Clinical Advances in Obsessive Compulsive Disorder: A Position Statement by The International College Of Obsessive Compulsive Spectrum Disorders.

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Abstract

In this position statement, developed by The International College of Obsessive-Compulsive Spectrum Disorders, a group of international experts responds to recent developments in the evidence based management of obsessive-compulsive disorder (OCD). The position statement presents selected therapeutic advances judged to be of utmost relevance to the treatment of OCD, based on new and emerging evidence from clinical and translational science. Areas covered include refinement in the methods of clinical assessment, the importance of early intervention based on new staging models and the need to provide sustained well-being involving effective relapse prevention. The relative benefits of psychological, pharmacological and somatic treatments are reviewed and novel treatment strategies for difficult to treat OCD, including neurostimulation, as well as new areas for research such as problematic internet use, novel digital interventions, immunological therapies, pharmaco-genetics and novel forms of psychotherapy are highlighted.

Keywords

Obsessive-compulsive disorder, evidence based, treatments, position statement
Once a neglected illness, obsessive-compulsive disorder (OCD) is now recognised as a common, highly disabling and potentially treatable early-onset brain disorder. Clinical and translational research in OCD grows apace, and over the past 10 years has contributed to substantial advances in understanding of the phenomenology, brain-based biology and treatment response, leading to innovations in nosological conceptualisations, therapeutic interventions and services. Recent changes in the DSM-5 (American Psychiatric Association, 2013) and ICD-11 (World Health Organisation, 2018) diagnostic classification have set OCD at the head of a new family of obsessive compulsive (OC) spectrum disorders, including body dysmorphic, hoarding, hair-pulling, skin picking, and olfactory reference disorders as well as hypochondriasis, all sharing compulsive behaviour as a cardinal characteristic. Serotonin reuptake inhibitors (selective serotonin reuptake inhibitors (SSRIs), clomipramine) or cognitive-behavioural therapy (CBT) involving exposure and response prevention (ERP), represent the mainstay of contemporary treatment for OCD, with emerging evidence suggesting early intervention produces better outcomes (Fineberg et al., 2019). However, a large minority of patients still fail to respond and treatment-resistant OCD has become a fruitful research focus for clinical treatment and specialist services development, worldwide.

A number of evidence-based clinical guidelines for managing OCD have been published (Baldwin et al., 2014; Bandelow et al., 2012; Sookman and Fineberg, 2015). However, recent feedback from topic experts and stakeholders (National Institute for Health and Care Excellence, 2019) has identified the need for an update, highlighting that clinical practice has progressed in many areas. This includes evidence of efficacy for new pharmacological interventions and augmentation therapies amongst treatment-resistant groups, advances in invasive and non-invasive neuro-stimulation technology as well as rapid advances in information technology and telecommunications and the introduction of technology-enhanced interventions. Yet, in many parts of the world, access to recommended treatments and specialist care services, in particular for children, remains limited.

The International College of Obsessive Compulsive Spectrum Disorders (www.ICOCS.org) is a global network of expert clinicians, researchers and “experts by experience of OCD”, whose principal objective is to support and stimulate the
study and treatment of obsessive-compulsive spectrum disorders. In recognition of
the need for updated clinical guidance on the treatment of OCD, the ICOCS has
developed this position statement, based on expert consensus and including a
balanced representation of genders, child versus adult psychiatrists, and early
career scientists, with global and ethnic diversity. We have selected those recent
therapeutic advances judged to be of most relevance to the treatment of OCD,
based on new and emerging evidence from clinical and translational science.

Global Assessment Of OCD

A comprehensive assessment of OCD requires that trained clinicians perform direct
interviews with the patient and, whenever possible, with the family, so that an
accurate diagnosis can be determined and individualised treatment can be
tailored. In adults, the hallmarks of OCD are obsessions (recurrent intrusive,
unwanted thoughts, images or impulses) and compulsions (repetitive behaviours or
mental acts that the individual feels compelled to perform). The most common
symptom dimensions of OCD are contamination/ washing, aggression/checking,
symmetry/ordering/arranging, sexual/religious (also known as “taboo thoughts”),
and hoarding (Rosario-Campos et al., 2006). Importantly, according to DSM-5, a
diagnosis of Hoarding Disorder should be assigned when symptoms pertain to this
single dimension (American Psychiatric Association, 2013). The presence and
severity of symptoms can be measured by validated instruments (Goodman et al.,
1989; Rosario-Campos et al., 2006; Storch et al., 2010), which is relevant to tailor
the behavioural treatment and monitor treatment response objectively.

Obsessions and compulsions tend to occur concomitantly in the vast majority of
subjects (Shavitt et al., 2014). In addition, compulsions can be preceded not only
by obsessions, but also by subjective experiences of incompleteness or “not feeling
just-right”, or so-called “sensory phenomena”, present in about 60% of subjects
with OCD (Shavitt et al., 2014). We could expect these sensory phenomena to be
targeted by cognitive-behavioural techniques in a way similar to the premonitory
urges in the behavioural treatment of tic disorders (McGuire et al., 2015).
Another relevant clinical feature that merits attention when assessing subjects with OCD is the degree of insight, meaning the extent to which the person recognizes that his/her beliefs are not true (Eisen et al., 1998). In general, subjects with OCD have at least good insight, with only a minority presenting poor insight or delusional OCD (Shavitt et al., 2014). Finally, the clinician must obtain information regarding avoidance, which commonly occurs as a means to handle the distress elicited by the obsessions and constitutes one of the main targets of the cognitive-behavioural treatment for this disorder (Drummond, 2014). Functional impairment varies in OCD. It is an important domain that reflects clinical severity and constitutes an indirect measure of improvement during treatment. It and can be measured indirectly with the OCD severity scales or with specific measures (for example, the WHODAS - (Ustun, Tevfik Bedirhan, Kostanjesek, N, Chatterji, S, Rehm, 2010) or the CAOIC-13 (Dittrich et al., 2011).

Comorbidity is the rule rather than the exception in OCD. The assessment of specific comorbidities, like tic disorders, anxiety and depressive disorders, disruptive disorders, eating disorders, autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD), schizophrenia (Zohar, 1997) is essential in guiding the formulation of an effective treatment strategy. A recent study in 4645 OCD patients found different genotypes to be associated with different OCD comorbidities; OCD comorbid with bipolar disorders were associated with COMT, OPRM1 and GRK1 genotypes; OCD and depressive disorders were associated with OPRM1 and CYP3A4/5 genotypes; OCD comorbid with ADD/ADHD were associated with 5HT2C genotypes; and OCD comorbid with anxiety were associated with CYP3A4/5 genotypes (Nezgovorova et al., 2018). However, this finding should be viewed with caution, as the “candidate gene” approach, in which specific genes are tested for association with specific disorders, chosen for the biological plausibility of their relationship, using relatively small samples of affected subjects and healthy controls, has been criticized for overestimating the statistical associations. Attempts to replicate the findings have tended to produce disappointing results. Therefore, more unbiased forms of association study, such as genome-wide association studies (GWAS), that test the association between a disease and multiple genetic variants across the whole genome, are to be
preferred (Gordon, 2018; National Advisory Mental Health Council Workgroup on Genomics, 2019.)

Interestingly, comorbid disorders that start before the onset of OCD symptoms seem to influence the occurrence of additional comorbidities over time: In a cohort of 1001 patients with OCD, separation anxiety disorder preceded OCD in 17.5% of subjects and was associated with a higher lifetime frequency of post-traumatic stress disorder; attention deficit hypersactivity disorder (ADHD) preceded OCD in 5.0% of subjects, and was associated with higher lifetime frequencies of substance abuse and dependence; tic disorders preceded OCD in 4.4% of subjects and was associated with higher lifetime frequencies of OCD spectrum disorders (de Mathis et al., 2013). In children and adolescents, in addition to the considerations for the adult subjects, a history of paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) should be taken, as this could also have treatment implications (Wilbur et al., 2019). Taken together, these findings emphasise the importance of identifying comorbid disorders, as they may serve as markers of different biological or clinical substrates of potential relevance for treatment planning (see future directions, section 11).

OCD needs to be differentiated from: Anxiety disorders presenting with recurrent fears (as in the phobias) and excessive worry (as in generalized anxiety disorder); ruminations accompanying depressive mood in depressive disorders; OCD-related disorders like body dysmorphic disorder (where there are specific concerns with one’s appearance), hair pulling disorder (the only compulsion), tic disorders; eating disorders (concerns focused on weight and food); psychotic disorders (especially in poor-insight OCD), and obsessive-compulsive personality disorder (with the hallmarks of enduring rigidity and perfectionism over the lifetime) (American Psychiatric Association, 2013).

Along with the identification of the most bothersome symptoms, the clinician should investigate the age of onset of symptoms and the age when a diagnosis of OCD has been determined, since this data can help to predict the prognosis
(Fineberg et al., 2019). OCD frequently emerges in childhood, in which group accurate diagnosis is essential for care-planning. Paediatric clinicians can ask simple screening questions such as “do you ever have unwanted thoughts or worries that won’t go away? Are there things you have to do over and over again, even though you don’t want to or that don’t make sense?” The formal diagnosis should be made with a structured interview and the nationwide translated versions of the standardized Children’s Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), which has very good reliability (López-Pina et al., 2015a, 2015b).

Awareness of other conditions associated with the onset and course of OCD symptoms, can also be of help in treatment planning, since OCD frequently follows a chronic course, with most patients reporting residual symptoms, or present an episodic course with long symptom-free periods (Skoog and Skoog, 1999). For example, a cross-cultural study has shown an association between reproductive cycle events and the onset (mostly menarche) or exacerbation of OCD during the pre-menstruum, pregnancy, postpartum, and menopause (Guglielmi et al., 2014). Relevant to prevention strategies, exacerbation during or after first pregnancy posed a significant risk to exacerbation in or after a subsequent pregnancy. The underlying factors responsible for triggering exacerbation remain to be studied, especially the role of oestrogen and oxytocin (Guglielmi et al., 2014).

Information on the family history of OCD, tics and other psychiatric disorders, the understanding of OCD among family members and family accommodation is also relevant to treatment-planning and adherence. Evidence shows that successful treatment depends on the reduction of the participation of the family members in the patient’s compulsive behaviours (accommodation) (Gomes et al., 2017). Moreover, a recent analysis suggested that children with a family history of OCD have a six times lower response to CBT (Garcia et al., 2010).

Suicidality cannot be left aside when assessing subjects with OCD (Dell’Osso et al., 2018). Among 582 patients with OCD, 36% reported lifetime suicidal thoughts, 20% had made suicidal plans, 11% had already attempted suicide, and 10% presented with current suicidal thoughts (Torres et al., 2011). In another study of 425
outpatients, recruited by the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS) network, 14.6% of the sample reported at least one suicide attempt during their lifetime (DellOsso et al, 2018). In the study by Torres et al (2011), comorbid depressive disorder and posttraumatic stress disorder were associated with all aspects of suicidal behaviours. Sexual/religious symptoms and comorbid substance use disorders were associated with suicidal thoughts and plans, while impulse-control disorders were associated with current suicidal thoughts, suicide plans and attempts. In the study by Dell’Osso et al (2018), comorbid tic disorders as well as medical disorders and a previous history of hospitalisation, as well as living in Europe and South Africa, were also associated with increased suicidality.

Neuropsychological assessment of patients with OCD suggests that there are deficits in several domains. A recent meta-analysis found that patients with symptoms related to symmetry and orderliness were more likely to have poorer performance on memory, visuospatial ability, verbal working memory and cognitive flexibility tests, whereas patients with doubting and checking were more likely to perform poorly on memory and verbal memory tasks (Bragdon et al., 2018). It must be considered that comorbid neurodevelopmental disorders, such as Autism Spectrum Disorders (ASD) (Postorino et al., 2017) are expected to influence performance on distinct tests, especially in youth.

Behavioural analysis of OCD involves obtaining a history to ascertain the specific situations that provoke obsessive, anxiogenic thoughts or uncomfortable feelings and then separating out the compulsions or anxiolytic behaviours. This is important, as during therapy the patient needs to face up to the anxiety-provoking thoughts or uncomfortable feelings while resisting the urge to “put this right” using compulsive thoughts, behaviours or avoidance. Full descriptions of behavioural analysis are given elsewhere (Drummond, 2014). From the cognitive perspective, there have been several theories about the underlying beliefs that may trigger OCD, such as the failure to challenge underlying beliefs sufficiently (Emmelkamp et al., 1988); inflated responsibility and guilt if compulsions were not acted upon and negative consequences occurred (Salkovskis, 1999, 1985); or an
Early Intervention In OCD

OCD frequently has an onset early in life (Fineberg et al., 2019). Childhood onset and adolescent onset accounted for more than 50% of the sample in a recent International multisite report (Dell’Osso et al., 2016). Unfortunately, early onset is not associated with early help-seeking and recognition of the illness. OCD has been consistently associated with a long duration of untreated illness (DUI), around 7 years, on average (Dell’Osso et al., 2019), with this period accounting, in many cases, for more than half of the overall duration of illness (Albert et al., 2019; Dell’Osso et al., 2019). Longer DUI implies late interventions and poor therapy-response, particularly in relation to pharmacological treatment (Albert et al., 2019; Dell’Osso et al., 2010). The need for service investment in early intervention for OCD is further highlighted by studies indicating that OCD is among the top ten most disabling of all disorders, accounting for 2.2% of all years lost to disability (Ayuso-Mateos, 2006), with economic costs to society that are long-lasting and profound. It has been estimated that in the USA, over $10 billion dollars per year are spent on treatments for OCD alone (Hollander et al., 2016).

OCD has been traditionally viewed as a secretive illness with some phenotypes (e.g. with sexual, religious or aggressive content) particularly associated with reluctance to seek help (Dell’Osso et al., 2015). There may also be difficulty detecting the disorder in childhood (Storch et al., 2014). Nonetheless, a greater effort needs to be made at multiple levels (e.g. education, service development, screening of “at risk” individuals) to implement effective strategies for prevention, early diagnosis and intervention. For instance, there have been reports indicating that the earliest symptoms shown by OCD patients belong to the symmetry and ordering dimension (Kichuk et al., 2013) and these can represent a red flag for early detection of subthreshold/early symptoms.
Children of individuals with OCD represent another high-risk group deserving attention and potentially needing preventive interventions. The presence of tic, paediatric acute-onset neuropsychiatric syndrome (PANS), obsessive-compulsive personality disorder and impulse control disorders may be indicators for comorbid OCD or herald the subsequent development of OCD (Fineberg et al., 2019). Staging models may also be useful (Fineberg et al., 2019; Fontenelle and Yücel, 2019), with four major stages proposed (from stage 0 “increased risk, asymptomatic” to stage 4 “severe illness”). However, their clinical utility and applicability remain to be investigated. Interventions such as psychoeducation and reduction of family accommodation represent promising areas for prevention and early intervention when OCD is at its early stages in high-risk groups (Brakoulias et al., 2018). One Australian health service (Brakoulias, 2018) has recently begun using existing early intervention services for psychosis to provide early intervention to patients with OCD (Brakoulias, 2018) (Western Sydney Obsessive-Compulsive and Related Disorders Service).

