HHS Public Access

Author manuscript

Curr Top Behav Neurosci. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

Curr Top Behav Neurosci. 2021 ; 49: 331–384. doi:10.1007/7854_2020_204.

Pharmacotherapeutic strategies and new targets in OCD

Christopher Pittenger, MD, Ph.D.

Department of Psychiatry, Yale University School of Medicine, 34 Park Street, 333b, New Haven, CT 06524, USA

Abstract

Effective pharmacological and psychotherapeutic treatments are well established for obsessive-compulsive disorder (OCD). Serotonin reuptake inhibitors (SRIs) are first-line treatment and are of benefit to about half of patients. Augmentation of SRI treatment with low-dose neuroleptics is an evidence-based second-line strategy. Specialty psychotherapy is also used as both first-line and second-line treatment and can benefit many. However, a substantial number of patients do not respond to these treatments. New alternatives are urgently needed. This review summarizes evidence for these established pharmacotherapeutic strategies, and for others that have been investigated in refractory disease but are not supported by the same level of evidence. We focus on three neurotransmitter systems in the brain: serotonin, dopamine, and glutamate. We summarize evidence from genetic, neuroimaging, animal model, and other lines of investigation that probe these three systems in patients with OCD. We also review recent work on predictors of response to current treatments. While many studies suggest abnormalities that may provide insight into the pathophysiology of the disorder, most studies have been small, and non-replication of reported findings has been common. Nevertheless, the gradual accrual of evidence for neurotransmitter dysregulation may in time lead the way to new pharmacological strategies.

1. Introduction

Obsessive-compulsive disorder (OCD) affects approximately one person in 40 over the course of a lifetime and causes significant morbidity, worldwide (Ruscio, Stein et al. 2010, Kessler, Petukhova et al. 2012, Hollander, Doernberg et al. 2016, Torres, Fontenelle et al. 2017). Once considered rare (Rasmussen and Eisen 1990), OCD is now recognized as a significant source of both personal suffering and public health impact (Ruscio, Stein et al. 2010, Hollander, Doernberg et al. 2016, Boisseau, Schhwartzman et al. 2017, Torres, Fontenelle et al. 2017) and is the focus of substantial research, as epitomized by the current volume. Pharmacological and psychotherapeutic treatments for OCD are well established and supported by a robust evidence base (Skapinakis, Caldwell et al. 2016). Unfortunately, a substantial minority of patients, perhaps as many as a third, get little benefit from available treatments. Remission of symptoms is rare in those with moderate to severe disease, even with the best treatments we currently have to offer. There is thus an urgent need for new insights into the causes and pathophysiology of the disorder, and new strategies for treatment, prevention, and cure.

203-974-7675, christopher.pittenger@yale.edu.

This chapter provides a critical review of available pharmacological treatments for OCD. The goal is not to present an exhaustive summary of the current literature or a practical guide for clinicians; these have been recently provided by others (Fineberg, Reghunandanan et al. 2015, Skapinakis, Caldwell et al. 2016, Pittenger 2017, Reid, Reghunandanan et al. 2017). The focus on psychopharmacology should not be construed as implying that medication treatment of OCD is all that is needed in most cases; specialized cognitive-behavioral therapy is a first-line treatment and is often a critical component of an optimal treatment program (Excellence 2006, Koran, Hanna et al. 2007). Here, however, the focus is on pharmacology, and more specifically on pharmacology in adults. We review current evidence-based treatments, and some other treatment strategies that are sometimes used clinically in refractory disease despite a weaker evidence base. We then consider what these strategies may be telling us about the underlying mechanisms of disease, and other lines of evidence (genetics, neuroimaging, pharmacological challenge studies, animal models) that may help inform our understanding of these mechanisms.

Importantly, the efficacy of a particular drug cannot by itself identify specific pathophysiological mechanisms. Pharmacological treatment may act by reversing a core disease-associated abnormality, as when levothyroxine supplementation replaces missing thyroid hormone in primary hypothyroidism, or L-DOPA treatment increases dopamine production to compensate for dopamine depletion in Parkinson's disease. In such a case, extrapolation from the mechanism of action of a drug to inferences about pathophysiology is straightforward. But a medication can also treat disease by indirectly counteracting pathophysiology through its downstream effects; for example, interferon gamma has historically been used to cure hepatitis C by stimulating the immune system to eliminate the virus, but this does not imply that hepatitis is caused by interferon deficiency. Finally, a medication can compensate for disease pathophysiology without reversing it. For instance, diuretics such as furosemide are a mainstay of treatment for congestive heart failure (CHF) but act on the kidney, not the heart; they do not reverse heart failure but rather mitigate some of its consequences by removing fluid, thus achieving a new, more functional equilibrium. It would be an error to infer that, because furosemide provides clinical benefit in patients, CHF must be, at its core, a disease of excessive fluid retention by the kidney.

Similarly, in the case of OCD, we cannot facilely conclude from the well-established efficacy of selective serotonin reuptake inhibitors (SSRIs) (Soomro, Altman et al. 2008, Issari, Jakubovski et al. 2016) that serotonin deficiency or dysregulation is central to the underlying pathophysiology of the condition. Indeed, as further discussed below, evidence from other sources (genetics, neuroimaging; see chapters "The Future of Obsessive-Compulsive Spectrum Disorders: A Research Perspective", " Genetics of OCD and Related Disorders; Searching for Shared Factors", " Recent Developments in the Habit Hypothesis of OCD and Compulsive Disorders", and " Invasive and Non-invasive Neurostimulation for OCD") provides limited support for this theory. Nevertheless, thoughtful consideration of the pattern of medication response may provide some hints as to what is happening in the brain in patients, or at least facilitate the framing of new hypotheses.

It is widely appreciated, but nevertheless important to state, that OCD is an extremely heterogeneous disorder. This creates challenges both to studies of pathophysiology and

to the development and validation of new treatments. It is clear that OCD does not have a unitary cause. Genetic factors, which determine 40–50% of the risk (Davis, Yu et al. 2013), are complex and not well understood (Fernandez, Leckman et al. 2018), and developmental or environmental contributors are even more mysterious (see chapters “The Future of Obsessive-Compulsive Spectrum Disorders: A Research Perspective”, “ On the Development of OCD”, “Genetics of OCD and Related Disorders; Searching for Shared Factors”, and “New Directions for Surgical Ablation Treatment of Obsessive Compulsive Disorder”). Given this causal complexity, and presumed heterogeneity, group-level studies may obscure important truths. For example, a recent genetic analysis identified 2 candidate rare genetic causes of OCD and suggested the existence of as many as 400 similar rare, large-effect mutations, each explaining a tiny fraction of cases (Cappi, Oliphant et al. 2019). Such rare causes may be determinative in individual cases but will never be seen in a population study (Stewart, Yu et al. 2013, Mattheisen, Samuels et al. 2015, International Obsessive Compulsive Disorder Foundation Genetics and Studies 2018), as they explain too little of the population variance.

This heterogeneity in turn complicates the search for new treatments, pharmacological or otherwise. In the extreme case, a treatment might be curative in patients who carry a particular causal mutation but completely ineffective in those who do not; such a treatment will never show statistically significant benefit in the heterogeneous clinical populations enrolled in large controlled treatment studies. It may be necessary to stratify studies by underlying pathophysiology in order to reach the ultimate ‘precision medicine’ goal of identifying the optimal treatment for each patient. Such stratification by individual characteristics may be a realistic near-term goal in the treatment of cancer (for example) (Friedman, Letai et al. 2015), but we are far from achieving this precision in the treatment of OCD, or any other psychiatric syndrome.

It is possible that clinical OCD represents a final common pathway that individuals can reach through a range of different trajectories (Pittenger, Gruner et al. 2017). Alternatively, it may not be a unitary condition at all but rather a multidimensional spectrum (Bloch, Landeros-Weisenberger et al. 2008, Olatunji, Ebesutani et al. 2017), or a collection of phenomenologically overlapping pathophysiological entities that share no common core. We must be modest in what we can expect of group-level pharmacological treatment studies; given the heterogeneity of OCD, it is unlikely that any treatment will produce dramatic benefit in all patients. Indeed, this prediction matches experience: SSRIs, the mainstay of the pharmacological treatment of OCD, are of significant benefit in 40–50% of patients, but of limited benefit in others, and none at all in a distressingly large minority.

With this context in mind – and these caveats – we turn to a review of current pharmacological treatments, and the brain systems that they implicate.

2. Serotonin reuptake inhibitors

Efficacy of serotonin reuptake inhibitors (SRIs).

Clomipramine, a tricyclic antidepressant that potently blocks serotonin reuptake (Wishart, Feunang et al. 2018), was first identified as a potential treatment for OCD in the 1960s

(Fernandez Cordoba and Lopez-Ibor Alino 1967, Fineberg and Gale 2005). Randomized, placebo-controlled trials began to appear in the early 1980s (Marks, Stern et al. 1980, Insel, Murphy et al. 1983), and two definitive multi-center trials were completed at the end of that decade, with robustly positive results (DeVeaugh-Geiss, Landau et al. 1989, Katz, DeVeaugh-Geiss et al. 1990, Group 1991). Meta-analysis of multiple controlled studies unambiguously demonstrates benefit from clomipramine treatment (Skapinakis, Caldwell et al. 2016). However, clomipramine is not recommended as a first-line agent in current treatment guidelines, because of its problematic side effect profile (Baldwin, Anderson et al. 2005, Excellence 2006, Koran, Hanna et al. 2007).

The selective serotonin reuptake inhibitors (SSRIs) – fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, and escitalopram – are the mainstay of the pharmacotherapy of OCD and the first-line pharmacological recommendation in all major treatment guidelines (Baldwin, Anderson et al. 2005, Excellence 2006, Koran, Hanna et al. 2007, Fineberg, Reghunandanan et al. 2015). They were first shown to be efficacious in the late 1980s (Perse, Greist et al. 1987, Goodman, Price et al. 1989, Montgomery, McIntyre et al. 1993); efficacy has now been shown across multiple double-blind, placebo-controlled studies and is unambiguously supported by meta-analysis (Soomro, Altman et al. 2008, Issari, Jakubovski et al. 2016, Skapinakis, Caldwell et al. 2016). The SSRIs appear to be slightly less efficacious than clomipramine (Skapinakis, Caldwell et al. 2016), though this has never been demonstrated in a head-to-head comparison. Nevertheless, their favorable side effect and safety profile makes them the first choice for pharmacological treatment in most or all cases (Excellence 2006, Koran, Hanna et al. 2007, Fineberg, Reghunandanan et al. 2015).

The six available SSRIs have all been shown to be efficacious in the treatment of OCD. Fluoxetine, fluvoxamine, sertraline, and paroxetine are approved by the United States Food and Drug Agency and by parallel regulatory agencies in other countries for this indication; escitalopram is also approved in Europe. Citalopram and escitalopram (in the United States) are often used off-label (Excellence 2006, Koran, Hanna et al. 2007, Fineberg, Reghunandanan et al. 2015, Reid, Reghunandanan et al. 2017). Head-to-head comparisons between these agents are sparse and have not shown differential efficacy; meta-analysis similarly shows no difference between them (Soomro, Altman et al. 2008, Issari, Jakubovski et al. 2016, Skapinakis, Caldwell et al. 2016).

SSRI dosage.

Optimal SSRI response in OCD is achieved at high doses (Bloch, McGuire et al. 2010), and doses in excess of the approved antidepressant dose range are often used. For example, treatment guidelines suggest doses of fluoxetine of up to 120 mg/dy, fluvoxamine up to 450 mg/dy, and sertraline up to 400 mg/dy (Koran, Hanna et al. 2007, Reid, Reghunandanan et al. 2017). The clinical importance of this guidance is clear but should not be exaggerated; more typical SSRI doses are of benefit to many, and the added benefit of raising them beyond the usual range is modest, at the population level. That said, in the absence of problematic side effects and or other contraindications, it is good practice to push to high doses before declaring a trial a failure, lest a potentially beneficial treatment be abandoned

prematurely. The highest doses are typically tried when more typical doses produce partial response without problematic side effects.

A caveat to this guidance arose about a decade ago with the observation that high doses of citalopram are sometimes associated with an increase in the QTc interval on the EKG (FDA 2012), which could in principle lead to dangerous arrhythmias. This led to a recommendation by the U.S. Food and Drug Administration that citalopram not be dosed above 40 mg/dy, or above 20 mg/dy in those over 60 years old (Services 2012). Similar concerns have been raised for escitalopram. Subsequent analyses have not revealed a clear association between citalopram use and negative cardiac outcomes (Zivin, Pfeiffer et al. 2013, Hasnain and Vieweg 2014, Hutton, Cave et al. 2017); evidence remains equivocal. Nevertheless, the FDA warning (and similar guidance in Canada and the United Kingdom (Service 2011)) complicates the use of high-dose citalopram, and perhaps escitalopram, for OCD; at the very least, medicolegal considerations must be taken into account, and EKG monitoring is advisable. These factors have steered many prescribers away from the use of high-dose citalopram in OCD, despite the clear evidence for efficacy (Bloch, McGuire et al. 2010, Issari, Jakubovski et al. 2016).

Duration of SSRI treatment.

Full clinical response to SSRI pharmacotherapy in OCD often takes many weeks (Soomro, Altman et al. 2008). Treatment guidelines therefore recommend trials of 8–12 weeks before a particular medication can be declared ineffective (Baldwin, Anderson et al. 2005, Koran, Hanna et al. 2007). This can be a source of frustration for both prescribers and patients, as it may entail continuation of ineffective treatment for many weeks before moving on to an alternative strategy. There is evidence that SRI benefit begins early in treatment; in the largest, best-powered of the early clomipramine efficacy trials benefit was seen as early as 2 weeks (DeVeaugh-Geiss, Landau et al. 1989); and a recent meta-analysis including data from more than 3200 patients concluded that benefit begins shortly after treatment initiation and indeed is greatest in the early weeks (Issari, Jakubovski et al. 2016) (though it takes several weeks to accumulate to the point of being statistically detectable in clinical studies). Partial early response may therefore be a useful indicator of the likelihood of later benefit; indeed, one study examining this issue found that only 20% of patients who did not show partial response at 4 weeks went on to develop a full clinical response (≥35% improvement) at 12 weeks (da Conceicao Costa, Shavitt et al. 2013). Early response may therefore be a clinically useful indicator of the likely ultimate benefit from a particular drug trial, though with some risk of premature termination in a fraction of patients who would ultimately respond to a full-length trial.

Optimization of SSRI treatment.

Unfortunately, a substantial fraction of patients – close to half – do not respond to a first SSRI trial. There are several reasonable strategies to optimize SRI response. While our focus in this review is on pharmacotherapy, evidence-based psychotherapy should always be considered in this context (Koran, Hanna et al. 2007, Simpson, Foa et al. 2013). If response is partial, further escalation of SSRI dose or extension of a trial is a reasonable strategy. Higher doses are often more effective, as noted above (Bloch, McGuire et al.

2010, Issari, Jakubovski et al. 2016); and in some patients, full response becomes apparent only after many months (Rasmussen, Hackett et al. 1997). Intravenous SRI treatment has been used in a few studies as a way to rapidly achieve high doses; there is some evidence of benefit in those who have not responded to standard dosing (Fallon, Liebowitz et al. 1998, Pallanti, Quercioli et al. 2002, Karameh and Khani 2015), but this is not a widely available therapeutic strategy. Switching to a second SSRI may be of benefit in some patients, although the likelihood of response declines with subsequent trials (Reid, Reghunandanan et al. 2017). Switching from an SSRI to clomipramine is more likely to be of benefit, and clomipramine should therefore be considered as a second- or third-line intervention, when initial SSRI monotherapy is ineffective (Koran, Hanna et al. 2007). Other strategies, such as combination of two different SSRIs, or of an SSRI and clomipramine, have been investigated in small trials (Reid, Reghunandanan et al. 2017), but the evidence is insufficient to support any of these as a clear next step after initial nonresponse. Such combination regimens increase the risk of drug-drug interactions and problematic side effects.

3. Other serotonergic agents.

The efficacy of monotherapy with serotonin reuptake inhibitors (clomipramine and SSRIs) has motivated trials of other serotonergic strategies, especially in patients who do not respond to an initial SSRI trial. No other agents have been definitively shown to be effective; but most trials have been small, and the evidence for other serotonergic agents is thus best considered equivocal, rather than negative.

Serotonin-norepinephrine dual reuptake inhibitors.

A few studies have investigated the dual reuptake inhibitor venlafaxine as monotherapy in OCD, with mixed results. An early study reported that patients who failed initial SSRI treatment were more likely to respond if they were switched to venlafaxine treatment than if they were switched to an alternative SSRI (L, U et al. 2001); but a subsequent crossover study found the opposite result (Denys, van Megen et al. 2004). More recently, an observational study from India found a high rate of response to venlafaxine treatment in SSRI nonresponders (Balachander, Kodancha et al. 2019). There are no published trials of desvenlafaxine in OCD. Duloxetine treatment of OCD has been reported in a number of case reports, and in one controlled trial that found similar response to duloxetine versus a second SSRI after failure of response to a first SSRI trial (Mowla, Boostani et al. 2016). It is difficult to draw firm conclusions from these small studies.

Serotonin agonists and antagonists.

Buspirone is a partial agonist of the 5-HT1A receptor, with some affinity for dopamine D3 and D4 receptors. It is marketed for the treatment of generalized anxiety disorder. Controlled data in OCD are limited, and largely negative (Koran, Hanna et al. 2007). High doses of buspirone are advocated by some experts as an augmentation strategy for SSRI-resistant OCD symptoms; however, this strategy has not been rigorously tested in controlled studies.

Pindolol is both a 5-HT1A and a beta-adrenergic antagonist. Small, early controlled studies reported some benefit from either monotherapy or augmentation of SSRI treatment (Koran, Hanna et al. 2007). A recent meta-analysis of controlled augmentation studies showed a trend towards symptom improvement with pindolol augmentation, but it did not reach statistical significance (Sassano-Higgins and Pato 2015). More research is needed to establish the therapeutic role of this agent, if any.

Mirtazapine is an alpha-2 adrenergic agonist and an antagonist of the serotonin 2A, 2C, and 3 receptors. Two controlled studies have studied its effects in OCD and suggest that it may produce some benefit, or may accelerate the response to a concomitantly prescribed SSRI (Pallanti, Quercioli et al. 2004, Koran, Gamel et al. 2005). Again, more work is needed before clear conclusions can be drawn.

Ondansetron is an agonist of the 5-HT3 serotonin receptor; it is indicated for the treatment of nausea. Five controlled studies examined its use in OCD, with some evidence of benefit even at very low doses (Serata, Kotzalidis et al. 2015). This motivated a large, multi-site study by Transcept Pharmaceuticals (NCT01275248). Unfortunately, this trial failed to meet its primary efficacy endpoint (BioSpace 2012) (though it remains unpublished). The appropriate role of ondansetron in the treatment of OCD therefore remains unclear.

4. Serotonin dysregulation in OCD.

The clear benefit of SRI treatment in OCD has motivated interest in serotonin dysregulation as a pathophysiological contributor (Graat, Figee et al. 2017, Szechtman, Harvey et al. 2020). This has been one motivation for the many (largely inconclusive) trials of other serotoninergic agents summarized above. Importantly, the fact that SRIs often produce therapeutic benefit does not constitute proof that serotonin abnormalities are causally related to OCD symptoms, as noted earlier in this article; this remains an empirical question.

Genetic findings have suggested that alleles of genes involved in serotonergic neurotransmission, as a group, may contribute to OCD risk, though they have not yet unambiguously identified specific alleles or genes with adequate statistical confidence (Sinopoli, Burton et al. 2017).

The serotonin reuptake transporter.

Clomipramine and the SSRIs block the action of the serotonin reuptake transporter, also known as 5-HTT or SERT, which is encoded by the *SLC6A4* gene on chromosome 17. This is therefore an obvious candidate actor in the pathophysiology of OCD, and it has been intensively investigated.

Polymorphisms in the *SLC6A4* gene appear to make a small contribution to OCD risk. An intensively studied polymorphism in the promoter region of the gene influences expression levels and has been associated with neuroticism, depression, and the response to stress or trauma (Caspi, Sugden et al. 2003, Risch, Herrell et al. 2009, Clarke, Flint et al. 2010, Talati, Odgerel et al. 2017). Multiple candidate gene association studies have examined this polymorphism in OCD. Early results were mixed (Bloch, Landeros-Weisenberger et

al. 2008); but more recent meta-analysis suggests a positive association, with an odds ratio of approximately 1.25 (i.e. carriers of the risk allele have a 25% higher likelihood of developing OCD than those without) (Taylor 2013). It is important to note that candidate gene studies have a checkered history in neuropsychiatry, with most failing to replicate (Altshuler, Daly et al. 2008). In OCD, out of well over a hundred candidate gene studies, most have not replicated (Fernandez, Leckman et al. 2018). Such associations must therefore be interpreted with caution. Genome-wide association studies (GWAS), which can largely avoid the pitfalls of candidate gene studies, have not to date identified either *SLC6A4* or any other serotonin-related genes as leading candidate risk loci in OCD (International Obsessive Compulsive Disorder Foundation Genetics and Studies 2018), but much larger studies are needed to provide a comprehensive characterization of the genetic architecture of OCD risk.

Interestingly, the association of risk-associated polymorphisms in the promoter region with neuroticism appears to be quantitatively similar to the association with OCD (Talati, Odgerel et al. 2017), and the genetic correlation between neuroticism and major OCD symptom dimensions is substantial (Bergin, Verhulst et al. 2014). Therefore, while there does seem to be a statistically significant association between this polymorphism and OCD, it is unclear that this is a specific effect, rather than a more general association with neuroticism and related symptomatology (depression, anxiety, stress reactivity). Comparison with other psychiatric diagnoses does suggest some specificity to the association with OCD (Taylor 2016), but this analysis is limited by the specific discrete disorders examined; neuroticism was not included.

A parallel set of molecular brain imaging studies has examined 5-HTT protein in the brain. Importantly, while genetic associations provide prima facie evidence for a causal contribution of the implicated alleles in the development of disease, establishing the association of brain imaging findings with pathophysiology is a more complex undertaking: receptor abnormalities could be the cause of symptoms, but they could as easily be a consequence of either symptoms or treatment, a compensation, or an epiphenomenon that correlates with disease without contributing to it. Early studies with the positron emission tomography (PET) ligand ^{11}C-McN 5652 and the single photon emission computerized tomography (SPECT) ligand ^{123}I-β-CIT produced equivocal results, suggesting either elevated (Pogarell, Hamann et al. 2003) or unchanged 5-HTT levels (Simpson, Lombardo et al. 2003) relative to healthy controls (Nikolaus, Muller et al. 2016).

5-HTT is expressed at high levels in platelets, and studies examining receptor levels/binding here have been more consistent, with most showing reduced 5-HTT ligand binding in patients (Bastani, Arora et al. 1991, Marazziti, Hollander et al. 1992, Weizman, Mandel et al. 1992, Marazziti, Rossi et al. 1996, Sallee, Richman et al. 1996, Marazziti, Pfanner et al. 1997, Marazziti, Dell'Osso et al. 1999, Delorme, Chabane et al. 2004), and some showing correlation of this reduced binding with symptom severity (Marazziti, Pfanner et al. 1997) or relationships with treatment outcome (Marazziti, Pfanner et al. 1997, Delorme, Chabane et al. 2004). The challenge here is, of course, to understand the relationship between these peripheral measures and what is happening in the brain. The status of brain 5-HTT in OCD remains unclear.

