Review

A Clinical Staging Model for Obsessive–Compulsive Disorder: Is It Ready for Prime Time?

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ABSTRACT

Recent changes to the diagnostic classification of obsessive–compulsive disorder (OCD), including its removal from the anxiety/neurotic, stress-related and somatoform disorders chapters of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and International Classification of Diseases 11th Revision (ICD-11), are based on growing evidence of unique pathogenic signatures and linked diagnostic and treatment approaches. In this review, we build on these recent developments and propose a 'clinical staging model' of OCD that integrates the severity of symptoms and phase of illness for personalised case management. A clinical staging model is especially relevant for the early identification and management of subthreshold OCD - a substantial and largely neglected portion of the population who, despite having milder symptoms, experience harms that may impact personal relationships, work-related functioning and productivity. Research on the pathogenesis, classification and management of such cases is needed, including the development of new outcomes measures that prove sensitive to changes in future clinical trials. Early intervention strategies in OCD are likely to yield better long-term outcomes.

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1. Introduction

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Obsessive–compulsive disorder (OCD) is both common and disabling. Recent changes to its classification, including its removal from

the anxiety/neurotic, stress-related and somatoform disorder chapters of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and International Classification of Diseases 11th Revision (ICD-11), are based on growing evidence of unique pathogenic signatures, such as its broader neurocircuitry-based dysfunction involving the basal ganglia (as opposed to primarily the amygdala, as seems to be the case in anxiety disorders) and linked diagnostic and treatment approaches [1]. While there have been recent advances in the management of OCD, such as implanted electrodes providing deep brain stimulation (DBS) [2], neuroimaging guided psychiatric surgery [3], and the use of specific transcranial magnetic stimulation (rTMS) devices [4], these approaches are only relevant to the more severe (frequently treatment refractory) patients. For the greatest majority of OCD patients who are neither sufficiently severe nor treatment refractory, the best available treatments remain being exposure and response prevention (EX/RP) and high dose serotonin reuptake inhibitors (SRIs) [5], which are typically unavailable or inaccessible (e.g., rely on highly trained personnel), or associated with several short and long term side effects, respectively.

While the combined prevalence of the new group of obsessive–compulsive and related disorders (OCRDS), including OCD, body dysmorphic disorder, hoarding disorder, hair pulling disorder and excoriation disorder, is still unknown, there is a substantial and largely neglected portion of the population (28.2% in the study by Ruscio [6]) who, despite having OCD subthreshold symptoms and not meeting criteria for OCD, also experience substantial harms, including significant impairments to their quality of life. For these individuals, traditional treatments (including EX/RP, SRIs, DBS or ablative psychiatric surgery) seem largely inappropriate. Further, although most individuals with subthreshold OCD will never convert to full blow OCD [7], they will nevertheless suffer substantial harms. Indeed, over two thirds of individuals with OCD who seek treatment display a protracted course of subthreshold symptoms before reaching clinical levels of severity [8]. Thus, while the characterisation of an "at ('ultra-high') risk" phenotype for OCD along the lines of psychosis [9] seems presently elusive, its most critical clinical component may well be the presence of subthreshold OCD symptoms.

It seems likely that a combination of inherited and environmental risk factors (e.g. perinatal complications, reproductive cycle, and stressful life events) interact with other risk factors to precipitate OCD in individuals with subthreshold symptoms [10]. Although, to the best of our knowledge, there is no randomised controlled trial (RCT) investigating whether the eradication of modifiable risk factors (e.g. parental rearing practices) impact on conversion rates of individuals thought to be at risk for full-blown OCD, treatment and follow-up studies of patients with diagnosed OCD have shown that duration of untreated illness is associated with worse treatment response [11], as well as a more delayed [12] and less frequent remission [13]. Thus, the available evidence suggests that, compared to primary prevention, early intervention is of greater immediate importance to practicing clinicians.

