A Brief Insight About Obsessive-Compulsive Disorder Treatment

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Abstract
Obsessive-compulsive disorder (OCD) as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM5TR), involve a complex and heterogeneous collection of thoughts, behaviors, and their interplay obsessive compulsive disorder (OCD) is a neuropsychiatric disorder affecting approximately 1–3% of the population and it is characterized by the occurrence of either obsessions, compulsive rituals or, most commonly both. The disorder is rarely limited to a single episode or to recurrent episodes. It usually arises in late adolescence or early adulthood, although onset in childhood or late adulthood can occur. Cognitive theories of OCD developed from research showing that negative intrusive thoughts are common experiences. OCD symptoms are produced by specific beliefs that pertain to responsibility and perfectionism, namely that one has a personal responsibility for protection against harm and that one should strive for perfection. Although the concept of obsessive-compulsive related disorders was initially developed on the basis of the apparent similarity of symptoms of some disorders (e.g., repetitive thinking and repetitive behavior), its proponents assert that these disorders also overlap in their neurobiology, patterns of comorbidity, familial patterns, and effective treatments. First line treatments for OCD include both pharmacotherapy (selective serotonin reuptake inhibitors SSRIs – and, among the tricyclic antidepressants, only the serotonin reuptake inhibitor –SRI - clomipramine) and cognitive behavior therapy (CBT) – in the forms of exposure and response prevention (ERP) and/or cognitive restructuring.
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Introduction:

Obsessive compulsive disorder (OCD) is a debilitating psycho- logical condition often results in significant functional impairment and a poor quality of life **(1)**

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Obsessive–compulsive disorder (OCD) is a mental disorder where people feel the need to check things repeatedly, perform certain routines repeatedly (called "rituals"), or have certain thoughts repeatedly. People are unable to control either the thoughts or the activities for more than a short period of time These activities occur to such a degree that the person's daily life is negatively affected **(3)**

Obsessions:

Obsessions are thoughts that recur and persist despite efforts to ignore or confront them. People with OCD frequently perform tasks, or compulsions, to seek relief from obsession-related anxiety. Within and among individuals, the initial obsessions, or intrusive thoughts, vary in their clarity and vividness. A relatively vague obsession could involve a general sense of disarray or tension accompanied by a belief that life cannot proceed as normal while the imbalance remains. A more intense obsession could be a preoccupation with the thought or image of someone close to them dying or intrusions related to "relationship rightness". [8]Other obsessions concern the possibility that someone or something other than oneself—such as God, the Devil, or disease—will harm either the person with OCD or the people or things that the person cares about. Other individuals with OCD may experience the sensation of invisible protrusions emanating from their bodies or have the feeling that inanimate objects are ensouled. **(4)**

Clinical picture

The disorder is rarely limited to a single episode or to recurrent episodes. It usually arises in late adolescence or early adulthood, although onset in childhood or late adulthood can occur **(5).**

- Clinical presentation of the disorder in children and adults is generally similar **(6).**
- Obsessive-compulsive disorder has been identified in many different ethnic groups **(7).**
- The main features of the symptoms seem to be consistent over time; for example, obsessions about violations of social taboos concerning sexual behavior and aggression. **(8).**

However, cultural background could affect the content of obsessions and compulsions for example, religious obsessions and compulsions (e.g., blasphemous intrusive thoughts, compulsive praying, and cleaning compulsions) might be more common in ethnic groups that emphasize the importance of religious observance than in those in which religion has a less prominent role. *(9).*

Pathophysiology:

1. ***Neurochemistry and neuroanatomy:***

Obsessive-compulsive disorder has been linked to a disruption in

A. **The brain's serotonin system**.

Serotonin dysregulation has been implicated in many other psychological disorders, and whether these disorders differ from one another in the type of abnormality is unclear. Obsessive-compulsive disorder has been associated with hypersensitivity of postsynaptic serotonin receptors.Individuals with the disorder might have a specific dysfunction in the genes encoding for the serotonin transporter (5-HTT) and serotonin receptor (5HT2A but these have not been consistently identified. ***(10)***

B. **The glutamate system** might also be dysfunctional in obsessive-compulsive disorder.

Preliminary research has implicated glutamate transporter genes such as Sapap3 and SLC1A1 in the disorder **(11)**

C. **The dopamine system** might be abnormal in obsessive-compulsive disorder, although results have been inconsistent regarding which dopamine genes are associated with the disorder.