Serotonin 2A receptor.

The serotonin 2A receptor (5-HT2A), encoded by the *HTR2A* gene, is a primarily postsynaptic, $G_{\alpha}q$-coupled metabotropic receptor. Like 5-HTT it has been intensively studied in candidate gene association studies in OCD. Meta-analysis suggests an association with two linked alleles, rs6311 in the promotor region and rs6313 in the 5' coding region (Taylor 2013, Taylor 2016). As noted above, candidate gene associations must be interpreted with caution; *HTR2A* has not emerged as a candidate from genome-wide association studies to date (Fernandez, Leckman et al. 2018).

5-HT2A has also been studied using PET imaging. An early study, using the tracer ^{18}F-altanserine, reported increased receptor availability in the caudate nucleus, bilaterally (Adams, Hansen et al. 2005). Of note, 5-HT2A levels are low in the basal ganglia, and between-group differences in this structure can thus be difficult to detect. In contrast, a smaller study with the tracer ^{11}C-MDL reported reduced receptor availability across multiple cortical regions; tracer binding in the caudate and putamen was not reported (Perani, Garibotto et al. 2008). Finally, a somewhat larger, methodologically rigorous 2011 study, also using ^{11}C-MDL, reported no differences between patients with OCD and controls in any brain region (Simpson, Slifstein et al. 2011). Exploratory analyses in the latter two studies reported correlations between tracer binding in the orbitofrontal cortex and different measures of disease (symptom severity in one case(Perani, Garibotto et al. 2008), earlier age of onset in the other (Simpson, Slifstein et al. 2011)). This heterogeneity of results, with one study reporting increased binding, one decreased binding, and one no change, leaves little clarity regarding the status of 5-HT2A receptors in adults with OCD.

Atypical antipsychotics are antagonists of the 5-HT2A (in addition to their blockade of dopamine D2 receptors), and it is possible that benefit from augmentation with agents such as aripiprazole relates to this binding. We return to the use of atypical antipsychotics in OCD treatment below, when discussing dopamine dysregulation in OCD. 5-HT2A is also targeted by psychedelic drugs such as LSD and psilocybin; they are potent agonists (Johnson, Hendricks et al. 2019), and this binding appears to be critical for their profound subjective effects (Kraehenmann, Pokorny et al. 2017, Preller, Herdener et al. 2017). Interest in psychedelic agents as potential therapeutics has been rekindled in recent years, and research in this area is accelerating (Reiff, Richman et al. 2020). A single small uncontrolled study suggests that psilocybin can have lasting benefits in some patients with OCD (Moreno, Wiegand et al. 2006); controlled studies are underway (NCT03300947; NCT03356483).

Serotonin 1A receptor.

The serotonin 1A receptor (5-HT1A), encoded by the *HTR1A* gene, is a $G_{\alpha}i$-coupled somatodendritic autoreceptor on both serotonergic neurons, where it mediates negative feedback in the locus coeruleus, and on other neurons throughout the brain. Desensitization of 5-HT1A receptors is thought to be an important event in the response to SSRIs (El Mansari and Blier 2005). 5-HT1A receptors have not been extensively studied in OCD. No genetic studies have implicated polymorphisms in *HTR1A* as increasing risk, and no PET studies have examined the expression of the receptor.

5-HT1A is the primary target of buspirone. As noted above, buspirone is sometimes used as a tertiary pharmacological agent in OCD, although controlled data supporting this strategy are lacking (Koran, Hanna et al. 2007).

Serotonin 1B/1D receptor.

The 1B/1D receptor, encoded by the *HTR1B* gene, is a $G_{\alpha}i$-coupled receptor that is primarily localized to axon terminals, both on serotonergic neurons themselves (where it can also contribute to negative feedback regulation of transmitter release) and on other neuronal types (Sari 2004). Some candidate gene association studies have implicated *HTR1B* in OCD risk, but these have not been consistently replicated and are not supported by meta-analysis (Taylor 2013).

An older literature examined the impact of 5-HT1B/1D agonists on OCD symptoms. Agonists such as sumatriptan have been reported to worsen either symptoms of OCD or neurochemical abnormalities in several studies (Koran, Pallanti et al. 2001, Gross-Isseroff, Cohen et al. 2004, Zohar, Kennedy et al. 2004), though not in all (Pian, Westenberg et al. 1998, Boshuisen and den Boer 2000). In rodents, agonists of the 5-HT1B receptor impair prepulse inhibition (PPI) and increase anxiety and perseverative behavior, all of which have been argued to reflect aspects of an OCD-like response (Shanahan, Holick Pierz et al. 2009, Woehrle, Klenotich et al. 2013).

A single PET imaging study has examined 5-HT1B binding in unmedicated patients with OCD, using the tracer ^{11}C-P943. There was no difference in binding between 12 adults with OCD and 12 matched healthy controls (Pittenger, Adams et al. 2016). Motivated by the ability of 5-HT1B agonists to impair PPI in animals (Shanahan, Holick Pierz et al. 2009), the authors examined the relationship between ^{11}C-P943 binding and PPI in patients and controls, and an interesting pattern emerged: there was no correlation between PPI and ^{11}C-P943 binding in cortical regions in controls, but a strong positive correlation in individuals with OCD. In subcortical structures the pattern was quite different: a positive correlation between PPI and ^{11}C-P943 binding in controls was lost in OCD, and even reversed in some structures (pallidum, thalamus) (Pittenger, Adams et al. 2016). This result requires replication, and its import is unclear, but it suggests a subtle reorientation of the serotonergic system in OCD that may not be apparent in simple between-group analyses.

Serotonin-3 receptors.

The 5-HT3 receptor is unique among serotonin receptors in that it is a heteropentameric ligand-gated ion channel, rather than a metabotropic G-protein-coupled receptor. Interest in this receptor in OCD derives from treatment studies using 5-HT3 agonists such as ondansetron. As reviewed above, initial studies with these agents were promising, but a large double-blind, placebo controlled study (NCT01275248) did not hit its primary efficacy endpoint (BioSpace 2012). There are five 5-HT3 genes, two of which (*HTR3A* and *HTR3B*) are expressed at significant levels in the brain. No genetic studies to date have implicated these genes as risk alleles in OCD.

Interestingly, ondansetron reduces activity in cortical circuitries involved in interoception and sensorimotor processing, suggesting potential utility in the treatment of OCD symptoms

associated with disgust and/or sensory hypersensitivity (Stern, Shahab et al. 2019). A controlled study to test this possibility is underway (NCT03239210).

Serotonin levels in OCD?

Some of the findings reviewed above have been interpreted as suggesting that levels of serotonin itself are dysregulated in individuals with OCD. Unfortunately, serotonin in and around synapses is not accessible to experimental measurement in humans using currently available technologies, and so arguments for dysregulated serotonin levels are necessarily indirect.

The simplest explanation of the efficacy of SRI medications is that serotonin is low in OCD, and SRI treatment, by blocking serotonin reuptake, normalizes it. Consistent with this idea, the 5-HTT promoter allele associated with OCD risk – the L_a allele (Taylor 2013) – is more efficiently transcribed and thus can produce more 5-HTT protein in the brain (Heinz, Jones et al. 2000). This increased protein leads to more efficient reuptake of serotonin, at least in lymphoblasts (Lesch, Bengel et al. 1996), suggesting that L_a allele carriers may have reduced basal serotonin levels.

Studies in animals with a 5-HT neurotoxin have shown that orbitofrontal serotonin depletion can produce cognitive inflexibility (Clarke, Dalley et al. 2004). Brain serotonin can be acutely reduced in humans using tryptophan depletion, a dietary manipulation. If low brain serotonin contributes directly to symptomatology, then tryptophan depletion should exacerbate symptoms. The literature using this technique is small, and mixed. Early studies found no effect on core OCD symptoms after tryptophan depletion in SRI-treated patients, though depression and/or subjective distress were worsened in most studies (Barr, Goodman et al. 1994, Smeraldi, Diaferia et al. 1996, Berney, Sookman et al. 2006, Kulz, Meinzer et al. 2007). In contrast, a recent small controlled study found tryptophan depletion to acutely worsen some OCD symptoms, increasing interfering thoughts and decreasing perceived control over them (Hood, Broyd et al. 2017).

Brain 5-HT levels can be indirectly measured by quantifying the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF). An old literature took this approach; again, results are mixed. One early study found reduced 5-HIAA in a group of obsessional patients (Insel, Mueller et al. 1985). However, other studies have not identified any 5-HIAA abnormalities in patients, though there may be an association between pre-treatment CSF 5-HIAA levels and response to SRI treatment (Baumgarten and Grozdanovic 1998).

Neurotransmitter levels can be inferred from PET imaging, with caveats. PET measures the specific binding of radiolabeled ligand to its molecular target. When a ligand binds to the same site on a neurotransmitter receptor as the transmitter itself, radioligand binding reflects a combination of the amount of receptor present, its affinity for the ligand (which can be modulated by molecular changes such as covalent posttranslational modifications or allosteric interactions), and competition with endogenous neurotransmitter. With appropriate experimental design it is possible to isolate the contribution of competition with endogenous neurotransmitter, and thus to make inferences about relative neurotransmitter levels

between experimental groups. This strategy has been extensively used in measurements of endogenous dopamine, as further discussed below (Denys, de Vries et al. 2013). However, comparable methods are not as well established to measure serotonin levels, and so, while some authors have made claims about endogenous serotonin concentrations from PET signal, any such inferences remain tentative. Furthermore, as reviewed above, the PET literature on both the serotonin transporter and serotonin receptors in OCD is quite mixed, with no clear consensus as to dysregulation of any individual serotonin-related protein.

In sum, the literature attempting to directly or inferentially measure serotonin levels in OCD is quite mixed, and firm conclusions are difficult to draw. The robust therapeutic response to SRI medications is the clearest finding in the treatment literature on OCD (Soomro, Altman et al. 2008, Issari, Jakubovski et al. 2016), and characterization of endogenous serotonin levels and dynamics therefore remains a compelling goal. Unfortunately, such characterization is limited by available technology; brain serotonin cannot be directly assayed in humans, except in rare circumstances. This is an important area for future research.

5. Dopaminergic agents in the treatment of OCD.

While SRI antidepressants are the mainstay and the universally endorsed first-line pharmacological treatment for OCD, nonresponse and limited response are distressingly common. There is thus a clear clinical need for second-line treatments and augmentation strategies. Pharmacologically, much attention has focused on modulators of dopaminergic neurotransmission. Clinically it is of course always important to consider expert cognitive behavioral therapy, either as an augmentation strategy or as a stand-alone treatment; but our focus here remains on pharmacological strategies.

D2 antagonist monotherapy.

Neuroleptics – dopamine D2 antagonists – have been investigated for the treatment of OCD. While the total number of studies is not large, the consensus in the field is that neuroleptic monotherapy is ineffective (Koran, Hanna et al. 2007). A study in the 1950s, before modern diagnostic criteria were developed, examined chlorpromazine in 75 patients with obsessive-compulsive symptoms and reported at least some benefit in nearly half (Trethowan and Scott 1955); but the lack of modern diagnostic criteria and of quantitative measures of symptom change complicates extrapolation from these early results to modern clinical practice. Case reports of typical and atypical neuroleptic monotherapy have been mixed (Hussain and Ahad 1970, O'Regan 1970, Rivers-Bulkeley and Hollender 1982, Chiou, Lin et al. 2015). An open-label study in the 1990s examined clozapine monotherapy and found significant side effects but no benefit (McDougle, Barr et al. 1995). A more recent open label study examined aripiprazole monotherapy and found some patients to benefit; side effects were again a problem (Connor, Payne et al. 2005). Small sample size and open label design limit the interpretability of these studies. More rigorous examination of neuroleptic monotherapy would be valuable; however, the limited evidence for benefit, both in the published literature and in the experience of expert clinicians, provides little motivation for such studies.

In fact, neuroleptic monotherapy can sometimes induce or exacerbate OCD symptoms (Grillault Laroche and Gaillard 2016, Poyurovsky 2017). This is particularly clear in the case of clozapine (Lykouras, Alevizos et al. 2003, Schirmbeck and Zink 2012, Grillault Laroche and Gaillard 2016) but may also be true of other atypical/second-generation neuroleptics, perhaps because of their antagonism of the 5-HT2A receptor (Schirmbeck and Zink 2013, Poyurovsky 2017). There is some evidence that specific genetic polymorphisms may contribute to this susceptibility (Cai, Zhang et al. 2013), though this finding is based on a candidate gene approach, which is historically problematic, and has yet to be replicated (Schirmbeck, Nieratschker et al. 2012).

D2 antagonist augmentation.

In contrast, addition of neuroleptics to stable SRI treatment – that is, pharmacological augmentation – has been shown to be of benefit in a number of studies. Early work focused on the typical neuroleptics haloperidol and pimozide, as well as risperidone, with generally positive results (Bloch, Landeros-Weisenberger et al. 2006). Meta-analysis of this early work confirmed overall benefit, with one positive study for haloperidol augmentation and three concordant controlled studies for risperidone (Bloch, Landeros-Weisenberger et al. 2006, Skapinakis, Papatheodorou et al. 2007). More recent work has largely examined atypical/second-generation neuroleptics. A 2014 meta-analysis of controlled studies of atypical neuroleptic augmentation found evidence for benefit from aripiprazole and risperidone, but not from olanzapine or quetiapine (Veale, Miles et al. 2014). A 2015 meta-analysis including all studies to date, of both typical and atypical neuroleptics, reached similar conclusions, with good evidence for benefit from augmentation with haloperidol, risperidone, and aripiprazole (Dold, Aigner et al. 2015). Based on this work, augmentation with these agents is included as a second-tier pharmacological intervention in all current treatment guidelines (Baldwin, Anderson et al. 2005, Koran, Hanna et al. 2007). The doses used are typically low; evidence for benefit from higher doses is quite limited. Restricting neuroleptic doses to the low end of the usual range can help mitigate the side effects of these agents, for which tolerability is often a limiting factor (Koran, Hanna et al. 2007).

It is important to note that this literature is not uniform, and only a minority of patients respond to neuroleptic augmentation. Indeed, a recent controlled trial of risperidone versus CBT for adults with OCD who had an inadequate response to SRI monotherapy found no benefit from risperidone augmentation, in contrast to clear benefit from CBT (Simpson, Foa et al. 2013). It is clinically advisable to monitor closely over the course of a trial of limited duration (4–6 weeks), and to discontinue the trial if there is not clear benefit of improvement.

What underlies this heterogeneity of response? As in all such cases, our understanding is limited. An early study suggested that OCD patients with current or historical tic comorbidity have a higher rate of response to augmentation with the typical/first-generation neuroleptic haloperidol.(McDougle, Goodman et al. 1994) This benefit was borne out by later meta-analysis.(Bloch, Landeros-Weisenberger et al. 2006) In contrast, meta-analysis of more recent studies of atypical/second-generation neuroleptics found no evidence for particular benefit in patients with comorbid tics (although a majority of the studies reviewed

did not stratify by tic comorbidity and thus this sub-analysis was of limited power) (Veale, Miles et al. 2014). One possible explanation is that the high D2 affinity of haloperidol makes it particularly efficacious in patients with tic comorbidity; low-dose haloperidol is a well-established monotherapy for tic disorders (Bloch 2008). It is also possible that the 5-HT2A antagonism that characterizes atypical/second-generation neuroleptics makes them less effective than the typical agents in the treatment of OCD patients with comorbid tics. A meta-regression analysis found benefit of antipsychotics to be related to their D2R/D3R affinity and not to their 5-HT2A affinity, supporting the former explanation (Ducasse, Boyer et al. 2014). More study is needed to place these speculations on a firmer foundation; based on current data, it may be appropriate to turn to the typical agents in patients with comorbid tics and to the atypical agents (specifically, aripiprazole) in those without this comorbidity.

Patients with OCD who have severe disease, limited insight, and/or bizarre obsessions can be both diagnostically and therapeutically quite challenging (Hamblin, Park et al. 2017, Poyurovsky 2017). It is intuitive to turn more quickly to neuroleptic augmentation in this context, in an effort to simultaneously target OCD and psychotic symptomatology. While this approach is clinically reasonable, it is important to recognize that it rests on a rather thin empirical basis. Most controlled studies have not stratified patients by schizotypy or level of insight. One that did, an early study of risperidone augmentation, did not find a higher rate of response in patients with OCD and comorbid schizotypy (McDougle, Epperson et al. 2000). One study found insight to predict poorer response to pharmacotherapy (Catapano, Sperandeo et al. 2001), but another found no relationship (Eisen, Rasmussen et al. 2001). Studies of body dysmorphic disorder (BDD), an OCD-related disorder that is similarly responsive to high-dose SSRI pharmacotherapy but in which impaired insight to the point of delusionality is much more common, provides a useful parallel. BDD patients with delusional levels of insight responded just as well as those with better insight to fluoxetine monotherapy in a placebo-controlled trial (Phillips, Albertini et al. 2002). The utility of neuroleptic augmentation in OCD with poor insight remains unclear.

Other dopaminergic agents.

Only small studies have examined other agents that target the brain’s dopamine system, and in no case is the evidence base sufficient for such agents to be considered standard-of-care. One small controlled study found benefit from both dextroamphetamine and caffeine in OCD, suggesting a potential role for stimulants in some patients (Koran, Aboujaoude et al. 2009). A recent larger controlled trial of fluvoxamine plus either extended-release methylphenidate or placebo found a higher response rate in the methylphenidate group (Zheng, Jia et al. 2019). However, both methylphenidate (Kouris 1998, Serby 2003, Woolley and Heyman 2003, Jhanda, Singla et al. 2016) and methamphetamine (Iyo, Sekine et al. 1999) have been reported to worsen OCD symptoms, so caution is warranted.

An open-label study of bupropion, which blocks both dopamine and norepinephrine reuptake, found no net benefit in OCD; some patients improved over 8 weeks of treatment, but others worsened (Vulink, Denys et al. 2005).

Interestingly, SSRIs at high doses can increase brain dopamine (Koch, Perry et al. 2002). Given that high SSRI doses are more efficacious in the treatment of OCD than typical

antidepressant doses (Soomro, Altman et al. 2008), it is plausible that dopamine reuptake blockade could contribute to therapeutic benefit (Graat, Figee et al. 2017). This speculation has yet to be rigorously tested.

7. Dopamine dysregulation in OCD.

As in the case of serotonin, the efficacy of dopaminergic drugs – specifically, pharmacological augmentation with D2 antagonists – has motivated interest in the dopamine system in the brain of individuals with OCD. The evidence for dopamine dysregulation is much clearer for Tourette syndrome (TS) and other tic disorders,(Williams, Bloch et al. 2013) which are often comorbid with OCD, and in tic-related OCD.(Pittenger 2017) In OCD without tics, evidence for DA dysregulation is ambiguous.

Animal studies.

Much of the evidence for a relationship between dopamine dysregulation and OCD-like phenomenology comes from animal models. The construction, evaluation, and interpretation of animal models of potential relevance to understanding the pathophysiology of tics and OCD is a complicated and sometimes vexing topic (Pittenger 2014, Bortolato and Pittenger 2017, Pittenger, Dulawa et al. 2017), which is treated in detail in chapter “Animal Models for OCD Research”. With that caveat, a range of dopamine agonists, precursors, reuptake blockers, and releasers – amphetamine; L-DOPA; bromocriptine; apomorphine – can lead to repetitive, stereotypic behaviors, which have been argued to be of relevance to the symptoms of OCD (Szechtman, Sulis et al. 1998, Denys, Zohar et al. 2004, Graat, Figee et al. 2017, Szechtman, Harvey et al. 2020). However, dopaminergic agonists can also ameliorate such behaviors in some contexts. For example, repetitive checking behaviors are induced by the dopamine D2/D3 agonist quinpirole (Szechtman, Sulis et al. 1998); but dopamine agonists can ameliorate apparently similar behaviors that occur naturally in some species (Vandebroek and Odberg 1997, Korff, Stein et al. 2008). It is of course possible that some repetitive behaviors in animals recapitulate the mechanisms underlying OCD in humans, and others do not. Such interpretative ambiguities, combined with the underlying complexity of the dopamine system – which comprises multiple circuits, receptors, and functional roles – make it difficult to draw any clear conclusions from this animal literature as to what role dopamine dysregulation may have in the development or maintenance of obsessions and compulsions in humans.

Genetics.

As noted elsewhere (see chapter “Genetics of OCD and Related Disorders; Searching for Shared Factors”), the genetics of OCD are not mature; early candidate gene association studies have largely failed to replicate, and GWAS studies are not yet of sufficient size to yield large convincing, statistically robust findings (Fernandez, Leckman et al. 2018). However, two findings of relevance to dopamine from candidate gene studies have been sufficiently well replicated as to merit discussion. Interestingly, both show sexually dimorphic effects, with evidence for a genetic contribution to OCD risk in males but not in females.

Catechol O-methyltransferase (COMT) metabolizes dopamine and other catecholamines, especially in the prefrontal cortex. A well characterized common polymorphism, rs4680 (Val158Met), has been studied extensively in OCD. The Met allele, which is associated with lower enzymatic activity and thus presumably with higher levels of dopamine, is over-represented in males with OCD (Taylor 2013). Monoamine oxidase A (MAO-A) is the primary enzyme that metabolizes dopamine in the basal ganglia. At a well characterized polymorphism, EcoRV (also called c1460C>T), the T allele appears to be over-represented in males (Taylor 2013). This allele is associated with lower enzymatic activity; again, therefore, carriers are predicted to have higher basal dopamine levels.

Several other alleles of dopamine-related genes examined in the same meta-analysis of candidate gene association studies showed suggestive relationships with OCD that failed to reach statistical significance; these include the dopamine transporter gene *DAT1* and the dopamine receptor gene *DRD3* (Taylor 2013). All of these associations – including the reported male-specific associations with COMT and MAOA polymorphisms – must be interpreted with great caution; non-replications of these findings continue to appear (Sampaio, Hounie et al. 2015). The field awaits better-powered studies to provide a comprehensive picture of the genetic architecture of OCD (Fernandez, Leckman et al. 2018).

Receptor imaging studies.

Dopamine binds to 5 distinct receptors, which fall into two classes: D1-like receptors (D1R and D5R) and D2-like receptors (D2R, D3R, and D4R). SPECT and PET imaging have been used to visualize these receptors. As in the case of serotonin receptors, reviewed above, studies to date have been small and findings somewhat variable, and it is difficult to draw specific conclusions with confidence.

Two studies using SPECT imaging reported elevation of the dopamine transporter in the striatum in OCD (Kim, Koo et al. 2003, van der Wee, Stevens et al. 2004); however, a third study reported reduced levels of the transporter (Hesse, Muller et al. 2005). The dopamine D1R receptor has been imaged using PET in two small studies of unmedicated patients with OCD, with evidence for reduced binding in the striatum and the anterior cingulate cortex (Olver, O'Keefe et al. 2009, Olver, O'Keefe et al. 2010). A single study examined dopamine metabolism using the PET tracer ^{18}F-DOPA, which labels dopaminergic vesicles, in five patients compared to six controls; increases in ^{18}F-DOPA uptake were seen in several cortical structures, though most were only at trend level (Hsieh, Lue et al. 2014).

