# EDITORIAL

# Current Psychopharmacology of Obsessive-Compulsive Spectrum Disorders

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Obsessive-compulsive spectrum disorders is a new chapter to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1]. This group of disorders is mainly characterised by repetitive thoughts, anxiety or preoccupation, emotional distress, and compulsive behaviours. The specific types of obsessions, anxiety symptoms, pursuance/avoidance, and compulsive/impulsive behaviours vary according to each disorder. The DSM-5 distinguishes five main obsessive-compulsive spectrum disorder diagnoses: obsessive-compulsive disorder (OCD), body dysmorphic disorder (BDD), hoarding disorder, hair-pulling disorder (trichotillomania) (TTM), and excoriation or skin-picking disorder (ED). Although these disorders have some similarities regarding patient characteristics, symptom presentation, neurobiological correlates, and treatment response, they are clearly distinct from one another. Their pharmacological treatment is faced with various difficulties, as cases of poor or no response to a first therapeutic approach are not uncommon. In fact, this group of disorders shows a great deal of drug treatment-resistance, defined as insufficient response to drug treatment after sufficiently long periods of doses and drugs considered to be effective in the condition being treated. This of course entails the trial of drugs with different mechanisms of action that are believed to be involved in the pathophysiology of the specific disorder. This issue has been tackled here by Del Casale *et al*., who also provided a simple algorithm to follow that might prove to be useful for practitioners.

OCD-related intrusive thoughts (obsessions), ritualistic behaviour, and urges to perform actions (compulsions), as well as other affective and cognitive symptoms causing personal distress and reduced global functioning impact negatively and significantly on public health system costs [1]. This disorder affects more than 1% of the general population worldwide [2, 3], with lifetime prevalence of 2-3% [4]. However, the proper epidemiological figures of OCD have to be reset since the disorder has been detached from hoarding disorder, which was previously incorporated in it; hence, the figures obtained when the two disorders were fused, should now be precisely redefined. This is sideways tackled in this Special Issue by Piacentino *et al*. in this issue. So, maybe the prevalence of OCD will be found to be a little less or much less than currently believed, but it could be that hoarding displays similar epidemiological figures with OCD, so the two disorders will have to split in about the middle due to some measures, like prevalence. The onset of OCD is bimodal, with a first peak in late childhood or early adolescence, and a second one in early adulthood [5, 6]. On the contrary, hoarding appears to be chronic and more prevalent elderly people.

The course of OCD is chronic and unstable, and the fluctuations of symptoms can relate to traumatic or stressful life events [7, 8]. Among OCD patients coming to clinician's consideration, less than 40% receive a pharmacological treatment specific for their illness, and less than 10% obtain an evidence-based approach [9, 10]. Diagnosis can be difficult, since about 50% of OCD patients have at least a comorbid anxiety, major depressive, or alcohol use disorder [11].

An important issue is the distinction between the prodromal OCD and developmentally determined behaviours that could be physiological [12, 13]. Although the prevalence of OCD in children is about 0.5-2.0%, around 10-15% of the paediatric population can show subclinical obsessive-compulsive symptoms [14, 15], which may predict the onset of OCD or other mental disorders later in life [16]. The generality and the non-specificity of the prodromal symptoms could lead to diagnostic delays of early onset forms [17], with long duration of untreated illness and possible persistent developmental and cognitive impairment. Early-onset OCD is a neurodevelopmental disorder with specific psychopathological features and treatment needs. Burchi and Pallanti in this issue deal with both these aspects and provide clues as to its neurobiology. Early diagnosis and treatment can correlate with better outcomes, also in light of the studies reporting that paediatric OCD remission rates are considerably higher than adult form. The same applies for symptom remission, which lasts longer in early onset forms [17, 18].

Another important topic is the need for specific considerations when OCD is comorbid with Tourette Syndrome (TS); this involves both symptom assessment and drug treatment. This issue is developed here by Rothenberger and Roessner. Difficulty in distinguishing borderline forms of tics from tic-like compulsions could partly explain the inconsistency of prevalence rates of OCD and comorbid TS [19, 20]. Additional diagnostic issues in patients with OCD and TS regard other possible comorbid mental disorders (or their

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1570-159X/19 $58.00+.00 

respective symptom dimensions), including attention deficit and hyperactivity disorder (ADHD), TTM, ED, and suicidality. In fact, although OCD has been traditionally considered to be associated with low risk of suicide [21-23], recent systematic reviews and meta-analyses have questioned this opinion, suggesting that suicide risk in OCD patients could be higher than the general population [24]. Albert *et al*. (this issue) provide a thorough overview of suicide risk factors in OCD.

Another common belief that lasted until the early nineties was that OCD did not respond to placebo [25]. However, this rapidly changed in the following years, with increasing evidence for the growth of placebo effect in clinical trials of depression [26] and bipolar disorder [27]. Other psychiatric disorders have been little investigated, but a multivariate meta-analysis of OCD trials showed placebo response to increase with time [28]. Kotzalidis *et al*. in this issue confirmed the trend of the placebo effect to grow in OCD drug trials over a wider time interval using jointpoint analysis, which has not been used as of now in similar studies. Their results show that patient populations are evolving with time and assume more placebo-responsive characteristics. This may have important potential implications for future drug development, as societal trends are towards the dismantling of older drugs to make room for the new ones. This is a point open to philosophical reflection.