For these reasons exposed above, research on the pathogenesis, classification and management of subthreshold and recently developed OCD is needed, including the adoption of alternative outcomes measures (e.g. quality of life indices) or the elaboration of new tools that prove sensitive to change in future clinical trials. The recognition of subthreshold and early stages of OCD is particularly relevant to the development of staging models, which may help establishing the extension, progression, and chronicity of OCD and, as a consequence, where an individual lies along the continuum on the course of the illness. Based on the existing approach to psychosis and severe mood disorders [14], we propose a new staging model for OCD that considers a number of clinical, potential (trait and state) biomarkers, and outcome characteristics thought to reflect different on-going pathophysiological processes that may prove relevant for personalised case management.

Search Strategy and Selection Criteria

References for this review were identified through searches of PubMed for articles by use of the terms "obsessive-compulsive", "severity", "duration", and "progression". The search was performed on September 14, 2018, with no start date restraint adopted. However, given the scope of the topic and the limited amount of space, special emphasis was given to meta-analysis and systematic reviews, whenever they were available. There were also no language restrictions.

2. Clinical Staging

The first step of our staging process is a clinical assessment for the presence of typical OCD symptoms and more rudimentary childhood compulsive-like behaviours resembling aspects of OCD, such as being iterative, inflexible and associated with anxiety and fearfulness (e.g. [15]). While the Adult [16] and Children's [17] Yale-Brown Obsessive–Compulsive Scale (Y-BOCS and CY-BOCS) Checklist may suffice for the identification of typical OCD symptoms in clinical samples, compulsive and habit behaviours exhibited by very young non-clinical children may be assessed with the Parent's Report Childhood Routines Inventory (CRI) [15]. These latter behaviours seem to be particularly common between age 2 and 4, and comprise "just right" phenomena (e.g. lining up objects in straight lines or symmetrical patterns) and repetitive behaviour/insistence on sameness factors (e.g. "acting out the same thing over and over in pretend play") [15].

Once OCD symptoms are identified, individuals are to be classified within stages I-III, based primarily on their YBOCS severity score [18]. Stage I would be classified as "Ultra-High Risk" (UHR) on the basis of subthreshold OCD leading to a score in the range of 1–13 on the Y-BOCS plus treatment seeking and one of the following: (i) the presence of a positive family history of OCD or tics; and/or (ii) the presence of at least one potential environmental OCD risk factor (e.g. birth complications, increased parental age, pregnancy and the postpartum period, infection, or recent stressful life events) [10]. In terms of symptom content, studies in children with the so-called "normative compulsivity" [15] and in OCD adults who were retrospectively assessed for course of illness [19] suggest the earliest OCD symptom to involve symmetry and ordering themes. However, stage I is also associated with other typical non-symmetry OCD dimensions, as well as with other frequent, but yet non-obligatory OCRDs, tic, anxiety, depressive, substance use, and psychotic symptoms (e.g. [20]).

Although epidemiological studies suggest that only few adults with subthreshold OCD ($\approx 3\%$) will develop OCD on the long term [7], one follow-up study found that children reporting obsessions/compulsions at age 11 were significantly more likely to meet diagnostic criteria for OCD 20 years later (OR = 5.90) [21]. Another study found that subthreshold OCD plus a family history for OCD or OCD symptoms were risk factors for later OCD in adolescents [22]. Further, the rates of conversion of subthreshold OCD to full blown OCD might be higher in treatment seeking samples (similarly to psychosis [23]). However, it might be difficult to establish when conversion from subthreshold symptoms to frank case-level symptoms occurs. This difficulty in temporal sensitivity is because OCD symptoms typically begin early and insidiously in childhood then follows a chronic, waxing and waning course. Nevertheless, a number of studies showed that, as severity of OCD increases, so does duration of illness [24,25] and the ensuing clinical complexity, including the number of associated physical [26] and psychiatric comorbidities [24] and the rates of depressive disorders (major depressive disorder or dysthymia) and social phobia [24,27]. Both severity and duration of illness were found to predict the insight an individual with OCD has into symptoms [28]. Similarly, a meta-analysis found increased

severity of OCD leads to increased "family accommodation" (or "participation" of family members in OCD individual's rituals) [29]. These studies attest the importance of illness progression, and of an early intervention in OCD.

