Clinical advances in obsessive-compulsive disorder: a position statement by the International College of Obsessive-Compulsive Spectrum Disorders

Naomi A. Fineberg[a,b,c], Eric Hollander[d], Stefano Pallanti[e,f], Susanne Walitza[g,h,i], Edna Grünblatt[g,h,i], Bernardo Maria Dell'Osso[j,k,l,m], Umberto Albert[n], Daniel A. Geller[o], Vlasios Brakoulias[p,q], Y.C. Janardhan Reddy[r], Shyam Sundar Arumugham[r], Roseli G. Shavitt[s], Lynne Drummond[t], Benedetta Grancini[b,j], Vera De Carlo[b,j], Eduardo Cinosi[a,b], Samuel R. Chamberlain[u,v], Konstantinos Ioannidis[u,v], Carolyn I. Rodriguez[k,w], Kabir Garg[b], David Castle[x], Michael Van Ameringen[y,z], Dan J. Stein[aa], Lior Carmi[bb,cc], Joseph Zohar[bb,dd] and Jose M. Menchon[ee]

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 article presents those 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, pharmacogenetics and novel forms of psychotherapy are discussed. *Int Clin Psychopharmacol* 35: 173–193 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

[a]University of Hertfordshire, Hatfield, [b]Hertfordshire Partnership University NHS Foundation Trust, Welwyn Garden City, Hertfordshire, [c]University of Cambridge School of Clinical Medicine, Cambridge, UK [d]Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York, USA, [e]Istituto di Neuroscienze, University of Florence, Firenze, Italy, [f]Albert Einstein College of Medicine, Bronx, New York, USA, [g]Department of Child and Adolescent Psychiatry and Psychotherapy, University Hospital of Psychiatry Zurich, University of Zurich, [h]Neuroscience Center Zurich, University of Zurich and ETH Zurich, [i]Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland, [j]University of Milan, Department of Biomedical and Clinical Sciences Luigi Sacco, Ospedale Sacco-Polo Universitario, ASST Fatebenefratelli-Sacco, Milan, Italy, [k]Department of Psychiatry and Behavioural Sciences, Stanford University, California, USA, [l]CRC 'Aldo Ravelli' for Neurotechnology and Experimental Brain Therapeutics, University of Milan, Milan, [m]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, [n]Department of Medicine, Surgery and Health Sciences, UCO Clinica Psichiatrica, University of Trieste, Trieste, Italy, [o]Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA, [p]Western Sydney Obsessive-Compulsive and Related Disorders Service, Western Sydney Local Health District, Blacktown Hospital, Blacktown, New South Wales, [q]Translational Research Health Institute (THRI), Clinical and Health Psychology Research Initiative (CaHPRI) and School of Medicine, Western Sydney University, Sydney, Australia, [r]OCD Clinic, Department of Psychiatry, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru, India, [s]OCD Spectrum Disorders Program, Institute and Department of Psychiatry, Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo-SP, Brazil, [t]Consultant Psychiatrist, SW London and St George's NHS Trust and St George's, University of London, London, [u]Department of Psychiatry, University of Cambridge, Cambridge, [v]Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK, [w]Veterans Affairs Palo Alto Health Care System, Palo Alto, California, USA, [x]St. Vincent's Hospital Melbourne and The University of Melbourne, Melbourne, Australia, [y]Department of Psychiatry and Behavioural Neurosciences, McMaster University, [z]Hamilton Health Sciences, Hamilton, Ontario, Canada, [aa]SA MRC Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry and Neuroscience Institute, University of Cape Town, Cape Town, South Africa, [bb]The Post Trauma Center, Chaim Sheba Medical Center, Ramat Gan, [cc]The Data Science Institute, The Interdisciplinary Center, Herzliya, [dd]Tel Aviv University, Tel Aviv-Yafo, Israel and [ee]Department of Psychiatry, Bellvitge University Hospital-IDIBELL, University of Barcelona, Cibersam, Barcelona, Spain

Correspondence to Kabir Garg, Hertfordshire Partnership University NHS Foundation Trust, Welwyn Garden City, Hertfordshire, UK
E-mail: kabir.garg@nhs.net