**CBT, SSRI Or Their Combination As First Line Treatment?**

Pharmacological therapies (selective serotonin reuptake inhibitors (SSRIs) and the tricyclic clomipramine) (Fineberg et al., 2012; Zohar et al., 1996) and psychological therapies (exposure and response prevention (ERP) and cognitive behaviour therapy (CBT)) (Abramowitz, 2006) are efficacious in treating OCD. As SSRIs and CBT are thought to have broadly similar efficacy in acute treatment, current guidelines recommend taking account of patient clinical features, needs and preference as well as service availability when choosing first line treatment (Baldwin et al., 2014). Monotherapy with CBT involving ERP is recommended as an initial treatment in those with mild to moderate OCD, in the absence of severe depression, in those who do not prefer medications and where this form of treatment is accessible, available and preferred by patients (National Institute for Health and Clinical Excellence, 2005; Health, 2006; Katzman et al., 2014; Koran et al., 2007; Reddy et al., 2017). SSRIs are recommended as a first-line treatment option in more severe OCD, in those who have comorbid depression, in those with previous history of good response to SSRIs, in those who are uncooperative with
CBT, or in situations where ERP/CBT is not available, accessible or preferred by patients. A combination of CBT involving ERP and SSRIs is often recommended in severe OCD, in the presence comorbid depression, and in poor responders to CBT or SSRIs alone (National Institute for Health and Clinical Excellence, 2005; Health, 2006; Hirschtritt et al., 2017; Reddy et al., 2017; Skapinakis et al., 2016b). In essence, most guidelines recognise SSRIs and CBT involving ERP as first-line monotherapies but prefer CBT involving ERP over SSRIs.

Several meta-analyses and systematic reviews have demonstrated SSRIs and clomipramine (Ackerman and Greenland, 2002; Skapinakis et al., 2016b; Soomro et al., 2008) and CBT involving ERP to be more effective than placebo (frequently waiting list in CBT trials) (Gava et al., 2007; Rosa-Alcázar et al., 2008). Although earlier meta-analysis suggested superiority of clomipramine over SSRIs (Ackerman and Greenland, 2002), a recent network meta-analysis has failed to demonstrate the superiority of clomipramine over SSRIs (Skapinakis et al., 2016b). Direct head-to-head comparisons of various medications are few and there seems to be no individual differences in efficacy among SSRIs (Skapinakis et al., 2016b).

Most studies of CBT involving ERP included symptomatic patients stabilized on antidepressants (Skapinakis et al., 2016b). Although the effect size of CBT is larger than the SSRIs and clomipramine, this superiority could well be attributed to the additive or synergistic effects of two effective treatment modalities. Therefore, it is not clear if the efficacy data of CBT involving ERP can be generalized to patients who are not on antidepressants. The efficacy of CBT as monotherapy therefore still needs to be established clearly in drug-naïve or drug-free patient population for it to be recommended as initial monotherapy in this population.

Some studies suggest that a combination of CBT and an SSRI may be superior to SSRI monotherapy, (Foa et al., 2005; Franklin et al., 2011; Liu et al., 2005; Meng et al., 2019; Romanelli et al., 2014) exposure monotherapy (Cottraux et al., 1990, Fineberg et al., 2018) or multi-modal CBT (Hohagen et al., 1998). However, it is uncertain whether combining ab initio CBT and a SSRI is advantageous compared to either treatment used alone (Albert et al., 2012). Confidence in the superiority of
the combination of medications and psychotherapy partly stems from the fact that most psychotherapy trials are considered variants of combination trials since most patients in these studies were stabilized on antidepressant treatment (Skapinakis et al., 2016b). Most guidelines and literature recommend a combination of SSRIs and CBT involving ERP in severe OCD, but the recommendation is based on evidence of its efficacy as an augmenting agent in patients who have clinically significant symptoms despite treatment with medications and not necessarily in severe OCD (Simpson et al., 2013, 2008). A recent randomised feasibility study that included patients treated in primary care found that whereas combined treatment with SSRI and ERP was associated with the largest improvement after 16 weeks, SSRI monotherapy was the most efficacious and cost effective treatment after 52 weeks (Fineberg et al., 2018a). If replicated, this finding would carry major implications for health services planning, especially where resources are limited, such as lower and middle income countries (LMIC).

The Critical Importance Of Adequate Treatment Of OCD In Children And Young Adults

For children and adolescents, CBT should always be the first line approach (Sánchez-Meca et al., 2014; Skapinakis et al., 2016a), ERP as core elements (Lewin et al., 2014). ERP is both highly effective and also an acceptable intervention for youth ages 3-8 years with OCD (Lewin et al., 2014). Children with a strong family history of OCD are reported to respond less well to conventional CBT (Garcia et al., 2010), possibly owing to family accommodation of their symptoms. Key adaptations for younger children include extensive parent involvement targeting family accommodation and frequent meetings while delivering a full course of ERP. According to the study of Sanchez-Meca et al. (2014), effect sizes were large for CBT (d+=1.742) and combined (medication plus CBT) interventions (d+=1.710) and moderate for pharmacological only treatments (d+=0.746) (Sánchez-Meca et al., 2014). Family-based CBT (Freeman et al., 2014; Piacentini et al., 2011) is also effective for children and adolescents with OCD, especially when there is a high degree of accommodation. The extant literature also supports CBT when delivered
in group settings. More recently the use of technical devices (smart phones and tablets) using App-delivered CBT seems promising.

Medication is indicated when symptoms are more severe, when CBT has failed, when skilled CBT is unavailable, when there is a comorbid disorder (e.g. depression) that may respond to medication, or when, in the judgment of the parent or clinician, earlier introduction of medicines is clinically indicated. Only SSRIs have been shown in randomised controlled trials to be safe and effective in youth (Geller et al., 2004; Skarphedinsson et al., 2015). Sertraline and fluvoxamine have been approved for children from 6 and 8 years of age. Dosing schedules should include low starting doses, slow titration schedules and maximum recommended doses. Following adequate response and stabilization, treatment should be reviewed after 6 to 12 months.

In case of non-response or inadequate response, another SSRI should be tried (Geller et al., 2012, 2004; Locher et al., 2017). Treatment with SSRIs in CBT-resistant patients may improve OCD symptoms. Although clomipramine may be effective, it is not recommended as a first-line treatment because of its potential side effects. However, if there are no cardiological contraindications, clomipramine is also an option in youth but requires electrocardiogram monitoring. In the case of insufficient efficacy of drug treatment with several SSRIs and clomipramine, augmentation with antipsychotics e.g. aripiprazole or risperidone in low dosage may be used. Minimal duration on neuroleptics is encouraged and close monitoring is required. Combined treatment is often the most effective treatment.

Relapse-prevention

Relapse-prevention strategies play an essential role for the optimal clinical management of OCD, considering its frequently chronic course and relapsing nature. Recovery occurs only in one fifth of adult cases, while for children the mean persistence rates for full or subthreshold OCD has been estimated around 60% (Maina et al., 2001; Stewart et al., 2004). Earlier age of OCD onset, increased illness-duration, inpatient status, the presence of comorbidities and a positive
family history seem to predict greater rates of persistence (Geller et al., 2003; Stewart et al., 2004). Furthermore, relapses in OCD are associated not only with considerable distress, significant functioning impairment and decrease of quality of life (Hollander et al., 2010), but also with a decreased response to a previous efficacious treatment (Maina et al., 2001).

To date, relapse-prevention studies in OCD have mainly investigated SRI as the maintenance treatment, with the duration of treatment under placebo-controlled conditions extending up to 12 months. Studies with a longer follow-up period or investigating relapse following CBT, are relatively scarce. Current evidence suggests that discontinuation of treatment is associated with a heightened relapse risk. Thus, the majority of relapse-prevention studies in adults have shown an overall superiority of SSRI compared to placebo in preventing relapse (Fineberg et al., 2007), suggesting that even a period of prolonged wellbeing under SSRI does not protect against relapse in the longer term. Relapse was particularly prominent in patients with comorbidities, which is the rule rather than the exception in children with OCD. As childhood and adolescence are critical periods for achievement of social, educational and occupational milestones, relapse-prevention is particularly relevant for this population (Fineberg et al., 2019). There has been one randomised controlled relapse-prevention study in paediatric OCD, which showed an advantage for paroxetine over placebo (Geller et al., 2004). As there is no available evidence suggesting a duration of treatment beyond which treatment can be discontinued safely, more recent guidelines emphasised the importance of maintaining medication for at least 12 months to reduce relapse-risk (Baldwin et al., 2014).

The clinician's role in enabling an informed choice about whether or not to discontinue medication at any particular time is challenging, considering the limitations of the available relapse-prevention studies. Strategies for safely managing emerging relapse, such as re-instating either 'booster' CBT or medication at the first sign of symptoms, do not have established evidence of efficacy. Nevertheless, it is advisable to establish a relapse-management plan, in cooperation with patients and their families based on vigilance for emergent
symptoms and rapid access to treatment previously known to be effective. If medication is to be discontinued, this should be done gradually, after a careful explanation of the potential consequences, such as withdrawal symptoms and relapse risk. SSRI tapering over a period of months, rather than weeks, is advisable in order to minimize the risk of withdrawal symptoms (Horowitz and Taylor, 2019).

**Treatment Resistant OCD - Novel Pharmacotherapies**

After well-supported first- and second-line treatments and strategies have been exhausted, some patients will continue to experience impairing OCD symptoms. Next-step treatment strategies may include continuing with the chosen SRI for an extended period of time, switching to another SRI, augmenting the SRI with a second-generation antipsychotic agent (SGA), or raising the dose of SRI to the highest tolerated level (Bandelow et al., 2008; Fineberg and Craig, 2007; Fineberg et al., 2012; Stein et al., 2012).

Although switching to another SRI is recommended in the depression literature, there is little evidence to support this approach in OCD. When a partial or moderate response has been achieved following adequate first-line treatment, there is randomized controlled trial (RCT) and meta-analytic evidence to support augmentation with an SGA (Brakoulias and Stockings, 2019; Dold et al., 2015; Stein et al., 2012; Zhou et al., 2019). Of these agents, risperidone is supported by the greatest number of studies, which have generally been positive (Brakoulias and Stockings, 2019). Two randomised controlled trials (Muscatello et al., 2011; Sayyah et al., 2012), several open-label studies (Ak et al., 2011; Connor et al., 2005; Pessina et al., 2009), and multiple case reports have demonstrated the efficacy of aripiprazole as an OCD treatment augmentation agent (Brakoulias & Stockings, 2019; Matsunaga et al., 2011; Higuma et al., 2012; Hou & Lai, 2014; Ercan et al., 2015; Akca & Yilmaz, 2016; Patra 2016). One meta-analysis also found a stronger effect size for aripiprazole than for risperidone: $D=1.11$ (aripiprazole) vs. $D=0.53$ (risperidone) (Veale et al., 2014). Quetiapine has been well-examined as an augmentation agent in OCD, but the evidence is conflicting. Despite several positive studies (Diniz et al., 2011; Atmaca et al., 2002; Denys et al., 2004; Vulink
et al., 2010), negative results have been found in the majority of placebo-controlled trials (Carey et al., 2005; Kordon et al., 2008; Fineberg et al., 2013).

Contrary to the depression literature, a meta-analysis of SRIs in OCD found that high doses (high end of recommended dosage, not higher than recommended doses) of SRIs were more effective than medium or low doses in the first-line treatment of OCD (Bloch et al., 2010). Response was more robust for patients with comorbid tics and in individuals who had received more than 12 weeks of maximal SRI monotherapy (Bloch et al., 2008). However, tolerability is a significant issue as compared with lower doses so that this strategy requires caution in a primary care setting (Stein et al., 2012). The Food and Drug Administration in the United States raised a safety warning in 2011 against citalopram doses higher than 40 mg/day due to a modest but probable risk of arrhythmias (US, 2012) however, a more recent meta-analysis identified only 18 cases where electrocardiogram QTc prolongation or torsades de pointes was associated with citalopram at doses between 20 and 60 mg/day. The authors concluded that these cardiac adverse events were infrequent (Tampi et al., 2015).

When an inadequate response persists, less well-supported treatment strategies (lacking multiple randomized, controlled trials or meta-analyses) may be considered for these cases (Koran et al., 2007; Koran and Simpson, 2013), including glutamate modulators, d-amphetamine, and oral morphine sulfate.

Glutamate modulators like memantine, riluzole, topiramate, lamotrigine, N-acetylcysteine, and ketamine have varying levels of support (Koran et al., 2007; Koran and Simpson, 2013; Pittenger, 2015; Pittenger et al., 2011). Memantine augmentation showed benefit in case studies and open-label trials (Aboujaoude et al., 2009; Bakhla et al., 2013; Feusner et al., 2009; Pasquini and Biondi, 2006; Poyurovsky et al., 2005; Stewart et al., 2010). In addition, two randomized controlled trials of memantine showed exceptionally high response rates (100% in one study), inconsistent with the literature (Ghaleiha et al., 2013; Haghighi et al., 2013). Riluzole augmentation showed promise in a case series and open-label trial (Coric et al., 2005, 2003). Subsequent small controlled studies have been mixed
(Emamzadehfard et al., 2016; Pittenger et al., 2008). While topiramate augmentation showed promise in case studies and open label trials (Rubio et al., 2006; Van Ameringen et al., 2006; Van Ameringen and Patterson, 2015), small randomized controlled trials have produced mixed results (Afshar et al., 2014; Berlin et al., 2011; Mowla et al., 2010). Lamotrigine augmentation showed mixed results in case reports (Arrojo-Romero et al., 2013; Hussain et al., 2015; Kumar and Khanna, 2000; Uzun, 2010) and benefit in two small randomized controlled trials (Bruno et al., 2012; Khalkhali et al., 2016). Limited data suggests that N-acetylcysteine is of benefit in some cases of refractory OCD (Lafleur et al., 2006), with mixed data in four randomized controlled trials (Afshar et al., 2012; Costa et al., 2017; Paydary et al., 2016; Sarris et al., 2015). A single intravenous dose of ketamine has been reported to be of rapid (in hours) and robust benefit in unmedicated adults with OCD in case report and open label studies (Rodriguez et al., 2016, 2011) and a randomized controlled cross-over study (Rodriguez et al., 2013). In an open label trial of medicated OCD adults with multiple comorbidities, depression improved on ketamine but improvement in OCD symptoms was minimal, and two patients developed new-onset irritability and suicidal ideation (Bloch et al., 2012; Niciu et al., 2013). Experience with intranasal ketamine in OCD is very limited (Adams et al., 2017; Rodriguez et al., 2017). Ketamine should only be performed at sites with expertise in this approach, with appropriate precautions including monitoring for side effects and screening individuals who have current or history of substance abuse (Sanacora et al., 2017).