2.1. Why Not Simply Use Endophenotypes to Characterise UHR OCD?

Endophenotypes (EDs) have been defined as measurable components unseen by the unaided eye along the pathway between disease and distal genotype [30]. They are generally thought to be highly heritable, state independent traits that co-segregate with illnesses, but also to occur in non-affected family members [30]. Although such candidate EDs have been suggested to be useful to delineate the first stage of a number of neuropsychiatric disorders, including individuals who are at risk for developing OCD [31], there are a number of difficulties with the use of EDs in staging systems. Firstly, individuals who show sporadic forms of OCD, which constitute the majority (78 to 95%) of OCD individuals [32], are systematically excluded from "at risk samples" in ED studies. Yet, many subjects who lack a family history for OCD and tics may be at an increased risk for OCD for being exposed to environmental factors [30], such as acute bacterial (e.g. group A beta-haemolytic streptococcus) and viral infections, traumatic brain injury, substances of abuse, and even genetic mutations. Unfortunately, the role of environmental factors in EDs is often neglected.

Secondly, studies on EDs comprise complex and specific laboratory paradigms that are typically difficult to employ in clinical practice, often involving costly imaging techniques and relevant expertise, both of which are often not available to clinicians. Thirdly, with a few exceptions, there are few studies from independent groups replicating specific EDs for OCD. Lastly, and in the context of clinical staging, it is doubtful whether an ED would be more practical than simply having a positive family history of OCD, which could be sufficient to characterise a subgroup of individuals who are at risk for OCD. Thus, a more clinically useful alternative to EDs for staging OCD would be the assessment of traits that are present across the majority of OCD individuals, irrespective of whether or not there is a positive family history of OCD. Such traits can be more easily integrated and adopted into clinical practice, and have been extensively investigated by different groups.

3. Potential Biomarkers

3.1. "Trait" Biomarkers: Genetics and IQ to Identify Individuals at Risk for OCD?

3.1.1. Genetics

Family studies found OCD to be significantly more common among first-degree relatives of OCD adults (from 2.6 to 11.7%) and children (from 5.0 to 22.7%) as compared to first-degree relatives of appropriate controls [1.3 to 2.7% and 0.0 to 0.9%, respectively (for a review, see [32])]. One study suggested three OCD phenotypes to be particularly familial, i.e. an early-onset type of OCD that is comorbid with tics (i.e. Tourette syndrome and/or chronic tics), an early-onset type of OCD without tics, and a later-onset form of OCD without tics [33], While family studies do not prove that genetic factors are necessary for the occurrence of OCD, twin studies provide unequivocal evidence for the role of genetics in OCD. A recent meta-analysis found that additive genetic factors (the influence of many genes) and non-shared environment effects (e.g. a stressful life event experience by just one twin) explain most of the variance (37–41% and 50–52%, respectively) in obsessive–compulsive symptoms, while shared environment (e.g. upbringing styles, affecting both twins) and non-additive genetic effects (epistatic or dominance effects) made little or no contribution (5–6% and 9–10%, respectively) [34].

It is now clear that the occurrence of certain genetic variants associated with the major neurotransmitter systems increase the risk for OCD. Candidate genes involved in brain functional [e.g. serotonergic (5HTT

and SLC6A4), dopaminergic (COMT, DAT1, and DRD3), and glutamatergic (SLC1A1) neurotransmission] (see meta-analysis by Taylor et al. [35]) and structural features (e.g. OLIG2) had their role in pathogenesis of OCD suggested by different association studies. However, these findings have proven difficult to replicate due partly to the limitations inherent to studies' methods, particularly the low probability of any single gene contributing to a complex multifactorial disorder like OCD. Genome-wide studies have been performed in OCD, including linkage (e.g. [36]) and association studies (e.g. [37]); GWAS studies of OCD vs. Tourette syndrome [38], of quantitative obsessive–compulsive symptoms [39], and of rare copy number variants in OCD [40]; and whole exome sequencing (targeting coding regions) [41] and target sequencing studies (which also captures regulatory regions) [42].

