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

Introduction

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 *GRIK1* 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 (accomodation) (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

overinflated idea of danger (Jones and Menzies, 1998) (See Novel forms of Psychotherapy below).

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 adaptions 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 un-medicated 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 un-medicated 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 (≤1 Hz) (LF-rTMS) is thought to inhibit the activity of underlying cortical regions, while high frequency rTMS (HF-rTMS), provided at ≥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 Abdolhosseinzadeh et al., 2019; S Abdolhosseinzadeh 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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NF declares; In the past 12 months I have held research or networking grants from the ECNP, UK NIHR, EU H2020. In the past 12 months I have accepted travel and/or hospitality expenses from the BAP, ECNP, RCPsych, CINP, International Forum of Mood and Anxiety Disorders, World Psychiatric Association, Indian Association for Biological Psychiatry. In the past 12 months I have received payment from Taylor and Francis and Elsevier for editorial duties. Previously, I have accepted paid speaking engagements in various industry supported symposia and have recruited patients for various industry-sponsored studies in the field of OCD treatment. I

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

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