

An Examination of the Effectiveness of SSRIs with Clomipramine on OCD Patients

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ABSTRACT

Most psychiatrists begin pharmacotherapy for Obsessive Compulsive Disorder (OCD) treatment with Selective Serotonin Reuptake Inhibitors (SSRIs) because they tend to lead to fewer side effects than other symptom-alleviating medications such as clomipramine. SSRIs have been shown to produce response rates of up to 60% in patients with OCD (Paxos, 2022). However, this leaves a considerable number of patients in need of other treatments. clomipramine may be used as either a monotherapy or in combination with an SSRI, as evidence has highlighted the positive impact it has on patients with OCD (Andrade, 2013). Previous research shows that clomipramine and SSRIs are roughly equivalent in benefit when taken alone (Mago, 2017). That said, less is known about the combination of these two medicines. This review will examine the literature comparing individuals with OCD medicated by either SSRIs or clomipramine alone, as well as those taking both in tandem in order to see which prescription best augments exposure and response prevention-based treatment. In addition, this review will briefly describe alternate treatments to examine other possible approaches to effective psychopharmacology.

Introduction

Today, it is estimated that 70 million individuals have experienced Obsessive Compulsive Disorder (OCD), globally (Wolmark, 2023). Researchers began developing medication for OCD about 50 years ago and, despite the lack of information on the condition, accumulating knowledge on serotonin made scientists confident that targeting the serotonergic system would be the most effective treatment for the illness (Washington, 2020). For this reason, psychiatrists typically prescribe Selective Serotonin Reuptake Inhibitors (SSRIs) as the first-line medicinal treatment for OCD, due to the higher general tolerability of the drug. Despite their effectiveness for many, SSRIs do not work in about 40% of OCD patients (Paxos, 2022). Because many patients have not seen a full recovery with SSRIs alone, psychiatrists have been jointly prescribing clomipramine with SSRIs, as clomipramine targets an additional neurotransmitter (norepinephrine), along with serotonin (National Center for Biotechnology Information, 2023). When taken individually, both SSRIs and clomipramine have similar impacts on OCD; however, there is minimal research on the utility of taking these medications together and addressing this gap may offer a new pathway for individuals struggling to see improvement after taking an SSRI alone. This review examines both the biology and mechanisms of taking these medications alone and together. By comparing data from clinical trials and scientific reviews, this review proposes that this combination-based treatment reduces symptoms of OCD, even though taking these medications in tandem increases side effects. However, it's important to note that combining SSRIs and clomipramine is not the only option for OCD patients who do not experience relief from SSRIs alone, so this review concludes by examining alternative options as well.

Methods

In order to examine the effects of SSRIs and clomipramine on OCD treatment, I conducted systematic searches on PubMed, ERIC, Web of Science, and Google Scholar. Throughout my search process, I relied on several search terms, including OCD, selective serotonin reuptake inhibitor, clomipramine, neurotransmitter, and neuroanatomy. This review synthesized results from scholarly research articles, scholarly review essays, and reports from medical institutions or academic research centers. To capture research on the evolution of modern diagnostic measures for OCD and combination-based treatments, the review included articles from 1997 to the present. The primary mechanism of analysis was identifying and interpreting patterns across the literature, with particular focus on the benefits and consequences of combining SSRIs and clomipramine.

The review excluded studies that investigated the use of clomipramine among patients with both OCD and another disorder, whether a mood disorder, personality disorder, tic disorder, psychosis, neurodevelopmental disorder, or eating disorder. Many researchers considered the effects of augmenting clomipramine with medications like lamotrigine and aripiprazole, and these studies were excluded because they introduced confounding variables. Besides a few tertiary sources used to establish context on OCD symptoms and explain its side effects, this review excluded gray literature, such as magazine articles, newspaper articles, and blogs.