Introduction

Once a neglected illness, obsessive-compulsive disorder (OCD) is now recognized 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 conceptualizations, therapeutic interventions and services. Recent changes in the DSM-5 (American Psychiatric Association, 2013) and ICD-11 (WHO, 2018) diagnostic classification systems have set OCD at the head of a new family of obsessive-compulsive spectrum disorders [otherwise known as Obsessive-Compulsive or Related Disorders, or, Obsessive-Compulsive and Related Disorders (OCRDs)], including body dysmorphic, hoarding, hair-pulling, skin picking and olfactory reference disorders and 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 that early intervention produces better outcomes (Fineberg *et al.*, 2019). However, a substantial minority of patients still fail to respond either in any meaningful way, or in terms of residual symptoms. 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 (Bandelow *et al.*, 2012; Baldwin *et al.*, 2014; Sookman *et al.*, 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 among treatment-resistant groups, advances in invasive and noninvasive neurostimulation 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 (ICOCS; 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. Agreement was reached on the key issues to be covered at a series of meetings, and the authors of each section were chosen based on their expertise in that area. An initial draft was prepared, based on a literature review, and circulated first among the authors and then to all ICOCS members and iterative edits were incorporated. In sum, we have selected those recent therapeutic advances judged by a range of experts to be of most relevance to the treatment of OCD, including products that are not licensed or labelled for treatment of OCD by the US Food and Drug Administration (FDA) (Table 1), which are marked with an asterisk (*) throughout the article, based on new and emerging evidence from clinical and translational science

Global assessment of obsessive-compulsive disorder

A comprehensive assessment of OCD requires trained clinicians who perform direct interviews with the patient and, whenever possible, with family members, so that an accurate diagnosis can be determined and individualized treatment can be tailored. 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), these can present together or separately. 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 tailoring the behavioural treatment and monitoring treatment response objectively. For the OCD diagnosis, while free-form interviews by clinicians are commonly used, structured interviews offer advantages in terms of objectivity and psychometric properties (Rapp *et al.*, 2016). Suitable interviews for the diagnosis of OCD in adulthood include the Structured Clinical Interview for DSM-5 Disorders (First *et al.*, 2016), or the Mini International Neuropsychiatric Interview (Sheehan *et al.*, 1998). The Yale–Brown Obsessive-Compulsive Scale (Y-BOCS) is the gold-standard for assessing symptom severity in diagnosed adult patients, and incorporates a detailed checklist for individual symptoms (Goodman *et al.*, 1989). For initial screening, six brief questions can be used. These include as follows: (1) Do you wash or clean a lot? (2) Do you check things a lot? (3) Is there any thought that keeps bothering you that you would like to get rid of but can't? (4) Do your daily activities take a long time to finish? (5) Are you concerned about orderliness or symmetry? (6) Do these problems trouble you? Positive response to one or more statements would indicate a need for more detailed assessment (Fineberg *et al.*, 2008).

Table 1 **The US Food and Drug Administration status of treatments covered in this article**

	FDA status for treatment of OCD	
Treatment	Adults	Children and adolescents
Serotonin reuptake inhibitors		
Clomipramine	Approved	Approved from 10 years of age
Fluoxetine	Approved	Approved from 8 years of age
Fluvoxamine	Approved	Approved from 8 years of age
Sertraline	Approved	Approved from 6 years of age
Paroxetine	Approved	Not approved
Citalopram	Not approved	
Escitalopram	Not approved	
Second-generation antipsychotics		
Risperidone	Not approved	
Aripiprazole	Not approved	
Quetiapine	Not approved	
Novel pharmacotherapies		
Glutamate modulators (memantine, riluzole, topiramate, lamotrigine, N-Acetylcysteine, Ketamine)	Not approved	
d-amphetamine	Not approved	
Morphine	Not approved	
Pindolol	Not approved	
Clonazepam	Not approved	
Buspirone	Not approved	
Lithium	Not approved	
Ondansetron	Not approved	
Noninvasive brain stimulation		
Low-frequency r-TMS at supplementary motor area	Not approved	
Low-frequency r-TMS at orbitofrontal cortex	Not approved	
High-frequency-deep rTMS over the dorsomedial prefrontal cortex/anterior cingulate cortex	Approved for treatment of resistant OCD	
Transcranial direct current stimulation	Not approved	
Electroconvulsive therapy	Not approved	
Invasive procedures		
Deep brain stimulation	Humanitarian device exemption for severe refractory OCD	
Stereotactic neurosurgical procedures	Not approved	

FDA, the US Food and Drug Administration; OCD, obsessive-compulsive disorder; r-TMS, recurrent-transcranial magnetic stimulation.