In two double-blind, placebo controlled studies, d-amphetamine was superior to placebo in unmedicated OCD adults (Insel et al., 1983; Joffe et al., 1991). A subsequent double-blind comparison of SSRI augmentation with d-amphetamine versus high dose caffeine showed benefit of both drugs (Koran et al., 2009). Oral morphine showed benefit in a case series (Warneke, 1997) and in a double-blind crossover study (Koran et al., 2005) in adults with OCD. Precautions should be taken in the case of both d-amphetamine and morphine to screen out individuals who have current or history of substance abuse (Koran et al., 2007).
Other drugs, such as pindolol, clonazepam, buspirone, or lithium, have been tested but the results have been mixed and/or placebo-controlled trials have not found positive results. Some promising results have been found with the 5HT3 antagonist ondansetron but clinical double-blind placebo-controlled trials with larger sample sizes are needed (Serata et al., 2015). A more recent research line with some positive results is the use of immunological modulators, such as celecoxib (Shalbafan et al., 2015); however, the evidence of its usefulness in OCD is still insufficient.

**Treatment Resistant OCD - Non Invasive Neurostimulation**

Non-invasive neuro-modulatory interventions targeting the cortico-striato-thalamo-cortical (CSTC) circuits hold promise as augmenting intervention for treatment-resistant OCD (Lusicic et al., 2018). Repetitive Transcranial Magnetic Stimulation (rTMS) is the best studied non-invasive modulatory intervention in OCD. rTMS delivered at low frequency ($\leq 1$ Hz) (LF-rTMS) is thought to inhibit the activity of underlying cortical regions, while high frequency rTMS (HF-rTMS), provided at $\geq 5$ Hz, enhances cortical activity (Lefaucheur et al., 2014). Conventional rTMS, provided through the figure-8 coil, is highly focal and modulates superficial cortical regions over a depth of around 2 cm (Lefaucheur et al., 2014). LF-rTMS protocols targeting the supplementary motor area (SMA) have been found to be helpful in multiple randomized controlled trials and meta-analyses (Gomes et al., 2012; Hawken et al., 2016; Mantovani et al., 2010; Rehn et al., 2018; Zhou et al., 2017). This effect has been found to last up to 3 months (Gomes et al., 2012). A recent trial demonstrated superior efficacy of this protocol over antipsychotic augmentation in treatment-resistant OCD subjects (Pallanti et al., 2016). However, given recent inconsistent reports on inhibitory rTMS protocols targeting the SMA (Arumugham et al., 2018; Harika-Germaneau et al., 2019; Pelissolo et al., 2016), there is a need for large multi-center trials to confirm its efficacy.

LF-rTMS targeting the orbitofrontal cortex (OFC) has also shown promise in small randomised controlled trials (Nauczyciel et al., 2014; Ruffini et al., 2009). There is a need for larger trials targeting the OFC to confirm its efficacy and tolerability.
Randomised controlled trials targeting the dorsolateral prefrontal cortex have, in contrast and unlike in major depressive disorder, shown highly inconsistent findings in OCD (Lusicic et al., 2018). A multisite randomized sham-controlled trial found HF-deep rTMS, using the H7 coil, over the dorsomedial prefrontal cortex/anterior cingulate cortex to be efficacious and well-tolerated in a treatment resistant population (Carmi et al., 2019). This resulted in FDA approval and CE certification for this device for the treatment of resistant OCD. However, considering the increased cost of this device, there is a need for replication studies confirming the efficacy of the above protocol, which included personalised symptom-provocation as an interventional component. Less expensive deep coils, which have shown promise in targeting the dorsomedial prefrontal cortex in open-label trials on OCD (Dunlop et al., 2016; Modirrousta et al., 2015), are yet to be evaluated under controlled conditions.

Transcranial Direct Current Stimulation (tDCS) involves administration of low-amplitude (1-2mA) electric current to the brain between a cathode and anode. Anodal tDCS is thought to enhance cortical excitability and cathodal tDCS to have an inhibitory effect (Rachid, 2019). The SMA and OFC are key targets. A randomized sham-controlled trial (n=24 treatment-resistant OCD subjects) demonstrated efficacy for anodal tDCS administered over bilateral pre-SMA and cathodal tDCS over right supra-orbital regions (Gowda et al., 2019). However, another randomized crossover trial (n=12) found clinical improvement with cathodal tDCS over pre-SMA, while anodal tDCS was ineffective (D’urso et al., 2016). Thus, replication studies are needed to determine the optimal stimulation protocol for tDCS over SMA in OCD. Another randomized sham-controlled trial (n=21 treatment-resistant OCD patients) showed efficacy for cathodal tDCS delivered over the OFC and the anode over the right cerebellum, but the effect was not sustained at follow-up (Bation et al., 2019). Other promising results in treatment-resistant OCD for protocols targeting OFC and other cortical regions, such as dorsolateral prefrontal cortex and dorsomedial prefrontal cortex, are found in case reports and small uncontrolled studies and have to be confirmed in well-designed trials (Brunelin et al., 2018; Rachid, 2019). Furthermore, studies present significant heterogeneity and methodological differences in sample
selection criteria, concomitant treatment and tDCS stimulation protocols (da Silva et al., 2019; Rachid, 2019). Some authors suggest that overall, cathodal tDCS may be better than anodal in treating OCD (Rapinesi et al., 2019).

Currently, there are no RCTs to support the efficacy of electroconvulsive therapy (ECT) in OCD (Fontenelle et al., 2015). Hence, ECT may be recommended only for acute treatment of comorbid conditions such as depression or psychosis.

To summarize, LF-rTMS delivered over the SMA (with figure-8 coil) and HF-rTMS over the dorsomedial prefrontal cortex/anterior cingulate cortex (with H7 coil) appear promising interventions in treatment-resistant OCD. There is a need for large replication studies and evaluation of long-term effects/maintenance protocols. The evidence for tDCS is so far highly preliminary and further studies are encouraged.

**Treatment Resistant OCD - Deep Brain Stimulation and Ablative Neurosurgery**

A significant number (10-40%) of patients do not respond to any available therapy and suffer from severe, enduring symptoms and dysfunction (Denys, 2006; Fineberg and Gale, 2005; Gupta et al., 2018). For this highly refractory patient group, ablative neurosurgery and deep brain stimulation (DBS) remain modalities to be considered. These procedures are usually delivered as an adjunct to existing pharmacological treatments and CBT is frequently also administered, either during the acute treatment phase or follow-up.

Stereotactic neurosurgical procedures for intractable OCD have been available for more than fifty years (Miguel et al., 2019). The procedures include dorsal anterior cingulotomy and anterior capsulotomy and are reserved for the most severe treatment non-responsive patients. A systematic review involving 10 studies and 193 participants suggested both procedures were efficacious (Brown et al., 2016). The authors reported a mean Y-BOCS reduction of 37% for cingulotomy and 57% for capsulotomy. Another recent review of publications on anterior capsulotomy spanning over five decades (Pepper et al., 2019), reported ‘significant clinical
response’ in 73-90% of patients and ‘remission’ in 24-39% of patients with treatment resistant OCD.

DBS was investigated as a partially reversible alternative to surgical ablation (Nuttin et al., 1999). The original stimulation target was similar to the site of anterior capsulotomy i.e. ventral capsule/ventral striatum (VC/VS). Three reasonably sized studies have provided evidence in favour of the acute efficacy of DBS in the VC/VS. The first involved 24 patients who were followed up to four years and reported a 37% median improvement in baseline Y-BOCS scores (Luyten et al., 2016). ‘ON’ phases of stimulation were compared with ‘OFF’ phases (no stimulation), demonstrating that improvements were unlikely to represent ‘placebo’ effects. The second study investigated 16 patients, initially as open label, reporting a 46% reduction in baseline Y-BOCS at 8 months as well as a significant difference (25%) in Y-BOCS scores when compared with sham stimulation in a subsequent month long double-blind phase (Denys et al., 2010). A recent 12-month multi-center study of 30 patients given VC/VS DBS (Menchón et al., 2019) reported a mean reduction of baseline Y-BOCS of 42%. 60% of patients responded (reduction in baseline Y-BOCS > 40%).

The long term benefits of VC/VS DBS are less certain. An open label follow up study of 10 patients (Greenberg et al., 2006) reported a reduction in mean Y-BOCS from 34.67 at baseline (severe) to 22.37 (moderate) at 36 months. In addition significant improvements in global functioning, depression and anxiety persisted.

The anteromedial subthalamic nucleus (amSTN) has been identified as another promising target for DBS in OCD. Sixteen patients were randomized according to a crossover design to either 3 months active or sham treatment, resulting in a significantly greater reduction in mean Y-BOCS in the stimulation versus sham group (endpoint 19±8 vs. 28±7)(Mallet et al., 2008). It remains unclear whether VC/VS holds any advantage over amSTN DBS. A recent ‘mechanism of effect’ study of six OCD patients in which electrodes were implanted in both sites found differential improvements in mood (VC/VS) and cognitive flexibility (am STN),
suggesting that DBS exerts therapeutic effects at these targets via different brain networks (Tyagi et al., 2019).

There have been no head-to-head trials comparing ablative neurosurgery with DBS. A recent review (Pepper et al., 2015) retrospectively evaluated 20 studies of varying methodological quality involving 62 patients who underwent DBS of the VC/VS or the Nucleus Accumbens and 108 patients who underwent anterior capsulotomy. The capsulotomy group showed a significantly higher (51%) mean reduction in Y-BOCS than the DBS group (40%). No difference in surgical complication rates was observed. Adverse events across both modalities included intra-cranial haemorrhage (2-5%), persisting postoperative side effects (5-7%), cognitive and personality changes (7-13%) and suicide (1-2%). Weight gain (defined by an increase >10%) was significantly higher in the capsulotomy group (29% vs 3%).

In summary, studies of both DBS and ablative neurosurgery have shown these techniques are clinically effective for this highly refractory extremely chronically disabled patient group. However, there is as yet insufficient evidence to determine which technique to choose at an individual patient level. Further clarification of the differential effects of ablation and stimulation across the different candidate neural targets, as well as better understanding of the interaction between somatic, pharmacological and psychological interventions, have the potential to advance the field toward a personalised approach. Agreement over standardised patient selection and treatment protocols that would allow clinical outcomes data to be collected and compared across treatment centres, represents an achievable milestone toward this goal (e.g. Menchón et al., 2019). Meanwhile, technological innovations e.g. MRI-guided focused ultrasound, laser interstitial thermal therapy (Miguel et al., 2019), offer potential for safer and more cost effective surgical approaches.

**Future Directions For Research**

**Problematic Usage Of The Internet**
Problematic Use of the Internet (PUI), is an umbrella term for a range of repetitive functionally impairing compulsive behaviours including excessive and gambling, gaming, sexual behaviour, shopping, video-streaming or social media use. While advances have been made into defining diagnostic criteria and developing rating scales for some forms of PUI (e.g. Gaming Disorder) (Kiraly et al., 2015), a considerable amount of research is needed to understand better the broad range of PUI phenomena, and translate the known behavioural phenotypes into valid and reliable diagnostic criteria and assessment tools, to facilitate the systematic investigation of aetiological factors and brain-based mechanisms, as a platform for the development of preventative and therapeutic interventions (Fineberg et al., 2018b).

**Novel Digital interventions in OCD**

The digital era and the technology accompanying it offer new opportunities for monitoring and interventions. The extensive use of smartphones and vast amounts of information they contain has positioned them as a proxy for behaviour and social interactions (World Health Organisation, 2016). Harnessing smartphone technology along with smart wearables (e.g., smart watches) is expected to be a valuable source of continuous, objective and reliable data for clinical characterization, behavioural monitoring and treatment support (Marzano et al., 2015). This is true for several disorders but especially true for obsessive-compulsive disorders such as PUI, as the digital media that is directly linked to the disorder is the same one that can accurately monitor the behaviour (Ferreri et al., 2019).

Accordingly, using digital technology along with big data analyses may enable the potential to characterize the ‘digital phenotype’ of the disorder (Ferreri et al., 2019) and to identify those individuals most at risk (e.g., by monitoring online internet usage in comparison with changes in diurnal variation, lack of human contact, lack of geographical movement, restricted circles of friends etc). A potential research step in this direction could be to alert the individual whenever
a “compulsive pattern” of online activity emerges, help him/her to adjust his behaviour accordingly, to monitor and to feedback his progress.

Other forms of active online intervention have become increasingly available for OCRD (Whiteside et al., 2013). Specifically, incorporating digital tools can enhance and facilitate the treatment compliance of the patient in the treatment due to its continues manner (Andersson et al., 2014; Marzano et al., 2015). For example, interventions may include WhatsApp groups comprising a given patient and staff members (who know and work with him), in which the patient reports in real-time their difficulties, daily achievement and progress. Such digital groups enable continuing communication, real-time reports, enable prompt responses and rapid intervention when needed. In addition, the digital intervention may serve as a platform for continuous monitoring of tasks delivered in face-to-face meetings.

Another example of existing digital interventions is the proactive use of webcams and smartphone cameras. Using this domain and upon patient’s consent, the clinician may get the opportunity to monitor patients in their natural environment. As the digital platform bridges the elapsed time between therapeutic sessions, it can also overcome geographical distances and enables therapeutic practice in the patient’s natural environment (World Health Organisation, 2016), where symptoms are manifested daily (rather than in the neutral clinic).