Theories of Obsessive-Compulsive Disorder

Understanding the biological and neurological roots of OCD can help pinpoint medications that might be effective in reducing symptoms. Scientists have formed three compelling theories regarding the biological origins of OCD. The first is that there is dysfunction within a neuronal loop that stretches from the orbital frontal cortex to the thalamus. This theory is derived from and supported by neurosurgical research; interfering with the neuronal loop seems to benefit treatment-resistant OCD patients. The second theory places the origin of OCD on genetics and has its backstory in twin studies that revealed a connection between OCD and family history. The last and most relevant theory for the purposes of this review proposes that serotonergic neurotransmitters experience unusual activity, which is supported by the realization that clomipramine (a serotonin reuptake inhibitor) reduced OCD symptoms, whereas other non-serotonergic medications did not (“Understanding Obsessive-Compulsive,” n.d.). Despite these many theories, scientists agree upon some specific brain abnormalities associated with OCD. These include changes within the basal ganglia and orbitofrontal cortices. Changes in grey matter volume include volumetric increases in subcortical structures and decreases in the cortex. Reduced cortical thickness in the frontal, temporal, and parietal lobes is another neurological indicator of OCD. And lastly, there are communication issues between the cortex, striatum, and thalamus (“Understanding Obsessive-Compulsive,” n.d.). All of these structural changes to the brain present as the symptoms that characterize OCD.

Diagnosing Obsessive-Compulsive Disorder

Both the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) address the symptoms, signs, and mechanisms characterizing OCD. The Y-BOCS is a structured interview psychologists and other providers use to diagnose OCD by going through the common obsessions and compulsions present in the disorder (Scahill, et al., 1997). Obsessions are intrusive, unwanted, disturbing thoughts that appear recurrently in the mind of a person with OCD (American Psychiatric Association, 2013, p. 237). Compulsions are repetitive, unrelated actions done in an attempt to soothe, get rid of, or prevent the obsession from happening. In practice, many people with OCD possess multiple obsessions and compulsions. Y-BOCS categorizes obsessions into eight groups and compulsions into seven groups. The eight obsessive groups are the following: aggressive, contamination, sexual, hoarding/saving, religious, symmetry/exactness, somatic, and miscellaneous. The seven compulsive groups are cleaning/washing, checking, repeating, counting, ordering/arranging, hoarding/collect-

ing, and miscellaneous (Scahill, et al., 1997). The *DSM-5* stresses that, in order to get an OCD diagnosis, one's symptoms cannot be explained by the usage of substances, the presence of another mental disorder, or the side effects of a current prescription. After ruling out these possibilities, physicians must confirm that the amount of time spent on obsessions and compulsions exceeds an hour per day for OCD to be considered clinically significant (American Psychiatric Association, 2013, p. 237).

Medicinal Development

After diagnosing a patient with OCD, antidepressants are one of the first lines of defense against the condition, and they have continued to be critical treatments since their development back in the 1950s and 1960s. Interestingly, this category of drug emerged out of chance. Scientists were testing tuberculosis medication, Iproniazid, when they observed fewer depression symptoms in hospital patients around 70 years ago. This drug later became the first pharmacological depression treatment on the market due to its abilities as a monoamine oxidase (MAO) inhibitor. MAO blocks chemical signals for messengers, including serotonin, norepinephrine, and dopamine, so inhibiting it helps restore the activity of these neurotransmitters (Washington, 2020). This discovery, along with the creation of the first tricyclic antidepressant (imipramine), characterized psychopharmacological discovery in the 1950s (Hillhouse & Porter, 2015). Imipramine's development in 1957 led to the creation of many similar drugs, categorized as tricyclic antidepressants. In 1961, scientists began modifying the chemical structure of imipramine to create other tricyclics, such as amitriptyline and desipramine. Starting in 1963, these offshoots of imipramine began being prescribed globally. In 1964, clomipramine was synthesized as a result of previous tricyclic developments (Pereira, 2018). Relatedly, when researchers tested tricyclic antidepressants on patients with schizophrenia, they realized they showed better results on people with depression. These findings shaped the popularization of a theory called the monoamine hypothesis throughout the mid-20th century. This hypothesis postulates that patients with depression possess lower concentrations of serotonin, norepinephrine, and dopamine (Hillhouse & Porter, 2015). The monoamine hypothesis led to many discoveries that continue to influence pharmacological innovation, including developments in treatment methods for OCD.

The monoamine hypothesis informed one treatment that remains common today: SSRIs. SSRIs target the serotonin reuptake process (Silvestro & Varvatsis, 2021). In the average brain, once a neuron's action potential travels down its axon, it triggers the presynaptic neuron to release neurotransmitters into the synaptic cleft. The neurotransmitter binds to the postsynaptic neuron's neurotransmitter receptor. For serotonin, a reuptake transporter will eventually bring the neurotransmitter back into the presynaptic neuron and into a synaptic vesicle where it will be stored until the next action potential. SSRIs target serotonin's reuptake process, leaving the neurotransmitter in the synaptic cleft for longer so that it can repeatedly bind to the receptor and keep the signal going (Wrobel, 2007). Because serotonin is a feel-good chemical, its reuptake leads to increased happiness.

