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Obsessive-Compulsive Disorder: Current and Emerging Treatment Options

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ABSTRACT

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder that can result in significant functional impairment. The cost to society is both direct due to increased healthcare costs and indirect due to reduced productivity. For patients, it can lead to profound disability and greatly affect their quality of life. Due to the complex nature of the disorder, both diagnosis and treatment are often delayed, leading to poorer outcomes. Currently, first-line treatments for OCD consist of psychotherapy, medications or both. Unfortunately, both interventions, in conjunction or as monotherapy, take several months to take effect. In addition, only a fraction of patients with OCD sees a sufficient response to treatment. As a result, it is important for researchers and health care providers to continue investigating new treatments that may be more efficacious or reduce the time it takes for patients to respond. Three such treatments - the Bergen 4-day treatment, ketamine, and transcranial magnetic stimulation - will be discussed as well as reviewing the currently recommended treatments.

Introduction

Obsessive compulsive disorder (OCD) is a chronic, debilitating psychiatric disorder that affects more than 1% of the population (Rasmussen & Eisen, 1994; Ruscio et al., 2010), with a lifetime prevalence of 2-3% (Kessler et al., 2005). The World Health Organization (WHO) and the Global Burden of Disease Study determined that patients with OCD experienced more years of disability than patients with multiple sclerosis and Parkinson disease combined (WHO, 2008). OCD is associated with significant direct health care costs to society as well as indirect costs such as decreased productivity and reduced income (Fineberg et al., 2019).

As defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5*) (APA, 2013), OCD is characterized by obsessions and compulsions. Obsessions refer to repetitive and persistent thoughts, urges, or images that cause anxiety. Compulsions are repetitive behaviors that patients perform in an attempt to diminish or neutralize their obsessions. They are often very time-consuming and cause significant limitations. Compulsions are performed in a certain way or a specific number of times and need to be repeated if not done exactly in the "right" way or order. If a patient is interrupted during his or her compulsion, the entire compulsion must be started over from the beginning. Alternately, some patients repeat their compulsions until it feels "just right", or the "uncomfortable" feeling goes away. In addition, some patients will resort to avoidance behaviors in order to decrease the need for performing compulsions. For instance, if a doorknob is contaminated, avoiding touching the doorknob allows the patient to not have to perform the often extensive compulsion associated with that particular obsession. Although patients realize that the obsessions are not logical, the anxiety caused by them compels patients to perform compulsions or exhibit avoidance behaviors which only serve to provide temporary relief (Szechtman et al., 2020).

Due to a general increase in mental health awareness in recent years, it is more well known that OCD is associated with contamination, hand washing, and frequent checking such as repeatedly checking that the stove is turned off. However, there are several subtypes of OCD that are not as well known. The general subtypes

are: symmetry, superstition, and perfectionism; somatic fears; contamination and cleaning; taboo thoughts or fears; and hoarding (Katerberg et al., 2010). Due to the wide array of obsessions and manifestations of compulsions, OCD is often not recognized or misdiagnosed. In addition, there is a significant component of self-stigma in the form of shame, embarrassment, or guilt experienced by patients (Hirschtritt et al., 2017) that prevents patients from seeking professional help at the onset of symptoms. As a result, there are still significant delays in diagnosis and treatment – with an average of approximately 8 years between diagnosis and pharmacologic treatment and at least 8 years between onset of symptoms and formal diagnosis (Dell'Osso et al., 2019). Because numerous studies have shown that delayed treatment results in poorer outcomes (Fineberg et al., 2019), it is important that patients receive appropriate treatment as soon as it is warranted to decrease the severity of the illness and improve functional disability.

Current Treatments

When patients are diagnosed with OCD, a common standardized questionnaire used to assess patients is the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Stein et al., 2019). Scores range from 0 to 40, with a score of 8 to 15 indicating mild symptoms, 16 to 23 moderate symptoms, 24 to 31 severe symptoms, and 32 to 40 extreme symptoms. Scores below 8 are considered subclinical symptoms. Most scientific studies use the Y-BOCS to determine the effectiveness of various treatments and medications. For OCD studies, a treatment that results in a decrease of 35% in the Y-BOCS score is considered to be an effective treatment.

