Evidence based Psychiatric Care
Journal of the Italian Society of Psychiatry

Società Italiana di Psichiatria

Towards Italian guidelines for the pharmacological treatment of Obsessive-Compulsive Disorder (OCD) in adults: a preliminary draft

Umberto Albert[1], Bernardo Dell'Osso[2,3,4], Giuseppe Maina[5]

[1] Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum University of Bologna, Italy; [2] Department of Biomedical and Clinical Sciences, University of Milan, Psychiatric Unit 2, ASST Fatebenefratelli-Sacco, Milan, Italy; [3] Department of Psychiatry and Behavioral Sciences, Stanford University, CA, USA; [4] CRC "Aldo Ravelli" for Neurotechnology and Experimental Brain Therapeutics, University of Milan, Milan,Italy; [5] Rita Levi Montalcini Department of Neuroscience, University of Torino, Italy

Introduction

Obsessive-compulsive disorder (OCD) is a heterogeneous psychiatric disorder with a lifetime prevalence in the general population of approximately 2-3% [1]. It is currently classified by the DSM-5 within the chapter of "Obsessive-Compulsive and Related Disorders" (OCRDs), where it is the "*nosological organizer*", together with Body Dysmorphic Disorder, Hoarding Disorder, Trichotillomania (Hair-Pulling Disorder) and Excoration (Skin-Picking) Disorder. ICD-11 will follow the DSM-5 and create an analogue chapter adding Olfactory Reference Disorder and Hypocondriasis (Health Anxiety Disorder) to the other OCRDs [2].
The diagnosis of OCD is made by the presence of recurrent or persistent, upsetting thoughts, images, or urges, that are experienced, at some time during the illness, as intrusive and unwanted (obsessions), and that cause anxiety or distress (at least in most individuals, although with time subjects may respond with compulsions before experiencing anxiety); the individual attempts to ignore or suppress the obsessions or to neutralize them by performing a compulsion. Compulsions, which follow obsessions in the vast majority of patients [3], are repetitive behaviors or mental acts performed in response to obsessions. By definition, compulsions are finalized behaviors (aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situations), unlike other repetitive acts like tics which are purposeless. Moreover, compulsions are intentional [4]. Together with obsessions and compulsions, avoidance behaviors are usually present, and such signs and symptoms interfere with individual functioning and consume time (at least one hour per day for the diagnosis).
Family members are also usually involved in symptoms, as they often directly participate in compulsions and in avoidance behaviors. The term family accommodation has been proposed to refer to family responses specifically related to obsessive-compulsive symptoms: it encompasses behaviours, such as directly participating to compulsions and/or assisting a relative with OCD when he/she is performing a ritual (e.g. controlling that the patient with OCD is "*correctly*" taking a shower without touching nothing "*dirty*" or potentially "*contaminating*"; having to pass towels to the patient taking particular care that they do not touch "*contaminated*" surfaces) or helping him/her avoiding triggers that may precipitate obsessions and compulsions (the relative has to respect rules that OCD imposes on the patient; e.g. for a patient with contamination obsessions, having to undress before entering home and putting the "*dirty*" clothes in a specific place at home, avoiding to "*contaminate*" the house with "*dirty clothes*" and having to immediately wash themselves before entering "*uncontaminated*" rooms) [5].
OCD has generally an early age at onset, in childhood or early adult life [6], with an earlier age at onset in males; the early age at onset may greatly impact on

Address for correspondence:

Umberto Albert

Department of Biomedical and Neuromotor Science, Section of Psychiatry,
Alma Mater Studiorum University of Bologna,
Viale C. Pepoli 5, 40123, Bologna, Italy
Phone: +39-051-2083058
Fax: +39-051-521030.

E-mail: umberto.albert@unibo.it

the ability of patients with OCD to gain normal skills and abilities to function in adult life [7]. OCD tends to have, in the majority of cases (up to 75% of patients), a chronic course; the picture is further complicated by the long duration of untreated illness, usually of 10 years or even longer [8,9]. OCD tends to run in families, because of a shared genetic predisposition combined with shared obsessive beliefs as cognitive vulnerability factors [10,11]. Cases of early onset, particularly in male patients, can show a high degree of comorbidity with tic disorders and attention deficit hyperactivity disorder (ADHD) [12].