Side Effects

Although adjusting the serotonin reuptake process can be beneficial, it can also often lead to adverse experiences. Because SSRIs are the category of drug most popularly prescribed for depression, clinicians have noticed a range of responses to the medication, but clomipramine often has more severe side effects. 40% of people on SSRIs report weight gain, drowsiness, and sexual dysfunction (Cascade, et al., 2009). Weight gain and drowsiness are readily identifiable symptoms, but sexual dysfunction can range from difficulty maintaining or obtaining an erection or difficulty reaching orgasm during sex. Other common side effects can include dizziness, blurred vision, nausea or vomiting, and emotional disturbances, such as heightened anxiety or agitation. However, the benefit of SSRIs is that most of these reactions are not overly bothersome to the patient and sometimes can even go away within the first few weeks of being on medication as the body adjusts (Cascade, et al., 2009). Unfortunately, because many people underestimate these

symptoms, they refrain from telling their prescribers and general physicians about their responses to a new SSRI, preventing opportunities for practitioners to identify other medications that might work (Cascade, et al., 2009). There is some overlap between the side effects of SSRIs and clomipramine: drowsiness, dizziness, stomach problems, sexual dysfunction, and weight changes (Cipriani, et al., 2018). However, more severe side effects specific to clomipramine include sleep problems, lessened mental acuity, raised blood sugar levels, increased seizure risk, and prolongation of the QTc wave on an EKG, which can be linked to tachycardia (Andrade, 2013). Despite the side effects that occur in some cases, SSRIs and clomipramine can have substantial positive impacts on mood when taken together and individually.

Primary and Secondary Treatments

Before being prescribed an antidepressant, most clinicians recommend that OCD patients try therapy first, as it is completely non-invasive and, at times, effective. The gold-standard psychotherapy intervention for OCD is Exposure and Response Prevention therapy (ERP). ERP involves introducing someone to a triggering stimulus and delaying the urge to perform a compulsion in response to this stressor. Despite the fact that ERP has been proven helpful in treating OCD on the whole, a large portion of patients do not receive optimal benefits from the treatment. In addition, OCD patients often quit ERP therapy before it works due to discomfort with the approach (Law & Boisseau, 2019). This review has already described how psychiatrists tend to prescribe SSRIs as a next step.

However, some patients are not adequately aided by SSRIs alone, so clomipramine may be added to their SSRI prescription. Most doctors only consider clomipramine after two to three failed trials of SSRIs. In many cases, SSRIs can partially ease symptoms, but adding clomipramine heightens the effect of both drugs (“Medications for OCD,” n.d.). In Australia, a study found that five percent of all SSRIs were prescribed in conjunction with another antidepressant, such as clomipramine. In Canada, this percentage was nine (Gillman, 2009). A chart review conducted in Canada involved six pediatric patients with OCD. Upon reviewing these patients’ medical records, combining clomipramine with the SSRI fluvoxamine was found to be effective (Fung, et al., 2021). A similar case study on seven patients with OCD discovered that the combination of these two medications was more effective than their previous monotherapy approach, even though these subjects did experience some of the side effects listed above (Figuroa, et al., 1998). Finally, a review of nine trials involving over 800 children with OCD discovered that the combination of an SSRI and clomipramine had its greatest positive effect after the first few weeks of treatment (Varigonda, et al., 2016). For some patients, alleviating OCD symptoms is a trial-and-error process, but the combination of clomipramine and SSRIs has proven to be one of the most successful approaches.

Aside from clomipramine, there are two other classes of drugs that doctors commonly utilize with an SSRI to treat OCD. The first of these is a class of medications called antipsychotics. Antipsychotics have been shown to block some of the brain’s dopamine receptors, which is helpful because OCD has been linked to higher concentrations of dopamine in the brain (“The Effects of Dopamine and Antipsychotic Drugs,” 2019). Studies state that one in three people who don’t respond to SSRIs improve when adding an antipsychotic prescription to their current regime. Of antipsychotics, risperidone and aripiprazole have the greatest evidence pointing to their success in OCD treatment. Another alternate drug that can be combined with an SSRI is ketamine, a medication taken via infusion that has effects on the glutamate system. At high doses, ketamine acts as an anesthetic by blocking glutamate. At low doses, ketamine enhances glutamate production, which helps regenerate neuronal connections lost due to stress and depression (Yin, n.d.). A case study revealed that, within 30 minutes post-treatment, a patient experienced a complete stop to obsessions that did not return fully for 7 days (Rodriguez, et al., 2011). A different study highlighted the realization that ketamine infusions lasted for approximately two weeks (White, 2017). While these are all medications that can be added to primary medications, there are also a slew of non-invasive procedures that augment the effects of both SSRIs and clomipramine.