In practice, this approach breaks down the traditional terminology of “outpatient”, “in-patient” and “day hospitalization”, by allowing real time, objective and continuous monitoring (World Health Organisation, 2016). This kind of digital monitoring and communication could be considered as “virtualized hospitalization”, as it offers more comprehensive and intensive treatment. This key aspect of continues monitoring is specifically important as crucial element of the treatment can take place while the patient is located in their natural environment, where the OCD usually occurs, and not within the artificial setting of the clinic. Thus, therapeutic utilization of digital tools may change the landscape of treatment in OCRD, providing potentially cost effective alternatives to hospitalization or outpatient clinics.
**Immunological Therapies**

Inflammation and release of inflammatory cytokines affect brain circuitry involving both reward and threat-sensitivity, producing potentially adaptive and beneficial behavioral responses (Raison and Miller, 2013). There is growing evidence of dysfunctional immunological function in the pathogenesis of a significant subset of OCD patients. Basal ganglia antibodies have been reported as five times more likely to be detected in OCD compared to control groups. Translocator protein distribution volume, a marker of the microglial component of neuro-inflammation, was found to be significantly elevated in the cortico-striato-thalamo-cortical (CSTC) circuit of OCD subjects compared with healthy controls, demonstrating inflammation within the neuro-circuitry and extending beyond the basal ganglia, affecting the adult population rather than solely childhood OCD (Attwells et al., 2017). Significantly more CSF autoantibodies directed against basal ganglia and thalamus were found among drug-naive OCD patients, and were associated with increased levels of CSF glutamate and glycine, indicating underpinning abnormalities in excitatory neurotransmission that correlated with hyperactivity in the ventral cognitive circuit (Bhattacharyya et al., 2009).

A common genetic link may explain an excess of some autoimmune comorbidities. For example, in the acute pediatric onset subset of children (PANDAS) there is immunological cross-reactivity with epitopes associated with streptococcal infection expressed on the surface of basal ganglia neurons. About 20% of the mothers of children fulfilling criteria for PANDAS (Chang et al., 2015) had at least one auto-immune disease. Multigenerational studies also show that 43% of OCD relatives are more likely to have an auto-immune disease such as Sjogren’s syndrome 94%, celiac disease 76%, Guillian Barrè 71%, Crohn’s disease 66%, Hashimotos Thyroiditis 59%, Type I diabetes mellitus 56%, ulcerative colitis 41%, multiple sclerosis 41%, and psoriasis vulgaris 32% (Mataix-Cols et al., 2018). A subset of patients with PANDAS with motor symptoms demonstrated anti-neural antibodies against dopamine (D1) receptors as well as elevated antibodies against tubulin, lysoganglioside and higher activation of calmodulin-dependent protein kinase II (Cox et al., 2015).
Immunomodulatory therapy represents a new field of investigation. While treatment with antimicrobials has delivered inconsistent results (Burchi and Pallanti, 2018), non-specific non-steroidal anti-inflammatory drugs have produced some positive effects, though only in a subset of youth (Spartz et al., 2017). Clinicians should consider genetic and immunological profile differences to advance precise individualized therapy for OCD.

**Novel forms of psychotherapy**

Although it may seem logical to try to tackle OCD using cognitive therapy, little evidence suggests that it offers any advantage to graded exposure and self-imposed response prevention (Tyagi et al., 2010; Ougrin, 2011). Poorly applied cognitive therapy, such as that expecting patients to re-evaluate actual dangers, may make some patients with OCD worse. This is because the process of looking for evidence to confirm or refute the obsessions can become incorporated into rituals. Cognitive therapy may also turn out to be less cost-efficient, as it requires more training and supervision for the therapist and usually takes more time in therapy. It is therefore probably best used in situations where there is OCD refractory to ERP (Drummond and Edwards, 2018).

Rational Emotive Therapy, on the other hand, has been shown to have some possible beneficial effects (Emmelkamp et al., 1988). Also using Rational Emotive Therapy but with instructions not to undergo Exposure, an Australian group has demonstrated good outcomes in some small controlled trials using Danger Ideation Reduction Therapy (DIRT) for patients with contamination fears (Jones and Menzies, 1998; Krochmalik et al., 2001). A recent case report of patients refractory to OCD also reviewed the literature on DIRT showing some positive outcomes (Maqbool et al., 2017). The techniques used in DIRT include: Cognitive restructuring using Rational Emotive Therapy (Ellis, 1962), filmed interviews with people who work in feared situations, corrective information about the real risks of “contamination” as opposed to the deleterious effects of overzealous hand-
washing, attentional focusing whereby patients are taught to focus the mind away from the danger-related intrusive thoughts.

In recent years the so-called Third Wave Therapies have been used in a number of psychiatric conditions. The therapy of this type most commonly used in OCD is mindfulness, which teaches an individual to focus on the world around them rather than their internal dialogue. A recent study demonstrated that both cognitive restructuring and also mindfulness led to a small improvement in Y-BOCS score when compared with waiting list controls. Indeed, the strength of efficacy for both treatments appeared to be less than that generally found with ERP (Rupp et al., 2019).

Many OCD patients describe their compulsions as habitual i.e. fixed ‘stimulus-response ’acts that, through habit learning, occur automatically in response to a specific environmental trigger. Habit Reversal Therapy (HRT) (Azrin and Nunn, 1973) is a long-established form of therapy that helps patients challenge habitual performance through a variety of behavioural methods. HRT is reported to be efficacious for the treatment of Tourette Syndrome and Tic Disorders and has more recently been applied in Obsessive Compulsive and Related Disorders such as trichotillomania and skin picking behaviours. However, there remains a scarcity of evidence from controlled trials supporting the efficacy of HRT in OCRDs in general, and OCD in particular, apart from a few studies reporting benefit in Tic Disorder with secondary OCD wherein the effects on OCD was not fully reported (Lee et al., 2019). Emerging neurosciences evidence identifying faulty habit learning in OCD (Fineberg et al., 2017) suggests further study of HRT in OCD would be worthwhile.

**Pharmaco-genetics**

Pharmacogenetic or pharmacogenomics define genetic variants that influence either drug metabolism, delivery, affinity to receptors or transporters etc., which may contribute in predicting drug efficacy and/or toxicity, promoting precision medicine (Hess et al., 2015). Since approximately one quarter of OCD patients do
not respond to treatment with either SSRIs and/or CBT (Hirschtritt et al., 2017), it has been suggested that pharmacogenetics may contribute to better drug-response prediction and side effect tolerance (Zai et al., 2014).

Currently, several pharmacogenetic approaches using hypothesis-free GWAS have been conducted into the association between candidate genes and drug response in OCD patients (Setareh Abdolhosseinizadeh et al., 2019; S Abdolhosseinizadeh et al., 2019; Alizadeh et al., 2019; Denys et al., 2007; Di Bella et al., 2002; Grünblatt et al., 2014; Lisoway et al., 2018; Mas et al., 2016; Miguita et al., 2011; MJ et al., 2017; Qin et al., 2016; Sina et al., 2018; Umehara et al., 2016, 2015; Van Nieuwerburgh et al., 2009; Zai et al., 2014). The candidate genes investigated belong to: (a) pharmacokinetic regulating genes, such as the CYP450 liver enzyme with CYP2D6 and CYP2C19; (b) serotonergic systems, such as SLC6A4 and its promoter, HTTLPR, HTR2A, HTR2C, HTR1B and TPH2; (c) glutamatergic systems, such as SLC1A1, DLGAP2, DLGAP2, GRIN2B, GRIK2, SLIT, SLITRK5; (d) dopaminergic systems, such as COMT, MAOA, DRD2 and DRD4; (e) other systems, such as BDNF, NTRK3, MOG, OLIG2, DISP1 etc.

Yet, currently no consensus with sufficiently robust results exists in the field of pharmacogenetics of OCD, due to the fact that many studies used naturalistic approaches, did not employ double blinded designs or crossed over with the tested drug, used a variety of drugs and doses, as well as used various cut-offs and measures determining response. Though there is still a need to systematically assess the pharmaco-genetic link between treatment response (to SSRIs, tricyclic antipsychotic /clomipramine, antipsychotics etc.) and certain genes, some data is already available, though very limited, on the Internet (e.g. https://www.pharmgkb.org; Whirl-Carrillo et al., 2012) summarizing some findings on pharmacogenetics of some drugs and giving some recommendations aligning with the US Food and Drug Administration (FDA), European Medicine Agency (EMA), Pharmaceutical and Medical Devices Agency, Japan (PMDA) and Health Canada (Sante Canada) HCSC.

Conclusion
Until just 40 years ago, OCD was considered rare (prevalence 0.05%), of psychological origin and without effective treatment. Now, all has changed; the finding in early 70s' that serotonergic medication (clomipramine at that time) is effective (Zohar et al., 1987; Zohar and Insel, 1987) opened the door to great interest in OCD (Zohar, 2012). This led to the development of specific forms of psychological intervention (CBT) which replaced the dynamic approach and to a focus on the serotonergic system in the treatment and pathophysiology of OCD. As a result of neuroscience insights including endophenotype-based approaches (reviewed in Fineberg et al., 2018), OCD has been removed from the Anxiety Disorder grouping in the DSM-5 (American Psychiatric Association, 2013) and ICD-11 (World Health Organisation, 2018) and now stands at the head of a new family of obsessive-compulsive and related disorders (OCRD).

The realization that OCRDs as a group are different from other anxiety disorders has led to significant changes in understanding their impact (the prevalence of OCRD in the population is more than 9%) (Carmi et al., 2019, in submission) and to refinement of the treatment approach (e.g. focusing on the urge to perform compulsions and the need for higher doses of serotonergic medication).

This position statement highlights the “tectonic” changes that have been taking place in the last few years in the field of OCD, in terms of conceptualization, diagnosis, assessment, intervention (with focus on early intervention), strategies for optimizing the efficacy of specific pharmacological intervention (SRI) with specific psychological intervention (ERP), the critical role of treatment of children and young adults and the importance of maintenance of wellbeing.

As new neuroscience insights are revealed, new therapeutic interventions are being explored (e.g. ketamine, glutamatergic agents, dopaminergic modulators etc.). This position statement also highlights invasive and non-invasive neuro-modulation as experimental interventions, including dTMS (achieving FDA indication for OCD in 2019).
Looking ahead to the future, other exciting avenues for investigation include the use of digital tools to monitor (and eventually to diagnose OCRD), advanced genetic methods, and new pharmacological domains (e.g. immunological systems). Indeed, it seems that the future was never so bright for OCRD patients. We trust that this position statement has managed to capture, describe, explain and shed light on many of these developments, including those in the front line of understanding and treatment of OCRD in the future.

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lead an NHS treatment service for OCD. I hold Board membership for various registered charities linked to OCD. I give expert advice on psychopharmacology to the UK MHRA.

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Authors’ contributions

All authors were involved in drafting the manuscript and agreed to its publication. All authors read and approved their sections of the final version of the manuscript.

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References

Abdolhosseinzadeh, S, Alizadeh, N., Shams, J., Asadi, S., Ahmadiani, A., 2019. BDNF association study with obsessive-compulsive disorder, its clinical characteristics, and response to fluvoxamine-treatment in Iranian patients. Exp. Clin. Psychopharmacol.
Abdolhosseinzadeh, Setareh, Sina, M., Ahmadiani, A., Asadi, S., Shams, J., 2019. Genetic and pharmacogenetic study of glutamate transporter (SLC1A1) in Iranian patients with obsessive-compulsive disorder. J. Clin. Pharm. Ther. 44, 39-48.

Aboujaoude, E., Barry, J.J., Gamel, N., 2009. Memantine augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial. J. Clin. Psychopharmacol. 29, 51-55.

Abramowitz, J.S., 2006. The Psychological Treatment of Obsessive—Compulsive Disorder. Can. J. Psychiatry 51, 407-416.

Ackerman, D.L., Greenland, S., 2002. Multivariate meta-analysis of controlled drug studies for obsessive-compulsive disorder. J. Clin. Psychopharmacol. 22, 309-317.

Adams, T., Bloch, M., Pittenger, C., 2017. Intranasal Ketamine and Cognitive-Behavioral Therapy for Treatment Refractory Obsessive-Compulsive Disorder. J. Clin. Psychopharmacol. 37, 269.

Afshar, H., Akuchekian, S., Mahaky, B., Zarean, E., 2014. Topiramate augmentation in refractory obsessive-compulsive disorder: A randomized, double-blind, placebo-controlled trial. J. Res. Med. Sci. Off. J. Isfahan Univ. Med. Sci. 19, 976.

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

Albert, U., Barbaro, F., Aguglia, A., Maina, G., Bogetto, F., 2012. Combined treatments in obsessive-compulsive disorder: current knowledge and future prospects. Riv. Psichiatr. 47, 255-268.

Albert, U., Barbaro, F., Bramante, S., Rosso, G., De Ronchi, D., Maina, G., 2019. Duration of untreated illness and response to SRI treatment in Obsessive-Compulsive Disorder. Eur. Psychiatry 58, 19-26.

Alizadeh, N., Nosrat, N., Jahani, Z., Ahmadiani, A., Asadi, S., Shams, J., 2019. Association of HTR1A gene polymorphisms with obsessive-compulsive disorder and its treatment response: the influence of sex and clinical characteristics. Int. J. Neurosci. 129, 264-272.
American, P.A., 2013. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub.

Andersson, G., Cuijpers, P., Carlbring, P., Riper, H., Hedman, E., 2014. Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. World Psychiatry 13, 288-295.

Arrojo-Romero, M., Tajes Alonso, M., de Leon, J., 2013. Lamotrigine augmentation of serotonin reuptake inhibitors in severe and long-term treatment-resistant obsessive-compulsive disorder. Case Rep. Psychiatry 2013.

Arumugham, S.S., Subhasini, V.S., Madhuri, H.N., Vinay, B., Ravi, M., Sharma, E., Thirthalli, J., Reddy, Y.C.J., 2018. Augmentation effect of low-frequency repetitive transcranial magnetic stimulation over presupplementary motor area in obsessive-compulsive disorder: A randomized controlled trial. J. ECT 34, 253-257.

Attwells, S., Setiawan, E., Wilson, A.A., Rusjan, P.M., Mizrahi, R., Miler, L., Xu, C., Richter, M.A., Kahn, A., Kish, S.J., 2017. Inflammation in the neurocircuitry of obsessive-compulsive disorder. JAMA psychiatry 74, 833-840.

Ayuso-Mateos, J.L., 2006. Global burden of obsessive-compulsive disorder in the year 2000. World Heal. Organ.

Azrin, N.H., Nunn, R.G., 1973. Habit-reversal: a method of eliminating nervous habits and tics. Behav. Res. Ther. 11, 619-628.

Bakhla, A.K., Verma, V., Soren, S., Sarkhel, S., Chaudhury, S., 2013. An open-label trial of memantine in treatment-resistant obsessive-compulsive disorder. Ind. Psychiatry J. 22, 149.