More studies have examined the D2R family of receptors in OCD, and in tic disorders. An early SPECT study using the tracer iodobenzamide indicated lower D2 receptors in the left caudate (Denys, van der Wee et al. 2004), although a subsequent study found this effect only in patients with comorbid social anxiety disorder (Schneier, Martinez et al. 2008). A pair of PET imaging studies with the D2R/D3R antagonist ^{11}C-raclopride similarly found reduced D2/D3 binding in the caudate-putamen (Perani, Garibotto et al. 2008, Denys, de Vries et al. 2013), making this the best replicated evidence for a dopaminergic abnormality in OCD.

Dopamine levels.

Several of the findings reviewed above could be consistent with alterations in basal dopamine levels. As with serotonin, the most direct way to assay dopamine levels is to examine dopamine and its metabolites in cerebrospinal fluid, serum, or urine of patients with OCD. Here the literature is sparse and inconclusive. An early study found homovanillic acid (HVA), a primary metabolite of dopamine, to be no different in the CSF of patients with OCD than in controls, though it was elevated in Tourette syndrome (Leckman, Goodman et al. 1995). A study in patients with normal pressure hydrocephalus found both elevated HVA and elevated obsessive-compulsive symptoms, but the two were not obviously correlated with one another (Markianos, Lafazanos et al. 2009). In small studies, HVA is reduced after treatment of patients with OCD with clomipramine (Altemus, Swedo et al. 1994) or risperidone (Yoshimura, Kaneko et al. 2006). It is difficult to draw any overall conclusions from this heterogeneous literature.

The alleles of COMT and MAO-A that are associated with increased OCD risk, in males, have lower metabolic activity and are therefore consistent with elevated dopamine levels. And the reduced D1R and D2R receptor binding seen in several PET studies, summarized above, may suggest increased basal dopamine levels, and thus greater competition between dopamine and the PET tracers.

A classic way of measuring dopamine is through PET imaging before and after challenge with amphetamine. By releasing large amounts of dopamine, amphetamine floods the receptors with transmitter, displacing the radioligand and thus reducing PET signal. Modeling of this reduced PET signal in a within-subject design allows inferences about baseline dopamine levels. A single study has used this approach in patients with OCD, compared to a group with Tourette syndrome, using the D2/D3 antagonist tracer raclopride. Baseline raclopride binding in the caudate-putamen was reduced in both OCD and TS; it was unchanged after amphetamine challenge. TS symptoms worsened after amphetamine challenge and correlated with changes in raclopride signal (and thus presumably with dopamine release) in the ventral striatum; no such relationships were seen in OCD (Denys, de Vries et al. 2013). This study thus provides clearer support for dopaminergic pathophysiology in TS than OCD. This is however a single, small study; further work is needed to permit clear conclusions.

In summary, the evidence for dysregulated dopamine, dopamine homeostasis, or dopamine receptors in the pathophysiology of OCD is equivocal. It may be that dopamine dysregulation contributes to disease in some patients but not in others. Indeed, given the clearer evidence for striatal dopamine abnormalities in tic disorders (Williams, Bloch et al. 2013), it may be that OCD with comorbid tics is characterized by dopaminergic pathology, while OCD without tics is not. However, this remains speculative; better powered studies that are more able to discriminate plausible pathophysiological subtypes are needed.

7. Glutamate modulators in the treatment of refractory OCD.

The evidence-based algorithm for the pharmacological treatment of OCD is distressingly limited: only the SRIs (clomipramine and the selective serotonin reuptake inhibitors)

and augmentation thereof with certain neuroleptics are supported by sufficiently robust evidence to be considered the clear standard of care. Symptoms that are refractory to these interventions are unfortunately common. Investigational use of other agents, either as monotherapy or (more often) as augmentation of SRI treatment, therefore represents an important area of research. Some of these studies have been summarized above in the discussions of serotonin and dopamine-centered mechanisms.

Much recent work has focused on the hypothesis that glutamate imbalance contributes to OCD, and that glutamate modulators may have therapeutic utility in treatment of otherwise refractory disease (Pittenger, Krystal et al. 2006, Pittenger, Bloch et al. 2011, Pittenger 2015, Marinova, Chuang et al. 2017). It is important to note that these two claims are not equivalent: glutamate modulators may be of therapeutic benefit even if glutamate dysregulation is not central to pathophysiology; and glutamate abnormalities might contribute causally to the development of OCD and yet glutamate modulators not be therapeutically effective. In this section we briefly summarize recent work on glutamate modulators; this material has been recently reviewed in more detail, with more specific clinical guidance, elsewhere (Pittenger 2015, Marinova, Chuang et al. 2017, Pittenger 2017).

Memantine.

The most studied glutamate modulator for the treatment of refractory OCD is the NMDA receptor antagonist memantine. Memantine is a low-affinity open-pore blocker with a rapid off-rate; these characteristics may explain why its effects differ from those of a higher-affinity blocker, ketamine, which is further discussed below.

Early uncontrolled studies in both adults and children suggested that some OCD sufferers benefit from memantine augmentation (Aboujaoude, Barry et al. 2009, Feusner, Kerwin et al. 2009, Hezel, Beattie et al. 2009, Stewart, Jenike et al. 2010). More recently, a series of placebo-controlled trials has suggested a large benefit, with a response rate of 81% in memantine-treated patients (Ghaleiha, Entezari et al. 2013, Haghighi, Jahangard et al. 2013, Sahraian, Jahromi et al. 2017, Modarresi, Sayyah et al. 2018). These studies have recently been summarized in a systematic review and meta-analysis, suggesting substantial benefit from memantine treatment in adults with OCD (Modarresi, Chaibakhsh et al. 2019). However, this conclusion has been questioned on methodological grounds (Andrade 2019). The four placebo-controlled trials of memantine are individually small and were performed in the same geographic area, in Iran. They produced effects larger than those seen in open-label studies performed elsewhere, with response rates in individual studies of up to 100%, raising questions about their generalizability. Given these concerns, memantine cannot be considered to be an established treatment for OCD at this point; larger studies, from a wider geographical range and with optimally rigorous methodology, are needed (Andrade 2019).

Riluzole.

Riluzole is a glutamate modulator developed for the treatment of amyotrophic lateral sclerosis. It has several mechanisms; at physiologically realistic concentrations, the two most significant appear to be a reduction in synaptic glutamate release and an enhancement of glial reuptake of perisynaptic glutamate (Pittenger, Coric et al. 2008). An open label trial

(Coric, Taskiran et al. 2005), a retrospective case series (Pittenger, Kelmendi et al. 2008), and two small controlled studies (Pittenger, Bloch et al. 2015, Emamzadehfard, Kamaloo et al. 2016) suggest some benefit in adults, though only one of the controlled studies reached its primary efficacy endpoint (Emamzadehfard, Kamaloo et al. 2016), and both were small and had methodological limitations. A controlled study in pediatric OCD showed no evidence of benefit (Grant, Joseph et al. 2014). As in the case of memantine, more and higher-quality studies are needed before any firm recommendations can be made as to the use of riluzole in OCD refractory to other pharmacological treatments.

Recently, a riluzole prodrug, troriluzole, has been developed and tested for several indications. A large, multi-site controlled study of troriluzole augmentation in SRI-refractory OCD (NCT03299166) recently showed promising evidence of benefit, though it did not hit its primary efficacy endpoint.(Pharmaceuticals)

Ketamine.

The dissociative anesthetic drug ketamine has garnered much recent interest due to the observation that it can produce a rapid-onset, lasting antidepressant effect, sometimes after a single dose (Berman, Cappiello et al. 2000, Zarate, Singh et al. 2006, Krystal, Abdallah et al. 2019). In OCD, the literature is sparse and the benefit is less clear. A first open-label trial in treatment-refractory patients found a clear improvement in depressive symptoms but no clinically significant change in OCD symptoms after a single dose of ketamine (Bloch, Wasylink et al. 2012). However, a controlled trial in less ill patients (no significant comorbidities, no other medication) found benefit in many, lasting over a week (Rodriguez, Kegeles et al. 2011, Rodriguez, Kegeles et al. 2013). Ongoing work has consisted mostly of case studies, investigating the combination of ketamine with other interventions such as memantine (Rodriguez, Levinson et al. 2016) or CBT (Rodriguez, Wheaton et al. 2016, Adams, Bloch et al. 2017). Clinical experience suggests that repeated ketamine treatments may be helpful in a minority of treatment-refractory OCD patients (Sharma, Thamby et al. 2020); but repeated dosing has not been systematically studied in OCD. Again, large controlled studies are needed to more clearly establish the role of ketamine treatment, if any, in a comprehensive OCD treatment algorithm.

Other glutamatergic agents.

A number of other agents that can modulate brain glutamate have been investigated in the treatment of refractory OCD (Pittenger 2015, Marinova, Chuang et al. 2017). These include the anti-epileptic drugs topiramate (Berlin, Koran et al. 2011, Afshar, Akuchekian et al. 2014, Sahraian, Bigdeli et al. 2014) and lamotrigine (Kumar and Khanna 2000, Uzun 2010, Bruno, Mico et al. 2012, Arrojo-Romero, Tajes Alonso et al. 2013, Hussain, Dar et al. 2015, Khalkhali, Aram et al. 2016, Naguy, Alamiri et al. 2016), the nutraceuticals N-acetylcysteine (Lafleur, Pittenger et al. 2006, Afshar, Roohafza et al. 2012, Yazici and Percinel 2015, Paydary, Akamaloo et al. 2016, Costa, Diniz et al. 2017, Ghanizadeh, Mohammadi et al. 2017) and sarcosine (Wu, Tang et al. 2011), and the amino acid glycine (Greenberg, Benedict et al. 2009). Of these, N-acetylcysteine is perhaps the most promising; its efficacy is supported by a recent meta-analysis (Gadallah, Ebada et al. 2020) (see chapter “Inflammation, Obsessive-Compulsive Disorder, and Related Disorders” for a description

of the anti-inflammatory effects of N-acetylcysteine in relation to OCD). In the other cases there are some promising studies but others that are equivocal, and there have been no large, placebo-controlled studies of sufficient quality to produce definitive treatment recommendations.

An interesting agent in this category is D-cycloserine (DCS), a partial agonist of the glycine site on the NMDA receptor. DCS has been found in animal studies to potentiate NMDA-dependent plasticity and NMDA-dependent extinction learning (Richardson, Ledgerwood et al. 2004, Kaplan and Moore 2011). This has motivated investigations of whether DCS pretreatment can potentiate the response to extinction-based psychotherapies in OCD, and in other disorders in which dysregulated anxiety is prominent. This is a complex literature, and beyond our scope to review in detail here (see chapter “Innovations in the Delivery of Exposure and Response Prevention for Obsessive-Compulsive Disorder” for a review of the use of DCS to augment CBT for OCD). Recent meta-analyses suggested no significant benefit (Burkner, Bittner et al. 2017) or only subtle benefits (Mataix-Cols, Fernandez de la Cruz et al. 2017) from DCS augmentation of CBT in OCD. However, studies have differed enormously in the dose of DCS and, critically, in the temporal relationship of DCS dosage with CBT. In appropriately selected patients and with optimal dosing, DCS may be of some clinical benefit; but studies to date do not allow clear specification of which patients these might be, or of the optimal dosage and timing to produce clinical benefit. For these reasons, despite the theoretical attractiveness of the concept of pharmacologically augmenting effective behavioral treatments, DCS has not entered widespread clinical use.

8. Glutamate dysregulation in the pathophysiology of OCD.

Several lines of evidence suggest that glutamate dysregulation may contribute to the pathophysiology of OCD. None of these is definitive – as in the case of serotonin and dopamine contributions to pathophysiology, reviewed above, studies are mixed and our understanding remains woefully incomplete. Nevertheless, a brief review of this literature helps to frame potentially fruitful future avenues for intervention development. More detailed descriptions of the glutamate system and how it may be perturbed in patients with OCD can be found elsewhere (Ting and Feng 2008, Pittenger, Bloch et al. 2011, Karthik, Sharma et al. 2020).

It is important to recognize in framing this discussion the ways that the function and organization of glutamatergic neurotransmission in the mammalian brain differs from the serotonin and dopamine systems. Serotonin and dopamine are modulatory neurotransmitters. In both cases, a relatively small number of neurons located in a specific brain area (the dorsal raphe nuclei for serotonin; the substantia nigra/ventral tegmental area for dopamine) project widely throughout the brain and modulate the function of other circuitries. It is reasonable to think of these modulatory transmitters as being involved in a small set of discrete processes. It is thus coherent, though doubtless a huge simplification, to think of excess or deficiency of these transmitters as a cause of disease or as an important aspect of pathophysiology.

Glutamate, in contrast, is the primary excitatory neurotransmitter in the mammalian brain. It is used as a neurotransmitter by over half of the neurons and in every structure and circuit in the central nervous system, and thus it is involved in virtually everything the brain does. A global excess or deficiency in glutamate would be likely to have dramatic, widespread effects. Conversely, pathological activity of virtually any circuit in the brain could be reflected in a local disruption of glutamate levels.

Glutamate-related genes in OCD.

Much attention has focused on the possible role of polymorphisms in glutamate-related genes as determinants of OCD risk (see chapters " The Future of Obsessive-Compulsive Spectrum Disorders: A Research Perspective", " Genetics of OCD and Related Disorders; Searching for Shared Factors", and " Invasive and Non-invasive Neurostimulation for OCD" for a more detailed review). An early focus was the glutamate transporter EAAT3, encoded by the *SLC1A1* gene (Escobar, Wendland et al. 2019). The *SLC1A1* region was initially identified as an OCD risk locus in two linkage studies (Hanna, Veenstra-VanderWeele et al. 2002, Willour, Yao Shugart et al. 2004); reports of several different polymorphisms in the gene itself in patients OCD accumulated over the next several years (Escobar, Wendland et al. 2019). The fact that *SLC1A1* arose as a risk gene from genome-wide linkage studies, rather than a specific a priori hypothesis about pathophysiology, makes these association studies somewhat more compelling than most studies of serotonergic and glutamatergic genes (Taylor 2013, Taylor 2016). OCD-associated alleles have been reported to modulate *SLC1A1* expression levels (Wendland, Moya et al. 2009). However, distinct alleles have been identified in different studies, weakening the statistical association of any one allele with OCD; perhaps as a result, the association is not supported by meta-analysis (Stewart, Mayerfeld et al. 2013). Furthermore, *SLC1A1* has not emerged as a risk locus in more recent genome-wide association studies (Stewart, Mayerfeld et al. 2013, International Obsessive Compulsive Disorder Foundation Genetics and Studies 2018). The association is thus equivocal; *SLC1A1* alleles may contribute to risk in some cases and some contexts, but more work is needed to confirm the role of this gene and to clarify the details of its role.

As noted above, the two GWAS studies completed in OCD to date have not identified any disease-associated loci that reached genome-wide statistical significance (Stewart, Yu et al. 2013, Mattheisen, Samuels et al. 2015, International Obsessive Compulsive Disorder Foundation Genetics and Studies 2018). However, examination of loci that approach significance allows some tentative conclusions about the genetic structure of OCD risk, even if individual risk alleles remain elusive. Glutamate-related genes are strikingly over-represented amongst these borderline-significant alleles. One of the strongest associations is with the *GRID2* gene, an orphan receptor with significant homology to ionotropic glutamatergic receptors. A slightly less strong association is with *GRIK2*, a subunit of the kainate receptor class of ionotropic glutamate receptors. Finally, the *DLGAP1* gene, which is involved in the structural organization of the postsynaptic glutamate receptors and associated proteins, may be associated with OCD risk (International Obsessive Compulsive Disorder Foundation Genetics and Studies 2018).

Again, none of these alleles have reached genome-wide statistical significance, and thus more data are needed before any of these associations can be considered definitive. Nevertheless, the prominent representation of glutamate-related genes amongst probable risk alleles is striking. Since genetic contributors to pathophysiology are necessarily causes, at the level of a single organism, these associations – if replicated – constitute suggestive evidence that glutamate dysregulation may contribute to OCD pathophysiology, in at least some cases.

Glutamate receptors and related proteins in OCD.

No PET or SPECT imaging studies of glutamate receptors in OCD have been reported. This is in contrast to the literature on dopamine and serotonin reviewed above.

A recent post-mortem study, on the other hand, focused on glutamate receptors and other glutamate-related transcripts in the orbitofrontal cortex and basal ganglia (also see chapter n) (Piantadosi, Chamberlain et al. 2019). RNA for the gene *DLGAP1* and the related gene *DLGAP2*, also involved in the organization of the glutamatergic synapse, were both reduced in orbitofrontal cortex. So was *SLC1A1*. The total number of subjects in this study remains low (8 OCD, 8 controls), and more work is needed to confirm and extend these findings, but the preliminary work is supportive of a role for glutamate dysregulation in the pathophysiology of OCD, especially in the orbitofrontal cortex.

CSF and brain glutamate levels.

Two studies, from a single group, have examined glutamate levels in spinal fluid in unmedicated adults with OCD. Both found CSF glutamate to be elevated in a subset of patients (Chakrabarty, Bhattacharyya et al. 2005, Bhattacharyya, Khanna et al. 2009). This is a striking finding. Because glutamate is involved in so many circuits and processes, and because excess glutamate is toxic to neurons, glutamate homeostasis is tightly regulated. Spillover of enough glutamate to be detectable in lumbosacral CSF suggests a significant disruption of these homeostatic mechanisms. However, this elevation is seen in only a minority of OCD patients; most have CSF glutamate levels indistinguishable from healthy controls. It remains to be established whether those with elevated glutamate represent a subset with distinct pathophysiology.

Brain glutamate levels in patients with OCD have been measured using magnetic resonance spectroscopy (MRS), which takes advantage of the fact that the electromagnetic environment of protons in the glutamate molecule creates a unique magnetic resonance signature. (Brennan, Rauch et al. 2013) Most studies measure a composite of glutamate and the related amino acid glutamine, which are difficult to disambiguate in the MRS signal using standard techniques. Importantly, MRS measures total tissue glutamate, including intracellular and metabolic pools. This differs from other techniques, such as CSF sampling and inferences from PET imaging, which measure extracellular pools of transmitter.

Early MRS studies suggested that children with OCD have elevated glutamate/glutamine levels in the striatum (Rosenberg, MacMaster et al. 2000), and reduced glutamate/glutamine in the anterior cingulate cortex (Rosenberg, Mirza et al. 2004) (for a review of MRS studies in OCD please see chapter “Magnetic Resonance Spectroscopy (MRS) and Positron

Emission Tomography (PET) Imaging in Obsessive-Compulsive Disorder"). Caudate glutamate/glutamine levels normalized after pharmacotherapy with paroxetine (Rosenberg, MacMaster et al. 2000). These findings spurred great interest and a large number of follow-up MRS studies in both children and adults – indeed, these early studies were largely responsible for kindling interest in glutamate dysregulation as a potential pathophysiological mechanism in OCD (Rosenberg, MacMillan et al. 2001). However, subsequent findings have been equivocal, with many more negative studies than positive ones (Brennan, Rauch et al. 2013). It remains unclear whether this is because glutamate dysregulation observable by MRS is unique to pediatric OCD (most subsequent studies have been in adults), is seen in only a subset of patients, is sensitively dependent on technical variables that differ between studies, or was a false positive in the early work.

One recent study has combined MRS measures of brain glutamate with prediction of treatment response, with intriguing early results (O'Neill, Piacentini et al. 2017). O'neill and colleagues found MRS-measured glutamate in the pregenual anterior cingulate cortex to decline after cognitive behavioral therapy in children with OCD. On the other hand, baseline glutamate in the ventral posterior cingulate cortex predicted treatment response (O'Neill, Piacentini et al. 2017). If this latter finding proves to be robust, such a baseline predictor of response may help stratify patients and select individualized treatment protocols, moving us towards precision medicine in psychiatry – a topic to which we return below.

Animal studies.

A number of animal studies of the circuitry thought to be perturbed in OCD have implicated glutamatergic mechanisms. We review this work only briefly; it has been summarized in more detail elsewhere (see chapter "Animal Models for the Study of OCD") (Pittenger, Bloch et al. 2011, Pittenger 2014, Ahmari and Dougherty 2015, Ahmari 2016, Szechtman, Ahmari et al. 2017). As noted above and reviewed in detail in the chapter by Chamberlain and Ahmari (this volume), the use of animal models to shed light on the pathophysiology of OCD, or of any complex neuropsychiatric disease, raises complex interpretative issues (Pittenger 2014, Bortolato and Pittenger 2017, Pittenger, Dulawa et al. 2017). Furthermore, since glutamate is involved in virtually every brain circuit, it is hardly surprising that circuit manipulations in animals may measurably perturb measures of glutamate function, and that alterations of glutamatergic neurotransmission may produce circuit abnormalities. Nevertheless, the convergence of several lines of animal work on the conclusion that glutamatergic pathophysiology within cortico-striatal circuits can lead to repetitive behaviors merits brief discussion in this chapter as well.

One of the best-studied animal models of repetitive behavior is the *Sapap3* knockout mouse, which has been interpreted as a mouse model of OCD (Welch, Lu et al. 2007) (see also chapter "Animal Models for the Study of OCD"). The mouse SAPAP proteins are orthologs of human DLGAPs and are important constituents of the postsynaptic protein network that coordinates and stabilizes glutamate receptors at synapse. As noted above, *DLGAP1* and *DLGAP2* have been tentatively implicated in initial genetic (International Obsessive Compulsive Disorder Foundation Genetics and Studies 2018) and postmortem (Piantadosi, Chamberlain et al. 2019) studies of OCD, which renders a connection between SAPAP

disruption in mice and OCD-relevant abnormalities intrinsically plausible. *Sapap3* knockout mice exhibit repetitive behavior and anxiety, both of which are responsive to treatment with fluoxetine, and abnormalities in glutamatergic synapses in the cortico-striatal circuitry (Welch, Lu et al. 2007).

Other targeted disruptions of glutamate-related genes have similarly produced repetitive behaviors in mice. For example, targeted disruption of the *Slc1a1* gene in mice reduced repetitive stereotypical behaviors after amphetamine in mice (Zike, Chohan et al. 2017), while overexpression of *Slc1a1* leads to anxiety and behavioral stereotypy (Delgado-Acevedo, Estay et al. 2019), supporting a role for appropriate dosing of this gene in normal maintenance of behavioral flexibility. Mutation of the neural signaling molecule *Slitrk5*, which regulates the maturation of glutamatergic synapses (among other functions), produces an excessive grooming phenotype quite similar to that seen in the *Sapap3* knockout mice, reinforcing the conclusion that abnormal glutamatergic synapses can produce repetitive behaviors (Shmelkov, Hormigo et al. 2010).

In sum, multiple convergent lines of evidence suggest that glutamate dysregulation may contribute to the development of OCD, and OCD-relevant brain circuit abnormalities. In conjunction with accumulating evidence that glutamate modulators can mitigate otherwise refractory OCD symptoms (Pittenger 2015, Marinova, Chuang et al. 2017), this suggests that targeting glutamate neurotransmission may be a fruitful avenue forward for the development of new pharmacological treatment strategies.