Current recommendations for the first-line treatment of OCD include cognitive behavioral therapy (CBT) with exposure response prevention (ERP) and/ or pharmacotherapy with a selective serotonin reuptake inhibitor (SSRI) or clomipramine, a tricyclic antidepressant (TCA) that also inhibits serotonin reuptake. The 2005 National Institute for Health and Care Excellence (NICE) guidelines recommend treatment of mild OCD symptoms with CBT including ERP, moderate symptoms with more intensive CBT with ERP or an SSRI, and a combination of both for severe symptoms (NICE, 2005).

CBT with ERP

In 2007, the American Psychiatric Association (APA) released practice guidelines that indicated that, among the various CBT techniques, ERP was the most effective (Koran et al., 2007). It is now the most commonly used psychotherapy for OCD (Hirschtritt et al., 2017). CBT is a form of psychotherapy that focuses on efforts to change thinking patterns and behavioral patterns. The goal of ERP is to identify and gradually reduce and eliminate the compulsive or avoidance behaviors that are associated with obsessions. Working with a therapist, patients first identify all of their obsessions and compulsions and rank them in order in terms of how much anxiety is caused by each obsession. Using this ranking system, obsessions and compulsions that cause the least amount of anxiety are tackled first. The patient is then "exposed" to the situation or element that causes the least amount of anxiety and instructed not to engage in the associated compulsion ("response prevention"). ERP is based on a behavioral principle known as habituation whereby physiological or emotional responses to stimuli decrease after repeated exposure.

Different phases of this therapy include first imagining the situation, then seeing someone else in the situation, and finally, engaging directly in the situation. For instance, if a doorknob is contaminated, the patient may first just picture the doorknob and not engage in the associated compulsion. Then, the patient may watch someone else touch the doorknob. Finally, he or she might touch the doorknob for 5 minutes and then 15 minutes and gradually increase the amount of time spent touching the contaminated item without engaging in the associated compulsion. In this way, patients are purposefully exposed to the feared situation and led to face the situation without performing the associated compulsion that would normally follow. Once low-level anxiety situations are mastered, situations that evoke higher levels of anxiety are addressed.

Multiple studies have shown that ERP is an effective treatment for patients with OCD (Stein et al., 2019; Reid et al., 2021; Koran et al., 2007). This treatment can be used in both inpatient and outpatient settings with varying frequencies (Stein et al., 2019). However, the treatment is highly dependent on patients continuing the exposure and response prevention exercises on their own in between sessions with their therapist. Studies have shown that patients usually need 16 to 20 sessions, and consistently attending therapy sessions and practicing ERP in between sessions are the strongest predictor of response to this treatment (Simpson et al., 2011; Stein et al., 2019).

SSRI's and Clomipramine

As mentioned earlier, SSRI's and clomipramine are also among first-line treatments recommended for patients, especially in areas where access to clinicians equipped to administer ERP is limited. Between SSRI's and clomipramine, SSRI's are currently used more frequently due to the their side effect profile being more favorable than clomipramine's at therapeutic doses.

The efficacy of clomipramine for OCD was a fortuitous discovery in the mid-1960s. At that time, psychiatrists were using clomipramine to treat depression and noticed that it resulted in an improvement in obsessive thoughts (Szechtman et al., 2020). This discovery led to many other TCA's being investigated for OCD treatment. However, other TCA's were not found to be as effective, and this was determined to be the result of clomipramine's unique characteristic of being a strong inhibitor of serotonin reuptake while other TCA's do not affect serotonin reuptake as much or at all. Based on the efficacy of clomipramine and SSRI's, it is now known that low serotonin levels are associated with OCD, since the mechanism of these medications is increasing serotonin levels. However, the exact relationship of serotonin to OCD is still unknown.

In the United States, clomipramine and only four SSRI's (fluoxetine, fluvoxamine, paroxetine, and sertraline) are currently approved by the Food and Drug Administration (FDA) for treating OCD. However, additional SSRI's, escitalopram and citalopram, have been shown to be equally effective in the treatment of OCD (Del Casale et al., 2019).

For patients with OCD, treatment with an SSRI or clomipramine is typically started at a low dose and slowly increased as tolerated to the recommended dosage, which is significantly higher than the dosages used for depression (Stein et al., 2019). Currently, the APA recommends at least 8-12 weeks of treatment (with at least 4-6 weeks at the maximum tolerable dose) before considering a change in medications (APA, 2007). Unlike depression, where medication dosages are often decreased over time, for OCD, long term treatment for 24-52 weeks is recommended to decrease the probability of relapse (Fineberg et al., 2007).