Baldwin, D.S., Anderson, I.M., Nutt, D.J., Allgulander, C., Bandelow, B., den Boer, J.A., Christmas, D.M., Davies, S., Fineberg, N., Lidbetter, N., 2014. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J. Psychopharmacol. 28, 403-439.

Bandelow, B., Sher, L., Bunevicius, R., Hollander, E., Kasper, S., Zohar, J., Möller, H.J., 2012. WFSBP Task Force on Mental Disorders in Primary Care; WFSBP Task Force on Anxiety Disorders, OCD and PTSD. Guidelines for the pharmacological
treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. Int J Psychiatry Clin Pr. 16, 77-84.

Bandelow, B., Zohar, J., Hollander, E., Kasper, S., Möller, H.-J., Disorders, W.T.F. on T.G. for A.O.-C.P.-T.S., Bandelow, B., Zohar, J., Hollander, E., Kasper, S., 2008. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders-first revision. World J. Biol. Psychiatry 9, 248-312.

Bation, R., Mondino, M., Le Camus, F., Saoud, M., Brunelin, J., 2019. Transcranial direct current stimulation in patients with obsessive compulsive disorder: A randomized controlled trial. Eur. Psychiatry 62, 38-44.

Berlin, H.A., Koran, L.M., Jenike, M.A., Chaplin, W., Pallanti, S., Hollander, E., 2011. Double-blind, placebo-controlled trial of topiramate augmentation in treatment-resistant obsessive-compulsive disorder. J. Clin. Psychiatry.

Bhattacharyya, S., Khanna, S., Chakrabarty, K., Mahadevan, A., Christopher, R., Shankar, S.K., 2009. Anti-brain autoantibodies and altered excitatory neurotransmitters in obsessive-compulsive disorder. Neuropsychopharmacology 34, 2489.

Bloch, M.H., Landeros-Weisenberger, A., Rosario, M.C., Pittenger, C., Leckman, J.F., 2008. Meta-analysis of the symptom structure of obsessive-compulsive disorder. Am. J. Psychiatry 165, 1532-1542.

Bloch, M.H., McGuire, J., Landeros-Weisenberger, A., Leckman, J.F., Pittenger, C., 2010. Meta-analysis of the dose-response relationship of SSRI in obsessive-compulsive disorder. Mol. Psychiatry 15, 850.

Bloch, M.H., Wasylink, S., Landeros-Weisenberger, A., Panza, K.E., Billingslea, E., Leckman, J.F., Krystal, J.H., Bhagwagar, Z., Sanacora, G., Pittenger, C., 2012. Effects of ketamine in treatment-refractory obsessive-compulsive disorder. Biol. Psychiatry 72, 964-970.

Bragdon, L.B., Gibb, B.E., Coles, M.E., 2018. Does neuropsychological performance in OCD relate to different symptoms? A meta-analysis comparing the symmetry and obsessing dimensions. Depress. Anxiety. https://doi.org/10.1002/da.22785

Brakoulias, V., 2018. Western Sydney Obsessive-Compulsive and Related Disorders
Brakoulias, V., Perkes, I.E., Tsalamandis, E., 2018. A call for prevention and early intervention in obsessive-compulsive disorder. Early Interv. Psychiatry 12, 572-577.

Brakoulias, V., Stockings, E., 2019. A systematic review of the use of risperidone, paliperidone and aripiprazole as augmenting agents for obsessive-compulsive disorder. Expert Opin. Pharmacother. 20, 47-53.

Brown, L.T., Mikell, C.B., Youngerman, B.E., Zhang, Y., McKhann, G.M., Sheth, S.A., 2016. Dorsal anterior cingulotomy and anterior capsulotomy for severe, refractory obsessive-compulsive disorder: a systematic review of observational studies. J. Neurosurg. 124, 77-89.

Brunelin, J., Mondino, M., Bation, R., Palm, U., Saoud, M., Poulet, E., 2018. Transcranial Direct Current Stimulation for Obsessive-Compulsive Disorder: A Systematic Review. Brain Sci. 8, 37. https://doi.org/10.3390/brainsci8020037

Bruno, A., Micò, U., Pandolfo, G., Mallamace, D., Abenavoli, E., Di Nardo, F., D’Arrigo, C., Spina, E., Zoccali, R.A., Muscatello, M.R.A., 2012. Lamotrigine augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. J. Psychopharmacol. 26, 1456-1462.

Burchi, E., Pallanti, S., 2018. Antibiotics for PANDAS? Limited Evidence: Review and Putative Mechanisms of Action. Prim. care companion CNS Disord. 20.

Carmi, L., Fineberg, N., Ben Arush, O., J, Z., n.d. Obsessive Compulsive Disorder, in: Geddes, J., Andreasen, N., Goodwin, G. (Eds.), New Oxford Textbook of Psychiatry. Oxford University Press.

Carmi, L., Tendler, A., Bystritsky, A., Hollander, E., Blumberger, D.M., Daskalakis, J., Ward, H., Lapidus, K., Goodman, W., Casuto, L., 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 appi-ajp.

Chang, K., Frankovich, J., Cooperstock, M., Cunningham, M.W., Latimer, M.E.,
Murphy, T.K., Pasternack, M., Thienemann, M., Williams, K., Walter, J., 2015. Clinical evaluation of youth with pediatric acute-onset neuropsychiatric syndrome (PANS): recommendations from the 2013 PANS Consensus Conference. J. Child Adolesc. Psychopharmacol. 25, 3-13.

Coric, V., Milanovic, S., Wasylink, S., Patel, P., Malison, R., Krystal, J.H., 2003. Beneficial effects of the antiglutamatergic agent riluzole in a patient diagnosed with obsessive-compulsive disorder and major depressive disorder. Psychopharmacology (Berl). 167, 219-220.

Coric, V., Taskiran, S., Pittenger, C., Wasylink, S., Mathalon, D.H., Valentine, G., Saksa, J., Gueorguieva, R., Sanacora, G., Malison, R.T., 2005. Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial. Biol. Psychiatry 58, 424-428.

Costa, D.L.C., Diniz, J.B., Requena, G., Joaquim, M.A., Pittenger, C., Bloch, M.H., Miguel, E.C., Shavitt, R.G., 2017. Randomized, Double-Blind, Placebo-Controlled Trial of N-Acetylcysteine Augmentation for Treatment-Resistant Obsessive-Compulsive Disorder. J. Clin. Psychiatry 78, e766-e773.

Cottraux, J., Mollard, E., Bouvard, M., Marks, I., Sluys, M., Nury, A.M., Douge, R., Cialdella, P., 1990. A controlled study of fluvoxamine and exposure in obsessive-compulsive disorder. Int. Clin. Psychopharmacol.

D’urso, G., Brunoni, A.R., Mazzaferro, M.P., Anastasia, A., de Bartolomeis, A., Mantovani, A., 2016. Transcranial direct current stimulation for obsessive-compulsive disorder: A randomized, controlled, partial crossover trial. Depress. Anxiety 33, 1132-1140.

da Silva, R. de M.F., Brunoni, A.R., Miguel, E.C., Shavitt, R.G., 2019. Transcranial direct current stimulation for Obsessive-Compulsive Disorder: patient selection and perspectives. Neuropsychiatr. Dis. Treat. 15, 2663.

de Mathis, M.A., Diniz, J.B., Hounie, A.G., Shavitt, R.G., Fossaluza, V., Ferrão, Y., Leckman, J.F., de Bragança Pereira, C., do Rosario, M.C., Miguel, E.C., 2013. Trajectory in obsessive-compulsive disorder comorbidities. Eur. Neuropsychopharmacol. 23, 594-601. https://doi.org/10.1016/j.euroneuro.2012.08.006

Dell’Osso, B., Benatti, B., Arici, C., Palazzo, C., Altamura, A.C., Hollander, E., Fineberg, N., Stein, D.J., Nicolini, H., Lanzagorta, N., 2018. Prevalence of
suicide attempt and clinical characteristics of suicide attempters with obsessive-compulsive disorder: a report from the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS). CNS Spectr. 23, 59-66.

Dell’Osso, B., Benatti, B., Grancini, B., Vismara, M., De Carlo, V., Cirnigliaro, G., Albert, U., Viganò, C., 2019. Investigating duration of illness and duration of untreated illness in obsessive compulsive disorder reveals patients remain at length pharmacologically untreated. Int. J. Psychiatry Clin. Pract. 1-3.

Dell’Osso, B., Benatti, B., Hollander, E., Fineberg, N., Stein, D.J., Lochner, C., Nicolini, H., Lanzagorta, N., Palazzo, C., Altamura, A.C., 2016. Childhood, adolescent and adult age at onset and related clinical correlates in obsessive-compulsive disorder: A report from the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS). Int. J. Psychiatry Clin. Pract. 20, 210-217.

Dell’Osso, B., Benatti, B., Oldani, L., Spagnolin, G., Altamura, A.C., 2015. Differences in duration of untreated illness, duration, and severity of illness among clinical phenotypes of obsessive-compulsive disorder. CNS Spectr. 20, 474-478.

Dell’Osso, B., Buoli, M., Hollander, E., Altamura, A.C., 2010. Duration of untreated illness as a predictor of treatment response and remission in obsessive-compulsive disorder. World J. Biol. Psychiatry 11, 59-65.

Denys, D., 2006. Pharmacotherapy of obsessive-compulsive disorder and obsessive-compulsive spectrum disorders. Psychiatr. Clin. North Am. 29, 553-584.

Denys, D., Mantione, M., Figee, M., Van Den Munckhof, P., Koerselman, F., Westenberg, H., Bosch, A., Schuurman, R., 2010. Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. Arch. Gen. Psychiatry 67, 1061-1068.

Denys, D., Nieuwerburgh, F., Van, Deforce, D., Westenberg, H.G.M., 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, 747-753.

Di Bella, D., Erzegovesi, S., Cavallini, M.C., Bellodi, L., 2002. Obsessive-compulsive disorder, 5-HTTLPR polymorphism and treatment response. Pharmacogenomics J. 2, 176.
Dittrich, W.H., Johansen, T., Fineberg, N.A., 2011. Cognitive assessment instrument of obsessions and compulsions (CAIOC-13)—a new 13-item scale for evaluating functional impairment associated with OCD. Psychiatry Res. 187, 283-290.

Dold, M., Aigner, M., Lanzenberger, R., 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.

Drummond, L.M., 2014. CBT for adults: a practical guide for clinicians. RCPsych Publications.

Drummond, L.M., Edwards, L.J., 2018. Obsessive compulsive disorder: All you want to know about OCD for people living with OCD, carers, and clinicians. Cambridge University Press.

Dunlop, K., Woodside, B., Olmsted, M., Colton, P., Giacobbe, P., Downar, J., 2016. Reductions in cortico-striatal hyperconnectivity accompany successful treatment of obsessive-compulsive disorder with dorsomedial prefrontal rTMS. Neuropsychopharmacology 41, 1395.

Eisen, J.L., Phillips, K.A., Baer, L., Beer, D.A., Atala, K.D., Rasmussen, S.A., 1998. The brown assessment of beliefs scale: reliability and validity. Am. J. Psychiatry 155, 102-108.

Ellis, A., 1962. Reason and emotion in psychotherapy.

Emamzadehfard, S., Kamaloo, A., Paydary, K., Ahmadipour, A., Zeinoddini, Arefeh, Ghaleiha, A., Mohammadinejad, P., Zeinoddini, Atefeh, 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, 332-341.

Emmelkamp, P.M.G., Visser, S., Hoekstra, R.J., 1988. Cognitive therapy vs exposure in vivo in the treatment of obsessive-compulsives. Cognit. Ther. Res. 12, 103-114. https://doi.org/10.1007/BF01172784

Excellence, N.I. for C., 2005. Obsessive-compulsive Disorder: Core Interventions in the Treatment of Obsessive-compulsive Disorder and Body Dysmorphic Disorder. Quick Reference Guide. National Institute for Clinical Excellence.

Ferreri, F., Bourla, A., Peretti, C.-S., Segawa, T., Jaafari, N., Mouchabac, S., 2019.
How New Technologies Can Improve Prediction, Assessment, and Intervention in Obsessive-Compulsive Disorder (e-OCD). JMIR Ment. Heal. 6, e11643.

Feusner, J.D., Kerwin, L., Saxena, S., Bystritsky, A., 2009. Differential efficacy of memantine for obsessive-compulsive disorder vs. generalized anxiety disorder: an open-label trial. Psychopharmacol Bull 42, 81-93.

Fineberg, N.A., Apergis-Schoute, A.M., Vaghi, M.M., Banca, P., Gillan, C.M., Voon, V., Chamberlain, S.R., Cinosi, E., Reid, J., Shahper, S., 2017. Mapping compulsivity in the DSM-5 obsessive compulsive and related disorders: cognitive domains, neural circuitry, and treatment. Int. J. Neuropsychopharmacol. 21, 42-58.

Fineberg, N.A., Baldwin, D.S., Drummond, L.M., Wyatt, S., Hanson, J., Gopi, S., Kaur, S., Reid, J., Marwah, V., Sachdev, R.A., 2018a. Optimal treatment for obsessive compulsive disorder: a randomized controlled feasibility study of the clinical-effectiveness and cost-effectiveness of cognitive-behavioural therapy, selective serotonin reuptake inhibitors and their combination in the mana. Int. Clin. Psychopharmacol. 33, 334.

Fineberg, N.A., Brown, A., Reghunandanan, S., Pampaloni, I., 2012. Evidence-based pharmacotherapy of obsessive-compulsive disorder. Int. J. Neuropsychopharmacol. 15, 1173-1191. https://doi.org/10.1017/S1461145711001829

Fineberg, N.A., Craig, K.J., 2007. Pharmacological treatment for obsessive-compulsive disorder. Psychiatry 6, 234-239.

Fineberg, N.A., Dell’Osso, B., Albert, U., Maina, G., Geller, D., Carmi, L., Sireau, N., Walitza, S., Grassi, G., Pallanti, S., 2019. Early intervention for obsessive compulsive disorder: An expert consensus statement. Eur. Neuropsychopharmacol. 29, 549-565.

Fineberg, N.A., Demetrovics, Z., Stein, D.J., Ioannidis, K., Potenza, M.N., Grünblatt, E., Brand, M., Billieux, J., Carmi, L., King, D.L., 2018b. Manifesto for a European research network into Problematic Usage of the Internet. Eur. Neuropsychopharmacol. 28, 1232-1246.

Fineberg, N.A., Gale, T.M., 2005. Evidence-based pharmacotherapy of obsessive-compulsive disorder. Int. J. Neuropsychopharmacol. 8, 107-129.