9. Towards personalized medicine in the treatment of OCD.

In OCD, as in most of psychiatry, we have a collection of treatments – SRI medications; neuroleptic augmentation; specialized cognitive-behavioral therapy – that are helpful for many patients, but ineffective for many others. An important goal is the development of predictors and algorithms to determine, in advance, which patients are most likely to respond to which interventions, thus sparing them weeks or months spent in trials of treatments that ultimately prove to be ineffective. This goal of precision or personalized medicine has been identified by the U.S. National Institute of Mental Health as a key research priority (NIMH 2020, Goal 3.2).

We are far from achieving this goal in practice (Hazari, Narayanaswamy et al. 2016). However, several studies have made initial steps. This final section reviews these efforts at prediction of individual treatment outcomes.

Phenomenological, symptomatic, and cognitive predictors of treatment response.

The most clinically useful predictor of treatment response would be one that is apparent on clinical evaluation, without the need for specialized testing.

Symptom content has been investigated as a predictor of treatment response in a number of studies. Several findings emerge from this literature. Hoarding symptoms, which were considered a part of OCD prior to the publication of DSM-5 in 2013 (American Psychiatric Association. and American Psychiatric Association. DSM-5 Task Force. 2013), predict poor

response to both psychotherapy and pharmacotherapy in most studies, and in meta-analysis (Bloch, Bartley et al. 2014). This poorer response may be mitigated by the deployment of more recently developed therapeutic strategies specifically targeting hoarding symptoms; this is not yet clear. Among the major dimensions of OCD symptomatology (Bloch, Landeros-Weisenberger et al. 2008), somatic (Erzegovesi, Cavallini et al. 2001) and sexual/religious obsessions and compulsions (Ferrao, Shavitt et al. 2006) have been associated with poor response to pharmacotherapy. However, another study found good response to SSRI treatment among those with sexual and religious and, especially, harm-related obsessions and compulsions (Landeros-Weisenberger, Bloch et al. 2010), while yet another found washing rituals to be predictive of poor outcome (Ravizza, Barzega et al. 1995). This inconsistency is striking. Symptom subtype does not appear to be a strong predictor of response to pharmacotherapy in OCD.

One early study found that high scores on particular component scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman, Price et al. 1989, Goodman, Price et al. 1989), the most widely used instrument for rating of OCD symptom severity, predicted good response to clomipramine. Specifically, clomipramine response was predicted by high scores on item #3 (distress caused by obsessions) and item #8 (distress caused if a patient is prevented from engaging in a compulsion) (Ackerman, Greenland et al. 1996). This suggests that pharmacotherapy, at least with clomipramine, is most effective in treating distress associated with OCD, and may be less effective in treating OCD symptoms that are more automatic or integrated into normal patterns of behavior. This speculation requires more investigation.

Some studies suggest that OCD with comorbid tics is less likely to respond to SSRI monotherapy (McDougle, Goodman et al. 1993). As noted above, early studies of neuroleptic augmentation suggested that haloperidol is of greater benefit in patients with comorbid tics (McDougle, Goodman et al. 1994). While this finding has not been robustly replicated, it remains significant in meta-analysis (Bloch, Landeros-Weisenberger et al. 2006). This may guide a prescriber towards haloperidol augmentation in patients with significant comorbid tics. More robust studies are needed to confirm this practice and to quantify what the differential benefit in patients with tics may be.

Other baseline clinical characteristics have been reported to predict poor SRI response. These include:

- early age of onset (Ravizza, Barzega et al. 1995, Ackerman, Greenland et al. 1996, Erzegovesi, Cavallini et al. 2001);
- duration and chronicity of illness (DeVeaugh-Geiss, Katz et al. 1990, Ravizza, Barzega et al. 1995, Ferrao, Shavitt et al. 2006, Stein, Andersen et al. 2007);
- severity of symptoms (Mataix-Cols, Marks et al. 2002, Denys, Burger et al. 2003, Ferrao, Shavitt et al. 2006, Storch, Larson et al. 2006, Stein, Andersen et al. 2007);
- comorbid depression (Ackerman, Greenland et al. 1996) or OCPD (Cavedini, Erzegovesi et al. 1997);

- poor insight (Catapano, Sperandeo et al. 2001, Erzegovesi, Cavallini et al. 2001) [though see (Eisen, Rasmussen et al. 2001) for a contrary finding]; and
- previous failure to respond to psychopharmacology (Ackerman, Greenland et al. 1998).

It should be noted, however, that most of these reported effects are small. Furthermore, the ability to identify patients who are less likely to respond to treatment is not of great practical use, in the absence of guidance as to what they are likely to respond to.

SSRI trials in OCD are typically lengthy. Characteristics of early response that predict long-term benefit could be of great utility if they permitted clinical decisions (e.g. to continue the trial, increase the dose, or switch strategies) to be made more quickly. As discussed above, there is increasing evidence that early clinical response predicts ultimate benefit with reasonable accuracy (da Conceicao Costa, Shavitt et al. 2013, Issari, Jakubovski et al. 2016). There is also evidence, from trials of both clomipramine (Ackerman, Greenland et al. 1996) and fluoxetine (Ackerman, Greenland et al. 1998) that side effects early in a drug trial may predict ultimate clinical benefit. This may be because some side effects reflect individual sensitivity to the serotonergic effects of these drugs, which ultimately contribute to therapeutic response.

Cognitive measures have been investigated as predictors of response to both CBT and SSRIs. In a study of 38 adults randomized to receive either CBT or SSRI treatment, verbal IQ, verbal memory, and performance on the Stroop color-word conflict task predicted better response to both psychotherapy and pharmacotherapy (D'Alcante, Diniz et al. 2012). These may be nonspecific markers of better overall neuropsychological status. Cognitive flexibility is impaired in OCD (Gruner and Pittenger 2017) (See also chapter "Cognitive Inflexibility in OCD and Related Disorders"); preserved cognitive flexibility (operationalized as perseveration on the California Verbal Learning Test) predicted better response to CBT, but worse response to SSRIs (D'Alcante, Diniz et al. 2012). Another small study produced a consistent finding: impaired performance on the Wisconsin Card Sort task, a different measure of cognitive flexibility, predicated good response to pharmacotherapy (Fontenelle, Marques et al. 2001). A more recent study found an association between executive function scores and response to CBT in children (Hybel, Mortensen et al. 2017). These studies suggest that measures of cognitive flexibility might be able to provide the sort of guidance a clinician needs: preserved cognitive flexibility may indicate that CBT is appropriate, while impaired cognitive flexibility may steer treatment towards pharmacotherapy. This guidance is not yet ready for broad clinical use, as the studies are small, measures of cognitive flexibility vary and are not readily deployed in clinical practice, and the effect sizes and predictive value of measures of cognitive inflexibility are not established. Nevertheless, these studies suggest that sort of approach that might inform treatment algorithms in the future.

Genetic predictors of treatment response and side effects.

(See also Chapter "Pharmacogenetics of Obsessive-Compulsive Disorder: An Evidence-Update") With rapid advances in clinical genetics of the past two decades, a persistent hope is that genetic testing will assist with treatment decisions in complex disorders such as OCD.

Indeed, a number of companies will provide patients with genetic testing, and use it to derive specific treatment recommendations. Unfortunately, these recommendations rest on a thin evidence base and are rarely useful to guide treatment decisions, at this point. The evidence-based integration of genetic information into OCD treatment algorithms awaits further refinement of our understanding of the genetic architecture of the disorder.

Nevertheless, a few studies have examined genetic predictors of treatment response in OCD, and these merit brief mention here. As in the discussion of the genetics of serotonin, dopamine, and glutamate reviewed above, it is important to note that early candidate gene studies have been plagued by non-replication; GWAS and other studies that interrogate the whole genome are needed to identify genetic predictors of treatment response with confidence.

Candidate gene studies have focused on the CYP enzymes of the liver, which are responsible for the first-pass metabolism of many therapeutic drugs, and on some of the genes in the serotonin, dopamine, and glutamate systems (Brandl, Muller et al. 2012, Zai, Brandl et al. 2014). Suggestive results have been reported for the serotonin transporter (*SLC6A4*), the 5-HT1B and 5-HT2A receptors, and the EAAT3 glutamate receptor encoded by *SLC1A1* (Brandl, Muller et al. 2012). Targeted testing of CYP enzymes suggests an association between CYP2D6 metabolizer status and the likelihood of non-response to SSRIs, as well as the incidence of side effects after venlafaxine treatment (Brandl, Tiwari et al. 2014). However, replication is required before any of these reports can be interpreted with confidence, or deployed in clinical practice.

A single study suggests that alternate alleles of *SLC6A4*, the serotonin transporter gene, differentially predict response to paroxetine versus venlafaxine (Denys, Van Nieuwerburgh et al. 2007). This result, if replicated, is the sort of finding that may have clinical utility, as it could steer clinical decision making (i.e. choice of drug). However, it should be noted that the evidence supporting venlafaxine as a first-line agent in the treatment of OCD is equivocal, as reviewed above. A genetic predictor of response to venlafaxine would have to be quite strong to justify using it in preference to an SSRI, when the latter are so much better supported by the treatment literature.

A single genome-wide association study has examined genetic predictors of self-reported response to pharmacotherapy in adult OCD (Qin, Samuels et al. 2016). Top hits in this analysis included SNPs near the genes *DISP1* and *PCDH10*, neither of which leads immediately to a mechanistic model. Pathway analysis of all possible and probable genetic loci suggested involvement of the glutamatergic and serotonergic systems. Much more work of this type is needed if we are to move towards actionable genetic predictors of treatment response.

Structural and functional neuroimaging predictors of treatment response.

A number of studies have examined structural and functional brain imaging measures as predictors of treatment response. While this work, too, has not converged on clinically actionable insights, it may provide initial clues as to what such imaging-informed treatment algorithms might look like in the future.

Structural neuroimaging has been examined as a predictor of treatment response in a few small studies. Attention has generally been focused on the corticostriatal loops implicated in OCD by functional neuroimaging studies (Brennan and Rauch 2017). One comparative study found gray matter density (measured using voxel based morphometry, or VBM) in the orbitofrontal cortex (OFC) to predict response to pharmacotherapy, while VBM in the medial prefrontal cortex predicted response to psychotherapy (Hoexter, Dougherty et al. 2013). A follow up analysis from the same group found thickness of the orbitofrontal cortex was found to predict treatment response in two small cohorts of patients (Hoexter, Diniz et al. 2015). A more recent study examined cortical morphology across the whole brain using structural covariance analysis and identified a network of structures in which cortical surface area and/or thickness predicted response to pharmacotherapy with 89% accuracy (Yun, Jang et al. 2015). This supports the potential of brain structural analyses to predict treatment response; but much more work is needed before such approaches can be used clinically.

More studies have examined measures of brain function as predictors of treatment response. Again, the focus has largely been on the frontal corticostriatal circuitry; early PET studies of brain metabolism have converged on the importance of the OFC. The first such study found lower right OFC metabolism to predict response to clomipramine at the end of 2 months of treatment (Swedo, Schapiro et al. 1989), though not at one year (Swedo, Pietrini et al. 1992). In a subsequent study, higher metabolic activity in the left OFC was found to predict better response to behavioral therapy, but worse response to fluoxetine (Brody, Saxena et al. 1998). A later study from the same group found concordant results: lower baseline OFC metabolism (bilaterally) was associated with better response to paroxetine (Saxena, Brody et al. 1999). Finally, in yet another study, lower baseline metabolism in the OFC and higher metabolism in the posterior cingulate cortex (PCC) predicted response to paroxetine (Rauch, Shin et al. 2002). The association of low relative metabolism in the OFC as a predictor of response to pharmacotherapy appears robust across these studies.

A pair of studies have found similar relationships with activity of the caudate nucleus, another node within the cortico-striatal circuitry canonically implicated in OCD (Brennan and Rauch 2017). In one, using PET imaging at baseline, higher pretreatment metabolism in the right caudate was found to predict response to paroxetine in patients with OCD; there was no such relationship in patients with major depressive disorder, suggesting some specificity to the effect (Saxena, Brody et al. 2003). A study using SPECT imaging found similar results: perfusion in the right caudate, as well as in the dorsal anterior cingulate, predicted response to sertraline in OCD (Hendler, Goshen et al. 2003). In contrast, another study using SPECT found baseline perfusion in the right cerebellum, as well as in the brain as a whole, to be predictive of response to fluvoxamine (Ho Pian, van Megen et al. 2005).

Interestingly, the two nodes most robustly identified as predictors of response to treatment using metabolic imaging – the OFC and the caudate – are also the brain regions whose activity has most consistently been shown to be modulated by treatment (van der Straten, Denys et al. 2017). This concordance increases confidence that these relationships are meaningful, despite the fact that most individual studies have been small.

Compared to PET, fMRI is more widely available, cheaper, and less invasive; it thus has greater theoretical potential for broad clinical use. On the other hand, fMRI typically has a lower signal-to-noise than PET and generally produces relative measures, rather than absolute ones, with sensitive dependence on the behavioral task used and other details of acquisition that may complicate clinical deployment. A single study has examined brain activation during symptom provocation as a predictor of response to 12 weeks of fluvoxamine treatment (Sanematsu, Nakao et al. 2010). Activation in the right cerebellum and left superior temporal gyrus – not regions that figure prominently in the larger OCD neuroimaging literature – predicted response.

fMRI can also be used to make inferences about brain functional connectivity and network organization. This analysis can be performed on data collected while subjects are at rest, rather than engaged in a task, which reduces the complexity of data collection and may make such approaches more appropriate for clinical deployment in the future. Several recent studies have applied this approach to baseline characterization in OCD (e.g. Harrison, Soriano-Mas et al. 2009, Harrison, Pujol et al. 2013, Anticevic, Hu et al. 2014, Shin, Jung et al. 2014). Others have used this approach to investigate predictors of treatment response. fMRI-derived functional connectivity at rest between the dorsal raphe nuclei and the left medial temporal gyrus has been reported to be elevated in OCD, and the degree of elevation predicts nonresponse to SSRI treatment (Kim, Kwak et al. 2019).

Several studies have examined baseline resting-state predictors of response to CBT. Low functional connectivity between the basolateral amygdala and the ventromedial prefrontal cortex, both structures known to be involved in OCD and in emotion regulation more generally, was found to predict response to CBT in a large sample of adults with OCD (Fullana, Zhu et al. 2017). Using a brain-wide machine learning-based analysis of functional connectivity, another study found connectivity patterns within the brain's default mode network to predict CBT response (Reggente, Moody et al. 2018). Functional connectivity analyses have also been used to investigate predictors of response to surgical treatment of refractory OCD (Yin, Zhang et al. 2018) and to an experimental neurofeedback approach (Scheinost, Stoica et al. 2014).

Neurochemical predictors of treatment response.

Finally, a number of studies have examined neurochemical measures as potential predictors of response. The focus has again been on serotonin, dopamine, and glutamate.

Measurement of plasma or platelet serotonin provides one accessible assay of serotonergic function, though its relationship with brain serotonin levels and homeostasis is not fully understood. As reviewed above, a number of studies have found platelet expression of the serotonin transporter, 5-HTT, to be reduced in patients with OCD. In one of these, higher whole blood serotonin concentration was found to predict response to SRI treatment (Delorme, Chabane et al. 2004). Plasma serotonin levels decline with treatment; interestingly, another study found that rapid decline in plasma serotonin was associated with poor response to clomipramine or paroxetine, while a more gradual decline predicted clinical improvement (Humble, Bejerot et al. 2001).

Finally, MRS measurement of glutamate and related compounds in the posterior cingulate cortex has been found in a single study to predict response to CBT in children, as reviewed above (O'Neill, Piacentini et al. 2017). MRS is an attractive modality for such studies, as it is non-invasive and can be targeted to specific brain areas, potentially providing more relevant measures than (for example) peripheral blood. More studies of this sort are needed.

In sum, many different approaches have been used to identify potential predictors of both pharmacotherapy and psychotherapy in OCD, and there are a number of promising leads. The most robustly replicated predictors of poor response appear to be the presence of comorbid hoarding symptoms (Bloch, Bartley et al. 2014) and the baseline metabolic activity of the orbitofrontal cortex; most other measures reviewed are more equivocal, or are supported by only a few studies. More work is needed to develop these predictors to the point that they can be deployed in widespread clinical practice. Importantly, prediction of which patients are likely to respond poorly is of limited utility; ultimately, we need measures that will help the clinician decide between available treatments. Algorithms based on such measures could bring relief more quickly than the trial-and-error method that is typically used today and would represent a significant step towards the long-term goal of personalized medicine in psychiatry.

10. Conclusion.

Pharmacotherapeutic options for the treatment of OCD are distressingly limited. Clear evidence supports the use of serotonin reuptake inhibitors – the selective serotonin reuptake inhibitors (SSRIs) and the older drug clomipramine – as monotherapy (Koran, Hanna et al. 2007, Soomro, Altman et al. 2008, Issari, Jakubovski et al. 2016, Skapinakis, Caldwell et al. 2016). Somewhat weaker but still convincing evidence supports the use of neuroleptics, especially haloperidol, risperidone, and aripiprazole, as augmentation of stable SRI treatment when symptom response is incomplete (Bloch, Landeros-Weisenberger et al. 2006, Skapinakis, Papatheodorou et al. 2007, Veale, Miles et al. 2014). But these strategies, together with expert cognitive-behavioral psychotherapy, leave many patients – perhaps as many as a third – with significant ongoing symptoms and attendant suffering. The need for new treatment options is clear.

In this chapter we have reviewed the evidence behind both standard-of-care and less well established pharmacological treatment strategies. We have focused on three neurotransmitter systems in the brain: serotonin, dopamine, and glutamate. This focus is necessarily myopic. These neurotransmitter systems do not operate in isolation, either in the course of normal brain function or during the response to pharmacotherapy. Rather, they interact with one another, both developmentally and in the adult, to modulate complex brain circuitries whose function and dysfunction underpins both normal behavior and the symptoms and course of neuropsychiatric disease. Furthermore, even keeping this heuristic focus on specific neurochemical systems, OCD surely involves other aspects of brain function: GABA (Simpson, Shungu et al. 2012); histamine (Baldan, Williams et al. 2014, Pittenger 2017); neuropeptides (McDougle, Barr et al. 1999, Marroni, Nakano et al. 2007, Dietrich, Zimmer et al. 2017); and others. However, more treatment and neurobiological research has focused on serotonin, dopamine, and glutamate than on any other neurochemical systems. They are

thus an appropriate place to start a consideration of the current state of pharmacological treatment of OCD, and possible ways forward.

Several conclusions arise from this review.

First, OCD is an extremely complex and heterogeneous disease entity. This complicates the formulation of any general models of how it develops, manifests, and is treated (Pittenger, Gruner et al. 2017, Szechtman, Harvey et al. 2020). As our understanding matures, we are likely to appreciate that two patients with a diagnosis of OCD may have quite different underlying pathophysiology. Indeed, some hints of possible subdivisions of the diagnosis have begun to emerge. Tic-related OCD may be genetically distinct (Davis, Yu et al. 2013) and may be characterized by more dopaminergic pathophysiology than non-tic associated OCD (Pittenger 2017), which may motivate earlier use of a augmentation with high-affinity D2 antagonist such as haloperidol. Glutamate dysregulation may characterize only a subset of patients (Chakrabarty, Bhattacharyya et al. 2005, Bhattacharyya, Khanna et al. 2009) and may prove to predict treatment response (O'Neill, Piacentini et al. 2017). Future study is likely to refine these distinctions and identify new ones, complexifying our conception of OCD as a diagnosis but also placing it on a firmer foundation. As we better understand the heterogeneity of OCD and how it may predict treatment response, algorithms for personalized medicine will become all the more important.

Second, much larger and more careful studies of novel agents for the treatment of refractory disease are needed. In many cases initial work suggests the possibility of therapeutic benefit, but without better-powered investigations treatment guidelines cannot be formulated with confidence. The case of ondansetron is an informative cautionary tale: several small controlled studies suggested that it led to improvement in patients with OCD (Serata, Kotzalidis et al. 2015), but a better-powered, more definitive study did not show benefit (NCT01275248). It remains to be seen whether initial promising studies with such agents as memantine (Andrade 2019, Modarresi, Chaibakhsh et al. 2019) and riluzole (Pittenger, Coric et al. 2008, Pittenger, Bloch et al. 2015, Emamzadehfard, Kamaloo et al. 2016) will replicate in well-powered studies, which are desperately needed.

Third, our understanding of the neurobiological underpinnings of OCD remains woefully incomplete. Throughout this review we have been forced over and over again to repeat the mantra 'more work is needed'. Often small studies suggest a neurobiological insight, but subsequent work fails to replicate it, or at least suggests greater complexity. For example, PET studies of the 5-HT2A receptor have shown it to be increased (Adams, Hansen et al. 2005), reduced (Perani, Garibotto et al. 2008), or unchanged (Simpson, Slifstein et al. 2011) in patients with OCD. Early MRS studies suggested an important contribution of dysregulated brain glutamate in patients (Rosenberg, MacMaster et al. 2000, Rosenberg, Mirza et al. 2004), but follow-up studies have been largely negative (Brennan, Rauch et al. 2013). Early genetic findings have hinted at potentially important new insights, such as the implication of mutations in *Slc1a1* in OCD (Hanna, Veenstra-VanderWeele et al. 2002, Willour, Yao Shugart et al. 2004), but follow-up studies have been heterogeneous and more equivocal (Stewart, Mayerfeld et al. 2013).

Lack of ready replication of the simple conclusions drawn by early studies may mean that the early work was incorrect, or that technical differences between studies are muddying the waters. But this heterogeneity of results may simply be a reflection of the complexity of the underlying condition. For example, if glutamate dysregulation characterizes only a fraction of patients with OCD, as suggested by CSF measures (Chakrabarty, Bhattacharyya et al. 2005, Bhattacharyya, Khanna et al. 2009), then it is to be expected that measures of glutamate function will be variable depending on the chance composition of the specific population being examined, especially in small studies. Much larger, rigorous studies can simultaneously yield reproducible results in which we can have confidence – most obviously in the case of genetics, but also in imaging and other neurobiological modalities. Insights from such well powered descriptive studies may pave the way to the identification of more homogeneous groups of patients for future investigations of treatment, making it easier to detect meaningful signal in modestly sized therapeutic trials.

Fourth, pathophysiology and treatment may not map cleanly onto one another. SRI medications are the best pharmacological treatment we have for OCD, and the evidence for the efficacy is unequivocal (Soomro, Altman et al. 2008, Issari, Jakubovski et al. 2016, Skapinakis, Caldwell et al. 2016). But neuroimaging (Pogarell, Hamann et al. 2003, Simpson, Lombardo et al. 2003) and genetic evidence (Taylor 2013, Taylor 2016) for dysregulation of the serotonin transporter, the target of SRI medications, as a key contributor to OCD pathophysiology is decidedly weak. Given the inadequacy of our current understanding of the pathophysiology of OCD, it is perhaps fortunate that the development of new treatments need not wait for more complete knowledge and rational design, which may be long in coming.