Obsessions and compulsions tend to occur concomitantly in the vast majority of people with OCD (Shavitt *et al.*, 2014). In addition, compulsions are commonly preceded not only by obsessions but also by subjective experiences of incompleteness, or 'not feeling just-right', or so-called sensory phenomena (perceptual experiences that precede or accompany compulsions) (Shavitt *et al.*, 2014). We could expect these 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). Insight (good or fair insight, poor insight, absent insight/ delusional beliefs) is a diagnostic specifier for OCD, body dysmorphic disorder (BDD) and hoarding disorder in the DSM-5 (American Psychiatric Association, 2013). In general, subjects with OCD have at least good insight, with only a minority presenting poor insight or delusional OCD (Shavitt *et al.*, 2014). The presence of tic symptomatology represents another clinically relevant diagnostic specifier in the DSM-5, as tic may predict a more favourable response to dopamine antagonist agents (Bloch *et al.*, 2006). Finally, the clinician must obtain information regarding avoidance behaviours, which commonly occurs

as a means to handle the distress evoked 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. Impairment can be measured indirectly with OCD severity scales or with specific measures [e.g., the WHO Disability Assessment Schedule 2.0 (Üstün *et al.*, 2010) or the Cognitive Assessment Instrument of Obsessions and Compulsions (Dittrich *et al.*, 2011)].

Comorbidity is almost always present with OCD and is often 'phase-specific' (Pallanti and Grassi, 2014). Assessment of specific comorbidities, like tic disorders, anxiety and depressive disorders, disruptive disorders, eating disorders, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and schizophrenia (Zohar, 1997), is essential in guiding the formulation of an effective treatment strategy. Comorbidity has also been a focus of emerging genetic studies of OCD. For example, a recent study in 4645 OCD patients found different genotypes to be associated with different OCD comorbidities. Thus, OCD comorbid with bipolar disorders was associated with *COMT*, *OPRM1* and *GRIK1* genotypes; OCD and depressive disorders were associated with *OPRM1* and *CYP3A4/5* genotypes; OCD comorbid with ADD/ ADHD was associated with *5HT2C* genotypes; and OCD

comorbid with anxiety was associated with *CYP3A4/5* genotypes (Nezgovorova *et al.*, 2018). However, these findings 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 statistical associations. Attempts to replicate the findings have tended to produce disappointing results. Therefore, more unbiased forms of the association study, such as genome-wide association studies (GWAS), which 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). A recent meta-analysis of GWAS of eight psychiatric disorders identified a common genetic factor linking OCD, anorexia nervosa and Tourette's syndrome (Lee *et al.*, 2019b).

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 individuals and was associated with a higher lifetime frequency of posttraumatic stress 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 were 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 emphasize 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 section Future directions for research).

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 BDD (where there are specific concerns with one's appearance), hair-pulling disorder (the only compulsion); tic disorders; eating disorders (concerns focussed on weight and shape and food); psychotic disorders (especially in poor-insight OCD and so-called schizo-obsessive disorder) 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, because these 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 Y-BOCS (CY-BOCS), which has good reliability (López-Pina et al., 2015a,b).

Awareness of other conditions associated with the onset and course of OCD symptoms can also be of help in treatment planning, because 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 premenstruum, 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 understood, especially the role of oestrogen and oxytocin (Guglielmi *et al.*, 2014).

Information on the family history of OCD, tics and other psychiatric disorders and the understanding of OCD among family members and family accommodation are 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 (i.e., reduction of 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 should be included when assessing people with OCD (Dell'Osso *et al.*, 2018). A recent meta-analysis (Angelakis *et al.*, 2015) found that OCD patients showed relatively increased risk of 'suicidality', when compared with healthy controls. In terms of absolute risk, estimates vary. 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 ICOCS network, 14.6% of the sample reported at least one suicide attempt during their lifetime (Dell'Osso *et al.*, 2018). In the study by Torres *et al.* (2011), comorbid depressive disorder and posttraumatic stress disorder were associated with a range 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 of Dell'Osso *et al.* (2018), comorbid tic disorders as well as medical disorders and a previous history of hospitalization were also associated with increased suicidality.

Neuropsychological assessment of patients with OCD suggests that there are deficits across a broad range of domains (Fineberg *et al.*, 2018a). For example, a recent meta-analysis found that patients with symptoms related to symmetry and orderliness were more likely to have poor 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). Other meta-analyses have found cognitive flexibility and response inhibition to be impaired in OCD in general (all literature pooled), with medium–large effect sizes (Lipszyc and Schachar, 2010; Chamberlain *et al.*, 2019). It must be considered that comorbid neurodevelopmental disorders, such as ASD (Postorino *et al.*, 2017), or ADHD are expected to influence performance on distinct tests, especially but not exclusively in youth.