While these findings are difficult to synthesise, a recent meta-analysis of the two existing GWAS [43] reported associations between OCD and variants located in or near the genes ASB13, RSPO4, DLGAP1, PTPRD, GRIK2, FAIM2 and CDH20. The results of these approaches converge with association studies at the level of the biological pathways (e.g. glutamate signalling) rather than at the level of specific genes. As expected, these genetic variants are not specific for OCD, and seem to increase the risk for different neuropsychiatric disorders. These findings suggest that some heritable genetic variants, when interacting with certain environmental factors, may lead to OCD in susceptible individuals. Thus, within our staging model, the occurrence of certain genes in asymptomatic individuals may characterise stage 0, which may actually be shared by different disorders. In contrast, de novo mutations in sporadic cases of OCD, including rare copy number variations (CNVs) [44] and single-nucleotide variants (SNVs) [45], both involving high genotypic risks, may be less dependent on environmental risk factors.

3.1.2. Intelligence

Although there are many definitions of intelligence, IQ broadly tends to be a trait-like feature that remains mostly stable across the lifespan [46]. Further, despite the long held view that OCD is associated with increased IQ, a recent meta-analysis of intelligence studies in OCD has found individuals to show reduced IQ levels (particularly performance IQ), albeit still within the normative range [47]. It is unclear whether lower IQ increases the risk for OCD or OCD decreases IQ. Although reduced IQ in OCD has been suggested to reflect slowed information processing [47], data from the prospective Dunedin follow-up study on IQ in OCD samples found IQ to increase the risk for OCD [48]. These observations suggest that intellectual abilities could be, for instance, a trait-like biomarker characterising an at-risk OCD phenotype (stage 0). However, the use of IQ tests for these purposes poses significant problems, including the lack of a sufficient number of well-designed prospective studies, the fact that most OCD patients have average intellectual abilities, and the fact that lower IQ may increase the risk for many other non-OCD disorders. Taken together, the available studies suggest that, with the exception of common genetic polymorphisms with small genotypic risk and very rare CNVs/SNVs with high genotypic risk, the use of trait biomarkers that may work as risk factors for OCD remains elusive.

3.2. "State" Biomarkers: Neuroinflammation, Cognition and Neuroimaging

State biomarkers reflect severity and/or progression of illness, which also relate to each other [24] and to greater disability [49]. For instance, a handful of studies have found inflammatory markers (e.g. pro-inflammatory cytokines) to be increased in OCD samples compared to controls, and to correlate positively with severity of OCD symptoms [50], negatively with age at onset [51], and positively with duration of illness [51]. Similarly, some (but not all) neuropsychological studies have reported significant correlations between cognitive deficits and severity of both OCD [52] and associated depressive [53] symptoms. Further, follow-up assessments described deficits affecting different cognitive domains, some of which were remediated by treatment

(therefore being dependent on severity of symptoms) and others that persisted despite treatment (thus being more trait-like) [54]. There is a dearth of studies attempting to link duration of illness with cognitive deficits in OCD, with only one study reporting a negative impact of progression of illness in severity of impairment [55]. As such, despite some showing some potential, there is mixed evidence to justify the use of these biomarkers to identify individuals at UHR for OCD.

Although the routine use of neuroimaging to help diagnose "primary" psychiatric illness is uncertain, brain scans may prove to be useful for staging of different neuropsychiatric disorders, including OCD. Accordingly, a few studies have reported correlations between the volumes of different brain structures to progression of illness, either in relation to severity or to duration of illness. For instance, one study described that enlargement of striatal regions in OCD patients was driven by longer duration of illness and higher age [56]. A mega-analysis reported the lack of ageing-related reductions in the volumes of parts of the striatum and inferior frontal lobe in OCD patients [57], which were interpreted as resulting from chronic compulsive behaviours "increasing" putamen and striatum volumes or compensatory activation-induced neuroplasticity preserving inferior frontal cortex and anterior insula [57]. The same study found (para) limbic parts of the medial and lateral temporal cortex (regions that are relatively preserved in healthy ageing) to show greater ageing-related volume loss in OCD [57].

The Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Consortium found adult early onset OCD patients to exhibit larger pallidum than controls and [58] paediatric OCD to show decreased thickness of the parietal cortex, which tended to normalise with illness progression [59]. Grey matter density and duration of OCD correlated negatively in left hemisphere structures (including the post-central gyrus, the supra-marginal gyrus the pre-central gyrus, the middle and superior temporal gyrus, the inferior frontal gyrus) and the right inferior parietal lobule, while the insular and post-central gyrus correlated positively with the severity of OCD [60]. A study on treatment refractory OCD found duration of illness to be negatively correlated with bilateral hippocampal and left amygdala volumes and severity of OCD with the left hippocampus [61]. A recent DTI study found duration of illness to correlate with greater white matter changes in the anterior cingulate bundle bilaterally [62]. Finally, from the neurochemical point-of-view, increased duration of OCD correlated with decreased glutamate concentration in the anterior cingulate cortex [63] and, together with severity of illness, increased 5HT transporter availability in the thalamus–hypothalamus [64].

It was beyond the scope of this section to provide a systematic description of the neuroimaging literature of OCD, but instead to focus on larger-scale studies (like the ENIGMA and other mega-analysis) or smaller investigations felt to be more relevant for our staging model of OCD. As such, the available evidence suggests that increased duration of illness is related to perturbation on structures related to the cortico-striato-thalamo-cortical circuits, and tends to increase striatal volumes and to decrease the volumes of other (e.g. *hippocampus*) structures. It is difficult to speculate on the significance of these findings in light of the recent developments on the RDoC systems [31], but it seems that the more OCD is left untreated, the more likely OCD behaviours and cognitions are to be "entrenched" in habit systems. While promising, a challenge of course is always how to apply these "group-based" differences in neural morphology to individual level classifications with an acceptable level of sensitivity and specificity.

4. Response to Conventional Treatment

Treatment studies have suggested that late interventions lead to poorer outcomes in OCD subjects [65]. These findings have been demonstrated in naturalistic trials [e.g. The Brown Longitudinal Obsessive Compulsive Study (BLOCS) (e.g. [66])] from Western and non-Western cultures. Although a treatment bias effect, in which OCD patients with greater severity and duration are more likely to receive

psychiatric treatment [67] cannot be excluded in most studies performed in treatment seeking samples, a follow-up study of participants drawn from the general population of Zurich, Switzerland, who participated in a series of seven interviews over a period of 30 years [12] confirmed the links between earlier interventions and better outcomes. Further, studies using specific strategies (such as clomipramine, fluoxetine, clomipramine or fluoxetine, citalopram, and fluoxetine) [68] or cognitive-behavioural therapy [11] are also consistent with an association between longer duration of OCD and poorer response. Similarly, in most studies (e.g. [69]), milder severity of OCD symptoms has been associated with better outcomes.

Concerns have been recently raised on the face value of studies on treatment for OCD published in the last two decades, as they have systematically and progressively excluded the "typical" patient, who is characterised by a milder set of symptoms and presents with an unacceptable number and/or types of comorbidities [70]. In fact, it is unclear how informative studies that focus on the more severe end of adult samples of OCD subjects can be for early intervention programs. Since paediatric OCD may be less persistent than adult OCD in the long term [71], one could expect more evident benefits of earlier treatments. Indeed, studies on predictors of outcome of younger subjects that are both closer to illness onset and less chronic may be particularly informative for early intervention programs. However, the links between early intervention and better outcomes are also present in these more benign samples. For instance, in the first prospective study to examine course of OCD in a clinically representative sample of youth and adults with primary DSM-IV OCD [72], subjects who were less impaired and reported a shorter gap between onset of the disorder and initial treatment had higher rates of remission.