Unfortunately, approximately 50% of patients with OCD do not adequately respond to these treatments (CBT with ERP, medications, or both) (Fineberg et al., 2015; Hirschtritt et al., 2017). In addition, these treatments often take at least 6-12 weeks for patients to respond. As a result, there is ongoing research investigating alternate treatments and medications that may be effective for patients who do not respond adequately to currently recommended treatments or show effectiveness in a shorter time frame.

Emerging Treatments

The Bergen 4-Day Treatment (B4DT)

One such treatment is the Bergen 4-day treatment. Pioneered by Dr. Hansen and Dr. Kvale in Norway, the treatment is a concentrated exposure-based treatment delivered over the course of 4 consecutive days (Launes et al., 2019). Patients are treated in a group setting with 3-6 patients in a group and an equal number of therapists.

This allows for a 1:1 ratio of patients to therapists and ensures that the treatment is being administered properly and tailored to each patient's needs.

During the first day, patients are instructed on the rationale behind ERP and important principles for change. The anxieties and discomfort associated with obsessions and compulsions are reviewed as well as the need to confront these feelings and overcome them differently. The need for accepting varying degrees of uncertainty is addressed as well. Patients are taught how to "**LE**an into **T**he anxiety" (LET-technique) and introduced to loop tapes (repeated statements) to maximize uncertainty. The goal is to intentionally "let go" of the feeling of control that engaging in OCD behaviors provides (Launes et al., 2019). In contrast to ERP which relies on habituation, the B4DT encourages patients to embrace uncertainty, accept it, and then move on.

The second and third days are spent individualizing the exposures for each patient and practicing them with the therapist. Patients work individually with their therapist and also meet as a group in the morning, at lunch, and in the afternoon to report on their progress throughout the day. Some patients, as needed, will continue with their therapist using brief phone consultations in the evening. At the end of the third day, friends and family are invited to participate in a psycho-educative meeting (Launes et al., 2019). This aspect also differentiates the B4DT from ERP which does not necessarily include the involvement of friends and family as part of the treatment plan.

On the final (fourth) day, patients review the exposures they have completed and plan self-exposures for the folloowing three weeks. Patients are taught to be "their own therapists" (Launes et al., 2019) and are instructed to log their compliance with homework online without any therapist contact. Approximately 12 weeks after the 4-day treatment, patients have a final follow-up meeting to review their experience with the treatment and, if needed, to review strategies for fighting OCD.

Numerous studies have been conducted using this treatment technique and have shown that 90% of patients responded to the treatment and almost 70% of patients continued to show improvements up to 4 years post-treatment (Hansen et al., 2018; Hansen et al., 2019). In addition, a randomized controlled trial in 2019 showed a 94% response rate (defined as at least a 35% improvement in Y-BOCS score) to the B4DT compared to a 12.5% response rate in the self-help group and 0% response rate in the wait list group (Launes et al., 2019). A pilot study in Iceland (Davíðsdóttir et al., 2019) also demonstrated similar results.

A treatment that is this effective and can be delivered in just 4 days is a ray of hope for countless patients suffering from OCD for which current treatments take several months to take effect. Unfortunately, it is currently only available in Norway and Iceland. Plans to spread the treatment to the United States are currently on hold.

Ketamine

In addition to new psychotherapies that are currently being studied, alternate medications for the treatment of OCD are being investigated. Brain studies have shown that glutamate activity is associated with OCD and modulating levels using a class of medications known as N-methyl-D-aspartate (NMDA) receptor antagonists has emerged as a potential treatment for OCD, especially using ketamine (Rodriguez et al., 2013). It is still unknown exactly how ketamine reduces OCD symptoms. A possible explanation is that targeting NMDA receptor antagonists increases levels of gamma-aminobutyric acid (GABA) over time (Rodriguez et al., 2015). This increase in GABA downstream may result in a secondary glutamate release that activates hypo-functioning regions such as the parietal and frontostriatal regions (Bandeira et al., 2022). It is hypothesized that this downstream effect results in synaptic plasticity alterations in the cortico-striao-thalamo-cortical circuitry which is has been found to be imbalanced in patients with OCD.