Alternative Non-Invasive Treatments

Other approaches to treating OCD involve stimulating or capturing electrical information in the brain. Transcranial Magnetic Stimulation (TMS), for example, involves using a machine with an electromagnetic coil that generates highly concentrated magnetic fields which turn on and off very rapidly. These magnetic fields move into the brain and produce very small electrical currents, which activate cells that release neurotransmitters (“How does TMS Work,” n.d.). A review of 21 studies that included results from over 600 patients with OCD indicated that TMS effectively stimulated both the dorsolateral prefrontal cortex and medial frontal cortex at high and low frequencies alike (Fitzsimmons, et. al., 2022). Deep brain stimulation is another method of relieving OCD symptoms. This approach first entails undergoing a brain scan, which helps the practitioner establish which part of the patient’s brain has an abnormality that causes symptoms. Next, a device that delivers low-level electrical signals is placed in the problem-area of the brain. The signals this device administers help to ease severe OCD symptoms (Borders, et. al., 2018). One study, which reviewed 32 different research papers, concluded that out of 153 patients, most experienced relief when the deep brain stimulation targeted the nucleus accumbens or ventral cortex/ventral striatum (Borders, et. al., 2018). Finally, some OCD patients have found that neurofeedback can help improve their condition. Neurofeedback starts by placing a cap on the patient’s scalp that collects the electrical signals in the brain; this process is referred to as a Quantitative Electroencephalogram (qEEG). This method shows wave patterns in the brain, highlighting areas for improvement that can be addressed via targeted training activities (Marzbani, et. al, 2016). One study involving neurofeedback observed 36 drug-resistant subjects with OCD who participated in various numbers of sessions depending on the severity of their condition. Out of these 36, only three did not experience clinical improvement according to both their Y-BOCS and Clinical Global Impression (CGI) scores. When researchers followed up with these subjects after 26 months, 19 of the 33 maintained improvement, according to interviews conducted with either subjects or members of their families (Sürmeli & Ertem, 2011). Taken together, TMS and neurofeedback can be promising means of magnifying the impact of SSRIs and clomipramine for many OCD patients.

Conclusion

Ultimately, research has found that SSRIs and clomipramine tend to augment each other's characteristics– both in benefits and side effects (“Medications for OCD,” n.d.). Especially in patients with severe OCD or among those who are non-responsive to an SSRI, a joint approach has proven effective. It is, however, unclear if this combination is the ideal treatment method, as adding an antipsychotic to an SSRI could be similarly helpful for some patients. That said, side effects such as high bloodwork levels, nausea, and tachycardia, among others, can increase when taking multiple medicines. More research is needed on the combination of these medicines, as well as their long-term effects, especially in pediatric patients. Another area with room for growth is tailoring medicines to each person without needing a trial-and-error process, which is an approach similar to precision medicine. Because SSRIs and clomipramine react differently in each brain, it is important for researchers to examine the factors that trigger or worsen OCD, so that medications can better target these influences, whether genetic, environmental, or trauma related.

Limitations

While this review gathered information from a variety of sources from different databases, there is still a significant gap in knowledge on the impact of combination-based treatment methods for people with mental illness. In this case, the joint use of SSRIs and clomipramine needs to be the focus of more research, as long-term effects and physical side effects remain largely unclear. Because research on the combination of SSRIs and clomipramine is limited, this review needed to examine studies involving both children and adults. As the field develops, it would be helpful for scholars to consider the ways that children and adults present differently in terms of their OCD symptoms when prescribed both of these treatments. The sample sizes of existing studies varied immensely, and more large-scale research should

be done on this topic. Finally, this review collected findings from journals around the globe, which provided a robust sense of common combination-based treatment approaches, even though the scope of the review did not leave space to consider the ways countries differ in terms of treatment plans and diagnostic measures. All of these limitations establish the need for augmenting research on combining not only clomipramine and SSRIs, but also other medications to treat various mental illnesses. While previous research focused on the emotional benefits of these medications, the physical and cognitive side effects of combining psychiatric medications have been left largely unexplored. Because of this, it is essential that more attention is paid to combination-based pharmacotherapy for OCD, as it will pave the way for a more holistic research approach for other medicinal treatments.

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