Studies on duration of untreated illness (DUI) and the identification of risk factors for delayed treatment also seem particularly relevant for early intervention initiatives in OCD and related disorders. Most contemporary studies found DUI to range from 7 to 8 years, contingent on different variables [73]. For instance, the perception that OCD is caused by "stress" (including the threat of or an actual recent very unpleasant event, family or marital conflict or difficulty, grief or separation, or physical illness,) seem to shorten contact with mental health professions [73], whereas DUI for more than four years has been associated with lower rates of precipitating events and greater endorsement of the belief that OCD symptoms are not associated with an illness [74]. In contrast, aggressive-checking symptoms delay treatment-seeking [75], maybe because, among other things, subjects may fear being considered "crazy" or dangerous by family, friends or health providers. Another important finding from studies on DUI in OCD and other anxiety disorders is that affected individuals often make contact with mental health professionals for other issues before the self-reported onset of full-blown illness, creating an opportunity for early intervention [73]. Thus, early intervention programs may be particularly relevant for those individuals who believe their OCD is caused by non-stress related factors, that OCD is not a clinical condition and that exhibit aggressive-checking symptoms.

5. A Stepped Care Approach According to Staging

Clinical staging is largely based on stepped care models, whereby the clinician selects treatments for individuals in milder and/or earlier stages of an illness that are effective and yet scalable and less aggressive (i.e., less intensive and more tolerable) than treatments needed for more severe and/or end-state cases. Clinical staging is a desirable approach in the context of OCD, whose treatments can be poorly tolerable (e.g. SRIs), unavailable [e.g. exposure and response prevention (EX/RP)], or unacceptably invasive and/or expensive (e.g. neurostimulation). The perception that early intervention programs for subjects with other neuropsychiatric disorders (e.g. psychosis) have been successful have laid the roadmap for OCD researchers to recommend early diagnosis, stepped-care, and a personalised approach to create recovery-oriented

treatment programs and influence policy making for OCD [76]. Indeed, studies found a stepped care approach, whereby subjects with OCD receive bibliotherapy EX/RP (Step 1), followed by self-directed EX/RP with minimal therapist contact (Step 2) and intensive traditional therapist directed EX/RP (Step 3) only if needed, to be feasible, clinically relevant and cost-effective [77,78].

5.1. Stages 0 and I

Admittedly, our proposed clinical staging treatment algorithm (see Table 1) still finds mixed support in the literature. For instance, for healthy individuals without OCD symptoms, but a positive family history of the condition (and/or Tics; Stage 0), we recommend watchful observation by the parents and/or the subject themselves and psychoeducation. Although these strategies have not yet been comprehensively evaluated, there is some evidence that, even at the minimal doses, psychoeducation modifies the individual's conceptualisations of OCD, and therefore the outcomes [79]. In contrast, approaches for individuals with subthreshold OCD (Stage I) have included a 3-hour cognitive behavioural workshop, which in one clinical trial reduced number of OCD symptoms at 5-month follow-up, and the extent of thought action fusion (TAF) at 1 and 5-month follow-up [80]. In another trial, eight sessions of a mindfulness based meditation program showed decreases in Obsessive–Compulsive Inventory-Revised and TAF scores at the end of two months [81]. Based on research performed in clinical OCD samples (as reviewed by [82]) lifestyle interventions focusing on decreasing stress (e.g. kundalini yoga, acceptance and commitment therapy), eliminating sedentarism (physical exercise), improving diet, minimising alcohol ingestion, and ameliorating sleep need to be tested in this latter population in future trials.

5.2. Stages II and III

A detailed description of the established treatments for DSM-5 OCD (Stages II and III) is beyond the scope of this article. However, the utility of high dose SRI treatments for at least 12 weeks or a total of 20 h EX/RP sessions, both alone or in combination, has been widely demonstrated in the OCD literature [5]. No superiority of combined treatment over EX/RP has yet been demonstrated. EX/RP has been effectively delivered via bibliotherapy, Internet or just computer [83]. Although some clinicians have recommended the administration of antipsychotics to patients who failed to show at least 25–35% decrease in the scores of the YBOCS, one recent study showed resistant patients who were submitted to EX/RP to outperform subjects randomised to risperidone [84]. Indeed, although antipsychotics pose a number of health risks (including weight gain, diabetes, a cardiovascular problems), OCD patients may require these drugs for a few other reasons (e.g. severe tics) [5], EX/RP may not be available in some areas of the globe, and not all OCD patients are willing to face their fears and perform EX/RP. Yet, EX/RP proved helpful to patients who failed risperidone augmentation [85].