Behavioural analysis of OCD involves obtaining a history to ascertain the specific situations that provoke obsessions, anxious 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 a 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, 1985, 1999), or an overinflated idea of danger (Jones and Menzies, 1998) (see section Novel forms of psychotherapy below).

Early intervention in obsessive-compulsive disorder

OCD frequently has an onset early in life (Fineberg *et al.*, 2019). Childhood or 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 all too often 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 (Dell'Osso *et al.*, 2010; Albert *et al.*, 2019). The need for service investment in early intervention for OCD is further highlighted by studies indicating that OCD is among the top 10 most disabling of all disorders, accounting for 2.2% of all years lost to disability (Ayuso-Mateos, 2006), with economic costs to society including those associated with lost productivity, which 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) being 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 and 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 may 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, obsessive-compulsive personality disorder and impulse control disorders may be indicators of 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).

Cognitive behavioural therapy, selective serotonin reuptake inhibitor or their combination as a first-line treatment for adults with obsessive-compulsive disorder

Pharmacological therapies (SSRIs and the tricyclic clomipramine) (Zohar *et al.*, 1996; Fineberg *et al.*, 2012) and psychological therapies (ERP, CBT) (Abramowitz, 2006) are often efficacious in treating OCD in adults. As SSRIs

and CBT have been thought to have broadly similar efficacy in acute treatment, current guidelines recommend taking account of patients' clinical features, needs and preference as well as service availability when choosing a first-line treatment (Baldwin *et al.*, 2014). Monotherapy with CBT involving ERP is particularly 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, 2005a; Koran *et al.*, 2007; Katzman *et al.*, 2014; Janardhan Reddy *et al.*, 2017). In contrast, SSRIs are particularly 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, 2005b; Skapinakis *et al.*, 2016b; Hirschtritt *et al.*, 2017; Janardhan Reddy *et al.*, 2017). In essence, most guidelines recognize 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; Soomro *et al.*, 2008; Skapinakis *et al.*, 2016b) and CBT involving ERP to be more effective than placebo (frequently waiting list in CBT trials) in the treatment of OCD (Gava *et al.*, 2007; Rosa-Alcázar *et al.*, 2008). Although an earlier meta-analysis suggested superiority of clomipramine over SSRIs (Ackerman and Greenland, 2002), a recent network meta-analysis 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), although, of course, they may differ in side effect profiles.

Most studies of CBT involving ERP included symptomatic patients stabilized on antidepressants (Skapinakis *et al.*, 2016b). Although the observed effect size of CBT was 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 whether the efficacy data attributed to CBT with ERP can be generalized to patients who are not taking medication for OCD. The efficacy of CBT as monotherapy 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; Liu *et al.*, 2005; Franklin *et al.*, 2011; Romanelli *et al.*, 2014; Meng *et al.*, 2019), exposure monotherapy (Cottraux *et al.*, 1990, Fineberg *et al.*, 2018a) or multimodal CBT (Hohagen *et al.*, 1998). However, it is uncertain whether combining ab-initio CBT and an 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, as described above, most psychotherapy trials are considered variants of combination trials because most patients in these studies were stabilized on SSRI or clomipramine (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 strategy in patients who have clinically significant symptoms despite treatment with medications and not necessarily in severe OCD (Simpson et al., 2008, 2013). A recent randomized feasibility study that included patients treated in primary care found that although 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.*, 2018b). If replicated, this finding would carry major implications for health services planning, especially where resources are limited, such as lower and middle income countries.

The critical importance of adequate treatment of obsessive-compulsive disorder in children and young people

For children and young people, CBT should always be the first-line approach (Sánchez-Meca *et al.*, 2014; Skapinakis *et al.*, 2016a), with 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 parental involvement targeting family accommodation and frequent family meetings while delivering a full course of ERP. According to the study of Sánchez-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 ($d+ = 0.746$). Family-based CBT (Piacentini *et al.*, 2011; Freeman *et al.*, 2014) 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, however, indicated for children and young people when symptoms are more severe, CBT has failed, skilled CBT is unavailable, and there is a comorbid disorder (e.g., depression) that may respond to medication, or when, in the judgement of the parent or clinician, earlier introduction of medicines is clinically indicated. SSRIs have been shown in randomized controlled trials to be well tolerated and effective in youth (Geller *et al.*, 2004; Skarphedinsson *et al.*, 2015). Sertraline and fluvoxamine have been approved for children from 6 to 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 6–12 months.