Initial reports (Rodriguez et al., 2011; Bloch et al., 2012) of ketamine treatment involving one patient and ten patients, respectively, yielded mixed results. In Rodriguez et al.'s (2011) case study, a patient received one dose of intravenous (IV) ketamine at 0.5 mg/kg over 40 minutes. Post-infusion, the patient experienced a complete resolution of obsessive symptoms for 40 minutes. The symptoms gradually returned but did not return

to original levels until 7 days post-infusion. The ten patients in the Bloch et al. (2012) study received the same dose of IV ketamine over 40 minutes. Patients experienced a statistically significant reduction in OCD symptoms 3 days post-infusion but did not meet the clinical response criteria of at least 35% improvement in their Y-BOCS scores. The authors surmised that this may have been due to seven of the ten patients having co-morbid major depressive disorder.

In 2013, Rodriguez et al. published the first randomized, placebo-controlled, double-blind study of ketamine for OCD patients. The 15 patients were split into 2 groups: 8 patients received one IV infusion of ketamine at 0.5mg/kg over 40 minutes, and the remaining 7 patients received a placebo. The patients who were treated with ketamine showed a significant improvement in symptoms and met the treatment response criteria of at least a 35% decrease in Y-BCOS score at one week post-infusion. Meanwhile, none of the patients who received the placebo demonstrated any improvement in their symptoms. It was hypothesized that the difference in results compared to Bloch et al.'s (2012) study may have been that fewer patients had major depressive disorder as a co-morbidity (Bandeira et al., 2022).

Two additional studies (Adams et al., 2017; Sharma et al., 2020) investigated the effect of multiple ketamine infusions. The case report by Adams et al. (2017) involved one patient who received ketamine intranasally (50mg), twice a week for four weeks. He showed improvement in his symptoms but was also engaging in CBT at the same time. The second paper, by Sharma et al. (2020), was a retrospective chart review of 14 patients who had received multiple IV infusions of ketamine at 0.5mg/kg over 40 minutes. There were significant improvements in OCD symptoms, but only one patient met the treatment response criteria of at least 35% improvement in Y-BCOS score which lasted for three months. Three additional doses let to remission at 6 months follow up. Two other patient demonstrated partial responses defined as a 25-35% decrease in Y-BCOS scores (Bandeira at al., 2022).

When effective, the rapid onset of symptom improvement is very promising. However, effectiveness often faded, ranging from several hours to one week in the studies that have been conducted thus far (Bandeira et al., 2022). It is unknown whether alternate treatment protocols such as the twice a week for four weeks used by Adams et al. (2017) might prove to have longer lasting effects than just one or two infusions. In addition, it is still unknown whether IV ketamine or intranasal ketamine would be more effective, as the two have not been compared in a study. Perhaps ketamine could be used to initially, quickly improve symptoms, but then additional therapies, such as ERP, could be used to augment the neuro-plasticity aspect of treatment with ketamine to prolong the effects of the medication (Bottemanne & Arnould, 2021). Thus, appropriate dosing, treatment protocol, and possibly combining this treatment with others need to be investigated.

Transcranial Magnetic Stimulation (TMS)

In addition to CBT and pharmacologic treatments for OCD, different brain stimulating techniques such as transcranial magnetic stimulation are emerging as a possible adjunctive treatment for moderate to severe OCD. Repetitive TMS (rTMS) is a non-invasive treatment that delivers a series of electromagnetic pulses to different parts of the brain. High frequency rTMS is defined as 5-20 Hz, and low frequency rTMS is defined as 1 Hz or less. The treatment is delivered using a magnetic coil that is placed on the scalp to generate painless electromagnetic fields in different areas of the brain known to be affected by OCD. This alters the electrical activity within the area that is targeted. Researchers surmise that low frequency TMS leads to long-term depression while high frequency TMS results in behavioral change due to long-term potentiation (Lenz et al., 2016). In this way, the effects of the treatment persist beyond the treatment period.

Due to the various options in terms of frequency used and areas of the brain that are stimulated, there have been multiple studies investigating low frequency versus high frequency as well as treating different areas of the brain. Based on existing knowledge of the areas of the brain that are affected by OCD, the dorsolateral

prefrontal cortex (DLPFC), the supplementary motor area (SMA), the orbitofrontal cortex (OFC), and the medial prefrontal cortex (mPFC) have been targeted as areas for treatment with TMS. Most treatment protocols ranged from 2-4 weeks with treatments being administered daily. One meta-analysis showed that high frequency stimulation of the DLPFC and low frequency stimulation of the right DPLFC and the SMA were more effective than sham (Liang et al., 2021). Another meta-analysis of 26 studies by Perera et al. (2021) showed that TMS with either high or low frequency stimulation of the bilateral DLPFC had the greatest effect size. Meanwhile, a meta-analysis by Rapinesi et al. (2019) showed that low frequency stimulation may be more effective over the SMA or the OFC. These inconsistent findings are due to the various parameters used as well as the lack of robustness of the original studies being evaluated in the meta-analyses (Rapinesi et al., 2019; Kammen et al., 2022).