Since there is no absolute correlation between severity and chronicity or between severity and resistance to treatment, it seems appropriate to further subdivide OCD cases according to recurrence/persistence (stages IIA and IIB) and therapeutic response (stages IIIA and IIIB) levels. For instance, most clinicians have seen very severe OCD patients who have exhibited favourable, sometimes even complete response to first line treatments, either SRIs or EX/RP. Further, affected individuals who show some levels of resistance can be occasionally managed by modifying treatment approaches prescribed by stage II subjects, such as adding other drugs (e.g. clomipramine) to existing schemes or delivering intensive forms of EX/RP [86] in partial hospitalisation programs [87] that can also target at family accommodation [29] issues. The FDA has recently approved a specific deep TMS device for OCD based on a 6-week double blind multicentre RCT in patients resistant to SSRI or CBT showing both efficacy (54.7% in active TMS vs. 26.6% in sham TMS) and tolerability (10.6% drop out rate) [4].

The recommendation of DBS or psychiatric surgery (e.g., capsulotomy) to cases of OCD exclusively on the basis of severity is clearly inadequate. It is also unreasonable to submit OCD patients who are not severe enough to invasive and/or expensive approaches. Thus, only subjects who are both severe and refractory should be described as being stage III and treated with DBS or psychiatric surgery; Given the recent FDA approval [4], an attempt of rTMS before DBS or psychiatric surgery also seems reasonable; severe, but not refractory, OCD patients should be best categorised under a late stage II.

6. Potential Problems and Future Directions

One of the ultimate objectives of any clinical staging is avoiding progression of illness. As such, the identification of UHR OCD cases is a critical component of our proposal. There are however a number of problems with the concept of UHR OCD, including a phenotype that is presently more theoretical than practical and still difficult to delineate. For instance, some could argue that focusing on "traits" (such as behaviour inhibition in children [88]) or family history (e.g. maternal anxiousness [89]) rather than on "symptoms" (such as subthreshold OCD) to prevent progression to OCD would be an easier endeavour. Although the later phenotypes proved useful in the context of non-OCD anxiety disorders [88,89], subthreshold OCD provides a clinically useful continuity with full-blown OCD that wouldn't be possible with other "symptom-free" phenotypes.

Follow-up studies assessing the progression and proportion of cases throughout different stages of our system and their precipitating (risk) factors should also be performed. Likewise, randomised controlled trials testing the efficacy of specific interventions aimed at preventing transition to advanced stages of illness is also desirable, keeping in mind that the UHR OCD phenotype is likely show increased "placebo" response to any specific intervention, as is generally the case in individuals showing milder forms of psychopathology [90]. Thus, for the later "at risk" population, it seems appropriate to develop outcome measures that extend beyond the mere expression of OCD symptoms, including quality of life and well-being indexes, or even time to relapse.

In this report, we have also described, alongside the OCD staging criteria, a series of putative trait and state biomarkers that could provide biological validity to our model. While some would argue that the evidence supporting the use of biological measures in psychiatric practice is still in an embryonic stage, our approach to OCD is completely reliant on clinical definitions (YBOCS cut-offs). We expect biological data to feed this model over time, ideally resulting in more personalised treatments. Our staging system should also be flexibly used to allow the prompt identification of existing comorbidities, such as major depressive disorder and anxiety disorders, which may sometimes take over and become more clinically significant than OCD itself, thus requiring priority changes. For instance, many individuals with subthreshold OCD symptoms in the context of severe major depression [91–93] may sometimes require more specific and aggressive treatments (e.g. electroconvulsive therapy) [94]. We believe that our system prompts clinicians to be mindful of these possibilities by including associated symptoms to various degrees, particularly in stages II and III.

7. Conclusions

In this review, we have proposed a staging model for OCD that considers individuals at ultra-high risk for OCD, as well as individuals with DSM-5 OCD and OCD patients with refractory illness within a spectrum of severity that is likely to reflect a progressive underlying pathophysiological process affecting the habit-formation brain systems involving the basal ganglia and fronto-striato-thalamic circuits. Importantly, this staging model: (i) incorporates recent advances on the psychobiology of OCD into the clinic; (ii) emphasises the importance of early recognition of individuals with positive family histories, environmental risk factors and subthreshold OCD symptoms as samples at UHR; (iii)

Table 1
A proposed staging model for OCD.