In the case of nonresponse or inadequate response, another SSRI should be tried (Geller et al., 2004, 2012; 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 cardiac 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, or in the presence of tic disorder, augmentation with antipsychotics, for example, aripiprazole* or risperidone* in low dosage may be used. Minimal duration on antipsychotics (these medications are not approved or indicated for paediatric use) is encouraged and close monitoring is required.

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 in only about one-fifth of adult cases, while for children, the mean persistence rates for full or subthreshold OCD have been estimated at 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 functional impairment and impairment 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 SSRIs and clomipramine 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. In the case of adults, the majority of relapse prevention studies have shown an overall superiority of SSRI compared with placebo in preventing relapse (Fineberg *et al.*, 2007) and that discontinuation of maintenance treatment, even after a period of prolonged well-being under SSRI, is associated with a heightened relapse risk. 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 the younger patient population (Fineberg *et al.*, 2019). There has been one randomized 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 emphasized 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 reinstating 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, may reduce the risk of withdrawal symptoms (Horowitz and Taylor, 2019).

Treatment-resistant obsessive-compulsive disorder – novel pharmacotherapies tested in adults

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* or raising the dose of SRI to the highest tolerated level* (Fineberg and Craig, 2007; Bandelow *et al.*, 2008; Fineberg *et al.*, 2012; Stein *et al.*, 2012).

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

Contrary to the depression literature, a meta-analysis of SSRIs in OCD found that high doses (high end of recommended dosage, not higher than recommended doses) 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 SSRI monotherapy (Bloch et al., 2008). However, tolerability is a significant issue as compared with lower doses so that this strategy requires caution in primary care settings (Stein et al., 2012). The Food and Drug Administration in the USA raised a safety warning in 2011 against citalopram doses higher than 40 mg/day due to a modest but probable risk of arrhythmias (US Food and Drug Administration, 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 treatment response persists, less well supported treatment strategies (lacking multiple randomized, controlled trials or meta-analyses) may be considered (Koran et al., 2007; Koran and Simpson, 2013), including use of glutamate modulators*, d-amphetamine* or oral morphine sulfate*.

Glutamate modulators such as memantine*, riluzole*, topiramate*, lamotrigine*, N-acetylcysteine* and ketamine* have varying levels of support (Koran et al., 2007; Pittenger et al., 2011; Koran and Simpson, 2013; Pittenger, 2015). Memantine augmentation showed benefit in case studies and open-label trials (Poyurovsky et al., 2005; Pasquini and Biondi, 2006; Aboujaoude et al., 2009; Feusner et al., 2009; Stewart et al., 2010; Bakhla et al., 2013). In addition, two RCTs 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., 2003, 2005). Subsequent small controlled studies have been mixed (Pittenger et al., 2008; Emamzadehfard et al., 2016). 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 RCTs have also produced mixed results (Mowla et al., 2010; Berlin et al., 2011; Afshar et al., 2014). Lamotrigine augmentation showed mixed results in case reports (Kumar and Khanna, 2000; Uzun, 2010; Arrojo-Romero et al., 2013; Hussain et al., 2015) and benefits in two small RCTs (Bruno et al., 2012; Khalkhali et al., 2016). Limited data suggest that N-acetylcysteine is of benefit in some cases of refractory OCD (Lafleur et al., 2006), with mixed data in four RCTs (Afshar et al., 2012; Sarris et al., 2015; Paydary et al., 2016; Costa et al., 2017). N-acetylcysteine is generally well tolerated. 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., 2011, 2016) 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 administered at sites with expertise in this approach, with appropriate precautions including monitoring for side effects and screening individuals who have a current or past substance abuse problem (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 past 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 some of the placebo-controlled trials have not found positive results. Some promising results have been found with the 5HT3 antagonist ondansetron* (Serata *et al.*, 2015) and a clinical trial is currently underway (ClinicalTrials.gov, 2017) though a double-blind place-bo-controlled trial of low daily dosages of odansetron* (0.5 and 0.75 mg) in a relatively large sample was nega-tive (ClinicalTrials.gov, 2015).