From where are the next advances in the treatment of OCD likely to come? It remains unclear, and any predictions are fraught with uncertainty. The development of more robust predictors of response to currently available interventions may help to optimize treatment algorithms. It is important that these studies focus on predictors that inform treatment decisions, rather than simply predict higher or lower likelihood of response to a single intervention, and that they move beyond the fairly small proof of concept studies to better powered, more generalizable investigations. As to new agents, the glutamate modulators memantine and riluzole (and troriluzole; NCT03299166) are perhaps the most promising agents currently under investigation. Dopamine dysregulation in OCD is not particularly well understood, and only the typical and atypical neuroleptics have been investigated with any rigor; there may be room here for exploration of other agents. Brain stimulation techniques such as transcranial magnetic stimulation (Carmi, Tendler et al. 2019) show promise, though these lie beyond the primary focus of the current review. Finally, the use of pharmacological or other somatic manipulations to enhance the efficacy of CBT holds great theoretical promise, as it may allow us to take advantage of both the potency of neurobiological interventions and the individualized specificity of psychotherapy. The first attempt at such a mechanistic synergy, using D-cycloserine, has not proven to be of robust enough benefit to enter widespread use (Burkner, Bittner et al. 2017, Mataix-Cols, Fernandez de la Cruz et al. 2017), but it is a valuable proof of concept that may light the way for future work along the same conceptual line.

In sum, there is reason for both optimism and caution. We have a few robustly proven treatments for OCD, and these can benefit many patients and mitigate much suffering. But more is needed to help the severely affected and those whose symptoms are refractory to standard care. It is to be hoped that in the coming decade, developing insights such as those summarized in this volume will light the way towards the development of qualitatively new interventions, to the benefit of many.

References.

Aboujaoude E, Barry JJ and Gamel N (2009). "Memantine augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial." J Clin Psychopharmacol 29(1): 51–55. [PubMed: 19142108]

Ackerman DL, Greenland S and Bystritsky A (1996). "Use of receiver-operator characteristic (ROC) curve analysis to evaluate predictors of response to clomipramine therapy." Psychopharmacol Bull 32(1): 157–165. [PubMed: 8927667]

Ackerman DL, Greenland S and Bystritsky A (1998). "Clinical characteristics of response to fluoxetine treatment of obsessive-compulsive disorder." J Clin Psychopharmacol 18(3): 185–192. [PubMed: 9617976]

Ackerman DL, Greenland S, Bystritsky A and Katz RJ (1996). "Relationship between early side effects and therapeutic effects of clomipramine therapy in obsessive-compulsive disorder." J Clin Psychopharmacol 16(4): 324–328. [PubMed: 8835709]

Adams KH, Hansen ES, Pinborg LH, Hasselbalch SG, Svarer C, Holm S, Bolwig TG and Knudsen GM (2005). "Patients with obsessive-compulsive disorder have increased 5-HT2A receptor binding in the caudate nuclei." Int J Neuropsychopharmacol 8(3): 391–401. [PubMed: 15801987]

Adams TG, Bloch MH and Pittenger C (2017). "Intranasal Ketamine and Cognitive-Behavioral Therapy for Treatment-Refractory Obsessive-Compulsive Disorder." J Clin Psychopharmacol 37(2): 269–271. [PubMed: 28121735]

Afshar H, Akuchekian S, Mahaky B and Zarean E (2014). "Topiramate augmentation in refractory obsessive-compulsive disorder: A randomized, double-blind, placebo-controlled trial." J Res Med Sci 19(10): 976–981. [PubMed: 25538783]

Afshar H, Roohafza H, Mohammad-Beigi H, Haghighi M, Jahangard L, Shokouh P, Sadeghi M and Hafezian H (2012). "N-acetylcysteine add-on treatment in refractory obsessive-compulsive disorder: a randomized, double-blind, placebo-controlled trial." J Clin Psychopharmacol 32(6): 797–803. [PubMed: 23131885]

Ahmari SE (2016). "Using mice to model Obsessive Compulsive Disorder: From genes to circuits." Neuroscience 321: 121–137. [PubMed: 26562431]

Ahmari SE and Dougherty DD (2015). "Dissecting Ocd Circuits: From Animal Models to Targeted Treatments." Depress Anxiety 32(8): 550–562. [PubMed: 25952989]

Altemus M, Swedo SE, Leonard HL, Richter D, Rubinow DR, Potter WZ and Rapoport JL (1994). "Changes in cerebrospinal fluid neurochemistry during treatment of obsessive-compulsive disorder with clomipramine." Arch Gen Psychiatry 51(10): 794–803. [PubMed: 7524463]

Altshuler D, Daly MJ and Lander ES (2008). "Genetic mapping in human disease." Science 322(5903): 881–888. [PubMed: 18988837]

American Psychiatric Association. and American Psychiatric Association. DSM-5 Task Force. (2013). Diagnostic and statistical manual of mental disorders : DSM-5. Washington, D.C., American Psychiatric Association.

Andrade C (2019). "Augmentation With Memantine in Obsessive-Compulsive Disorder." J Clin Psychiatry 80(6).

Anticevic A, Hu S, Zhang S, Savic A, Billingslea E, Wasylink S, Repovs G, Cole MW, Bednarski S, Krystal JH, Bloch MH, Li CS and Pittenger C (2014). "Global resting-state functional magnetic resonance imaging analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder." Biol Psychiatry 75(8): 595–605. [PubMed: 24314349]

Arrojo-Romero M, Tajes Alonso M and de Leon J (2013). “Lamotrigine augmentation of serotonin reuptake inhibitors in severe and long-term treatment-resistant obsessive-compulsive disorder.” Case Rep Psychiatry 2013: 612459. [PubMed: 23936714]

Balachander S, Kodancha PG, Arumugham SS, Sekharan JT, Narayanaswamy JC and Reddy YCJ (2019). “Effectiveness of Venlafaxine in Selective Serotonin Reuptake Inhibitor-Resistant Obsessive-Compulsive Disorder: Experience From a Specialty Clinic in India.” J Clin Psychopharmacol 39(1): 82–85. [PubMed: 30516575]

Baldan LC, Williams KA, Gallezot JD, Pogorelov V, Rapanelli M, Crowley M, Anderson GM, Loring E, Gorczyca R, Billingslea E, Wasylink S, Panza KE, Ercan-Sencicek AG, Krusong K, Leventhal BL, Ohtsu H, Bloch MH, Hughes ZA, Krystal JH, Mayes L, de Araujo I, Ding YS, State MW and Pittenger C (2014). “Histidine decarboxylase deficiency causes tourette syndrome: parallel findings in humans and mice.” Neuron 81(1): 77–90. [PubMed: 24411733]

Baldwin DS, Anderson IM, Nutt DJ, Bandelow B, Bond A, Davidson JR, den Boer JA, Fineberg NA, Knapp M, Scott J, Wittchen HU and British Association for P (2005). “Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology.” J Psychopharmacol 19(6): 567–596. [PubMed: 16272179]

Barr LC, Goodman WK, McDougle CJ, Delgado PL, Heninger GR, Charney DS and Price LH (1994). “Tryptophan depletion in patients with obsessive-compulsive disorder who respond to serotonin reuptake inhibitors.” Arch Gen Psychiatry 51(4): 309–317. [PubMed: 8161291]

Bastani B, Arora RC and Meltzer HY (1991). “Serotonin uptake and imipramine binding in the blood platelets of obsessive-compulsive disorder patients.” Biol Psychiatry 30(2): 131–139. [PubMed: 1655071]

Baumgarten HG and Grozdanovic Z (1998). “Role of serotonin in obsessive-compulsive disorder.” Br J Psychiatry Suppl(35): 13–20. [PubMed: 9829022]

Bergin J, Verhulst B, Aggen SH, Neale MC, Kendler KS, Bienvenu OJ and Hettema JM (2014). “Obsessive compulsive symptom dimensions and neuroticism: An examination of shared genetic and environmental risk.” Am J Med Genet B Neuropsychiatr Genet 165B(8): 647–653. [PubMed: 25231027]

Berlin HA, Koran LM, Jenike MA, Shapira NA, Chaplin W, Pallanti S and Hollander E (2011). “Double-blind, placebo-controlled trial of topiramate augmentation in treatment-resistant obsessive-compulsive disorder.” J Clin Psychiatry 72(5): 716–721. [PubMed: 20816027]

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS and Krystal JH (2000). “Antidepressant effects of ketamine in depressed patients.” Biol Psychiatry 47(4): 351–354. [PubMed: 10686270]

Berney A, Sookman D, Leyton M, Young SN and Benkelfat C (2006). “Lack of effects on core obsessive-compulsive symptoms of tryptophan depletion during symptom provocation in remitted obsessive-compulsive disorder patients.” Biol Psychiatry 59(9): 853–857. [PubMed: 16213470]

Bhattacharyya S, Khanna S, Chakrabarty K, Mahadevan A, Christopher R and Shankar SK (2009). “Anti-brain autoantibodies and altered excitatory neurotransmitters in obsessive-compulsive disorder.” Neuropsychopharmacology 34(12): 2489–2496. [PubMed: 19675532]

BioSpace. (2012). “Transcept Pharmaceuticals, Inc.’s Drug for Obsessive Compulsive Disroder Fails Trial.” Retrieved May 22, 2020, from https://www.biospace.com/article/releases/transcept-pharmaceuticals-inc-s-drug-for-obsessive-compulsive-disorder-fails-trial-/.

Bloch MH (2008). “Emerging treatments for Tourette’s disorder.” Curr Psychiatry Rep 10(4): 323–330. [PubMed: 18627671]

Bloch MH, Bartley CA, Zipperer L, Jakubovski E, Landeros-Weisenberger A, Pittenger C and Leckman JF (2014). “Meta-analysis: hoarding symptoms associated with poor treatment outcome in obsessive-compulsive disorder.” Mol Psychiatry 19(9): 1025–1030. [PubMed: 24912494]

Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB and Leckman JF (2006). “A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder.” Mol Psychiatry 11(7): 622–632. [PubMed: 16585942]

Bloch MH, Landeros-Weisenberger A, Rosario MC, Pittenger C and Leckman JF (2008). "Meta-analysis of the symptom structure of obsessive-compulsive disorder." Am J Psychiatry 165(12): 1532–1542. [PubMed: 18923068]

Bloch MH, Landeros-Weisenberger A, Sen S, Dombrowski P, Kelmendi B, Coric V, Pittenger C and Leckman JF (2008). "Association of the serotonin transporter polymorphism and obsessive-compulsive disorder: systematic review." Am J Med Genet B Neuropsychiatr Genet 147B(6): 850–858. [PubMed: 18186076]

Bloch MH, McGuire J, Landeros-Weisenberger A, Leckman JF and Pittenger C (2010). "Meta-analysis of the dose-response relationship of SSRI in obsessive-compulsive disorder." Mol Psychiatry 15(8): 850–855. [PubMed: 19468281]

Bloch MH, Wasylink S, Landeros-Weisenberger A, Panza KE, Billingslea E, Leckman JF, Krystal JH, Bhagwagar Z, Sanacora G and Pittenger C (2012). "Effects of ketamine in treatment-refractory obsessive-compulsive disorder." Biol Psychiatry 72(11): 964–970. [PubMed: 22784486]

Boisseau CL, Schhwartzman CM and Rasmussen SA (2017). Quality of life and psychosocial functioning in OCD. Obsessive-Compulsive Disorder: Phenomenology, Pathophysiology, and Treatment. Pittenger C. New York, NY, Oxford University Press.

Bortolato M and Pittenger C (2017). "Modeling tics in rodents: Conceptual challenges and paths forward." J Neurosci Methods 292: 12–19. [PubMed: 28237575]

Boshuisen ML and den Boer JA (2000). "Zolmitriptan (a 5-HT1B/1D receptor agonist with central action) does not increase symptoms in obsessive compulsive disorder." Psychopharmacology (Berl) 152(1): 74–79. [PubMed: 11041318]

Brandl EJ, Muller DJ and Richter MA (2012). "Pharmacogenetics of obsessive-compulsive disorders." Pharmacogenomics 13(1): 71–81. [PubMed: 22176623]

Brandl EJ, Tiwari AK, Zhou X, Deluce J, Kennedy JL, Muller DJ and Richter MA (2014). "Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder." Pharmacogenomics J 14(2): 176–181. [PubMed: 23545896]

Brennan BP and Rauch SL (2017). A Review and Synthesis of Functional Neuroimaging Studies of Obsessive-Compulsive Disorder. Obsessive-copulsive disorder: Phenomenology, Pathophysiology, and Treatment. Pittenger C. New York, Oxford Univeristy Press.

Brennan BP, Rauch SL, Jensen JE and Pope HG Jr. (2013). "A critical review of magnetic resonance spectroscopy studies of obsessive-compulsive disorder." Biol Psychiatry 73(1): 24–31. [PubMed: 22831979]

Brody AL, Saxena S, Schwartz JM, Stoessel PW, Maidment K, Phelps ME and Baxter LR Jr. (1998). "FDG-PET predictors of response to behavioral therapy and pharmacotherapy in obsessive compulsive disorder." Psychiatry Res 84(1): 1–6. [PubMed: 9870412]

Bruno A, Mico U, Pandolfo G, Mallamace D, Abenavoli E, Di Nardo F, D'Arrigo C, Spina E, Zoccali RA and Muscatello MR (2012). "Lamotrigine augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study." J Psychopharmacol 26(11): 1456–1462. [PubMed: 22351381]

Burkner PC, Bittner N, Holling H and Buhlmann U (2017). "D-cycloserine augmentation of behavior therapy for anxiety and obsessive-compulsive disorders: A meta-analysis." PLoS One 12(3): e0173660. [PubMed: 28282427]

Cai J, Zhang W, Yi Z, Lu W, Wu Z, Chen J, Yu S, Fang Y and Zhang C (2013). "Influence of polymorphisms in genes SLC1A1, GRIN2B, and GRIK2 on clozapine-induced obsessive-compulsive symptoms." Psychopharmacology (Berl) 230(1): 49–55. [PubMed: 23660601]

Cappi C, Oliphant ME, Peter Z, Zai G, Conceicao do Rosario M, Sullivan CAW, Gupta AR, Hoffman EJ, Virdee M, Olfson E, Abdallah SB, Willsey AJ, Shavitt RG, Miguel EC, Kennedy JL, Richter MA and Fernandez TV (2019). "De Novo Damaging DNA Coding Mutations Are Associated With Obsessive-Compulsive Disorder and Overlap With Tourette's Disorder and Autism." Biol Psychiatry.

Carmi L, Tendler A, Bystritsky A, Hollander E, Blumberger DM, Daskalakis J, Ward H, Lapidus K, Goodman W, Casuto L, Feifel D, Barnea-Ygael N, Roth Y, Zangen A and Zohar J (2019). "Efficacy and Safety of Deep Transcranial Magnetic Stimulation for Obsessive-Compulsive

Disorder: A Prospective Multicenter Randomized Double-Blind Placebo-Controlled Trial." Am J Psychiatry 176(11): 931–938. [PubMed: 31109199]

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A and Poulton R (2003). "Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene." Science 301(5631): 386–389. [PubMed: 12869766]

Catapano F, Sperandeo R, Perris F, Lanzaro M and Maj M (2001). "Insight and resistance in patients with obsessive-compulsive disorder." Psychopathology 34(2): 62–68. [PubMed: 11244376]

Cavedini P, Erzegovesi S, Ronchi P and Bellodi L (1997). "Predictive value of obsessive-compulsive personality disorder in antiobsessional pharmacological treatment." Eur Neuropsychopharmacol 7(1): 45–49. [PubMed: 9088884]

Chakrabarty K, Bhattacharyya S, Christopher R and Khanna S (2005). "Glutamatergic dysfunction in OCD." Neuropsychopharmacology 30(9): 1735–1740. [PubMed: 15841109]

Chiou YJ, Lin PY and Lee Y (2015). "Risperidone as monotherapy for a patient with obsessive compulsive disorder comorbid with schizoaffective disorder: a case report." Clin Neuropharmacol 38(3): 114–116. [PubMed: 25970281]

Clarke H, Flint J, Attwood AS and Munafo MR (2010). "Association of the 5- HTTLPR genotype and unipolar depression: a meta-analysis." Psychol Med 40(11): 1767–1778. [PubMed: 20380781]

Clarke HF, Dalley JW, Crofts HS, Robbins TW and Roberts AC (2004). "Cognitive inflexibility after prefrontal serotonin depletion." Science 304(5672): 878–880. [PubMed: 15131308]

Connor KM, Payne VM, Gadde KM, Zhang W and Davidson JR (2005). "The use of aripiprazole in obsessive-compulsive disorder: preliminary observations in 8 patients." J Clin Psychiatry 66(1): 49–51. [PubMed: 15669888]

Coric V, Taskiran S, Pittenger C, Wasylink S, Mathalon DH, Valentine G, Saksa J, Wu YT, Gueorguieva R, Sanacora G, Malison RT and Krystal JH (2005). "Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial." Biol Psychiatry 58(5): 424–428. [PubMed: 15993857]

Costa DLC, Diniz JB, Requena G, Joaquim MA, Pittenger C, Bloch MH, Miguel EC and Shavitt RG (2017). "Randomized, Double-Blind, Placebo-Controlled Trial of N-Acetylcysteine Augmentation for Treatment-Resistant Obsessive-Compulsive Disorder." J Clin Psychiatry 78(7): e766–e773. [PubMed: 28617566]

D'Alcante CC, Diniz JB, Fossaluza V, Batistuzzo MC, Lopes AC, Shavitt RG, Deckersbach T, Malloy-Diniz L, Miguel EC and Hoexter MQ (2012). "Neuropsychological predictors of response to randomized treatment in obsessive-compulsive disorder." Prog Neuropsychopharmacol Biol Psychiatry 39(2): 310–317. [PubMed: 22789662]

da Conceicao Costa DL, Shavitt RG, Castro Cesar RC, Joaquim MA, Borcato S, Valerio C, Miguel EC and Diniz JB (2013). "Can early improvement be an indicator of treatment response in obsessive-compulsive disorder? Implications for early-treatment decision-making." J Psychiatr Res 47(11): 1700–1707. [PubMed: 23948637]

Davis LK, Yu D, Keenan CL, Gamazon ER, Konkashbaev AI, Derks EM, Neale BM, Yang J, Lee SH, Evans P, Barr CL, Bellodi L, Benarroch F, Berrio GB, Bienvenu OJ, Bloch MH, Blom RM, Bruun RD, Budman CL, Camarena B, Campbell D, Cappi C, Cardona Silgado JC, Cath DC, Cavallini MC, Chavira DA, Chouinard S, Conti DV, Cook EH, Coric V, Cullen BA, Deforce D, Delorme R, Dion Y, Edlund CK, Egberts K, Falkai P, Fernandez TV, Gallagher PJ, Garrido H, Geller D, Girard SL, Grabe HJ, Grados MA, Greenberg BD, Gross-Tsur V, Haddad S, Heiman GA, Hemmings SM, Hounie AG, Illmann C, Jankovic J, Jenike MA, Kennedy JL, King RA, Kremeyer B, Kurlan R, Lanzagorta N, Leboyer M, Leckman JF, Lennertz L, Liu C, Lochner C, Lowe TL, Macciardi F, McCracken JT, McGrath LM, Mesa Restrepo SC, Moessner R, Morgan J, Muller H, Murphy DL, Naarden AL, Ochoa WC, Ophoff RA, Osiecki L, Pakstis AJ, Pato MT, Pato CN, Piacentini J, Pittenger C, Pollak Y, Rauch SL, Renner TJ, Reus VI, Richter MA, Riddle MA, Robertson MM, Romero R, Rosario MC, Rosenberg D, Rouleau GA, Ruhrmann S, Ruiz-Linares A, Sampaio AS, Samuels J, Sandor P, Sheppard B, Singer HS, Smit JH, Stein DJ, Strengman E, Tischfield JA, Valencia Duarte AV, Vallada H, Van Nieuwerburgh F, Veenstra-Vanderweele J, Walitza S, Wang Y, Wendland JR, Westenberg HG, Shugart YY, Miguel EC, McMahon W, Wagner M, Nicolini H, Posthuma D, Hanna GL, Heutink P, Denys D, Arnold PD, Oostra BA, Nestadt G, Freimer NB, Pauls DL, Wray NR, Stewart SE, Mathews CA, Knowles JA, Cox NJ and Scharf

JM (2013). “Partitioning the heritability of Tourette syndrome and obsessive compulsive disorder reveals differences in genetic architecture.” PLoS Genet 9(10): e1003864. [PubMed: 24204291]

Delgado-Acevedo C, Estay SF, Radke AK, Sengupta A, Escobar AP, Henriquez-Belmar F, Reyes CA, Haro-Acuna V, Utreras E, Sotomayor-Zarate R, Cho A, Wendland JR, Kulkarni AB, Holmes A, Murphy DL, Chavez AE and Moya PR (2019). “Behavioral and synaptic alterations relevant to obsessive-compulsive disorder in mice with increased EAAT3 expression.” Neuropsychopharmacology 44(6): 1163–1173. [PubMed: 30622300]

Delorme R, Chabane N, Callebert J, Falissard B, Mouren-Simeoni MC, Rouillon F, Launay JM and Leboyer M (2004). “Platelet serotonergic predictors of clinical improvement in obsessive compulsive disorder.” J Clin Psychopharmacol 24(1): 18–23. [PubMed: 14709942]

Denys D, Burger H, van Megen H, de Geus F and Westenberg H (2003). “A score for predicting response to pharmacotherapy in obsessive-compulsive disorder.” Int Clin Psychopharmacol 18(6): 315–322. [PubMed: 14571151]

Denys D, de Vries F, Cath D, Figee M, Vulink N, Veltman DJ, van der Doef TF, Boellaard R, Westenberg H, van Balkom A, Lammertsma AA and van Berckel BN (2013). “Dopaminergic activity in Tourette syndrome and obsessive-compulsive disorder.” Eur Neuropsychopharmacol 23(11): 1423–1431. [PubMed: 23876376]

Denys D, van der Wee N, Janssen J, De Geus F and Westenberg HG (2004). “Low level of dopaminergic D2 receptor binding in obsessive-compulsive disorder.” Biol Psychiatry 55(10): 1041–1045. [PubMed: 15121489]

Denys D, van Megen HJ, van der Wee N and Westenberg HG (2004). “A double-blind switch study of paroxetine and venlafaxine in obsessive-compulsive disorder.” J Clin Psychiatry 65(1): 37–43.

Denys D, Van Nieuwerburgh F, Deforce D and Westenberg HG (2007). “Prediction of response to paroxetine and venlafaxine by serotonin-related genes in obsessive-compulsive disorder in a randomized, double-blind trial.” J Clin Psychiatry 68(5): 747–753. [PubMed: 17503984]

Denys D, Zohar J and Westenberg HG (2004). “The role of dopamine in obsessive-compulsive disorder: preclinical and clinical evidence.” J Clin Psychiatry 65 Suppl 14: 11–17.