OCD STAGING LEVELS		CLINICAL STAGING						POTENTIAL BIOMARKERS		TREATMENT APPROACH	
		Symptoms (YBOCS scores)	Risk factors	Other behaviours or symptoms	Course	Predominance OCD symptom content	Family accommo dation	Laboratory parameters	Pathophysiological process	Response to conventional Treatment	Proposed Treatment
Stage 0		NA (0)		NA	NA	NA	Absent		None	NA	Watchful observation,* psychoeducation
	Stage 0A		Family history of OCD or Tics					Genetic variants/ endophenotypes and other trait features			
	Stage 0B		Environmental risk factors*					Neuroinflammatory markers			
	Stage 0AB		Family history of OCD or Tics AND environmental risk factors*					Genetic variants/ endophenotypes and other trait features AND neuroinflammatory markers			
Stage I (UHR_OCD)		Subthreshold (1-13)	Family history of OCD or Tics AND/OR environmental risk factors*	Treatment seeking	Variable	Ordering and symmetry symptoms are remarkable	Absent	Genetic variants, neuroinflammation, cognition, imaging, key lifestyle indexes	None	NA	Psychoeducation ("cognitive behavioural workshops")**, meditation**, or exercise*
Stage II		Mild to moderate (14-34)	Variable	Mild to moderate anxiety or depression		Mixed but shameful thoughts /checking and/or contamination/washing symptoms are notable	Mild to moderate	Genetic variants and neuroinflammation, cognition, imaging, key lifestyle indices	CSTC hyperactivation w/out HPA hyperactivation	Potential	SSRIs*** and/or EX/RP***, TMS **
	Stage IIA				First episode OCD						
	Stage IIB				Multiple episodes or chronic OCD						
Stage III		Severe (35-40)	Variable	Moderate to severe anxiety or depression	Variable	Mixed but shameful thoughts /checking and/or contamination/washing symptoms are notable	Moderate to severe	Genetic variants and neuroinflammation, cognition, imaging, key lifestyle indices	CSTC hyperactivation w/ HPA hyperactivation		
	Stage IIIA									Potential	SSRIs*** and/or EX/RP***, TMS **
	Stage IIIB									Absent	Consider DBS*** or psychiatric surgery***

Footnote: NA = Not available; CSTC = Corticostriatal-thalamocortical systems; HPA = Hypothalamic–pituitary–adrenal axis; SSRI = Serotonin reuptake inhibitors; EX/RP = Exposure and response prevention; DBS = Deep brain stimulation; * = no evidence or preliminary evidence supporting efficacy, caution should be exercised here, as subjects with health anxiety issues may increase self-observation and show clinical deterioration; ** = moderate evidence supporting efficacy; *** = good quality evidence supporting efficacy; DBS or Psychiatric Surgery can, and sometimes should, be added to existing and on-going treatments for other less advanced stages. It is possible to consider DBS and psychiatric surgery in advanced stage II OCD. The colours green, yellow, orange and red attempt to illustrate the level of specialised attention required across different stages (low, moderate, high, and extreme, respectively).

integrates existing treatments for OCD (i.e. SRIs, EX/RP, DBS, rTMS, and psychiatric surgery) within a rational stepped care approach; and (iv) generates different testable hypothesis, including the potential of biomarkers for helping staging patients and whether watchful observation, psychoeducation, and lifestyle interventions may help subjects with less severe forms of OCD symptoms. Research on the pathogenesis, classification and management of such cases is badly needed, including the development of new outcomes measures that prove sensitive to changes in future clinical trials. Future studies should clarify is a similar clinical staging framework will prove beneficial for other OCRDs.

Authors' Contribution

The authors have made equal contributions to the conception of the work and the interpretation of the literature; drafted the work and revised it critically for important intellectual content; provided the final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Interests

The authors have no financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work, including employment, consultancies, stock ownership, honoraria, paid expert testimony, patents or patent applications, and travel grants, all within 3 years of beginning the work submitted.

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