Treatment-resistant obsessive-compulsive disorder – noninvasive neurostimulation

Noninvasive neuromodulatory interventions targeting the corticostriatothalamocortical (CSTC) circuits hold promise as augmenting intervention for treatment-re-sistant OCD (Lusicic *et al.*, 2018). Repetitive transcra-nial magnetic stimulation (rTMS)* is the best studied noninvasive modulatory intervention in OCD. rTMS delivered at low-frequency rTMS (≤1 Hz) (LF-rTMS) is thought to inhibit the activity of underlying cortical regions, while high-frequency rTMS, provided at ≥5 Hz, is thought to enhance cortical activity (Lefaucheur *et al.*, 2014). Conventional rTMS, provided through the fig-ure-8 coil, is relatively focal, modulating superficial cor-tical regions over a depth of around 2 cm (Lefaucheur *et al.*, 2014). LF-rTMS* protocols targeting the sup-plementary motor area (SMA) have been found to be helpful for OCD in multiple RCTs and meta-analyses (Mantovani *et al.*, 2010; Gomes *et al.*, 2012; Hawken *et al.*, 2016; Zhou *et al.*, 2017; Rehn *et al.*, 2018). This effect has been found to last up to 3 months (Gomes *et al.*, 2012). A recent trial demonstrated superior efficacy of this proto-col over antipsychotic augmentation in treatment-resist-ant OCD subjects (Pallanti *et al.*, 2016). However, given recent inconsistent reports on inhibitory rTMS proto-cols targeting the SMA (Arumugham *et al.*, 2018; Harika-Germaneau *et al.*, 2019; Pelissolo *et al.*, 2016), there is a need for large multicentre trials to confirm its efficacy at this location.

LF-rTMS targeting the orbitofrontal cortex (OFC)* has also shown promise in small RCTs (Ruffini *et al.*, 2009; Nauczyciel *et al.*, 2014). There is a need for larger trials targeting the OFC to confirm its efficacy and tolerability. RCTs 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 high-frequency deep rTMS, using an H7 coil, over the dorsomedial prefrontal cortex/anterior cingulate cor-tex to be efficacious and well tolerated in a treatment resistant OCD population (Carmi *et al.*, 2019). This FDA approval and CE (Conformité Européene) certification

device for the treatment of resistant OCD. However, considering the cost of this device, there is a need for replication studies confirming the efficacy of the above protocol, which included personalized symptom provo-cation as an interventional component. Less-expensive deep coils, which have shown promise in targeting the dorsomedial prefrontal cortex in open-label trials on OCD (Modirrousta *et al.*, 2015; Dunlop *et al.*, 2016), are yet to be evaluated under controlled conditions.

Transcranial direct current stimulation (tDCS)* involves administration of low-amplitude (1–2 mA) electric cur-rent 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 admin-istered over bilateral pre-SMA and cathodal tDCS over right supraorbital regions (Gowda *et al.*, 2019). However, another randomized crossover trial (*n* = 12) found clin-ical 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 sus-tained at follow-up (Bation *et al.*, 2019). Other promising results in treatment-resistant OCD for protocols target-ing 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 depres-sion or psychosis*.

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

Treatment-resistant obsessive-compulsive disorder – 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 (Fineberg and Gale, 2005; Denys, 2006; Gupta et al., 2019). 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. DBS is considered an experimental treatment, but has an FDA 'humanitarian device exemption' for severe refractory OCD (US Food and Drug Administration, 2009).

Stereotactic neurosurgical procedures for intractable OCD have been available for >50 years (Miguel et al., 2019). The procedures include dorsal anterior cingulotomy and anterior capsulotomy and are reserved for the most severe, treatment nonresponsive 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. The rates of serious or permanent adverse events were 5.2% in the cingulotomy studies and 21.4% in the capsulotomy studies. 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, that is, 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 multicentre study of 30 patients given VC/VS DBS (Menchón et al., 2019) reported a mean reduction of baseline Y-BOCS of 42%. Sixty percent of patients were 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 versus 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 these sites, found differential improvements in mood (VC/VS) and cognitive flexibility (amSTN), 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 intracranial 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 versus 3%). In other studies (Mallet et al., 2008; Menchón et al., 2019), hypomania after electrode implantation is commonly (6%) reported.

In summary, studies of both DBS and ablative neurosurgery have shown these techniques are clinically effective for this highly refractory and 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 towards a personalized approach. Agreement over standardized patient selection and treatment protocols that would allow clinical outcomes data to be collected and compared across treatment centres, represents an achievable milestone towards this goal (Menchón et al., 2019). Meanwhile, technological

innovations, for example, MRI-guided focussed 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 gambling, gaming, sexual behaviour, shopping, video-streaming or social media use. While advances have been made in defining diagnostic criteria and developing rating scales for some forms of PUI (e.g., Gaming Disorder) (Király *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 preventive and therapeutic interventions (Fineberg *et al.*, 2018c).

