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EXPERT OPINION

Why have early investigational therapies of obsessive–compulsive disorder failed to materialise?

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The mid-1980s brought about a revolution in the way in which clinicians approached the treatment of obsessive–compulsive disorder (OCD) pharmacologically. Indeed, clinicians adopted the use of selective serotonin (5-HT) re-uptake inhibitors, as treatment options, when it was demonstrated that OCD patients responded specifically to drugs enhancing 5-HT functioning in approximately 60% of all cases. Evidence to suggest a role for serotonergic compounds in OCD was further elucidated by increasing evidence in the following years. Since then, a number of different compounds that more or less directly modulate the 5-HT system have been proposed, although other therapeutic targets have also been considered. Unfortunately, despite our advancement in the understanding of this disorder, several of the treatment proposals never reached the clinic, staying at mere suggestion or not receiving sufficient development. The aim of this paper is to reflect and comment on the possible reasons that might have led to neglect or discarding these drugs that might have been effective in treating OCD.

Keywords: clomipramine, guidelines, obsessive–compulsive disorder, pharmacological treatment, selective serotonin re-uptake inhibitors

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1. Introduction

Obsessive–compulsive disorder (OCD) is a psychiatric condition characterised by the presence of obsessions and/or compulsions. Obsessions are defined as recurrent and persistent thoughts, impulses or images, which are experienced in an intrusive and inappropriate way. These thoughts cause marked anxiety and distress and persist despite all attempts to try to ignore, suppress or neutralise them. Compulsions are defined as repetitive behaviours or mental acts that a person feels driven to perform in response to an obsession or according to rigid rules, and which are generally aimed at preventing or reducing distress or a dreaded event. In the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), OCD has been recognised as a distinct nosological entity, separated from anxiety disorders. Furthermore, it has been specified that there might be different degrees of insight varying along a spectrum [1].

Without a doubt, the nosological autonomy of OCD is the consequence of renewed interest in this disorder, which was promoted by the great bulk of studies undertaken in the mid-1980s and which continued progressively in the following decades. Taken all together, the different findings contributed significantly to change both the scientific and common opinion of this condition that was, for too long, considered unresponsive or resistant to both psychological and pharmacological approaches. It also highlighted the fact that OCD is actually quite common all over the world and represents a major cause of disability to both patients and their families [2]. In spite of its prevalence, it became clear that OCD was not frequently

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diagnosed, and that patients would generally hide their symptoms for a long time before seeking help. It is clear that there is a need to improve the diagnosis and awareness of the illness among physicians, psychiatrists and common people, and several initiatives are being promoted to overcome this bias [3].

Most interestingly, OCD patients have been shown to respond to selective serotonin (5-HT) re-uptake inhibitors (SSRIs), as first observed with clomipramine reported in a paper in the 1960s [4], and which was further re-evaluated thereafter [5]. Furthermore, the pharmacological response of OCD patients drove attention towards the role of the 5-HT system in this disorder that represented and still represents a major focus of neurobiological research in this condition, although the possible involvement of other neurotransmitters and systems, such as dopamine, glutamate and oxytocin, has been highlighted and explored [6].

The available guidelines indicate that first-line treatments are mainly SSRIs at adequate dose (fluoxetine 20 – 80 mg/day, fluvoxamine 50 – 300 mg/day, paroxetine 20 – 60 mg/day, citalopram 20 – 60 mg/day and escitalopram up to 10 – 20 mg/day), as well as cognitive behavioural therapy (CBT) [7,8]. In the case that a response is achieved, generally seen within 2 months, the drug should be continued for at least 1 year, as only a long-term treatment can help to prevent relapses. Approximately 40 – 60% of OCD patients fail to respond to SSRI treatment, so it is important to have alternative strategies available. This may be achieved through substitution, association or augmentation. Indeed, the first step is the substitution with a second SSRI at an adequate dose for a period of at least 12 weeks. The second is the substitution with another SSRI at an adequate dose for at least 12 weeks. The third is the substitution with clomipramine p.o. (up to 300 mg/day) for a period of at least 12 weeks. The fourth is the association of one SSRI and clomipramine. If there is still little improvement, there is often the addition of haloperidol or pimozide, or perhaps a second-generation antipsychotic drug (risperidone, olanzapine and quetiapine), to either two SSRIs or one SSRI + venlafaxine, and, lastly, i.v. citalopram or clomipramine.