DeVeaugh-Geiss J, Katz R, Landau P, Goodman W and Rasmussen S (1990). “Clinical predictors of treatment response in obsessive compulsive disorder: exploratory analyses from multicenter trials of clomipramine.” Psychopharmacol Bull 26(1): 54–59. [PubMed: 2196627]

DeVeaugh-Geiss J, Landau P and Katz R (1989). “Preliminary results from a multicenter trial of clomipramine in obsessive-compulsive disorder.” Psychopharmacol Bull 25(1): 36–40. [PubMed: 2672070]

Dietrich MO, Zimmer MR, Bober J and Horvath TL (2017). “Hypothalamic Agrp Neurons Drive Stereotypic Behaviors beyond Feeding.” Cell 169(3): 559.

Dold M, Aigner M, Lanzenberger R and Kasper S (2015). “Antipsychotic Augmentation of Serotonin Reuptake Inhibitors in Treatment-Resistant Obsessive-Compulsive Disorder: An Update Meta-Analysis of Double-Blind, Randomized, Placebo-Controlled Trials.” Int J Neuropsychopharmacol 18(9).

Ducasse D, Boyer L, Michel P, Loundou A, Macgregor A, Micoulaud-Franchi JA, Courtet P, Abbar M, Leboyer M and Fond G (2014). “D2 and D3 dopamine receptor affinity predicts effectiveness of antipsychotic drugs in obsessive-compulsive disorders: a metaregression analysis.” Psychopharmacology (Berl) 231(18): 3765–3770. [PubMed: 24599398]

Eisen JL, Rasmussen SA, Phillips KA, Price LH, Davidson J, Lydiard RB, Ninan P and Piggott T (2001). “Insight and treatment outcome in obsessive-compulsive disorder.” Compr Psychiatry 42(6): 494–497. [PubMed: 11704942]

El Mansari M and Blier P (2005). “Responsiveness of 5-HT(1A) and 5-HT2 receptors in the rat orbitofrontal cortex after long-term serotonin reuptake inhibition.” J Psychiatry Neurosci 30(4): 268–274. [PubMed: 16049570]

Emamzadehfard S, Kamaloo A, Paydary K, Ahmadipour A, Zeinoddini A, Ghaleiha A, Mohammadinejad P, Zeinoddini A and Akhondzadeh S (2016). “Riluzole in augmentation of fluvoxamine for moderate to severe obsessive-compulsive disorder: Randomized, double-blind, placebo-controlled study.” Psychiatry Clin Neurosci 70(8): 332–341. [PubMed: 27106362]

Erzegovesi S, Cavallini MC, Cavedini P, Diaferia G, Locatelli M and Bellodi L (2001). “Clinical predictors of drug response in obsessive-compulsive disorder.” J Clin Psychopharmacol 21(5): 488–492. [PubMed: 11593074]

Escobar AP, Wendland JR, Chavez AE and Moya PR (2019). “The Neuronal Glutamate Transporter EAAT3 in Obsessive-Compulsive Disorder.” Front Pharmacol 10: 1362. [PubMed: 31803055]

Excellence, N. I. f. C. (2006). “Obsessive-compulsive disorder: Core interventions in the treatment of obsessive-compulsive disorder and body dysmorphic disorder.” Retrieved April 15, 2020, from https://www.nice.org.uk/guidance/cg31.

Fallon BA, Liebowitz MR, Campeas R, Schneier FR, Marshall R, Davies S, Goetz D and Klein DF (1998). “Intravenous clomipramine for obsessive-compulsive disorder refractory to oral clomipramine: a placebo-controlled study.” Arch Gen Psychiatry 55(10): 918–924. [PubMed: 9783563]

FDA, U. (2012). “FDA Drug Safety Comunication: Abnormal heart rhythms associated with high doses of celexa (citalopram hydrobromide).” Retrieved May 20, 2020, from http://www.fda.gov/Drugs/DrugSafety/ucm269086.htm.

Fernandez Cordoba E and Lopez-Ibor Alino J (1967). “[Use of monochlorimipramine in psychiatric patients who are resistant to other therapy].” Actas Luso Esp Neurol Psiquiatr 26(2): 119–147. [PubMed: 5628965]

Fernandez TV, Leckman JF and Pittenger C (2018). “Genetic susceptibility in obsessive-compulsive disorder.” Handb Clin Neurol 148: 767–781. [PubMed: 29478613]

Ferrao YA, Shavitt RG, Bedin NR, de Mathis ME, Carlos Lopes A, Fontenelle LF, Torres AR and Miguel EC (2006). “Clinical features associated to refractory obsessive-compulsive disorder.” J Affect Disord 94(1–3): 199–209. [PubMed: 16764938]

Feusner JD, Kerwin L, Saxena S and Bystritsky A (2009). “Differential efficacy of memantine for obsessive-compulsive disorder vs. generalized anxiety disorder: an open-label trial.” Psychopharmacol Bull 42(1): 81–93. [PubMed: 19204653]

Fineberg NA and Gale T (2005). “Evidence-based pharmacological treatments for obsessive-compulsive disorder.” International Journal of Neuropsychopharmacology 8: 107–129.

Fineberg NA, Reghunandanan S, Simpson HB, Phillips KA, Richter MA, Matthews K, Stein DJ, Sareen J, Brown A, Sookman D and D. Accreditation Task Force of The Canadian Institute for Obsessive Compulsive (2015). “Obsessive-compulsive disorder (OCD): Practical strategies for pharmacological and somatic treatment in adults.” Psychiatry Res 227(1): 114–125. [PubMed: 25681005]

Fontenelle L, Marques C, Engelhardt E and Versiani M (2001). “Impaired set-shifting ability and therapeutic response in obsessive-compulsive disorder.” J Neuropsychiatry Clin Neurosci 13(4): 508–510. [PubMed: 11748320]

Friedman AA, Letai A, Fisher DE and Flaherty KT (2015). “Precision medicine for cancer with next-generation functional diagnostics.” Nat Rev Cancer 15(12): 747–756. [PubMed: 26536825]

Fullana MA, Zhu X, Alonso P, Cardoner N, Real E, Lopez-Sola C, Segalas C, Subira M, Galfalvy H, Menchon JM, Simpson HB, Marsh R and Soriano-Mas C (2017). “Basolateral amygdala-ventromedial prefrontal cortex connectivity predicts cognitive behavioural therapy outcome in adults with obsessive-compulsive disorder.” J Psychiatry Neurosci 42(6): 378–385. [PubMed: 28632120]

Gadallah AHA, Ebada MA, Gadallah A, Ahmed H, Rashad W, Eid KA, Bahbah E and Alkanj S (2020). “Efficacy and safety of N-acetylcysteine as add-on therapy in the treatment of obsessive-compulsive disorder: A systematic review and meta-analysis.” J. OCD and Related Disorders 25: 100529.

Ghaleiha A, Entezari N, Modabbernia A, Najand B, Askari N, Tabrizi M, Ashrafi M, Hajiaghaee R and Akhondzadeh S (2013). “Memantine add-on in moderate to severe obsessive-compulsive disorder: randomized double-blind placebo-controlled study.” J Psychiatr Res 47(2): 175–180. [PubMed: 23063327]

Ghanizadeh A, Mohammadi MR, Bahraini S, Keshavarzi Z, Firoozabadi A and Alavi Shoshtari A (2017). “Efficacy of N-Acetylcysteine Augmentation on Obsessive Compulsive Disorder: A

Multicenter Randomized Double Blind Placebo Controlled Clinical Trial." Iran J Psychiatry 12(2): 134–141. [PubMed: 28659986]

Goodman WK, Price LH, Rasmussen SA, Delgado PL, Heninger GR and Charney DS (1989). "Efficacy of fluvoxamine in obsessive-compulsive disorder. A double-blind comparison with placebo." Arch Gen Psychiatry 46(1): 36–44. [PubMed: 2491940]

Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR and Charney DS (1989). "The Yale-Brown Obsessive Compulsive Scale. II. Validity." Arch Gen Psychiatry 46(11): 1012–1016. [PubMed: 2510699]

Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR and Charney DS (1989). "The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability." Arch Gen Psychiatry 46(11): 1006–1011. [PubMed: 2684084]

Graat I, Figee M and Denys D (2017). Neurotransmitter dysregulation in OCD. Obsessive-Compulsive Disorder: Phenomenology, Pathophysiology, and Treatment. Pittenger C. New York, Oxford University Press.

Grant PJ, Joseph LA, Farmer CA, Luckenbaugh DA, Lougee LC, Zarate CA Jr. and Swedo SE (2014). "12-week, placebo-controlled trial of add-on riluzole in the treatment of childhood-onset obsessive-compulsive disorder." Neuropsychopharmacology 39(6): 1453–1459. [PubMed: 24356715]

Greenberg WM, Benedict MM, Doerfer J, Perrin M, Panek L, Cleveland WL and Javitt DC (2009). "Adjunctive glycine in the treatment of obsessive-compulsive disorder in adults." J Psychiatr Res 43(6): 664–670. [PubMed: 19046587]

Grillault Laroche D and Gaillard A (2016). "Induced Obsessive Compulsive Symptoms (OCS) in schizophrenia patients under Atypical 2 Antipsychotics (AAPs): review and hypotheses." Psychiatry Res 246: 119–128. [PubMed: 27690134]

Gross-Isseroff R, Cohen R, Sasson Y, Voet H and Zohar J (2004). "Serotonergic dissection of obsessive compulsive symptoms: a challenge study with m-chlorophenylpiperazine and sumatriptan." Neuropsychobiology 50(3): 200–205. [PubMed: 15365215]

Group, C. C. S. (1991). "Clomipramine in the treatment of patients with obsessive-compulsive disorder. The Clomipramine Collaborative Study Group." Arch Gen Psychiatry 48(8): 730–738. [PubMed: 1883256]

Gruner P and Pittenger C (2017). "Cognitive inflexibility in Obsessive-Compulsive Disorder." Neuroscience 345: 243–255. [PubMed: 27491478]

Haghighi M, Jahangard L, Mohammad-Beigi H, Bajoghli H, Hafezian H, Rahimi A, Afshar H, Holsboer-Trachsler E and Brand S (2013). "In a double-blind, randomized and placebo-controlled trial, adjuvant memantine improved symptoms in inpatients suffering from refractory obsessive-compulsive disorders (OCD)." Psychopharmacology (Berl) 228(4): 633–640. [PubMed: 23525525]

Hamblin RJ, Park JM, Wu MS and Storch EA (2017). Variable insight in OCD. Obsessive-Compulsive Disorder: Phenomenology, Pathophysiology, and Treatment. Pittenger C. New York, Oxford University Press.

Hanna GL, Veenstra-VanderWeele J, Cox NJ, Boehnke M, Himle JA, Curtis GC, Leventhal BL and Cook EH Jr. (2002). "Genome-wide linkage analysis of families with obsessive-compulsive disorder ascertained through pediatric probands." Am J Med Genet 114(5): 541–552. [PubMed: 12116192]

Harrison BJ, Pujol J, Cardoner N, Deus J, Alonso P, Lopez-Sola M, Contreras-Rodriguez O, Real E, Segalas C, Blanco-Hinojo L, Menchon JM and Soriano-Mas C (2013). "Brain corticostriatal systems and the major clinical symptom dimensions of obsessive-compulsive disorder." Biol Psychiatry 73(4): 321–328. [PubMed: 23200527]

Harrison BJ, Soriano-Mas C, Pujol J, Ortiz H, Lopez-Sola M, Hernandez-Ribas R, Deus J, Alonso P, Yucel M, Pantelis C, Menchon JM and Cardoner N (2009). "Altered corticostriatal functional connectivity in obsessive-compulsive disorder." Arch Gen Psychiatry 66(11): 1189–1200. [PubMed: 19884607]

Hasnain M and Vieweg WV (2014). “QTc interval prolongation and torsade de pointes associated with second-generation antipsychotics and antidepressants: a comprehensive review.” CNS Drugs 28(10): 887–920. [PubMed: 25168784]

Hazari N, Narayanaswamy JC and Arumugham SS (2016). “Predictors of response to serotonin reuptake inhibitors in obsessive-compulsive disorder.” Expert Rev Neurother 16(10): 1175–1191. [PubMed: 27282021]

Heinz A, Jones DW, Mazzanti C, Goldman D, Ragan P, Hommer D, Linnoila M and Weinberger DR (2000). “A relationship between serotonin transporter genotype and in vivo protein expression and alcohol neurotoxicity.” Biol Psychiatry 47(7): 643–649. [PubMed: 10745057]

Hendler T, Goshen E, Tzila Zwas S, Sasson Y, Gal G and Zohar J (2003). “Brain reactivity to specific symptom provocation indicates prospective therapeutic outcome in OCD.” Psychiatry Res 124(2): 87–103. [PubMed: 14561427]

Hesse S, Muller U, Lincke T, Barthel H, Villmann T, Angermeyer MC, Sabri O and Stengler-Wenzke K (2005). “Serotonin and dopamine transporter imaging in patients with obsessive-compulsive disorder.” Psychiatry Res 140(1): 63–72. [PubMed: 16213689]

Hezel DM, Beattie K and Stewart SE (2009). “Memantine as an augmenting agent for severe pediatric OCD.” Am J Psychiatry 166(2): 237. [PubMed: 19188297]

Ho Pian KL, van Megen HJ, Ramsey NF, Mandl R, van Rijk PP, Wynne HJ and Westenberg HG (2005). “Decreased thalamic blood flow in obsessive-compulsive disorder patients responding to fluvoxamine.” Psychiatry Res 138(2): 89–97. [PubMed: 15766633]

Hoexter MQ, Diniz JB, Lopes AC, Batistuzzo MC, Shavitt RG, Dougherty DD, Duran FL, Bressan RA, Busatto GF, Miguel EC and Sato JR (2015). “Orbitofrontal Thickness as a Measure for Treatment Response Prediction in Obsessive-Compulsive Disorder.” Depress Anxiety 32(12): 900–908. [PubMed: 26032588]

Hoexter MQ, Dougherty DD, Shavitt RG, D’Alcante CC, Duran FL, Lopes AC, Diniz JB, Batistuzzo MC, Evans KC, Bressan RA, Busatto GF and Miguel EC (2013). “Differential prefrontal gray matter correlates of treatment response to fluoxetine or cognitive-behavioral therapy in obsessive-compulsive disorder.” Eur Neuropsychopharmacol 23(7): 569–580. [PubMed: 22841131]

Hollander E, Doernberg E, Shavitt R, Waterman RJ, Soreni N, Veltman DJ, Sahakian BJ and Fineberg NA (2016). “The cost and impact of compulsivity: A research perspective.” Eur Neuropsychopharmacol 26(5): 800–809. [PubMed: 27235690]

Hood SD, Broyd A, Robinson H, Lee J, Hudaib AR and Hince DA (2017). “Effects of tryptophan depletion on selective serotonin reuptake inhibitor-remitted patients with obsessive compulsive disorder.” J Psychopharmacol 31(12): 1615–1623. [PubMed: 29095069]

Hsieh HJ, Lue KH, Tsai HC, Lee CC, Chen SY and Kao PF (2014). “L-3,4-Dihydroxy-6-[F-18]fluorophenylalanine positron emission tomography demonstrating dopaminergic system abnormality in the brains of obsessive-compulsive disorder patients.” Psychiatry Clin Neurosci 68(4): 292–298. [PubMed: 24405478]

Humble M, Bejerot S, Bergqvist PB and Bengtsson F (2001). “Reactivity of serotonin in whole blood: relationship with drug response in obsessive-compulsive disorder.” Biol Psychiatry 49(4): 360–368. [PubMed: 11239907]

Hussain A, Dar MA, Wani RA, Shah MS, Jan MM, Malik YA, Chandel RK and Margoob MA (2015). “Role of lamotrigine augmentation in treatment-resistant obsessive compulsive disorder: a retrospective case review from South Asia.” Indian J Psychol Med 37(2): 154–158. [PubMed: 25969599]

Hussain MZ and Ahad A (1970). “Treatment of obsessive-compulsive neurosis.” Can Med Assoc J 103(6): 648 passim.

Hutton LMJ, Cave AJ, St-Jean R and Banh HL (2017). “Should We be Worried About QTc Prolongation Using Citalopram? A Review.” J Pharm Pract 30(3): 353–358. [PubMed: 26763342]

Hybel KA, Mortensen EL, Lambek R, Hojgaard D and Thomsen PH (2017). “Executive function predicts cognitive-behavioral therapy response in childhood obsessive-compulsive disorder.” Behav Res Ther 99: 11–18. [PubMed: 28881220]

Insel TR, Mueller EA, Alterman I, Linnoila M and Murphy DL (1985). "Obsessive-compulsive disorder and serotonin: is there a connection?" Biol Psychiatry 20(11): 1174–1188. [PubMed: 2413912]

Insel TR, Murphy DL, Cohen RM, Alterman I, Kilts C and Linnoila M (1983). "Obsessive-compulsive disorder. A double-blind trial of clomipramine and clorgyline." Arch Gen Psychiatry 40(6): 605–612. [PubMed: 6342562]

International Obsessive Compulsive Disorder Foundation Genetics, C. and O. C. D. C. G. A. Studies (2018). "Revealing the complex genetic architecture of obsessive-compulsive disorder using meta-analysis." Mol Psychiatry 23(5): 1181–1188. [PubMed: 28761083]

Issari Y, Jakubovski E, Bartley CA, Pittenger C and Bloch MH (2016). "Early onset of response with selective serotonin reuptake inhibitors in obsessive-compulsive disorder: a meta-analysis." J Clin Psychiatry 77(5): e605–611. [PubMed: 27249090]

Iyo M, Sekine Y, Matsunaga T, Tsukamoto T, Takei N and Mori N (1999). "Methamphetamine-associated obsessional symptoms and effective risperidone treatment: a case report." J Clin Psychiatry 60(5): 337–338.

Jhanda S, Singla N and Grover S (2016). "Methylphenidate-induced obsessive-compulsive symptoms: A case report and review of literature." J Pediatr Neurosci 11(4): 316–318. [PubMed: 28217153]

Johnson MW, Hendricks PS, Barrett FS and Griffiths RR (2019). "Classic psychedelics: An integrative review of epidemiology, therapeutics, mystical experience, and brain network function." Pharmacol Ther 197: 83–102. [PubMed: 30521880]

Kaplan GB and Moore KA (2011). "The use of cognitive enhancers in animal models of fear extinction." Pharmacol Biochem Behav 99(2): 217–228. [PubMed: 21256147]

Karameh WK and Khani M (2015). "Intravenous Clomipramine for Treatment-Resistant Obsessive-Compulsive Disorder." Int J Neuropsychopharmacol 19(2).

Karthik S, Sharma LP and Narayanaswamy JC (2020). "Investigating the Role of Glutamate in Obsessive-Compulsive Disorder: Current Perspectives." Neuropsychiatr Dis Treat 16: 1003–1013. [PubMed: 32368062]

Katz RJ, DeVeaugh-Geiss J and Landau P (1990). "Clomipramine in obsessive-compulsive disorder." Biol Psychiatry 28(5): 401–414. [PubMed: 2207219]

Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM and Wittchen HU (2012). "Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States." Int J Methods Psychiatr Res 21(3): 169–184. [PubMed: 22865617]

Khalkhali M, Aram S, Zarrabi H, Kafie M and Heidarzadeh A (2016). "Lamotrigine Augmentation Versus Placebo in Serotonin Reuptake Inhibitors-Resistant Obsessive-Compulsive Disorder: A Randomized Controlled Trial." Iran J Psychiatry 11(2): 104–114. [PubMed: 27437007]

Kim CH, Koo MS, Cheon KA, Ryu YH, Lee JD and Lee HS (2003). "Dopamine transporter density of basal ganglia assessed with [123I]IPT SPET in obsessive-compulsive disorder." Eur J Nucl Med Mol Imaging 30(12): 1637–1643. [PubMed: 14513291]

Kim M, Kwak S, Yoon YB, Kwak YB, Kim T, Cho KIK, Lee TY and Kwon JS (2019). "Functional connectivity of the raphe nucleus as a predictor of the response to selective serotonin reuptake inhibitors in obsessive-compulsive disorder." Neuropsychopharmacology 44(12): 2073–2081. [PubMed: 31189178]

Koch S, Perry KW, Nelson DL, Conway RG, Threlkeld PG and Bymaster FP (2002). "R-fluoxetine increases extracellular DA, NE, as well as 5-HT in rat prefrontal cortex and hypothalamus: an in vivo microdialysis and receptor binding study." Neuropsychopharmacology 27(6): 949–959. [PubMed: 12464452]

Koran LM, Aboujaoude E and Gamel NN (2009). "Double-blind study of dextroamphetamine versus caffeine augmentation for treatment-resistant obsessive-compulsive disorder." J Clin Psychiatry 70(11): 1530–1535. [PubMed: 19573497]

Koran LM, Gamel NN, Choung HW, Smith EH and Aboujaoude EN (2005). "Mirtazapine for obsessive-compulsive disorder: an open trial followed by double-blind discontinuation." J Clin Psychiatry 66(4): 515–520. [PubMed: 15816795]

Koran LM, Hanna GL, Hollander E, Nestadt G, Simpson HB and American Psychiatric A (2007). "Practice guideline for the treatment of patients with obsessive-compulsive disorder." Am J Psychiatry 164(7 Suppl): 5–53.

Koran LM, Pallanti S and Quercioli L (2001). "Sumatriptan, 5-HT(1D) receptors and obsessive-compulsive disorder." Eur Neuropsychopharmacol 11(2): 169–172. [PubMed: 11313163]

Korff S, Stein DJ and Harvey BH (2008). "Stereotypic behaviour in the deer mouse: pharmacological validation and relevance for obsessive compulsive disorder." Prog Neuropsychopharmacol Biol Psychiatry 32(2): 348–355. [PubMed: 17888556]

Kouris S (1998). "Methylphenidate-induced obsessive-compulsiveness." J Am Acad Child Adolesc Psychiatry 37(2): 135.

Kraehenmann R, Pokorny D, Vollenweider L, Preller KH, Pokorny T, Seifritz E and Vollenweider FX (2017). "Dreamlike effects of LSD on waking imagery in humans depend on serotonin 2A receptor activation." Psychopharmacology (Berl) 234(13): 2031–2046. [PubMed: 28386699]

Krystal JH, Abdallah CG, Sanacora G, Charney DS and Duman RS (2019). "Ketamine: A Paradigm Shift for Depression Research and Treatment." Neuron 101(5): 774–778. [PubMed: 30844397]

Kulz AK, Meinzer S, Kopasz M and Voderholzer U (2007). "Effects of tryptophan depletion on cognitive functioning, obsessive-compulsive symptoms and mood in obsessive-compulsive disorder: preliminary results." Neuropsychobiology 56(2–3): 127–131. [PubMed: 18259085]

Kumar TC and Khanna S (2000). "Lamotrigine augmentation of serotonin re-uptake inhibitors in obsessive-compulsive disorder." Aust N Z J Psychiatry 34(3): 527–528.

L R, U A and A C (2001). Venlafaxine in obsessive compulsive disorder. Fifth Internatonal Obsessive Compulsive Disorder Conference, Sardinia, Italy.