Significant cross-sectional associations between PUI and OCD symptoms have been found (Carli *et al.*, 2013). For example, in a two-site international online survey, ADHD and social anxiety disorder were associated with high PUI scores in young participants, whereas OCD and generalized anxiety disorder were associated with high PUI scores in older participants (Ioannidis *et al.*, 2018).

Novel digital interventions in obsessive-compulsive disorder
Digital technology offers new opportunities for monitoring and interventions. The extensive use of smartphones and the vast amounts of information they contain has positioned them as a proxy for behavioural and social interactions (WHO, 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 problems 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 research avenue in this direction is to use (real time) big data analysis, alongside machine learning algorithms,

to establish identifiable OCRD-specific illness patterns and use those real-time results to create an immediate feedback loop with the patient, which could then be used therapeutically by providing direct feedback on their behaviour and progress.

Other forms of active online intervention have become increasingly available for OCRD (Whiteside *et al.*, 2013) and may potentially enhance and facilitate treatment adherence (Andersson *et al.*, 2014; Marzano *et al.*, 2015). For example, WhatsApp group interventions, in which the patient reports to their clinician, in real time, their difficulties, daily achievement and progress, enable continual communication, real-time reporting, 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 with patient's consent, the clinician has the opportunity to monitor patients in their natural environment. As the digital platform bridges the elapsed time between therapeutic sessions, it overcomes geographical distances and enables therapeutic practice in the patient's natural environment (WHO, 2016), where symptoms are manifested daily. In addition to enriching the clinical picture by direct observation of symptoms, it confers the general assertive outreach benefits of telemedicine, which can be critical for otherwise difficult to treat socially isolated patients who cannot access help otherwise.

In practice, this approach breaks down the traditional terminology of 'outpatient', 'in-patient' and 'day hospitalization', by allowing real time, objective and continuous monitoring (WHO, 2016). The combination of digital monitoring and online communication produces a form of 'virtual hospitalization', enabling comprehensive and intensive treatment by offering continued monitoring and delivery of therapy in the patient's natural environment, where the OCD usually occurs, and not within the artificial setting of the clinic. While such approaches are still under development, digital tools seem to bear great potential and may change the landscape of treatment in OCRDs, 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 behavioural responses (Raison and Miller, 2013). There is growing evidence of dysfunctional immunological function in the pathogenesis of a significant subset of OCD patients. Elevated levels of basal ganglia antibodies have been detected in adult OCD patients' plasma compared with psychiatric control groups (Nicholson *et al.*, 2012). In

addition, significantly increased levels of 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 and correlating with hyperactivity in the ventral cognitive circuit (Bhattacharyya *et al.*, 2009). Translocator protein distribution volume, a marker of the microglial component of neuroinflammation, was found to be significantly elevated in the CSTC circuit of OCD subjects compared with healthy controls, demonstrating inflammation within the neurocircuitry extending beyond the basal ganglia, and affecting the adult population rather than solely childhood OCD (Attwells *et al.*, 2017).

A common genetic link may explain an excess of some autoimmune comorbidities. For example, in the acute paediatric 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 autoimmune disease. Multigenerational studies also show that OCD patients' relatives are more likely to have an autoimmune disease such as Sjögren's syndrome, coeliac disease, Guillian Barrè, Crohn's disease, Hashimotos Thyroiditis, type I diabetes mellitus, ulcerative colitis, multiple sclerosis and psoriasis vulgaris (Mataix-Cols *et al.*, 2018). A subset of patients with PANDAS with motor symptoms demonstrated antineural 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 in OCD. While treatment with antimicrobials has delivered inconsistent results (Burchi and Pallanti, 2018), other immunological modulators, such as celecoxib* (Shalbafan *et al.*, 2015) and nonspecific nonsteroidal anti-inflammatory drugs (Spartz *et al.*, 2017), have produced some positive findings, the latter only in a subset of young people. Thus, evidence of the usefulness of this approach in OCD remains insufficient. Nevertheless, researchers and clinicians should consider genetic and immunological profile differences in the search for 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 therapy (Drummond and Edwards, 2018).

Rational emotive therapy, on the other hand, has been shown to have some possible beneficial effects in OCD (Emmelkamp *et al.*, 1988). Australian researchers have developed danger ideation reduction therapy (DIRT), using rational emotive therapy but with instructions not to undergo exposure for patients with contamination fears; good outcomes in case reports and some small controlled trials have been found (Jones and Menzies, 1998; Krochmalik *et al.*, 2001; 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 and attentional focussing 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 (Pérez Álvarez, 2012). 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. However, the strength of efficacy for both treatments appeared to be less than that generally found with ERP (Rupp *et al.*, 2019). Despite promising results for metacognitive therapy in patients with OCD in case series, a full controlled trial has yet to be performed (Melchior *et al.*, 2019).