Treatment-resistant OCD is defined as a disorder, which does not present symptom improvement (Y-BOCS score reduction of 35%) after two trials with SSRIs given at adequate dose and for an adequate period of time. Refractory OCD is defined as a disorder that does not present an improvement of symptoms (Y-BOCS score reduction of 35 or 25%, depending on the authors) after two attempts with SSRIs at adequate doses and time, plus augmentation and alternative strategies.

Other non-pharmacological strategies have proven to be effective in resistant and/or refractory OCD, that is, CBT. Moreover, it is possible to consider ECT, especially if there is severe depression or suicidal risk, or repeated sessions of transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), as well as some neurosurgical techniques.

2. Expert opinion

The pharmacological treatment of OCD represents one of the most successful achievements towards the end of the previous millennium. Yet, just like with many other psychiatric disorders, one-third of patients do not respond to first-line drugs. In these cases, different strategies have been proposed with the aim of boosting the 5-HT system that seems crucial to OCD pharmacotherapy. More recently, different studies have described abnormalities of other neurotransmitters, such as dopamine, norepinephrine and glutamate. Additionally, there have also been abnormalities seen with neuropeptides, such as oxytocin, of the immune system as well as with secondary messengers, although these have had no real impact, as of yet, on clinical practice. It can be hypothesised that the heterogeneity of pathophysiological mechanisms, beyond the 5-HT paradigm, might underlie different clinical pictures, symptom patterns or dimensions that would require more tailored interventions. Moreover, the latest studies regarding the pharmacology of some SSRIs have shown that, in addition to sharing the common property of 5-HT re-uptake blockade, they also interact with other receptors and systems and are more heterogeneous than previously assumed. Furthermore, a few observations have proposed that sertraline and citalopram may be still effective in OCD patients resistant to other SSRIs. The limitations of the 5-HT paradigm are also evident in augmentation strategies that are mainly centred on this neurotransmitter, as most of the currently proposed strategies are based upon limited clinical observations that would need replication. No controlled clinical studies support the use of buspirone, lithium salts or tryptophan in resistant OCD. Alternative strategies, not related to the 5-HT system, must therefore be implemented. Yet the only convincing data currently available are those related to the modulation of the dopamine system with haloperidol, pimozide and risperidone, while no firm conclusion can yet be drawn on newer antipsychotics, because the available evidence is meagre. The same limitation is valid also for some alternative strategies, such as rTMS or DBS.

A critical issue with the treatment strategies commonly employed in OCD [9,10] is that there are few specific trials supporting them. Another issue is that these studies usually only use small sample sizes, with patients often not reflecting the complexity and heterogeneity of the clinical reality, as is the case with other psychiatric disorders. It is also surprising, given that OCD is a chronic disorder, which requires long-term treatment, that the drugs tested are only supported by findings of short-term, albeit controlled trials [10,11].

The need for effective long-term treatment has given attention towards the safety and side-effect profiles of different compounds. However, it is our opinion, particularly in the case of tricyclic compounds, such as clomipramine, that the side effects of these drugs have been overestimated by clinicians who continue to prefer SSRIs, as they are judged as

more tolerable [11,12]. Indeed, it may be true that head-to-head comparisons between clomipramine and SSRIs show a similar effectiveness but with a better tolerability profile than SSRIs. It is also true that clomipramine appears even more effective in some meta-analysis, or in studies that were not supported by pharmaceutical companies. In any case, the patients included in clomipramine or SSRI studies were not similar, as those enrolled in SSRIs had already failed to respond to previous serotonergic medications. Furthermore, the statistical analyses used in early SSRIs and clomipramine trials were different from those applied subsequently [13,14].