Currently, the most effective pharmacological treatment is believed to be a combination of a serotonin transporter inhibitor, be it a selective serotonin reuptake inhibitor or the tricyclic antidepressant clomipramine (but not other tricyclic antidepressant drugs), with cognitive behavioural therapy. Refractory OCD can improve with the intake of high dosages of serotonergic drugs or augmentation with an atypical antipsychotic, mainly risperidone and aripiprazole. The evidence on the usefulness of add-on treatments is currently inconsistent. The role of intervention strategies based on personalised medicine and pharmacogenomics are of promise, as in other fields of medicine, but needs corroboration. Furthermore, although OCD-related disorders have been customarily treated with the same drugs as OCD, other disorders within the spectrum may share the same (Hong *et al*., this issue) or require different treatment approaches (Piacentino *et al*.; Sani *et al*., this issue).

Neuroimaging studies revealed important neural structural and functional correlates of OCD, leading to the formulation of neurobiological and pathophysiological models of this disorder. Specific changes in cortical-subcortical circuits correlate with the manifestation of OCD symptomatology. Different studies showed "key brain regions" involved in the OCD pathophysiology, including the orbitofrontal cortex, thalamus, anterior cingulate cortex and caudate nucleus [29-31]. Atmaca in this special issue deals with how drug treatment affects neural structural and functional correlates of OCD.

Among other OCD-spectrum disorders, BDD is characterised by unrealistic beliefs that some aspect of one's own body is unpleasant, intolerable, or otherwise deformed. Many patients are unaware of the existence of effective treatments, and their self-stigma and feelings of guilt, blame or embarrassment lead them to hide or dissimulate their symptoms [32]. BDD symptoms may impair family and intimate relationships and negatively impact social [33], occupational, and intellectual functioning [34]. Treatment is frequently a challenge that is currently based on combinations of a selective serotonin reuptake inhibitor with cognitive behavioural therapy (Hong *et al*., this issue). Refractory BDD may benefit from non-invasive transcranial magnetic stimulation techniques. As for other OCD-spectrum disorders, TTM, also known as hair pulling disorder, is characterized by a long-term urge resulting in the pulling out of one's hair. ED, also known as skin-picking disorder or dermatillomania, which is repeated picking at one's own skin causing skin lesions and significant discomfort. The prevalence of TTM is about 0.5-2% [35], while that of ED ranges from 1.4% to 5.4% [36]. Onychophagia (nail biting) currently belongs to the obsessive-compulsive spectrum disorders along with lip biting and cheek chewing within the context of "body-focused repetitive behaviour disorder", for which there are no definite diagnostic criteria. Its prevalence is also uncertain, as nail-biting is very common in the general population but not always has clinical features allowing it to be diagnosed as onychophagia. Different interacting neurotransmitter systems have been involved in the neuropathophysiology of impulse control disorders, including the noradrenergic, serotonergic, dopaminergic, opioid peptide, and glutamatergic systems [37-39], indicating that drug trials should involve molecules able to act on these transmitter systems. This issue is dealt with in depth by Sani *et al.*

Another important topic regards the brain stimulation techniques added on to standard pharmacological treatment. Severe forms of refractory OCD could benefit from different types of brain stimulation, like the non-invasive repetitive transcranial magnetic stimulation, deep transcranial magnetic stimulation, and transcranial direct current stimulation, and the invasive deep brain stimulation [40-42], but evidence is still lacking for vagal nerve stimulation and electroconvulsive therapy (Rapinesi *et al*., this issue). Currently, there is increasing evidence of efficacy of some of these techniques, although inconsistency rules in this field. In fact, for each of these there is no consensus as to site of application, stimulation frequency and extent, treatment duration and need for maintenance sessions (nor for the timing and amount of this maintenance). The challenge now is to show how these techniques impact the pathophysiology and neurochemistry of OCD and how they can combine with drug treatment to obtain optimal benefit.

In conclusion, currently available obsessive-compulsive spectrum pharmacological treatments have fair efficacy in many patients, but there is also a significant proportion of patients who do not respond to treatment. To date, the rate of treatment-resistant or refractory patients is still significant, pointing to the existence of strong heterogeneity in each of these disorders. As often occurred in the past, pharmacological treatments that prove effective might act as probes for better understanding the pathophysiology of each patient and disentangle the different subtypes of the spectrum. In the

near future, the choice of therapeutic strategies will be supported by further development of personalised medicine, pharmacogenomics, and neuromodulation therapies.

## ACKNOWLEDGEMENTS

We wish to thank all contributors of this special issue for their dedication to our common task and commitment to provide the best possible work. We extend our thanks to the Editor of *Current Neuropharmacology* Prof. Tom Salt and to Ms. Rabia Moin for her editorial assistance.

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