Many OCD patients describe their compulsions as habitual, that is, 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 alter 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 with success in OCRDs such as trichotillomania and skin picking behaviours. However, there remains a scarcity of evidence from controlled trials to support the efficacy of HRT in OCRDs in general and OCD in particular (Lee *et al.*, 2019a). Emerging neurosciences evidence identifying faulty habit learning in OCD (Fineberg *et al.*, 2018a) suggests further study of HRT in OCD would be worthwhile.

Pharmacogenetics

Pharmacogenetics or pharmacogenomics define genetic variants that influence either drug metabolism, delivery, affinity to receptors or transporters may contribute to the prediction of drug efficacy or toxicity, promoting precision medicine (Hess *et al.*, 2015). Because approximately one-quarter of OCD patients do not respond to treatment with either SSRIs or CBT alone, or their combination (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 (Di Bella *et al.*, 2002; Denys *et al.*, 2007; Van Nieuwerburgh *et al.*, 2009; Miguita *et al.*, 2011; Grünblatt *et al.*, 2014; Zai *et al.*, 2014; Umehara *et al.*, 2015; Mas *et al.*, 2016; Qin *et al.*, 2016; Umehara *et al.*, 2016; Taj *et al.*, 2018; Lisoway *et al.*, 2018; Sina *et al.*, 2018; Abdolhosseinzadeh et al., 2019a,b; Alizadeh *et al.*, 2019). The candidate genes investigated belong to: (1) pharmacokinetic regulating genes, such as the CYP450 liver enzymes such as CYP2D6 and CYP2C19; (2) serotonergic systems, such as SLC6A4 and its promoter, HTTLPR, HTR2A, HTR2C, HTR1B and TPH2; (3) glutamatergic systems, such as SLC1A1, DLGAP2, DLGAP2, GRIN2B, GRIK2, SLIT, SLITRK5; (4) dopaminergic systems, such as COMT, MAOA, DRD2 and DRD4 and (5) other systems, such as BDNF, NTRK3, MOG, OLIG2 and DISP1.

Currently, no consensus with sufficiently robust results exists in the 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 cutoffs and measures determining response. Although there is still a need systematically to assess the pharmacogenetic link between treatment response (to SSRIs, tricyclics, antipsychotics, clomipramine, etc.) and certain genes, some data are 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 those of the FDA, European Medicine Agency, Pharmaceutical and Medical Devices Agency, Japan and Health Canada (Sante Canada).

Conclusion

Until just 40 years ago, OCD was considered rare, of psychological origin and without effective treatment. Now, all have changed; the finding in the 1970s and 1980s that serotonergic medication (clomipramine, followed by SSRIs) was effective (Montgomery, 1980; 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 (ERP) 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.*, 2018a), OCD has been removed from the anxiety disorder grouping in the DSM-5 (American Psychiatric Association, 2013) and ICD-11 (WHO, 2018) and now stands at the head of a new family of OCRDs.

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., focussing on the urge to perform compulsions and the need for higher doses of serotonergic medication).

This position statement highlights the major 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 well-being.

As new neuroscience insights are revealed, new therapeutic interventions are being explored (e.g., glutamatergic agents, dopaminergic modulators, etc.). This position statement also covers invasive and noninvasive neuromodulation as experimental interventions, including deep TMS (achieving FDA indication for OCD in 2018) (US Food and Drug Administration, 2018).

Looking to the future, other exciting avenues for investigation include the use of digital tools to monitor (and eventually to diagnose OCRDs), better understanding of links between excessive Internet use and OCRDs, 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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Conflicts of interest

Industries. He has served as a consultant to the Arlington Youth Counseling Center. He has served on the editorial board of *Annals of Clinical Psychiatry*. He has received honoraria from the Massachusetts Psychiatry Academy and the American Academy of Child and Adolescent Psychiatry. He has held stock options/ownership in Assurex Health and Revolutionary Road. R.G.G.S. receives a productivity grant from the National Council for Scientific and Technological Development, Brazilian Federal Government (CNPq). L.D. declares that she holds small investments in pharmaceutical and biotechnology firms, including AstraZeneca, Bioventic, Hikma Pharmaceutical, International Biotech Trust, Reneuron, Syncona and Yourgene. U.A. has received lecture honoraria from Lundbeck, Angelini, Janssen, Neuraxpharma and Innova Pharma. There are no conflicts of interest for the remaining authors.

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