- Two common features of obsessive-compulsive disorder (excessive doubting and repetitive actions) suggest that **specific brain regions** are involved in the condition: In particular,

a) The frontal orbitostriatal area (including the caudate nucleus)
b) The dorsolateral prefrontal cortex has been implicated in the inhibition of responses and in planning, organization, and verification of previous actions. ***(12)***

Treatment

Pharmacotherapy versus exposure and response prevention

First line treatments for OCD include both pharmacotherapy (selective

serotonin reuptake inhibitors SSRIs – and, among the tricyclic antidepressants, only the serotonin reuptake inhibitor –SRI - clomipramine) and cognitive behavior therapy (CBT) – in the forms of exposure and response prevention (ERP) and/or cognitive restructuring**.** Both the above-mentioned pharmacological and psychological approaches have been recognized as more effective than wait-list, inactive psychological treatments or placebo in individual randomized controlled trials (RCT)**. (13)**

Researchers have investigated the efficacy of medications versus exposure and response prevention. ***Foe and colleagues (14).*** compared the effect of:

Exposure and response prevention, Clomipramine alone, the combination of exposure and response prevention and clomipramine, placebo:

- **Exposure and response prevention** reduced Y-BOCS scores by 55%
- **Clomipramine** alone reduced it by 31%.

- **Combination of exposure and response prevention and clomipramine** reduced Y-BOCS scores by 58%, which was significantly greater than the effect of clomipramine alone, but not of exposure and response prevention alone.
- All active treatments were superior to **placebo** (11% Y-BOCS reduction). ***(14).***

Overall, the findings from randomized controlled trials suggest that exposure and response prevention whether delivered in daily or weekly sessions substantially improve obsessive-compulsive symptoms, and its effect is more than that produced by pharmacotherapy.

Symptom reduction is due to the specific techniques used in exposure and response prevention (i.e., exposure to fear-provoking stimuli while refraining from rituals) over and above the non-specific factors (e.g., expectations, attention) that are common to all psychological treatments.

Psychological treatments

Cognitive-behavioral therapy

The only empirically supported psychological treatment for obsessive-compulsive disorder involving (exposure and response prevention).

1) **Exposure** entails:

Systematic, repeated, and prolonged confrontation with stimuli that provoke anxiety and the urge to perform compulsive rituals.

- In situational exposure, the patient encounters actual feared stimuli e.g., toilets, cemeteries, and knives.
- In imaginal exposure, the patient confronts anxiety-provoking obsessional images (e.g., of molesting a child), thoughts (e.g., of a loved one's death), and doubts (e.g., "I might have hurt an innocent person by mistake") **(15).**

2) **Response prevention**

Definition: refraining from performing compulsive rituals.

For example, a patient who fears the number 13 because it will bring bad luck would practice writing this number and imagining causing bad luck. He or she would also refrain from performing any rituals to reduce anxiety or the chances of bad luck (e.g., saying prayers, checking for reassurance).

Aim of exposure and response prevention:

To teach patients with obsessive-compulsive disorder that his or her obsessional anxiety does not persist indefinitely, and that avoidance behavior and compulsive rituals are unnecessary for averting harm. Although exposure and response prevention is the only empirically supported psychological treatment for obsessive-compulsive disorder, additional motivational interventions are sometimes necessary for patients with very severe symptoms or for those with a limited ability to perceive that behaviors arising from obsessions are senseless. **(16)**

Although often effective, exposure and response prevention provoke anxiety in patients, and therefore approximately 25% of patients drop out of treatment. For patients who undergo exposure and response prevention, the effects of this treatment often last up to at least 2 years **(15).**

In conclusion, the combination ab initio of CBT and SSRIs has not been found to be clearly superior to either medication alone or CBT alone in most studies conducted in adult patients; the only exception is for patients with comorbid major depression, where the combination ab initio appeared superior to CBT alone. Our conclusion is that OCD patients with comorbid major depression should receive medication firstly, eventually associated with CBT; for all remaining patients there is clear evidence from the literature of no additive benefits of combining ab initio CBT and medication. Therefore, the routine use of a combination approach in all adult patients affected by OCD is not supported by the literature **(17)**

Pharmacotherapy

Randomized controlled trials have indicated that efficacious pharmacotherapies for obsessive-compulsive disorder include:

a) **Serotonin reuptake inhibitors**, such as clomipramine, and some **selective serotonin reuptake inhibitors**.