It should also be noted that the long-term use of SSRIs produces a series of invalidating, sometimes neglected, side effects such as asthenia, insomnia, nausea, gastro-intestinal distress and sexual problems (decreased libido, impotence and anorgasmia), as well emotional blunting in some cases [15]. Another advantage of clomipramine, which is not highlighted wholly by the specialised literature, is given by the possibility of its parenteral administration that may be particularly relevant in non-responder patients, especially as evidence suggests that side effects are generally more tolerable than when the drug is given orally. It is puzzling why no additional trials that compare clomipramine with SSRIs have been carried out in recent times. Similarly, no comparison between parenteral clomipramine and citalopram has ever been done. In any case, it is important to note that such trials involving two effective treatments would require large samples of patients (between 500 and 1000), and neither public agencies nor private organisations have the proper financial incentive to support studies with off-patent drugs, as they are SSRIs and clomipramine.

As far as resistant cases are concerned, available guidelines propose different options in these conditions, such as augmentation with the typical antipsychotics haloperidol and pimozide, or the atypical risperidone; there is also the potential use of some psychological techniques, in particular CBT and exposure and response prevention. No firm conclusion can yet be drawn on other newer antipsychotics, because the available evidence is scant [16]. The same applies to rTMS and DBS. The authors also highlight the fact, despite there being a wide range of compounds proposed as potential treatments for OCD, that most of them received only a little attention and/or were not developed sufficiently. We refer in particular to buspirone, lithium salts, tryptophan, ondansetron, anticonvulsants, pindolol, antibiotics and trazodone, as just a few interesting examples. Several others, such as calcium blockers, inositol, cyproheptadine, tramadol and sumatriptan, have also been suggested and should be at least considered [17]. Generally speaking, we can believe that augmentation trials are insufficient to detect clinically significant differences. When these trials are positive, but carried out in small samples (<50 patients), the observed effects might be due to poor methodology rather than to efficacy of the drugs. Conversely, it is also true that some effective drugs may not be developed further if they fail to reach significance in small trials.

Drugs like buspirone and pindolol have been neglected, discarded and forgotten with no apparent reason, despite their significant potentiality in OCD, as demonstrated by the preliminary clinical studies.

The reasons for this failure to implement further studies can be ascribed to different factors. First, there is a meagre interest by pharmaceutical companies for these drugs, given their relatively low costs compared with SSRIs, coupled with the increased costs of clinical trials in western countries. Second, it is felt that there is no need to broaden the spectrum of indications of some compounds, such as lithium salts, valproate, carbamazepine and trazodone, which are already widely used in several other disorders. Third, the evidence that OCD can be more or less treated and managed in a reasonable percentage of cases provides pharmaceutical companies with no incentive or need to use other compounds. We also cannot disregard those OCD patients who wish to hide their symptoms and who do not request timely treatment, as well as those who are adverse to taking medications or taking them for a long time.

On the other hand, suggestions of novel compounds for OCD targeting the glutamate system, such as riluzole, memantine and *N*-acetylcysteine, are progressively emerging, although the evidence for such drugs is not yet conclusive, as their effectiveness has been tested in uncontrolled trials. *N*-Acetylcysteine seems particularly appealing, as it is inexpensive, has no significant side effects and is available over-the-counter, but the evidence for benefit in OCD is still preliminary. Moreover, currently, there is a real difficulty in performing large, multisite trials with novel compounds in resistant and/or refractory OCD, given the problematic rating and assessment of the disorder.

We can conclude that economic reasons, due to the recession in most developed nations that face reduced research and mental health budgets, coupled with reduced interest of clinicians towards OCD treatment strategies and some patients' features prevent the further development of drugs previously investigated and suggested [18].

Given the current economic constraints, it is perhaps the right time to reconsider seriously if and how there might be place for early drugs proposed for OCD. Some drugs, in fact, risk remaining 'orphan' despite advancements in terms of pathophysiology, clinical descriptions and identified subtypes and the underlying dimensions of this disorder. Yet, it is also important to remember that OCD patients must not either be deprived of possible effective therapeutics.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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