Another type of TMS is deep transcranial magnetic stimulation (dTMS) which utilizes the same general principles as TMS. However, the treatment uses a different device that can penetrate deeper into the brain and encompasses a broader surface area. dTMS reaches a depth of 3.2 cm while rTMS reaches a depth of 0.7 cm. Both treatments have similar side effect profiles. A multi-center, sham-controlled randomized study that used high frequency dTMS to target the mPFC showed that 38% of the treatment group achieved at least a 30% reduction in Y-BOCS scores versus 11% in the sham group (Carmi et al., 2019). Based on this study, which included 99 patients, dTMS was approved by the FDA for patients with treatment-refractory OCD.

These findings, that both low and high frequencies and targeting multiple different areas of the brain have been shown to be effective, raise further questions about exactly what protocols should be recommended for patients. As mentioned earlier, there are several subtypes of OCD, and researchers have been able to link certain neural pathways to specific OCD symptomatology (Mataix-Cols et al., 2004). Nonetheless, studies that target areas based on the associated subtype of OCD have yet to be conducted. Subsequent studies that target specific symptom profiles may lead to more precise treatment recommendations in the future.

In addition, just as ketamine has been proposed to be potentially more effective when coupled with ERP, there is evidence that a similar principle may apply to TMS which aligns with both treatments affecting neuroplasticity. For several other conditions, such as bulimia, PTSD, and smoking cessation, TMS has been effective in reducing symptoms when administered after presenting images of food cues, trauma cues, and nicotine cues, respectively (Van Den Eynde, et al., 2010; Isserles, et al., 2013; Dinur-Klein et al., 2014). This methodology, of presenting triggering stimuli prior to treatment was used for the dTMS study targeting the mPFC (Carmi et al., 2019) which may have augmented the effects of dTMS. Thus, additional studies using this methodology and targeting specific areas of the brain associated with certain subtypes of OCD may lead to more effective and personally tailored treatments for patients.

Conclusion

OCD is a chronic condition that can become extremely debilitating if not treated promptly or appropriately. As a result, proper and timely treatment is key to mitigating the degree of severity and functional limitations. Currently, CBT/ ERP and SSRI's (plus clomipramine) are the gold standard for treating OCD. Unfortunately, these options sufficiently treat only approximately 50% of all patients with OCD. In addition, it typically takes months for these interventions to take effect. Treatments such as the B4DT, alternate medications like ketamine, and TMS have shown promising results in less time than ERP or SSRI's.

For the B4DT, hopefully geographic expansion will allow greater access to this highly effective treatment. Based on the results of the studies in Norway, the Norwegian government now provides reimbursement for the treatment. One of the reasons the plan for expansion in the United States was put on hold was due to lack of insurance reimbursement. Currently, to the knowledge of the author, there is only one therapist in the United States who is offering this treatment and does not accept insurance.

For ketamine, future studies that investigate optimal dosing, form of medication delivery, frequency

and number of doses need to be conducted. In addition, the efficacy of adjunctive therapies, such as ERP during treatment, need to be investigated. Finally, since neuroplasticity plays a part in the mechanism of action, perhaps presenting triggering stimuli prior to treatment could further augment the effects of ketamine just as is the case for TMS.

For TMS, future studies designed to specifically target neural pathways that are known to be affected in patients with certain subtypes of OCD need to be conducted. In addition, more robust, randomized, sham-controlled studies with much larger sample sizes need to be conducted. Presenting triggering stimuli prior to treatments should be evaluated as well as combining TMS with other treatments such as ERP.

Hopefully, further research will lead to additional treatments being recommended as first-line treatments for OCD so that clinicians will have more options to offer to patients. In addition, if further research can provide a more personally customized treatment plan for patients that is effective in a shorter period of time, it would significantly lessen the societal burden that OCD currently causes.

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