SSRI are the 1st line of treatment of OCD patients. However, these medications are effective only in some patients. A comprehensive meta-analysis of the pharmacotherapy publications for obsessive-compulsive disorder found that the mean effect size for obsessive compulsive symptoms across 18 randomized controlled trials of serotonin reuptake inhibitors was 0·91, which is a large effect. **(18)**

- However, most treatment responders showed residual symptoms after an adequate trial of treatment.
- Relapse after medication discontinuation is another issue:
- Relapse rates varied from 24% after discontinuation of sertraline
- To 31–89% after discontinuation of **clomipramine**
- Values which are much higher than the 12% relapse after completion of **exposure and response prevention therapy**.

In OCD patients there is a dysfunctional connectivity between raphe nucleus (RN) and other brain regions specially prefrontal(PFC) and temporal cortex. the results of the current study may suggest altered FC of the RN with brain regions comprising the CSTC circuit as a reflection of the pathophysiological mechanism in patients with OCD. However, considering that nearly half of patients with OCD show an insufficient therapeutic response to SSRIs and that neurotransmitter systems other than serotonin are also involved in OCD pathophysiology, patients with OCD under the current symptom-based diagnostic standard may be heterogeneous in the degree of serotonergic dysfunction and its contribution to the improvement of OC symptoms. Therefore, investigating brain-based biomarkers to predict SSRI responders would facilitate overcoming those heterogeneities and selecting an appropriate pharmacological agent from the beginning of treatment. We consistently found greater FC between the RN and the left MTG/STG in SSRI nonresponses than in responders,

suggesting that altered FC of the RN with the temporal cortices may be a useful brain-based biomarker of the SSRI response. **(19)**

A meta-analysis of nine double-blind randomized controlled studies (a total of 278 adult patients) showed that, for patients with obsessive-compulsive disorder who fail to fully respond to at least 3 months of treatment with serotonin reuptake inhibitors at their maximal tolerated dose, outcome can be significantly improved by:

b) **Adding an antipsychotic medication**.

Risperidone and haloperidol had additive effects that were especially beneficial for affected people with comorbid tics. Although these findings are encouraging, only a third of treatment refractory patients with obsessive-compulsive disorder show a clinically meaningful response to antipsychotic medication. Pharmacotherapy of pediatric obsessive-compulsive disorder has also been assessed in a meta-analysis, in which four serotonin reuptake inhibitors (paroxetine, fluoxetine, fluvoxamine, and sertraline), together with clomipramine, were investigated **(20)**

This study showed that, although treatment was effective compared with placebo, the effect sizes were generally modest (mean effect size=0·46), suggesting that these treatments were only partially effective.

c) Anti glutamatergic agents:

Evidence exists that the glutamate system is also dysregulated in obsessive-compulsive disorder. Accordingly, the efficacy of ant glutamatergic agents has been investigated; with small uncontrolled trials of Riluzole. Findings suggest that riluzole is associated with a modest reduction in obsessive-compulsive symptoms *(21)*

Psychotherapy and pharmacotherapy :(D-cycloserine)

Despite the hope that the combination of serotonin reuptake inhibitors and exposure and response prevention would lead to a more pronounced reduction of symptoms than that achieved with either monotherapy, this result has not been obtained.