Fineberg, N.A., Pampaloni, I., Pallanti, S., Ipser, J., Stein, D.J., 2007. Sustained
response versus relapse: the pharmacotherapeutic goal for obsessive-compulsive disorder. Int. Clin. Psychopharmacol. 22, 313-322.

Foa, E.B., Liebowitz, M.R., Kozak, M.J., Davies, S., Campeas, R., Franklin, M.E., Huppert, J.D., Kjernisted, K., Rowan, V., Schmidt, A.B., 2005. Randomized, placebo-controlled trial of exposure and ritual prevention, clomipramine, and their combination in the treatment of obsessive-compulsive disorder. Am. J. Psychiatry 162, 151-161.

Fontenelle, L.F., Coutinho, E.S., Lins-Martins, N.M., Fitzgerald, P.B., Fujiwara, H., Yücel, M., 2015. Electroconvulsive therapy for obsessive-compulsive disorder: a systematic review. J. Clin. Psychiatry 76, 949-957.

Fontenelle, L.F., Yücel, M., 2019. A Clinical Staging Model for Obsessive-Compulsive Disorder: Is It Ready for Prime Time? EClinicalMedicine.

Franklin, M.E., Sapyta, J., Freeman, J.B., Khanna, M., Compton, S., Almirall, D., Moore, P., Choate-Summers, M., Garcia, A., Edson, A.L., 2011. Cognitive behavior therapy augmentation of pharmacotherapy in pediatric obsessive-compulsive disorder: the Pediatric OCD Treatment Study II (POTS II) randomized controlled trial. JAMA 306, 1224-1232.

Freeman, J., Sapyta, J., Garcia, A., Compton, S., Khanna, M., Flessner, C., FitzGerald, D., Mauro, C., Dingfelder, R., Benito, K., 2014. Family-based treatment of early childhood obsessive-compulsive disorder: the Pediatric Obsessive-Compulsive Disorder Treatment Study for Young Children (POTS Jr)—a randomized clinical trial. JAMA psychiatry 71, 689-698.

Garcia, A.M., Sapyta, J.J., Moore, P.S., Freeman, J.B., Franklin, M.E., March, J.S., Foa, E.B., 2010. Predictors and moderators of treatment outcome in the Pediatric Obsessive Compulsive Treatment Study (POTS I). J. Am. Acad. Child Adolesc. Psychiatry 49, 1024-1033.

Gava, I., Barbui, C., Aguglia, E., Carlino, D., Churchill, R., De Vanna, M., McGuire, H., 2007. Psychological treatments versus treatment as usual for obsessive compulsive disorder (OCD). Cochrane Database Syst. Rev.

Geller, D.A., Biederman, J., Stewart, S.E., Mullin, B., Farrell, C., Wagner, K.D., Emslie, G., Carpenter, D., 2003. Impact of comorbidity on treatment response to paroxetine in pediatric obsessive-compulsive disorder: is the use of exclusion criteria empirically supported in randomized clinical trials? J. Child
Adolesc. Psychopharmacol. 13, 19-29.

Geller, D.A., March, J., (CQI), A.C. on Q.I., 2012. Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. Focus (Madison). 10, 360-373.

Geller, D.A., Wagner, K.D., Emslie, G., Murphy, T., Carpenter, D.J., Wetherhold, E., Perera, P., Machin, A., Gardiner, C., 2004. Paroxetine treatment in children and adolescents with obsessive-compulsive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. J. Am. Acad. Child Adolesc. Psychiatry 43, 1387-1396.

Ghaleiha, A., Entezari, N., Modabbernia, A., Najand, B., Askari, N., Tabrizi, M., Ashrafi, M., Hajiaghaee, R., Akhondzadeh, S., 2013. Memantine add-on in moderate to severe obsessive-compulsive disorder: randomized double-blind placebo-controlled study. J. Psychiatr. Res. 47, 175-180.

Gomes, J.B., Cordioli, A.V., Heldt, E., 2017. Obsessive-compulsive disorder and family accommodation: A 3-year follow-up. Psychiatry Res. 253, 107-109. https://doi.org/10.1016/j.psychres.2017.03.043

Gomes, P.V.O., Brasil-Neto, J.P., Allam, N., Rodrigues de Souza, E., 2012. A randomized, double-blind trial of repetitive transcranial magnetic stimulation in obsessive-compulsive disorder with three-month follow-up. J. Neuropsychiatry Clin. Neurosci. 24, 437-443.

Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Fleischmann, R.L., Hill, C.L., Heninger, G.R., Charney, D.S., 1989. The Yale-Brown obsessive compulsive scale: I. Development, use, and reliability. Arch. Gen. Psychiatry 46, 1006-1011.

Gordon, J., 2018. Towards a Genomic Psychiatry: Recommendations of the Genomics Workgroup of the NAMHC [WWW Document]. URL https://www.nimh.nih.gov/about/director/messages/2018/towards-a-genomic-psychiatry-recommendations-of-the-genomics-workgroup-of-the-namhc.shtml (accessed 12.24.19).

Gowda, S.M., Narayanaswamy, J.C., Hazari, N., Bose, A., Chhabra, H., Balachander, S., Bhaskarapillai, B., Shivakumar, V., Venkatasubramanian, G., Reddy, Y.C.J., 2019. Efficacy of pre-supplementary motor area transcranial direct current stimulation for treatment resistant obsessive compulsive
disorder: A randomized, double blinded, sham controlled trial. Brain Stimul.
Greenberg, B.D., Malone, D.A., Friehs, G.M., Rezai, A.R., Kubu, C.S., Malloy, P.F.,
Salloway, S.P., Okun, M.S., Goodman, W.K., Rasmussen, S.A., 2006. Three-Year
Outcomes in Deep Brain Stimulation for Highly Resistant Obsessive-Compulsive
Disorder. Neuropsychopharmacology 31, 2384–2393. https://doi.org/10.1038/
sj.npp.1301165
Grünblatt, E., Tschakarjan, S., Brezinka, V., Walitza, S., 2014. Extraordinarily fast
response to low-dose sertraline in a child with severe obsessive-compulsive
disorder and high functioning serotonin transporter genotype. J. Child Adolesc.
Psychopharmacol. 24, 102-104.
Guglielmi, V., Vulink, N.C.C., Denys, D., Wang, Y., Samuels, J.F., Nestadt, G.,
2014. Obsessive-compulsive disorder and female reproductive cycle events:
Results from the ocd and reproduction collaborative study. Depress. Anxiety
31, 979-987. https://doi.org/10.1002/da.22234
Gupta, A., Shepard, M.J., Xu, Z., Maiti, T., Martinez-Moreno, N., Silverman, J.,
Ilorio-Morin, C., Martinez-Alvarez, R., Barnett, G., Mathieu, D., 2018. An
International Radiosurgery Research Foundation Multicenter Retrospective
Study of Gamma Ventral Capsulotomy for Obsessive Compulsive Disorder.
Neurosurgery.
Haghighi, M., Jahangard, L., Mohammad-Beigi, H., Bajoghli, H., Hafezian, H.,
Rahimi, A., Afshar, H., Holsboer-Trachsler, E., 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, 633-640.
Harika-Germaneau, G., Rachid, F., Chatard, A., Lafay-Chebassier, C., Solinas, M.,
Thirioux, B., Millet, B., Langbour, N., Jaafari, N., 2019. Continuous theta burst
stimulation over the supplementary motor area in refractory obsessive-compulsive
disorder treatment: A randomized sham-controlled trial. Brain
Stimul. 12, 1565-1571.
Hawken, E., Dilkov, D., Kaludiev, E., Simek, S., Zhang, F., Milev, R., 2016.
Transcranial magnetic stimulation of the supplementary motor area in the
treatment of obsessive-compulsive disorder: a multi-site study. Int. J. Mol. Sci.
17, 420.
Health, N.C.C. for M., 2006. Core interventions in the treatment of obsessive compulsive disorder and body dysmorphic disorder (a guideline from the National Institute for Health and Clinical Excellence, National Health Service). London, England, Br. Psychiatr. Soc. R. Coll. Psychiatr.

Hirschtritt, M.E., Bloch, M.H., Mathews, C.A., 2017. Obsessive-compulsive disorder: advances in diagnosis and treatment. Jama 317, 1358-1367.

Hohagen, F., Winkelmann, G., Rasche-Räuchle, H., Hand, I., König, A., Münchau, N., Hiss, H., Geiger-Kabisch, C., Käppler, C., Schramm, P., 1998. Combination of behaviour therapy with fluvoxamine in comparison with behaviour therapy and placebo: results of a multicentre study. Br. J. Psychiatry 173, 71-78.

Hollander, E., Doernberg, E., Shavitt, R., Waterman, R.J., Soreni, N., Veltman, D.J., Sahakian, B.J., Fineberg, N.A., 2016. The cost and impact of compulsivity: a research perspective. Eur. Neuropsychopharmacol. 26, 800-809.

Hollander, E., Stein, D.J., Fineberg, N.A., Marteau, F., Legault, M., 2010. Quality of life outcomes in patients with obsessive-compulsive disorder: relationship to treatment response and symptom relapse. J. Clin. Psychiatry 71, 784-792.

Horowitz, M.A., Taylor, D., 2019. Tapering of SSRI treatment to mitigate withdrawal symptoms. The Lancet Psychiatry.

Hussain, A., Dar, M.A., Wani, R.A., Shah, M.S., Jan, M.M., Malik, Y.A., Chandel, R.K., Margoob, M.A., 2015. Role of lamotrigine augmentation in treatment-resistant obsessive compulsive disorder: a retrospective case review from South Asia. Indian J. Psychol. Med. 37, 154.

Insel, T.R., Hamilton, J.A., Guttmacher, L.B., Murphy, D.L., 1983. D-amphetamine in obsessive-compulsive disorder. Psychopharmacology (Berl). 80, 231-235.

Joffe, R.T., Swinson, R.P., Levitt, A.J., 1991. Acute psychostimulant challenge in primary obsessive-compulsive disorder. J. Clin. Psychopharmacol. 11, 237-241.

Jones, M.K., Menzies, R.G., 1998. Danger ideation reduction therapy (DIRT) for obsessive-compulsive washers. A controlled trial. Behav. Res. Ther. 36, 959-70.

Katzman, M.A., Bleau, P., Blier, P., Chokka, P., Kjernisted, K., Van Ameringen, M., 2014. Canadian Anxiety Guidelines Initiative Group of the Anxiety Disorders Association of Canada. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive
disorders. BMC Psychiatry 14, 1-83.
Khalkhali, M., Aram, S., Zarrabi, H., Kafie, M., Heidarzadeh, A., 2016. Lamotrigine augmentation versus placebo in serotonin reuptake inhibitors-resistant obsessive-compulsive disorder: a randomized controlled trial. Iran. J. Psychiatry 11, 104.
Kichuk, S.A., Torres, A.R., Fontenelle, L.F., Rosário, M.C., Shavitt, R.G., Miguel, E.C., Pittenger, C., Bloch, M.H., 2013. Symptom dimensions are associated with age of onset and clinical course of obsessive-compulsive disorder. Prog. Neuro-Psychopharmacology Biol. Psychiatry 44, 233-239.
Koran, L.M., Aboujaoude, E., Bullock, K.D., Franz, B., Gamel, N., Elliott, M., 2005. Double-blind treatment with oral morphine in treatment-resistant obsessive-compulsive disorder. J. Clin. Psychiatry 66, 353-359.
Koran, L.M., Aboujaoude, E., Gamel, N.N., 2009. Double-blind study of dextroamphetamine versus caffeine augmentation for treatment-resistant obsessive-compulsive disorder. J. Clin. Psychiatry 70, 1530-1535.
Koran, L.M., Hanna, G.L., Hollander, E., Nestadt, G., Simpson, H.B., Association, A.P., 2007. Practice guideline for the treatment of patients with obsessive-compulsive disorder. Am J Psychiatry 164, 5-53.
Koran, L.M., Simpson, H.B., 2013. Guideline watch (March 2013): practice guideline for the treatment of patients with obsessive-compulsive disorder. Arlington, VA Am. Psychiatr. Assoc.
Krochmalik, A., Jones, M.K., Menzies, R.G., 2001. Danger Ideation Reduction Therapy (DIRT) for treatment-resistant compulsive washing. Behav. Res. Ther. 39, 897-912. https://doi.org/https://doi.org/10.1016/S0005-7967(00)00063-2
Kumar, T.C.R., Khanna, S., 2000. Lamotrigine augmentation of serotonin re-uptake inhibitors in obsessive-compulsive disorder. Aust. N. Z. J. Psychiatry 34, 527-528.
Lafleur, D.L., Pittenger, C., Kelmendi, B., Gardner, T., Wasylink, S., Malison, R.T., Sanacora, G., Krystal, J.H., Coric, V., 2006. N-acetylcysteine augmentation in serotonin reuptake inhibitor refractory obsessive-compulsive disorder. Psychopharmacology (Berl). 184, 254-256.
Lee, M.T., Fineberg, N.A., Mpavaenda, D.N., 2019. Habit Reversal Therapy in Obsessive Compulsive Related Disorders: A Systematic Review of the Evidence
and CONSORT Evaluation of Randomized Controlled Trials. Front. Behav. Neurosci. 13, 79.
Lefaucheur, J.-P., André-Obadia, N., Antal, A., Ayache, S.S., Baeken, C., Benninger, D.H., Cantello, R.M., Cincotta, M., de Carvalho, M., De Ridder, D., 2014. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin. Neurophysiol. 125, 2150-2206.
Lewin, A.B., Park, J.M., Jones, A.M., Crawford, E.A., De Nadai, A.S., Menzel, J., Arnold, E.B., Murphy, T.K., Storch, E.A., 2014. Family-based exposure and response prevention therapy for preschool-aged children with obsessive-compulsive disorder: a pilot randomized controlled trial. Behav. Res. Ther. 56, 30-38.
Lisoway, A.J., Zai, G., Tiwari, A.K., Zai, C.C., Wigg, K., Goncalves, V., Zhang, D., Freeman, N., Müller, D.J., Kennedy, J.L., 2018. Pharmacogenetic evaluation of a DISP1 gene variant in antidepressant treatment of obsessive-compulsive disorder. Hum. Psychopharmacol. Clin. Exp. 33, e2659.
Liu, X., Liu, J., Long, J., 2005. Paroxetine combined with cognitive behavior therapy in treatment of obsessive-compulsive disorder. Chinese J. Heal. Psychol. 2, 86-87.
Locher, C., Koechlin, H., Zion, S.R., Werner, C., Pine, D.S., Kirsch, I., Kessler, R.C., Kossowsky, J., 2017. Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric disorders among children and adolescents: a systematic review and meta-analysis. Jama Psychiatry 74, 1011-1020.
López-Pina, J.A., Sanchez-Meca, J., López-López, J.A., Marin-Martinez, F., Núñez-Núñez, R.M., Rosa-Alcazar, A.I., Gomez-Conesa, A., Ferrer-Requena, J., 2015a. Reliability generalization study of the Yale-Brown Obsessive-Compulsive Scale for children and adolescents. J. Pers. Assess. 97, 42-54.
López-Pina, J.A., Sánchez-Meca, J., López-López, J.A., Marín-Martínez, F., Núñez-Núñez, R.M., Rosa-Alcázar, A.I., Gómez-Conesa, A., Ferrer-Requena, J., 2015b. The Yale-Brown Obsessive Compulsive Scale: A Reliability Generalization Meta-Analysis. Assessment 22, 619-628.
Lusicic, A., Schruers, K.R.J., Pallanti, S., Castle, D.J., 2018. Transcranial magnetic stimulation in the treatment of obsessive-compulsive disorder: current
perspectives. Neuropsychiatr. Dis. Treat. 14, 1721.