Lafleur DL, Pittenger C, Kelmendi B, Gardner T, Wasylink S, Malison RT, Sanacora G, Krystal JH and Coric V (2006). "N-acetylcysteine augmentation in serotonin reuptake inhibitor refractory obsessive-compulsive disorder." Psychopharmacology (Berl) 184(2): 254–256. [PubMed: 16374600]

Landeros-Weisenberger A, Bloch MH, Kelmendi B, Wegner R, Nudel J, Dombrowski P, Pittenger C, Krystal JH, Goodman WK, Leckman JF and Coric V (2010). "Dimensional predictors of response to SRI pharmacotherapy in obsessive-compulsive disorder." J Affect Disord 121(1–2): 175–179. [PubMed: 19577308]

Leckman JF, Goodman WK, Anderson GM, Riddle MA, Chappell PB, McSwiggan-Hardin MT, McDougle CJ, Scahill LD, Ort SI, Pauls DL and et al. (1995). "Cerebrospinal fluid biogenic amines in obsessive compulsive disorder, Tourette's syndrome, and healthy controls." Neuropsychopharmacology 12(1): 73–86. [PubMed: 7766289]

Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Muller CR, Hamer DH and Murphy DL (1996). "Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region." Science 274(5292): 1527–1531. [PubMed: 8929413]

Lykouras L, Alevizos B, Michalopoulou P and Rabavilas A (2003). "Obsessive-compulsive symptoms induced by atypical antipsychotics. A review of the reported cases." Prog Neuropsychopharmacol Biol Psychiatry 27(3): 333–346. [PubMed: 12691768]

Marazziti D, Dell'Osso L, Presta S, Pfanner C, Rossi A, Masala I, Baroni S, Giannaccini G, Lucacchini A and Cassano GB (1999). "Platelet [3H]paroxetine binding in patients with OCD-related disorders." Psychiatry Res 89(3): 223–228. [PubMed: 10708268]

Marazziti D, Hollander E, Lensi P, Ravagli S and Cassano GB (1992). "Peripheral markers of serotonin and dopamine function in obsessive-compulsive disorder." Psychiatry Res 42(1): 41–51. [PubMed: 1603880]

Marazziti D, Pfanner C, Palego L, Gemignani A, Milanfranchi A, Ravagli S, Lensi P, Presta S and Cassano GB (1997). "Changes in platelet markers of obsessive-compulsive patients during a double-blind trial of fluvoxamine versus clomipramine." Pharmacopsychiatry 30(6): 245–249. [PubMed: 9442546]

Marazziti D, Rossi A, Gemignani A, Giannaccini G, Pfanner C, Milanfranchi A, Presta S, Lucacchini A and Cassano GB (1996). "Decreased platelet 3H-paroxetine binding in obsessive-compulsive patients." Neuropsychobiology 34(4): 184–187. [PubMed: 9121618]

Marinova Z, Chuang DM and Fineberg N (2017). “Glutamate-Modulating Drugs as a Potential Therapeutic Strategy in Obsessive-Compulsive Disorder.” Curr Neuropharmacol 15(7): 977–995. [PubMed: 28322166]

Markianos M, Lafazanos S, Koutsis G, Sfagos C and Seretis A (2009). “CSF neurotransmitter metabolites and neuropsychiatric symptomatology in patients with normal pressure hydrocephalus.” Clin Neurol Neurosurg 111(3): 231–234. [PubMed: 19046799]

Marks IM, Stern RS, Mawson D, Cobb J and McDonald R (1980). “Clomipramine and exposure for obsessive-compulsive rituals: i.” Br J Psychiatry 136: 1–25. [PubMed: 6986939]

Marroni SS, Nakano FN, Gati CD, Oliveira JA, Antunes-Rodrigues J and Garcia-Cairasco N (2007). “Neuroanatomical and cellular substrates of hypergrooming induced by microinjection of oxytocin in central nucleus of amygdala, an experimental model of compulsive behavior.” Mol Psychiatry 12(12): 1103–1117. [PubMed: 17505467]

Mataix-Cols D, Fernandez de la Cruz L, Monzani B, Rosenfield D, Andersson E, Perez-Vigil A, Frumento P, de Kleine RA, Difede J, Dunlop BW, Farrell LJ, Geller D, Gerardi M, Guastella AJ, Hofmann SG, Hendriks GJ, Kushner MG, Lee FS, Lenze EJ, Levinson CA, McConnell H, Otto MW, Plag J, Pollack MH, Ressler KJ, Rodebaugh TL, Rothbaum BO, Scheeringa MS, Siewert-Siegmund A, Smits JAJ, Storch EA, Strohle A, Tart CD, Tolin DF, van Minnen A, Waters AM, Weems CF, Wilhelm S, Wyka K, Davis M, Ruck C, D. C. S. A. C. the, Altemus M, Anderson P, Cukor J, Finck C, Geffken GR, Golfels F, Goodman WK, Gutner C, Heyman I, Jovanovic T, Lewin AB, McNamara JP, Murphy TK, Norrholm S and Thuras P (2017). “D-Cycloserine Augmentation of Exposure-Based Cognitive Behavior Therapy for Anxiety, Obsessive-Compulsive, and Posttraumatic Stress Disorders: A Systematic Review and Meta-analysis of Individual Participant Data.” JAMA Psychiatry 74(5): 501–510. [PubMed: 28122091]

Mataix-Cols D, Marks IM, Greist JH, Kobak KA and Baer L (2002). “Obsessive-compulsive symptom dimensions as predictors of compliance with and response to behaviour therapy: results from a controlled trial.” Psychother Psychosom 71(5): 255–262. [PubMed: 12207105]

Mattheisen M, Samuels JF, Wang Y, Greenberg BD, Fyer AJ, McCracken JT, Geller DA, Murphy DL, Knowles JA, Grados MA, Riddle MA, Rasmussen SA, McLaughlin NC, Nurmi EL, Askland KD, Qin HD, Cullen BA, Piacentini J, Pauls DL, Bienvenu OJ, Stewart SE, Liang KY, Goes FS, Maher B, Pulver AE, Shugart YY, Valle D, Lange C and Nestadt G (2015). “Genome-wide association study in obsessive-compulsive disorder: results from the OCGAS.” Mol Psychiatry 20(3): 337–344. [PubMed: 24821223]

McDougle CJ, Barr LC, Goodman WK, Pelton GH, Aronson SC, Anand A and Price LH (1995). “Lack of efficacy of clozapine monotherapy in refractory obsessive-compulsive disorder.” Am J Psychiatry 152(12): 1812–1814. [PubMed: 8526253]

McDougle CJ, Barr LC, Goodman WK and Price LH (1999). “Possible role of neuropeptides in obsessive compulsive disorder.” Psychoneuroendocrinology 24(1): 1–24. [PubMed: 10098217]

McDougle CJ, Epperson CN, Pelton GH, Wasylink S and Price LH (2000). “A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder.” Arch Gen Psychiatry 57(8): 794–801. [PubMed: 10920469]

McDougle CJ, Goodman WK, Leckman JF, Barr LC, Heninger GR and Price LH (1993). “The efficacy of fluvoxamine in obsessive-compulsive disorder: effects of comorbid chronic tic disorder.” J Clin Psychopharmacol 13(5): 354–358. [PubMed: 8227493]

McDougle CJ, Goodman WK, Leckman JF, Lee NC, Heninger GR and Price LH (1994). “Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder. A double-blind, placebo-controlled study in patients with and without tics.” Arch Gen Psychiatry 51(4): 302–308. [PubMed: 8161290]

Modarresi A, Chaibakhsh S, Koulaeinejad N and Koupaei SR (2019). “A systematic review and meta-analysis: Memantine augmentation in moderate to severe obsessive-compulsive disorder.” Psychiatry Res 282: 112602. [PubMed: 31630042]

Modarresi A, Sayyah M, Razooghi S, Eslami K, Javadi M and Kouti L (2018). “Memantine Augmentation Improves Symptoms in Serotonin Reuptake Inhibitor-Refractory Obsessive-Compulsive Disorder: A Randomized Controlled Trial.” Pharmacopsychiatry 51(6): 263–269. [PubMed: 29100251]

Montgomery SA, McIntyre A, Osterheider M, Sarteschi P, Zitterl W, Zohar J, Birkett M and Wood AJ (1993). “A double-blind, placebo-controlled study of fluoxetine in patients with DSM-III-R obsessive-compulsive disorder. The Lilly European OCD Study Group.” Eur Neuropsychopharmacol 3(2): 143–152. [PubMed: 8364350]

Moreno FA, Wiegand CB, Taitano EK and Delgado PL (2006). “Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder.” J Clin Psychiatry 67(11): 1735–1740. [PubMed: 17196053]

Mowla A, Boostani S and Dastgheib SA (2016). “Duloxetine Augmentation in Resistant Obsessive-Compulsive Disorder: A Double-Blind Controlled Clinical Trial.” J Clin Psychopharmacol 36(6): 720–723. [PubMed: 27811556]

Naguy A, Alamiri B, Al-Khadhari S and Francis K (2016). “Lamotrigine Augmentation in Treatment-Resistant Pediatric Obsessive-Compulsive Disorder with a 16 Month Follow-up.” J Child Adolesc Psychopharmacol 26(8): 769–772. [PubMed: 26465832]

Nikolaus S, Muller HW and Hautzel H (2016). “Different patterns of 5-HT receptor and transporter dysfunction in neuropsychiatric disorders--a comparative analysis of in vivo imaging findings.” Rev Neurosci 27(1): 27–59. [PubMed: 26376220]

NIMH. (2020). Retrieved July 1, 2020, from https://www.nimh.nih.gov/about/strategic-planning-reports/goal-3-strive-for-prevention-and-cures.shtml.

O’Neill J, Piacentini J, Chang S, Ly R, Lai TM, Armstrong CC, Bergman L, Rozenman M, Peris T, Vreeland A, Mudgway R, Levitt JG, Salamon N, Posse S, Hellemann GS, Alger JR, McCracken JT and Nurmi EL (2017). “Glutamate in Pediatric Obsessive-Compulsive Disorder and Response to Cognitive-Behavioral Therapy: Randomized Clinical Trial.” Neuropsychopharmacology 42(12): 2414–2422. [PubMed: 28409563]

O’Regan JB (1970). “Treatment of obsessive--compulsive neurosis with haloperidol.” Can Med Assoc J 103(2): 167–168. [PubMed: 5430056]

Olatunji BO, Ebesutani C and Abramowitz JS (2017). “Examination of a Bifactor Model of Obsessive-Compulsive Symptom Dimensions.” Assessment 24(1): 45–59. [PubMed: 26310961]

Olver JS, O’Keefe G, Jones GR, Burrows GD, Tochon-Danguy HJ, Ackermann U, Scott A and Norman TR (2009). “Dopamine D1 receptor binding in the striatum of patients with obsessive-compulsive disorder.” J Affect Disord 114(1–3): 321–326. [PubMed: 18706700]

Olver JS, O’Keefe G, Jones GR, Burrows GD, Tochon-Danguy HJ, Ackermann U, Scott AM and Norman TR (2010). “Dopamine D(1) receptor binding in the anterior cingulate cortex of patients with obsessive-compulsive disorder.” Psychiatry Res 183(1): 85–88. [PubMed: 20538439]

Pallanti S, Quercioli L and Bruscoli M (2004). “Response acceleration with mirtazapine augmentation of citalopram in obsessive-compulsive disorder patients without comorbid depression: a pilot study.” J Clin Psychiatry 65(10): 1394–1399. [PubMed: 15491244]

Pallanti S, Quercioli L and Koran LM (2002). “Citalopram intravenous infusion in resistant obsessive-compulsive disorder: an open trial.” J Clin Psychiatry 63(9): 796–801. [PubMed: 12363120]

Paydary K, Akamaloo A, Ahmadipour A, Pishgar F, Emamzadehfard S and Akhondzadeh S (2016). “N-acetylcysteine augmentation therapy for moderate-to-severe obsessive-compulsive disorder: randomized, double-blind, placebo-controlled trial.” J Clin Pharm Ther 41(2): 214–219. [PubMed: 26931055]

Perani D, Garibotto V, Gorini A, Moresco RM, Henin M, Panzacchi A, Matarrese M, Carpinelli A, Bellodi L and Fazio F (2008). “In vivo PET study of 5HT(2A) serotonin and D(2) dopamine dysfunction in drug-naive obsessive-compulsive disorder.” Neuroimage 42(1): 306–314. [PubMed: 18511303]

Perse TL, Greist JH, Jefferson JW, Rosenfeld R and Dar R (1987). “Fluvoxamine treatment of obsessive-compulsive disorder.” Am J Psychiatry 144(12): 1543–1548. [PubMed: 3120604]

Pharmaceuticals B. from https://www.biohavenpharma.com/investors/news-events/press-releases/06-24-2020.

Phillips KA, Albertini RS and Rasmussen SA (2002). “A randomized placebo-controlled trial of fluoxetine in body dysmorphic disorder.” Arch Gen Psychiatry 59(4): 381–388. [PubMed: 11926939]

Pian KL, Westenberg HG, van Megen HJ and den Boer JA (1998). "Sumatriptan (5-HT1D receptor agonist) does not exacerbate symptoms in obsessive compulsive disorder." Psychopharmacology (Berl) 140(3): 365–370. [PubMed: 9877016]

Piantadosi SC, Chamberlain BL, Glausier JR, Lewis DA and Ahmari SE (2019). "Lower excitatory synaptic gene expression in orbitofrontal cortex and striatum in an initial study of subjects with obsessive compulsive disorder." Mol Psychiatry.

Pittenger C (2014). Animal models of Tourette syndrome and obsessive-compulsive disorder. Animal Models of Movement Disorders. LeDoux M. San Deigo, Elsevier: Academic Press: 748–766.

Pittenger C (2015). "Glutamate modulators in the treatment of obsessive-compulsive disorder." Psychiatr Ann 45(6): 308–315. [PubMed: 26236057]

Pittenger C (2017). "Histidine Decarboxylase Knockout Mice as a Model of the Pathophysiology of Tourette Syndrome and Related Conditions." Handb Exp Pharmacol 241: 189–215. [PubMed: 28233179]

Pittenger C (2017). The neurobiology of tic disorders and obsessive-compulsive disorder: human and animal studies. Nestler and Charney's Neurobiology of Mental Illness. Nestler EJ, Buxbaum JD, Sklar P and Charney DS. New York, Oxford University Press: 879–890.

Pittenger C (2017). The pharmacological treatment of refractory OCD. Obsessive-Compulsive Disorder: Phenomenology, Pathophysiology, and Treatment. Pittenger C. New York, NY, Oxford University Press.

Pittenger C, Adams TG Jr., Gallezot JD, Crowley MJ, Nabulsi N, James R, Gao H, Kichuk SA, Simpson R, Billingslea E, Hannestad J, Bloch M, Mayes L, Bhagwagar Z and Carson RE (2016). "OCD is associated with an altered association between sensorimotor gating and cortical and subcortical 5-HT1b receptor binding." J Affect Disord 196: 87–96. [PubMed: 26919057]

Pittenger C, Bloch MH, Wasylink S, Billingslea E, Simpson R, Jakubovski E, Kelmendi B, Sanacora G and Coric V (2015). "Riluzole augmentation in treatment-refractory obsessive-compulsive disorder: a pilot randomized placebo-controlled trial." J Clin Psychiatry 76(8): 1075–1084. [PubMed: 26214725]

Pittenger C, Bloch MH and Williams K (2011). "Glutamate abnormalities in obsessive compulsive disorder: neurobiology, pathophysiology, and treatment." Pharmacol Ther 132(3): 314–332. [PubMed: 21963369]

Pittenger C, Coric V, Banasr M, Bloch M, Krystal JH and Sanacora G (2008). "Riluzole in the treatment of mood and anxiety disorders." CNS Drugs 22(9): 761–786. [PubMed: 18698875]

Pittenger C, Dulawa S and Thompson SL (2017). Animal models of OCD: a conceptual framework. Obsessive-Compulsive Disorder: Phenomenology, Pathophysiology, and Treatment. Pittenger C. New York, Oxford University Press.

Pittenger C, Gruner P, Adams TA and Kelmendi B (2017). The dynamics of obsessive-compulsive disorder: A heuristic framework. Obsessive-Compulsive Disorder: Phenomenology, Pathophysiology, and Treatment. Pittenger C. New York, NY, Oxford University Press.

Pittenger C, Kelmendi B, Wasylink S, Bloch MH and Coric V (2008). "Riluzole augmentation in treatment-refractory obsessive-compulsive disorder: a series of 13 cases, with long-term follow-up." J Clin Psychopharmacol 28(3): 363–367. [PubMed: 18480706]

Pittenger C, Krystal JH and Coric V (2006). "Glutamate-modulating drugs as novel pharmacotherapeutic agents in the treatment of obsessive-compulsive disorder." NeuroRx 3(1): 69–81. [PubMed: 16490414]

Pogarell O, Hamann C, Popperl G, Juckel G, Chouker M, Zaudig M, Riedel M, Moller HJ, Hegerl U and Tatsch K (2003). "Elevated brain serotonin transporter availability in patients with obsessive-compulsive disorder." Biol Psychiatry 54(12): 1406–1413. [PubMed: 14675805]

Poyurovsky M (2017). Obsessive-compulsive symptoms in schizophrenia. Obsessive-Compulsive Disorder: Phenomenology, Pathophysiology, and Treatment. Pittenger C. New York, Oxford University Press.

Preller KH, Herdener M, Pokorny T, Planzer A, Kraehenmann R, Stampfli P, Liechti ME, Seifritz E and Vollenweider FX (2017). "The Fabric of Meaning and Subjective Effects in LSD-Induced States Depend on Serotonin 2A Receptor Activation." Curr Biol 27(3): 451–457. [PubMed: 28132813]

Qin H, Samuels JF, Wang Y, Zhu Y, Grados MA, Riddle MA, Greenberg BD, Knowles JA, Fyer AJ, McCracken JT, Murphy DL, Rasmussen SA, Cullen BA, Piacentini J, Geller D, Stewart SE, Pauls D, Bienvenu OJ, Goes FS, Maher B, Pulver AE, Valle D, Lange C, Mattheisen M, McLaughlin NC, Liang KY, Nurmi EL, Askland KD, Nestadt G and Shugart YY (2016). "Whole-genome association analysis of treatment response in obsessive-compulsive disorder." Mol Psychiatry 21(2): 270–276. [PubMed: 25824302]

Rasmussen S, Hackett E, DuBoff E, Greist J, Halaris A, Koran LM, Liebowitz M, Lydiard RB, McElroy S, Mendels J and O'Connor K (1997). "A 2-year study of sertraline in the treatment of obsessive-compulsive disorder." Int Clin Psychopharmacol 12(6): 309–316. [PubMed: 9547132]

Rasmussen SA and Eisen JL (1990). "Epidemiology of obsessive compulsive disorder." J Clin Psychiatry 51 Suppl: 10–13; discussion 14.

Rauch SL, Shin LM, Dougherty DD, Alpert NM, Fischman AJ and Jenike MA (2002). "Predictors of fluvoxamine response in contamination-related obsessive compulsive disorder: a PET symptom provocation study." Neuropsychopharmacology 27(5): 782–791. [PubMed: 12431852]

Ravizza L, Barzega G, Bellino S, Bogetto F and Maina G (1995). "Predictors of drug treatment response in obsessive-compulsive disorder." J Clin Psychiatry 56(8): 368–373. [PubMed: 7635854]

Reggente N, Moody TD, Morfini F, Sheen C, Rissman J, O'Neill J and Feusner JD (2018). "Multivariate resting-state functional connectivity predicts response to cognitive behavioral therapy in obsessive-compulsive disorder." Proc Natl Acad Sci U S A 115(9): 2222–2227. [PubMed: 29440404]

Reid JE, Reghunandanan S, Roberts A and Fineberg NA (2017). Standard evidence-based pharmacological treatment for OCD. Obsessive-Compulsive Disorder: Phenomenology, Pathophysiology, and Treatment. Pittenger C. New York, NY, Oxford University Press.