A meta-analysis of 85 randomized controlled trials comparing combined treatments with monotherapies of serotonin reuptake inhibitors or exposure and response prevention showed:

No clear benefit of combined treatment over either monotherapy alone. Animal research suggests that the N-methyl-d-aspartate (NMDA) glutamate receptors are important for the expression of conditioned fear responses in the basolateral amygdala and of conditioned fear extinctionin the amygdala.These findings are consistent with the view that fears extinction, similar to fear acquisition, is a form of learning. Accordingly, NMDA agonists administered before an exposure task might facilitate the extinction of fear responses. One such compound is **D-cycloserine**, which has been used for years in humans to treat tuberculosis and is not associated with significant side effects. Animal research has shown that this compound facilitates fear extinction after either systemic administration or intra amygdala infusion **(22)**

Research on humans suffering from either animal phobia or social anxiety disorder has provided preliminary evidence that D-cycloserine, administered shortly before an exposure session, can facilitate (i.e., speed up) fear extinction. With regard to obsessive compulsive disorder. **(23)**

Three studies have compared:

Exposure and response prevention (10–12 sessions) with D-cycloserine (100–250 mg) to exposure and response prevention with a placebo:

D-Cycloserine was not better than placebo in reducing obsessive-compulsive symptoms either immediately after treatment or at 1–3-month follow-up.

A recent study found that patients with OCD (moderate to severe) have better out come when adding amantadine to SSRI **(24).**

Brain stimulation and surgical interventions

Surgical interventions for obsessive-compulsive disorder involve cutting the tracts (circuits) between structures that might be important in the disorder (e.g., the sectioning of tracts connecting the orbital frontal cortex and anterior cingulate) **(25).**

These procedures include Anterior capsulotomy, anterior cingulotomy, subcaudatetractotomy and limbic leucotomy.

Indications of surgical treatments:

Patients who have failed to respond to pharmacological or psychological treatments for obsessive-compulsive disorder. However, even for these patients, safety and efficacy of surgical interventions remain controversial, and there has been a growing interest in alternative, non-ablative surgical procedures. **(25).**

Surgical intervention as:

Deep brain stimulation of the basal ganglia, (through surgically implanted electrodes)

Although initial results are promising, this intervention should be adequately assessed for safety and efficacy in the treatment of obsessive-compulsive disorder. Nowadays it has a promising pathway specially in treatment of refractory OCD. **(25).**

Although there are effective treatments available for many, probably most, patients with OCD, a significant number do not respond, or fail to experience a sustained beneficial response. For patients with such chronic, disabling and 'treatment-refractory' OCD, neurosurgical treatments may be considered. The best-established neurosurgical treatments are so-called ablative procedures, where targeted lesions are created with the intention of interrupting and modifying specific circuitry functions. There is a lengthy history of such procedures and a substantial literature although this is largely of an observational nature. However, both stereotactic radiosurgery (gamma knife) and MR-guided high intensity focused ultrasound are methods of lesion generation that lend themselves to the conduct of blinded randomized trial designs and these are beginning to be utilized. (Sometimes proposed as an alternative to neurosurgery **(26)**

A non-surgical brain stimulation as:

Repetitive transcranial magnetic stimulation, (in which electrical activity in the brain is altered by placing an external electromagnet over certain brain regions).

TMS is a non-invasive neuromodulation technique that has shown efficacy in the treatment of a variety of neurologic and psychiatric conditions and has FDA-approval for treatment refractory major depressive disorder, anxiety associated with depression, treatment-refractory OCD, smoking cessation, and migraine with aura **(27)**

Deep brain stimulation, there are multiple promising modalities to provide neuromodulation for the treatment of refractory OCD both non-invasively and invasively. DBS is of particular interest because it works to directly modulate the known networks continuously over longer timescales. **(28)**

ECT is also a method of treatment when OCD patient has comorbid severe depression that may lead to suicidal thoughts or attempts.

Studies had explicitly added two additional groupings of OCD-related disorders that are not based on descriptive nosology, but rather on etiologic considerations. One of these links acute OCD onset to environmental events such as the consequences of infection, traumatic brain injury, and other neurological disease insults**. (29)**

The other newly suggested OCD spectrum encompasses etiologies related to specific gene or narrow chromosome region-related syndromes a fourth genomic OCD-related group. Some of this latter group also overlaps with disorders such as Tourette syndrome, with its common tripartite combination of tic disorders, OCD, and ADHD. It is of interest that some considerations for *DSM-5* and future *DSMs* are beginning to show additional elements beyond clinical symptoms as bases for designation of an entity. These include biological, psychophysiological, and brain imaging data as well as potential etiological factors including genetic elements and brain neurocircuitry contributions**. (30).**

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