Luyten, L., Hendrickx, S., Raymaekers, S., Gabriëls, L., Nuttin, B., 2016. Electrical stimulation in the bed nucleus of the stria terminalis alleviates severe obsessive-compulsive disorder. Mol. Psychiatry 21, 1272.

Maina, G., Albert, U., Bogetto, F., 2001. Relapses after discontinuation of drug associated with increased resistance to treatment in obsessive-compulsive disorder. Int. Clin. Psychopharmacol. 16, 33-38.

Mallet, L., Polosan, M., Jaafari, N., Baup, N., Welte., M.-L., Fontaine, D., Montcel, S.T. du, Yelnik, J., Chéreau, I., Arbus, C., 2008. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N. Engl. J. Med. 359, 2121-2134.

Mantovani, A., Simpson, H.B., Fallon, B.A., Rossi, S., Lisanby, S.H., 2010. Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. Int. J. Neuropsychopharmacol. 13, 217-227.

Maqbool, M., Sengar, K.S., Vikas, Kumar, M., Uparikar, P.D., 2017. Efficacy of Danger Ideation Reduction Therapy in Obsessive-Compulsive Disorder Washer with Poor Insight: A Case Study and Literature Review. Indian J. Psychol. Med. 39, 523-526. https://doi.org/10.4103/0253-7176.211754

Marzano, L., Bardill, A., Fields, B., Herd, K., Veale, D., Grey, N., Moran, P., 2015. The application of mHealth to mental health: opportunities and challenges. The Lancet Psychiatry 2, 942-948.

Mas, S., Blázquez, A., Rodriguez, N., Boloc, D., Lafuente, A., Arnaiz, J.A., Lázaro, L., Gassó, P., 2016. Pharmacogenetic study focused on fluoxetine pharmacodynamics in children and adolescent patients: impact of the serotonin pathway. Pharmacogenet. Genomics 26, 487-496.

Mataix-Cols, D., Frans, E., Pérez-Vigil, A., Kuja-Halkola, R., Gromark, C., Isomura, K., de la Cruz, L.F., Serlachius, E., Leckman, J.F., Crowley, J.J., 2018. A total-population multigenerational family clustering study of autoimmune diseases in obsessive-compulsive disorder and Tourette's/chronic tic disorders. Mol. Psychiatry 23, 1652–1658.

McGuire, J.F., Piacentini, J., Scahill, L., Woods, D.W., Villarreal, R., Wilhelm, S., Walkup, J.T., Peterson, A.L., 2015. Bothersome tics in patients with chronic tic
disorders: Characteristics and individualized treatment response to behavior therapy. Behav. Res. Ther. 70, 56-63.

Menchón, J.M., Real, E., Alonso, P., Aparicio, M.A., Segalas, C., Plans, G., Luyten, L., Brunfaut, E., Matthijs, L., Raymakers, S., 2019. A prospective international multi-center study on safety and efficacy of deep brain stimulation for resistant obsessive-compulsive disorder. Mol. Psychiatry 1-14.

Meng, F.-Q., Han, H.-Y., Luo, J., Liu, J., Liu, Z.-R., Tang, Y., Hou, X., Wei, J., Shi, L.-L., Tang, M.-N., 2019. Efficacy of cognitive behavioural therapy with medication for patients with obsessive-compulsive disorder: A multicentre randomised controlled trial in China. J. Affect. Disord. 253, 184-192.

Miguel, E.C., Lopes, A.C., McLaughlin, N.C.R., Norén, G., Gentil, A.F., Hamani, C., Shavitt, R.G., Batistuzzo, M.C., Vattimo, E.F.Q., Canteras, M., 2019. Evolution of gamma knife capsulotomy for intractable obsessive-compulsive disorder. Mol. Psychiatry 24, 218-240.

Miguita, K., Cordeiro, Q., Shavitt, R.G., Miguel, E.C., Vallada, H., 2011. Association study between genetic monoaminergic polymorphisms and OCD response to clomipramine treatment. Arq. Neuropsiquiatr. 69, 283-287.

MJ, R.J.T., Ganesh, S., Shukla, T., Deolankar, S., Nadella, R.K., Sen, S., Purushottam, M., Reddy, Y.C.J., Jain, S., Viswanath, B., 2017. BDNF gene and obsessive compulsive disorder risk, symptom dimensions and treatment response. Asian J. Psychiatr.

Modirrousta, M., Shams, E., Katz, C., Mansouri, B., Moussavi, Z., Sareen, J., Enns, M., 2015. The efficacy of deep repetitive transcranial magnetic stimulation over the medial prefrontal cortex in obsessive compulsive disorder: results from an open-label study. Depress. Anxiety 32, 445-450.

Mowla, A., Khajeian, A.M., Sahraian, A., Chohedri, A.H., Kashkoli, F., 2010. Topiramate augmentation in resistant OCD: a double-blind placebo-controlled clinical trial. CNS Spectr. 15, 613-617.

Muscatoello, M.R.A., Bruno, A., Pandolfo, G., Micò, U., Scimeca, G., Romeo, V.M., Santoro, V., Settineri, S., Spina, E., Zoccali, R.A., 2011. Effect of aripiprazole augmentation of serotonin reuptake inhibitors or clomipramine in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. J. Clin. Psychopharmacol. 31, 174-179.
National, A.M.H.C.W. on G., n.d. Report of the National Advisory Mental Health Council Workgroup on Genomics [WWW Document]. URL https://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/report-of-the-national-advisory-mental-health-council-workgroup-on-genomics.shtml#acknowledgement (accessed 12.24.19).

National, C.C. for M.H., 2006. Core interventions in the treatment of obsessive compulsive disorder and body dysmorphic disorder (a guideline from the National Institute for Health and Clinical Excellence, National Health Service). London, England, Br. Psychiatr. Soc. R. Coll. Psychiatr.

National, I. for C.E., 2005a. Overview | Obsessive-compulsive disorder and body dysmorphic disorder: treatment | Guidance | NICE.

National, I. for C.E., 2005b. Obsessive-compulsive Disorder: Core Interventions in the Treatment of Obsessive-compulsive Disorder and Body Dysmorphic Disorder. Quick Reference Guide. National Institute for Clinical Excellence.

Nauczyciel, C., Le Jeune, F., Naudet, F., Douabin, S., Esquevin, A., Vérin, M., Dondaine, T., Robert, G., Drapier, D., Millet, B., 2014. Repetitive transcranial magnetic stimulation over the orbitofrontal cortex for obsessive-compulsive disorder: a double-blind, crossover study. Transl. Psychiatry 4, e436.

Nezgovorova, V., Rigby, N., Battles, J., Krause, D., Fineberg, N., Ameringen, M. Van, Hollander, E., 2018. Genetic variants of OCD phenotypes and comorbid conditions, ACNP Poster, 2018. The American College of Neuropsychopharmacology, Hollywood, Florida.

Niciu, M.J., Grunschel, B.D.G., Corlett, P.R., Pittenger, C., Bloch, M.H., 2013. Two cases of delayed-onset suicidal ideation, dysphoria and anxiety after ketamine infusion in patients with obsessive-compulsive disorder and a history of major depressive disorder. J. Psychopharmacol. 27, 651-654.

Nuttin, B., Cosyns, P., Demeulemeester, H., Gybels, J., Meyerson, B., 1999. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. Lancet 354, 1526.

Pallanti, S., Marras, A., Salerno, L., Makris, N., Hollander, E., 2016. Better than treated as usual: Transcranial magnetic stimulation augmentation in selective serotonin reuptake inhibitor-refractory obsessive-compulsive disorder, mini-review and pilot open-label trial. J. Psychopharmacol. 30, 568-578.
Pasquini, M., Biondi, M., 2006. Memantine augmentation for refractory obsessive-compulsive disorder. Prog. Neuro-Psychopharmacology Biol. Psychiatry 30, 1173-1175.

Paydary, K., Akamaloo, A., Ahmadipour, A., Pishgar, F., Emamzadehfard, S., 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, 214-219.

Pelissolo, A., Harika-Germaneau, G., Rachid, F., Gaudeau-Bosma, C., Tanguy, M.-L., BenAdhira, R., Bouaziz, N., Popa, T., Wassouf, I., Saba, G., 2016. Repetitive transcranial magnetic stimulation to supplementary motor area in refractory obsessive-compulsive disorder treatment: a sham-controlled trial. Int. J. Neuropsychopharmacol. 19.

Pepper, J., Hariz, M., Zrinzo, L., 2015. Deep brain stimulation versus anterior capsulotomy for obsessive-compulsive disorder: a review of the literature. J. Neurosurg. 122, 1028-1037.

Pepper, J., Zrinzo, L., Hariz, M., 2019. Anterior capsulotomy for obsessive-compulsive disorder: a review of old and new literature. J. Neurosurg. 1-10.

Piacentini, J., Bergman, R.L., Chang, S., Langley, A., Peris, T., Wood, J.J., McCracken, J., 2011. Controlled comparison of family cognitive behavioral therapy and psychoeducation/relaxation training for child obsessive-compulsive disorder. J. Am. Acad. Child Adolesc. Psychiatry 50, 1149-1161.

Pittenger, C., 2015. Glutamatergic agents for OCD and related disorders. Curr. Treat. options psychiatry 2, 271-283.

Pittenger, C., Bloch, M.H., Williams, K., 2011. Glutamate abnormalities in obsessive compulsive disorder: neurobiology, pathophysiology, and treatment. Pharmacol. Ther. 132, 314-332.

Pittenger, C., Kelmendi, B., Wasylink, S., Bloch, M.H., 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, 363-367.

Postorino, V., Kerns, C.M., Vivanti, G., Bradshaw, J., Siracusano, M., Mazzone, L., 2017. Anxiety Disorders and Obsessive-Compulsive Disorder in Individuals with Autism Spectrum Disorder. Curr. Psychiatry Rep. https://doi.org/10.1007/s11920-017-0846-y
Poyurovsky, M., Weizman, R., Weizman, A., Koran, L., 2005. Memantine for treatment-resistant OCD. Am. J. Psychiatry 162, 2191-a.

Qin, H., Samuels, J.F., Wang, Y., Zhu, Y., Grados, M.A., Riddle, M.A., Greenberg, B.D., Knowles, J.A., Fyer, A.J., McCracken, J.T., 2016. Whole-genome association analysis of treatment response in obsessive-compulsive disorder. Mol. Psychiatry 21, 270.

Rachid, F., 2019. Transcranial direct current stimulation for the treatment of obsessive-compulsive disorder? A qualitative review of safety and efficacy. Psychiatry Res. 271, 259-264.

Raison, C.L., Miller, A.H., 2013. Malaise, melancholia and madness: the evolutionary legacy of an inflammatory bias. Brain. Behav. Immun. 31, 1-8.

Rapinesi, C., Kotzalidis, G.D., Ferracuti, S., Sani, G., Girardi, P., Del Casale, A., 2019. Brain stimulation in obsessive-compulsive disorder (OCD): a systematic review. Curr. Neuropharmacol. 17, 787-807.

Reddy, Y.C.J., Sundar, A.S., Narayanaswamy, J.C., Math, S.B., 2017. Clinical practice guidelines for obsessive-compulsive disorder. Indian J. Psychiatry 59, S74.

Rehn, S., Eslick, G.D., Brakoulias, V., 2018. A meta-analysis of the effectiveness of different cortical targets used in repetitive transcranial magnetic stimulation (rTMS) for the treatment of obsessive-compulsive disorder (OCD). Psychiatr. Q. 89, 645-665.

Rodriguez, C., Lapidus, K., Zwerling, J., Levinson, A., Mahnke, A., Steinman, S., Kalanthroff, E., Simpson, H., 2017. Challenges Testing Intranasal Ketamine in Obsessive-Compulsive Disorder (OCD), in: NEUROPSYCHOPHARMACOLOGY. NATURE PUBLISHING GROUP MACMILLAN BUILDING, 4 CRINAN ST, LONDON N1 9XW, ENGLAND, pp. S128-S129.

Rodriguez, C.I., Kegeles, L.S., Flood, P., Simpson, H.B., 2011. Rapid resolution of obsessions after an infusion of intravenous ketamine in a patient with treatment-resistant obsessive-compulsive disorder: a case report. J. Clin. Psychiatry 72, 567.

Rodriguez, C.I., Kegeles, L.S., Levinson, A., Feng, T., Marcus, S.M., Vermes, D., Flood, P., Simpson, H.B., 2013. Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept.
Rodriguez, C.I., Levinson, A., Zwerling, J., Vermes, D., Simpson, H.B., 2016. Open-Label trial on the effects of memantine in adults with obsessive-compulsive disorder after a single ketamine infusion. J. Clin. Psychiatry 77, 688.

Romanelli, R.J., Wu, F.M., Gamba, R., Mojtabai, R., Segal, J.B., 2014. Behavioral therapy and serotonin reuptake inhibitor pharmacotherapy in the treatment of obsessive-compulsive disorder: A systematic review and meta-analysis of head-to-head randomized controlled trials. Depress. Anxiety 31, 641-652.

Rosa-Alcázar, A.I., Sánchez-Meca, J., Gómez-Conesa, A., Marín-Martínez, F., 2008. Psychological treatment of obsessive-compulsive disorder: A meta-analysis. Clin. Psychol. Rev. 28, 1310-1325.