Reiff CM, Richman EE, Nemeroff CB, Carpenter LL, Widge AS, Rodriguez CI, Kalin NH, McDonald WM, and B the Work Group on and a. D. o. t. A. P. A. C. o. R. Novel Treatments (2020). "Psychedelics and Psychedelic-Assisted Psychotherapy." Am J Psychiatry 177(5): 391–410. [PubMed: 32098487]

Richardson R, Ledgerwood L and Cranney J (2004). "Facilitation of fear extinction by D-cycloserine: theoretical and clinical implications." Learn Mem 11(5): 510–516. [PubMed: 15466301]

Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, Griem A, Kovacs M, Ott J and Merikangas KR (2009). "Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis." JAMA 301(23): 2462–2471. [PubMed: 19531786]

Rivers-Bulkeley N and Hollender MH (1982). "Successful treatment of obsessive-compulsive disorder with loxapine." Am J Psychiatry 139(10): 1345–1346. [PubMed: 7124992]

Rodriguez CI, Kegeles LS, Flood P and Simpson HB (2011). "Rapid resolution of obsessions after an infusion of intravenous ketamine in a patient with treatment-resistant obsessive-compulsive disorder." J Clin Psychiatry 72(4): 567–569. [PubMed: 21527129]

Rodriguez CI, Kegeles LS, Levinson A, Feng T, Marcus SM, Vermes D, Flood P and Simpson HB (2013). "Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept." Neuropsychopharmacology 38(12): 2475–2483. [PubMed: 23783065]

Rodriguez CI, Levinson A, Zwerling J, Vermes D and Simpson HB (2016). "Open-Label trial on the effects of memantine in adults with obsessive-compulsive disorder after a single ketamine infusion." J Clin Psychiatry 77(5): 688–689. [PubMed: 27249077]

Rodriguez CI, Wheaton M, Zwerling J, Steinman SA, Sonnenfeld D, Galfalvy H and Simpson HB (2016). "Can exposure-based CBT extend the effects of intravenous ketamine in obsessive-compulsive disorder? an open-label trial." J Clin Psychiatry 77(3): 408–409. [PubMed: 27046314]

Rosenberg DR, MacMaster FP, Keshavan MS, Fitzgerald KD, Stewart CM and Moore GJ (2000). "Decrease in caudate glutamatergic concentrations in pediatric obsessive-compulsive disorder patients taking paroxetine." J Am Acad Child Adolesc Psychiatry 39(9): 1096–1103. [PubMed: 10986805]

Rosenberg DR, MacMillan SN and Moore GJ (2001). “Brain anatomy and chemistry may predict treatment response in paediatric obsessive--compulsive disorder.” Int J Neuropsychopharmacol 4(2): 179–190. [PubMed: 11466168]

Rosenberg DR, Mirza Y, Russell A, Tang J, Smith JM, Banerjee SP, Bhandari R, Rose M, Ivey J, Boyd C and Moore GJ (2004). “Reduced anterior cingulate glutamatergic concentrations in childhood OCD and major depression versus healthy controls.” J Am Acad Child Adolesc Psychiatry 43(9): 1146–1153. [PubMed: 15322418]

Ruscio AM, Stein DJ, Chiu WT and Kessler RC (2010). “The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication.” Mol Psychiatry 15(1): 53–63. [PubMed: 18725912]

Sahraian A, Bigdeli M, Ghanizadeh A and Akhondzadeh S (2014). “Topiramate as an adjuvant treatment for obsessive compulsive symptoms in patients with bipolar disorder: a randomized double blind placebo controlled clinical trial.” J Affect Disord 166: 201–205. [PubMed: 25012432]

Sahraian A, Jahromi LR, Ghanizadeh A and Mowla A (2017). “Memantine as an Adjuvant Treatment for Obsessive Compulsive Symptoms in Manic Phase of Bipolar Disorder: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial.” J Clin Psychopharmacol 37(2): 246–249. [PubMed: 28099183]

Sallee FR, Richman H, Beach K, Sethuraman G and Nesbitt L (1996). “Platelet serotonin transporter in children and adolescents with obsessive-compulsive disorder or Tourette’s syndrome.” J Am Acad Child Adolesc Psychiatry 35(12): 1647–1656. [PubMed: 8973072]

Sampaio AS, Hounie AG, Petribu K, Cappi C, Morais I, Vallada H, do Rosario MC, Stewart SE, Fargeness J, Mathews C, Arnold P, Hanna GL, Richter M, Kennedy J, Fontenelle L, de Braganca Pereira CA, Pauls DL and Miguel EC (2015). “COMT and MAO-A polymorphisms and obsessive-compulsive disorder: a family-based association study.” PLoS One 10(3): e0119592. [PubMed: 25793616]

Sanematsu H, Nakao T, Yoshiura T, Nabeyama M, Togao O, Tomita M, Masuda Y, Nakatani E, Nakagawa A and Kanba S (2010). “Predictors of treatment response to fluvoxamine in obsessive-compulsive disorder: an fMRI study.” J Psychiatr Res 44(4): 193–200. [PubMed: 19758599]

Sari Y (2004). “Serotonin1B receptors: from protein to physiological function and behavior.” Neurosci Biobehav Rev 28(6): 565–582. [PubMed: 15527863]

Sassano-Higgins SA and Pato MT (2015). “Pindolol augmentation of selective serotonin reuptake inhibitors and clomipramine for the treatment of obsessive-compulsive disorder: A meta-analysis.” J Pharmacol Pharmacother 6(1): 36–38. [PubMed: 25709352]

Saxena S, Brody AL, Ho ML, Zohrabi N, Maidment KM and Baxter LR Jr. (2003). “Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression.” Am J Psychiatry 160(3): 522–532. [PubMed: 12611834]

Saxena S, Brody AL, Maidment KM, Dunkin JJ, Colgan M, Alborzian S, Phelps ME and Baxter LR Jr. (1999). “Localized orbitofrontal and subcortical metabolic changes and predictors of response to paroxetine treatment in obsessive-compulsive disorder.” Neuropsychopharmacology 21(6): 683–693. [PubMed: 10633474]

Scheinost D, Stoica T, Wasylink S, Gruner P, Saksa J, Pittenger C and Hampson M (2014). “Resting state functional connectivity predicts neurofeedback response.” Front Behav Neurosci 8: 338. [PubMed: 25309375]

Schirmbeck F, Nieratschker V, Frank J, Englisch S, Rausch F, Meyer-Lindenberg A, Rietschel M and Zink M (2012). “Polymorphisms in the glutamate transporter gene SLC1A1 and obsessive-compulsive symptoms induced by second-generation antipsychotic agents.” Psychiatr Genet 22(5): 245–252. [PubMed: 22531293]

Schirmbeck F and Zink M (2012). “Clozapine-induced obsessive-compulsive symptoms in schizophrenia: a critical review.” Curr Neuropharmacol 10(1): 88–95. [PubMed: 22942882]

Schirmbeck F and Zink M (2013). “Comorbid obsessive-compulsive symptoms in schizophrenia: contributions of pharmacological and genetic factors.” Front Pharmacol 4: 99. [PubMed: 23950745]

Schneier FR, Martinez D, Abi-Dargham A, Zea-Ponce Y, Simpson HB, Liebowitz MR and Laruelle M (2008). “Striatal dopamine D(2) receptor availability in OCD with and without comorbid social anxiety disorder: preliminary findings.” Depress Anxiety 25(1): 1–7. [PubMed: 17252580]

Serata D, Kotzalidis GD, Rapinesi C, Janiri D, Di Pietro S, Callovini G, Piacentino D, Gasperoni C, Brugnoli R, Ferri VR, Girardi N, Tatarelli R, Ferracuti S, Angeletti G, Girardi P and Del Casale A (2015). “Are 5-HT3 antagonists effective in obsessive-compulsive disorder? A systematic review of literature.” Hum Psychopharmacol 30(2): 70–84. [PubMed: 25676060]

Serby M (2003). “Methylphenidate-induced obsessive-compulsive symptoms in an elderly man.” CNS Spectr 8(8): 612–613. [PubMed: 12907924]

Service NH (2011). “Citalopram and escitalopram: QT interval prolongation.” Drug Safety Update 5(5): A1.

Services, U. D. o. H. a. H. (2012). “FDA Drug Safety Communications: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses.” Retrieved May 20, 2020, from http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm.

Shanahan NA, Holick Pierz KA, Masten VL, Waeber C, Ansorge M, Gingrich JA, Geyer MA, Hen R and Dulawa SC (2009). “Chronic reductions in serotonin transporter function prevent 5-HT1B-induced behavioral effects in mice.” Biol Psychiatry 65(5): 401–408. [PubMed: 19013555]

Sharma LP, Thamby A, Balachander S, Janardhanan CN, Jaisoorya TS, Arumugham SS and Reddy YCJ (2020). “Clinical utility of repeated intravenous ketamine treatment for resistant obsessive-compulsive disorder.” Asian J Psychiatr 52: 102183. [PubMed: 32554207]

Shin DJ, Jung WH, He Y, Wang J, Shim G, Byun MS, Jang JH, Kim SN, Lee TY, Park HY and Kwon JS (2014). “The effects of pharmacological treatment on functional brain connectome in obsessive-compulsive disorder.” Biol Psychiatry 75(8): 606–614. [PubMed: 24099506]

Shmelkov SV, Hormigo A, Jing D, Proenca CC, Bath KG, Milde T, Shmelkov E, Kushner JS, Baljevic M, Dincheva I, Murphy AJ, Valenzuela DM, Gale NW, Yancopoulos GD, Ninan I, Lee FS and Rafii S (2010). “Slitrk5 deficiency impairs corticostriatal circuitry and leads to obsessive-compulsive-like behaviors in mice.” Nat Med 16(5): 598–602, 591p following 602. [PubMed: 20418887]

Simpson HB, Foa EB, Liebowitz MR, Huppert JD, Cahill S, Maher MJ, McLean CP, Bender J Jr., Marcus SM, Williams MT, Weaver J, Vermes D, Van Meter PE, Rodriguez CI, Powers M, Pinto A, Imms P, Hahn CG and Campeas R (2013). “Cognitive-behavioral therapy vs risperidone for augmenting serotonin reuptake inhibitors in obsessive-compulsive disorder: a randomized clinical trial.” JAMA Psychiatry 70(11): 1190–1199. [PubMed: 24026523]

Simpson HB, Lombardo I, Slifstein M, Huang HY, Hwang DR, Abi-Dargham A, Liebowitz MR and Laruelle M (2003). “Serotonin transporters in obsessive-compulsive disorder: a positron emission tomography study with [(11)C]McN 5652.” Biol Psychiatry 54(12): 1414–1421. [PubMed: 14675806]

Simpson HB, Shungu DC, Bender J Jr., Mao X, Xu X, Slifstein M and Kegeles LS (2012). “Investigation of cortical glutamate-glutamine and gamma-aminobutyric acid in obsessive-compulsive disorder by proton magnetic resonance spectroscopy.” Neuropsychopharmacology 37(12): 2684–2692. [PubMed: 22850733]

Simpson HB, Slifstein M, Bender J Jr., Xu X, Hackett E, Maher MJ and Abi-Dargham A (2011). “Serotonin 2A receptors in obsessive-compulsive disorder: a positron emission tomography study with [11C]MDL 100907.” Biol Psychiatry 70(9): 897–904. [PubMed: 21855857]

Sinopoli VM, Burton CL, Kronenberg S and Arnold PD (2017). “A review of the role of serotonin system genes in obsessive-compulsive disorder.” Neurosci Biobehav Rev 80: 372–381. [PubMed: 28576508]

Skapinakis P, Caldwell DM, Hollingworth W, Bryden P, Fineberg NA, Salkovskis P, Welton NJ, Baxter H, Kessler D, Churchill R and Lewis G (2016). “Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis.” Lancet Psychiatry 3(8): 730–739. [PubMed: 27318812]

Skapinakis P, Papatheodorou T and Mavreas V (2007). “Antipsychotic augmentation of serotonergic antidepressants in treatment-resistant obsessive-compulsive disorder: a meta-analysis of the randomized controlled trials.” Eur Neuropsychopharmacol 17(2): 79–93. [PubMed: 16904298]

Smeraldi E, Diaferia G, Erzegovesi S, Lucca A, Bellodi L and Moja EA (1996). “Tryptophan depletion in obsessive-compulsive patients.” Biol Psychiatry 40(5): 398–402. [PubMed: 8874841]

Soomro GM, Altman D, Rajagopal S and Oakley-Browne M (2008). “Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD).” Cochrane Database Syst Rev(1): CD001765. [PubMed: 18253995]

Stein DJ, Andersen EW and Overo KF (2007). “Response of symptom dimensions in obsessive-compulsive disorder to treatment with citalopram or placebo.” Braz J Psychiatry 29(4): 303–307. [PubMed: 18200396]

Stern ER, Shahab R, Grimaldi SJ, Leibu E, Murrough JW, Fleysher L, Parides MK, Coffey BJ, Burdick KE and Goodman WK (2019). “High-dose ondansetron reduces activation of interoceptive and sensorimotor brain regions.” Neuropsychopharmacology 44(2): 390–398. [PubMed: 30116006]

Stewart SE, Jenike EA, Hezel DM, Stack DE, Dodman NH, Shuster L and Jenike MA (2010). “A single-blinded case-control study of memantine in severe obsessive-compulsive disorder.” J Clin Psychopharmacol 30(1): 34–39. [PubMed: 20075645]

Stewart SE, Mayerfeld C, Arnold PD, Crane JR, O’Dushlaine C, Fagerness JA, Yu D, Scharf JM, Chan E, Kassam F, Moya PR, Wendland JR, Delorme R, Richter MA, Kennedy JL, Veenstra-VanderWeele J, Samuels J, Greenberg BD, McCracken JT, Knowles JA, Fyer AJ, Rauch SL, Riddle MA, Grados MA, Bienvenu OJ, Cullen B, Wang Y, Shugart YY, Piacentini J, Rasmussen S, Nestadt G, Murphy DL, Jenike MA, Cook EH, Pauls DL, Hanna GL and Mathews CA (2013). “Meta-analysis of association between obsessive-compulsive disorder and the 3’ region of neuronal glutamate transporter gene SLC1A1.” Am J Med Genet B Neuropsychiatr Genet 162B(4): 367–379. [PubMed: 23606572]

Stewart SE, Yu D, Scharf JM, Neale BM, Fagerness JA, Mathews CA, Arnold PD, Evans PD, Gamazon ER, Davis LK, Osiecki L, McGrath L, Haddad S, Crane J, Hezel D, Illman C, Mayerfeld C, Konkashbaev A, Liu C, Pluzhnikov A, Tikhomirov A, Edlund CK, Rauch SL, Moessner R, Falkai P, Maier W, Ruhrmann S, Grabe HJ, Lennertz L, Wagner M, Bellodi L, Cavallini MC, Richter MA, Cook EH Jr., Kennedy JL, Rosenberg D, Stein DJ, Hemmings SM, Lochner C, Azzam A, Chavira DA, Fournier E, Garrido H, Sheppard B, Umana P, Murphy DL, Wendland JR, Veenstra-VanderWeele J, Denys D, Blom R, Deforce D, Van Nieuwerburgh F, Westenberg HG, Walitza S, Egberts K, Renner T, Miguel EC, Cappi C, Hounie AG, Conceicao do Rosario M, Sampaio AS, Vallada H, Nicolini H, Lanzagorta N, Camarena B, Delorme R, Leboyer M, Pato CN, Pato MT, Voyiaziakis E, Heutink P, Cath DC, Posthuma D, Smit JH, Samuels J, Bienvenu OJ, Cullen B, Fyer AJ, Grados MA, Greenberg BD, McCracken JT, Riddle MA, Wang Y, Coric V, Leckman JF, Bloch M, Pittenger C, Eapen V, Black DW, Ophoff RA, Strengman E, Cusi D, Turiel M, Frau F, Macciardi F, Gibbs JR, Cookson MR, Singleton A, C. North American Brain Expression, Hardy J, U. K. B. E. Database, Crenshaw AT, Parkin MA, Mirel DB, Conti DV, Purcell S, Nestadt G, Hanna GL, Jenike MA, Knowles JA, Cox N and Pauls DL (2013). “Genome-wide association study of obsessive-compulsive disorder.” Mol Psychiatry 18(7): 788–798. [PubMed: 22889921]

Storch EA, Larson MJ, Shapira NA, Ward HE, Murphy TK, Geffken GR, Valerio H and Goodman WK (2006). “Clinical predictors of early fluoxetine treatment response in obsessive-compulsive disorder.” Depress Anxiety 23(7): 429–433. [PubMed: 16841343]

Swedo SE, Pietrini P, Leonard HL, Schapiro MB, Rettew DC, Goldberger EL, Rapoport SI, Rapoport JL and Grady CL (1992). “Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Revisualization during pharmacotherapy.” Arch Gen Psychiatry 49(9): 690–694. [PubMed: 1514873]

Swedo SE, Schapiro MB, Grady CL, Cheslow DL, Leonard HL, Kumar A, Friedland R, Rapoport SI and Rapoport JL (1989). “Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder.” Arch Gen Psychiatry 46(6): 518–523. [PubMed: 2786402]

Szechtman H, Ahmari SE, Beninger RJ, Eilam D, Harvey BH, Edemann-Callesen H and Winter C (2017). “Obsessive-compulsive disorder: Insights from animal models.” Neurosci Biobehav Rev 76(Pt B): 254–279. [PubMed: 27168347]

Szechtman H, Harvey BH, Woody EZ and Hoffman KL (2020). “The Psychopharmacology of Obsessive-Compulsive Disorder: A Preclinical Roadmap.” Pharmacol Rev 72(1): 80–151. [PubMed: 31826934]

Szechtman H, Sulis W and Eilam D (1998). “Quinpirole induces compulsive checking behavior in rats: a potential animal model of obsessive-compulsive disorder (OCD).” Behav Neurosci 112(6): 1475–1485. [PubMed: 9926830]

Talati A, Odgerel Z, Wickramaratne PJ, Norcini-Pala A, Skipper JL, Gingrich JA and Weissman MM (2017). “Associations between serotonin transporter and behavioral traits and diagnoses related to anxiety.” Psychiatry Res 253: 211–219. [PubMed: 28391138]

Taylor S (2013). “Molecular genetics of obsessive-compulsive disorder: a comprehensive meta-analysis of genetic association studies.” Mol Psychiatry 18(7): 799–805. [PubMed: 22665263]

Taylor S (2016). “Disorder-specific genetic factors in obsessive-compulsive disorder: A comprehensive meta-analysis.” Am J Med Genet B Neuropsychiatr Genet 171B(3): 325–332. [PubMed: 26616111]

Ting JT and Feng G (2008). “Glutamatergic Synaptic Dysfunction and Obsessive-Compulsive Disorder.” Curr Chem Genomics 2: 62–75. [PubMed: 19768139]

Torres AR, Fontenelle LH, Shhavitt RG, Hoexter MQ, Pittenger C and Miguel EC (2017). Epidemiology, comorbidity, and burden of OCD. Obsessive-Compulsive Disorder: Phenomenology, Pathophysiology, and Treatment. Pittenger C. New York, NY, Oxford University Press.

Trethowan WH and Scott PA (1955). “Chlorpromazine in obsessive-compulsive and allied disorders.” Lancet 268(6868): 781–785. [PubMed: 14368870]

Uzun O (2010). “Lamotrigine as an augmentation agent in treatment-resistant obsessive-compulsive disorder: a case report.” J Psychopharmacol 24(3): 425–427. [PubMed: 19010977]

van der Straten AL, Denys D and van Wingen GA (2017). “Impact of treatment on resting cerebral blood flow and metabolism in obsessive compulsive disorder: a meta-analysis.” Sci Rep 7(1): 17464. [PubMed: 29234089]

van der Wee NJ, Stevens H, Hardeman JA, Mandl RC, Denys DA, van Megen HJ, Kahn RS and Westenberg HM (2004). “Enhanced dopamine transporter density in psychotropic-naive patients with obsessive-compulsive disorder shown by [123I]{beta}-CIT SPECT.” Am J Psychiatry 161(12): 2201–2206. [PubMed: 15569890]

Vandebroek I and Odberg FO (1997). “Effect of apomorphine on the conflict-induced jumping stereotypy in bank voles.” Pharmacol Biochem Behav 57(4): 863–868. [PubMed: 9259017]

Veale D, Miles S, Smallcombe N, Ghezai H, Goldacre B and Hodsoll J (2014). “Atypical antipsychotic augmentation in SSRI treatment refractory obsessive-compulsive disorder: a systematic review and meta-analysis.” BMC Psychiatry 14: 317. [PubMed: 25432131]

Vulink NC, Denys D and Westenberg HG (2005). “Bupropion for patients with obsessive-compulsive disorder: an open-label, fixed-dose study.” J Clin Psychiatry 66(2): 228–230. [PubMed: 15705009]

Weizman A, Mandel A, Barber Y, Weitz R, Cohen A, Mester R and Rehavi M (1992). “Decreased platelet imipramine binding in Tourette syndrome children with obsessive-compulsive disorder.” Biol Psychiatry 31(7): 705–711. [PubMed: 1318082]

Welch JM, Lu J, Rodriguiz RM, Trotta NC, Peca J, Ding JD, Feliciano C, Chen M, Adams JP, Luo J, Dudek SM, Weinberg RJ, Calakos N, Wetsel WC and Feng G (2007). “Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice.” Nature 448(7156): 894–900. [PubMed: 17713528]

Wendland JR, Moya PR, Timpano KR, Anavitarte AP, Kruse MR, Wheaton MG, Ren-Patterson RF and Murphy DL (2009). “A haplotype containing quantitative trait loci for SLC1A1 gene expression and its association with obsessive-compulsive disorder.” Arch Gen Psychiatry 66(4): 408–416. [PubMed: 19349310]

Williams K, Bloch MH, State MW and Pittenger C (2013). Tourette syndrome. Neurobiology of Mental Illness, 4th edition. C. DS, Buxbaum JD, Sklar P and Nestler EJ. New York, Oxford University Press.

Willour VL, Yao Shugart Y, Samuels J, Grados M, Cullen B, Bienvenu OJ 3rd, Wang Y, Liang KY, Valle D, Hoehn-Saric R, Riddle M and Nestadt G (2004). "Replication study supports evidence for linkage to 9p24 in obsessive-compulsive disorder." Am J Hum Genet 75(3): 508–513. [PubMed: 15272418]

Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, Sajed T, Johnson D, Li C, Sayeeda Z, Assempour N, Iynkkaran I, Liu Y, Maciejewski A, Gale N, Wilson A, Chin L, Cummings R, Le D, Pon A, Knox C and Wilson M (2018). "DrugBank 5.0: a major update to the DrugBank database for 2018." Nucleic Acids Res 46(D1): D1074–D1082. [PubMed: 29126136]

Woehrle NS, Klenotich SJ, Jamnia N, Ho EV and Dulawa SC (2013). "Effects of chronic fluoxetine treatment on serotonin 1B receptor-induced deficits in delayed alternation." Psychopharmacology (Berl) 227(3): 545–551. [PubMed: 23377022]

Woolley JB and Heyman I (2003). "Dexamphetamine for obsessive-compulsive disorder." Am J Psychiatry 160(1): 183.

Wu PL, Tang HS, Lane HY, Tsai CA and Tsai GE (2011). "Sarcosine therapy for obsessive compulsive disorder: a prospective, open-label study." J Clin Psychopharmacol 31(3): 369–374. [PubMed: 21508860]

Yazici KU and Percinel I (2015). "N-Acetylcysteine Augmentation in Children and Adolescents Diagnosed With Treatment-Resistant Obsessive-Compulsive Disorder: Case Series." J Clin Psychopharmacol 35(4): 486–489. [PubMed: 26066338]

Yin D, Zhang C, Lv Q, Chen X, Zeljic K, Gong H, Zhan S, Jin H, Wang Z and Sun B (2018). "Dissociable Frontostriatal Connectivity: Mechanism and Predictor of the Clinical Efficacy of Capsulotomy in Obsessive-Compulsive Disorder." Biol Psychiatry 84(12): 926–936. [PubMed: 29778276]

Yoshimura R, Kaneko S, Shinkai K and Nakamura J (2006). "Successful treatment for obsessive-compulsive disorder with addition of low-dose risperidone to fluvoxamine: implications for plasma levels of catecholamine metabolites and serum brain-derived neurotrophic factor levels." Psychiatry Clin Neurosci 60(3): 389–393. [PubMed: 16732759]

Yun JY, Jang JH, Kim SN, Jung WH and Kwon JS (2015). "Neural Correlates of Response to Pharmacotherapy in Obsessive-Compulsive Disorder: Individualized Cortical Morphology-Based Structural Covariance." Prog Neuropsychopharmacol Biol Psychiatry 63: 126–133. [PubMed: 26116795]

Zai G, Brandl EJ, Muller DJ, Richter MA and Kennedy JL (2014). "Pharmacogenetics of antidepressant treatment in obsessive-compulsive disorder: an update and implications for clinicians." Pharmacogenomics 15(8): 1147–1157. [PubMed: 25084207]

Zarate CA Jr., Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS and Manji HK (2006). "A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression." Arch Gen Psychiatry 63(8): 856–864. [PubMed: 16894061]

Zheng H, Jia F, Han H, Wang S, Guo G, Quan D, Li G and Huang H (2019). "Combined fluvoxamine and extended-release methylphenidate improved treatment response compared to fluvoxamine alone in patients with treatment-refractory obsessive-compulsive disorder: A randomized double-blind, placebo-controlled study." Eur Neuropsychopharmacol 29(3): 397–404. [PubMed: 30595354]

Zike ID, Chohan MO, Kopelman JM, Krasnow EN, Flicker D, Nautiyal KM, Bubser M, Kellendonk C, Jones CK, Stanwood G, Tanaka KF, Moore H, Ahmari SE and Veenstra-VanderWeele J (2017). "OCD candidate gene SLC1A1/EAAT3 impacts basal ganglia-mediated activity and stereotypic behavior." Proc Natl Acad Sci U S A 114(22): 5719–5724. [PubMed: 28507136]

Zivin K, Pfeiffer PN, Bohnert AS, Ganoczy D, Blow FC, Nallamothu BK and Kales HC (2013). "Evaluation of the FDA warning against prescribing citalopram at doses exceeding 40 mg." Am J Psychiatry 170(6): 642–650. [PubMed: 23640689]

Zohar J, Kennedy JL, Hollander E and Koran LM (2004). "Serotonin-1D hypothesis of obsessive-compulsive disorder: an update." J Clin Psychiatry 65 Suppl 14: 18–21.