Rosario-Campos, M.C., Miguel, E.C., Quatrano, S., Chacon, P., Ferrao, Y., Findley, D., Katsovich, L., Scahill, L., King, R.A., Woody, S.R., 2006. The Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS): an instrument for assessing obsessive-compulsive symptom dimensions. Mol. Psychiatry 11, 495.

Rubio, G., Jiménez-Arriero, M.A., Martínez-Gras, I., Manzanares, J., Palomo, T., 2006. The effects of topiramate adjunctive treatment added to antidepressants in patients with resistant obsessive-compulsive disorder. J. Clin. Psychopharmacol. 26, 341-344.

Ruffini, C., Locatelli, M., Lucca, A., Benedetti, F., Insacco, C., Smeraldi, E., 2009. Augmentation effect of repetitive transcranial magnetic stimulation over the orbitofrontal cortex in drug-resistant obsessive-compulsive disorder patients: a controlled investigation. Prim. Care Companion J. Clin. Psychiatry 11, 226.

Rupp, C., Jürgens, C., Doeblер, P., Andor, F., Buhlmann, U., 2019. A randomized waitlist-controlled trial comparing detached mindfulness and cognitive restructuring in obsessive-compulsive disorder. PLoS One 14, e0213895-e0213895. https://doi.org/10.1371/journal.pone.0213895

Salkovskis, P.M., 1999. Understanding and treating obsessive-compulsive disorder. Behav. Res. Ther. 37 Suppl 1, S29-52.

Salkovskis, P.M., 1985. Obsessional-compulsive problems: A cognitive-behavioural analysis. Behav. Res. Ther. 23, 571-583. https://doi.org/10.1016/0005-7967(85)90105-6

Sanacora, G., Heimer, H., Hartman, D., Mathew, S.J., Frye, M., Nemeroff, C.,
Beale, R.R., 2017. Balancing the promise and risks of ketamine treatment for mood disorders. Neuropsychopharmacology 42, 1179.

Sánchez-Meca, J., Rosa-Alcázar, A.I., Iniesta-Sepúlveda, M., Rosa-Alcázar, Á., 2014. Differential efficacy of cognitive-behavioral therapy and pharmacological treatments for pediatric obsessive-compulsive disorder: A meta-analysis. J. Anxiety Disord. 28, 31-44.

Sarris, J., Oliver, G., Camfield, D.A., Dean, O.M., Dowling, N., Smith, D.J., Murphy, J., Menon, R., Berk, M., Blair-West, S., 2015. N-acetyl cysteine (NAC) in the treatment of obsessive-compulsive disorder: A 16-week, double-blind, randomised, placebo-controlled study. CNS Drugs 29, 801-809.

Sayyah, Mehdi, Sayyah, Mohammad, Boostani, H., Ghaffari, S.M., Hoseini, A., 2012. Effects of aripiprazole augmentation in treatment-resistant obsessive-compulsive disorder (a double blind clinical trial). Depress. Anxiety 29, 850-854.

Serata, D., Kotzalidis, G.D., Rapinesi, C., Janiri, D., Di Pietro, S., Callovini, G., Piacentino, D., Gasperoni, C., Brugnoli, R., Ferri, V.R., 2015. Are 5-HT3 antagonists effective in obsessive-compulsive disorder? A systematic review of literature. Hum. Psychopharmacol. Clin. Exp. 30, 70-84.

Shalbafan, M., Mohammadinejad, P., Shariat, S.-V., Alavi, K., Zeinoddini, A., Salehi, M., Askari, N., Akhondzadeh, S., 2015. Celecoxib as an adjuvant to fluvoxamine in moderate to severe obsessive-compulsive disorder: A double-blind, placebo-controlled, randomized trial. Pharmacopsychiatry 48, 136-140.

Shavitt, R.G., de Mathis, M.A., Oki, F., Ferrao, Y.A., Fontenelle, L.F., Torres, A.R., Diniz, J.B., Costa, D.L.C., do Rosário, M.C., Hoexter, M.Q., 2014. Phenomenology of OCD: lessons from a large multicenter study and implications for ICD-11. J. Psychiatr. Res. 57, 141-148.

Simpson, H.B., Foa, E.B., Liebowitz, M.R., Huppert, J.D., Cahill, S., Maher, M.J., McLean, C.P., Bender, J., Marcus, S.M., Williams, M.T., 2013. Cognitive-behavioral therapy vs risperidone for augmenting serotonin reuptake inhibitors in obsessive-compulsive disorder: a randomized clinical trial. JAMA psychiatry 70, 1190-1199.
controlled trial of cognitive-behavioral therapy for augmenting pharmacotherapy in obsessive-compulsive disorder. Am. J. Psychiatry 165, 621-630.

Sina, M., Ahmadiani, A., Asadi, S., Shams, J., 2018. association of serotonin receptor 2a haplotypes with obsessive-compulsive disorder and its treatment response in iranian patients: a genetic and pharmacogenetic study. Neuropsychiatr. Dis. Treat. 14, 1199.

Skapinakis, P., Caldwell, D., Hollingworth, W., Bryden, P., Fineberg, N., Salkovskis, P., Welton, N., Baxter, H., Kessler, D., Churchill, R., 2016a. A systematic review of the clinical effectiveness and cost-effectiveness of pharmacological and psychological interventions for the management of obsessive-compulsive disorder in children/adolescents and adults. Health Technol. Assess. (Rockv). 20, 1-392.

Skapinakis, P., Caldwell, D.M., Hollingworth, W., Bryden, P., Fineberg, N.A., Salkovskis, P., Welton, N.J., Baxter, H., Kessler, D., Churchill, R., 2016b. Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. The Lancet Psychiatry 3, 730-739.

Skarphedinnson, G., Weidle, B., Ivarsson, T., 2015. Sertraline treatment of nonresponders to extended cognitive-behavior therapy in pediatric obsessive-compulsive disorder. J. Child Adolesc. Psychopharmacol. 25, 574-579.

Skoog, G., Skoog, I., 1999. A 40-year follow-up of patients with obsessive-compulsive disorder [see commetns]. Arch. Gen. Psychiatry 56, 121-7. https://doi.org/10.1001/archpsyc.56.2.121

Sookman, D., Fineberg, N.A., 2015. Specialized psychological and pharmacological treatments for obsessive-compulsive disorder throughout the lifespan: a special series by the Accreditation Task Force (ATF) of The Canadian Institute for Obsessive Compulsive Disorders (CIOCD, www.ciocd.ca). Psychiatry Res. 227, 74-77.

Soomro, G.M., Altman, D.G., Rajagopal, S., Browne, M.O., 2008. Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). Cochrane database Syst. Rev.

Spartz, E.J., Freeman Jr, G.M., Brown, K., Farhadian, B., Thienemann, M.,
Frankovich, J., 2017. Course of neuropsychiatric symptoms after introduction and removal of nonsteroidal anti-inflammatory drugs: A pediatric observational study. J. Child Adolesc. Psychopharmacol. 27, 652-659.

Stein, D.J., Koen, N., Fineberg, N., Fontenelle, L.F., Matsunaga, H., Osser, D., Simpson, H.B., 2012. A 2012 evidence-based algorithm for the pharmacotherapy for obsessive-compulsive disorder. Curr. Psychiatry Rep. 14, 211-219.

Stewart, S.E., Geller, D.A., Jenike, M., Pauls, D., Shaw, D., Mullin, B., Faraone, S.V, 2004. Long-term outcome of pediatric obsessive-compulsive disorder: a meta-analysis and qualitative review of the literature. Acta Psychiatr. Scand. 110, 4-13.

Stewart, S.E., Jenike, E.A., Hezel, D.M., Stack, D.E., Dodman, N.H., Shuster, L., Jenike, M.A., 2010. A single-blinded case-control study of memantine in severe obsessive-compulsive disorder. J. Clin. Psychopharmacol. 30, 34-39.

Storch, E.A., De Nadai, A.S., Jacob, M.L., Lewin, A.B., Muroff, J., Eisen, J., Abramowitz, J.S., Geller, D.A., Murphy, T.K., 2014. Phenomenology and correlates of insight in pediatric obsessive-compulsive disorder. Compr. Psychiatry 55, 613-620.

Storch, E.A., Rasmussen, S.A., Price, L.H., Larson, M.J., Murphy, T.K., Goodman, W.K., 2010. Development and psychometric evaluation of the Yale-Brown Obsessive-Compulsive Scale—Second Edition. Psychol. Assess. 22, 223.

Tampi, R.R., Balderas, M., Carter, K. V, Tampi, D.J., Moca, M., Knudsen, A., May, J., 2015. Citalopram, QTc prolongation, and torsades de pointes. Psychosomatics 56, 36-43.

Torres, A.R., Ramos-Cerqueira, A.T.A., Ferrão, Y.A., Fontenelle, L.F., do Rosário, M.C., Miguel, E.C., 2011. Suicidality in obsessive-compulsive disorder: prevalence and relation to symptom dimensions and comorbid conditions. J. Clin. Psychiatry 72, 17-26; quiz 119-20. https://doi.org/10.4088/JCP.09m05651blu

Tyagi, H., Apergis-Schoute, A.M., Akram, H., Foltynie, T., Limousin, P., Drummond, L.M., Fineberg, N.A., Matthews, K., Jahanshahi, M., Robbins, T.W., 2019. A randomized trial directly comparing ventral capsule and anteromedial subthalamic nucleus stimulation in obsessive-compulsive disorder: clinical and
imaging evidence for dissociable effects. Biol. Psychiatry 85, 726–734.

Tyagi, H., Drummond, L.M., Fineberg, N.A., 2010. Treatment for obsessive compulsive disorder. Curr. Psychiatry Rev. 6, 46-55.

Umehara, H., Numata, S., Kinoshita, M., Watanabe, S., Nakaaki, S., Sumitani, S., Ohmori, T., 2016. No association between BDNF Val66Met polymorphism and treatment response in obsessive-compulsive disorder in the Japanese population. Neuropsychiatr. Dis. Treat. 12, 611.

Umehara, H., Numata, S., Tajima, A., Kinoshita, M., Nakaaki, S., Imoto, I., Sumitani, S., Ohmori, T., 2015. No association between the COMT Val158Met polymorphism and the long-term clinical response in obsessive-compulsive disorder in the Japanese population. Hum. Psychopharmacol. Clin. Exp. 30, 372-376.

US, F. and D.A., 2012. FDA Drug Safety Communication: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses | FDA [WWW Document]. URL http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm (accessed 12.19.19).

Ustun, Tevfik Bedirhan, Kostanjesek, N, Chatterji, S, Rehm, J.& W.H.O., 2010. Measuring health and disability: manual for WHO Disability Assessment Schedule (WHODAS 2.0).

Uzun, Ö., 2010. Lamotrigine as an augmentation agent in treatment-resistant obsessive-compulsive disorder: a case report. J. Psychopharmacol. 24, 425-427.

Van Ameringen, M., Mancini, C., Patterson, B., Bennett, M., 2006. Topiramate augmentation in treatment-resistant obsessive-compulsive disorder: a retrospective, open-label case series. Depress. Anxiety 23, 1-5.

Van Ameringen, M., Patterson, B., 2015. Topiramate augmentation in a patient with obsessive-compulsive disorder. J. psychiatry Neurosci. JPN 40, E31.

Van Nieuwerburgh, F.C.W., Denys, D.A.J.P., Westenberg, H.G.M., Deforce, D.L.D., 2009. Response to serotonin reuptake inhibitors in OCD is not influenced by common CYP2D6 polymorphisms. Int. J. Psychiatry Clin. Pract. 13, 345-348.

Warneke, L., 1997. A Possible New Treatment Approach to Obsessive–Compulsive Disorder. Can. J. Psychiatry 42, 667-668.

Whirl-Carrillo, M., McDonagh, E.M., Hebert, J.M., Gong, L., Sangkuhl, K., Thorn,
C.F., Altman, R.B., Klein, T.E., 2012. Pharmacogenomics knowledge for personalized medicine. Clin. Pharmacol. Ther. 92, 414-417. https://doi.org/10.1038/clpt.2012.96

Whiteside, S., Ale, C., Vickers, K., Tiede, M., Dammann, J., 2013. Case Examples of Enhancing Pediatric OCD Treatment With a Smartphone Application. Clin. Case Stud. 13, 80-94. https://doi.org/10.1177/1534650113504822

Wilbur, C., Bitnun, A., Kronenberg, S., Laxer, R.M., Levy, D.M., Logan, W.J., Shouldice, M., Ann Yeh, E., 2019. PANDAS/PANS in childhood: Controversies and evidence. Paediatr. Child Heal. https://doi.org/10.1093/pch/pxy145

World, H.O., 2018. International classification of diseases for mortality and morbidity statistics (11th Revision)., International classification of diseases for mortality and morbidity statistics (11th Revision).

World, H.O., 2016. Monitoring and Evaluating Digital Health Interventions: A practical guide to conducting research and assessment, Who. https://doi.org/CC BY-NC-SA 3.0 IGO

Zai, G., Brandl, E.J., Müller, D.J., Richter, M.A., Kennedy, J.L., 2014. Pharmacogenetics of antidepressant treatment in obsessive-compulsive disorder: an update and implications for clinicians. Pharmacogenomics 15, 1147-1157.

Zhou, D.-D., Wang, W., Wang, G.-M., Li, D.-Q., Kuang, L., 2017. An updated meta-analysis: Short-term therapeutic effects of repeated transcranial magnetic stimulation in treating obsessive-compulsive disorder. J. Affect. Disord. 215, 187-196.

Zhou, D.-D., Zhou, X.-X., Lv, Z., Chen, X.-R., Wang, W., Wang, G.-M., Liu, C., Li, D.-Q., Kuang, L., 2019. Comparative efficacy and tolerability of antipsychotics as augmentations in adults with treatment-resistant obsessive-compulsive disorder: A network meta-analysis. J. Psychiatr. Res. 111, 51-58.

Zohar, J., 2012. Obsessive compulsive disorder: Current science and clinical practice. John Wiley & Sons.

Zohar, J., 1997. Is there room for a new diagnostic subtype—the schizo-obsessive subtype? CNS Spectr. 2, 49-50.

Zohar, J., Insel, T.R., 1987. Obsessive-compulsive disorder: psychobiological approaches to diagnosis, treatment, and pathophysiology. Biol. Psychiatry 22,
Zohar, J., Judge, R., Investigators, O.C.D.P.S., 1996. Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. Br. J. Psychiatry 169, 468-474.

Zohar, J., Mueller, E.A., Insel, T.R., Zohar-Kadouch, R.C., Murphy, D.L., 1987. Serotonergic responsivity in obsessive-compulsive disorder: comparison of patients and healthy controls. Arch. Gen. Psychiatry 44, 946-951.