Despite the availability of effective treatments for Obsessive-Compulsive Disorder (OCD), namely Cognitive-Behavioural Therapy (CBT) and serotonergic compounds (SSRIs and clomipramine) [13,14], there is a treatment gap (difference between those individuals with OCD needing treatment and those actually receiving it), estimated to be in Europe of 25% in 2004 (50% approximately in the world)[15]. The situation has not changed in more recent years: the proportion of subjects not being treated worldwide in more recent epidemiological studies, in fact, is estimated to vary between 22 and 92%, with 38-to-90% of individuals not even seeking treatment or advice for their OCD [16]. The phenomenon is then relevant. Even when subjects with OCD do seek help, the mean delay in help-seeking behaviours is substantial: it is estimated that individuals with OCD take up to 11 years to seek professional help [9,16,17]. Moreover, the interval between help seeking and receiving an *adequate treatment* for OCD is also significant (approximately 2 years for pharmacological treatment [18-20]). This means that a significant challenge exists for physicians and/or mental health professionals in recognizing and diagnosing OCD appropriately, or in prescribing or offering an *adequate* treatment (it may be that psychological therapies other than CBT with exposure and response prevention are applied, or that antidepressants other than clomipramine or SSRIs are prescribed, or for less than the required 12 weeks, or at sub-therapeutic doses). There is thus a strong need for early recognition, appropriate diagnosis and administration of adequate treatments for patients with OCD [20].

As a consequence, the duration of untreated illness (DUI), defined, in most investigations, as the interval between the onset of a specific psychiatric disorder and the administration of the first pharmacological treatment at standard dosages and for an adequate period of time, in adherent subjects, is remarkable in OCD patients. Indeed, DUI in OCD has been consistently demonstrated to count among the longest for any psychiatric disorder – in recent years ranging between seven and ten years in adults [17,19,21,22,23]. In addition, Italian studies found that the longer the DUI (≥ 2 years), the lower is the response to pharmacological treatments [9,19], suggesting a possible *damaging* effect of untreated symptoms even in OCD, as seen for psychotic disorders.

There is then a strong need for evidence-based, country-specific treatment guidelines that can help Italian clinicians to correctly prescribe and monitor treatments for individuals with OCD.

The aim of the present paper is to provide an overview of the state-of-the-art treatment of OCD, with a focus on the pharmacological treatment, and a preliminary draft for the development of Italian guidelines for the treatment of patients with OCD.

Evidence-based first-line treatments

First-line treatments for OCD include 1) pharmacotherapy with selective serotonin reuptake inhibitors - SSRIs – and, among the tricyclic antidepressants, only the serotonin reuptake inhibitor –SRI – clomipramine, and 2) cognitive behavior therapy (CBT) – in the forms of exposure and response prevention (ERP) and/or cognitive restructuring [24-33]. Both the above-mentioned pharmacological and psychological approaches have been recognized more effective than wait-list, inactive psychological treatments or placebo in double-blind randomized controlled trials (RCTs) and meta-analyses.

Pharmacotherapy, CBT or both? How to choose the personalized first-line treatment

Since both approaches are valid first-line treatments, a logical question is which approach is indicated for which patient and whether the combination *ab initio* of pharmacotherapy and CBT is more effective in reducing symptoms as compared to either monotherapy (medications only or CBT only). A recent systematic review [34] identified ten controlled studies assessing the efficacy of combination treatments ab initio *versus* CBT alone and six evaluating combination strategies ab initio *versus* medications alone. The combination *ab initio* of CBT and SRIs was not been found to be clearly superior to either monotherapy alone in most studies conducted in the field, except for patients with severe depression who might benefit more from the combination *versus* CBT only and children/adolescents.

OCD patients with comorbid major depression should then receive medication firstly, eventually associated with CBT; for all remaining patients, there is clear evidence from the literature of no additive benefits of combining *ab initio* CBT and medication. Therefore, the routine use of a combination approach in all adult patients affected by OCD is not supported by the literature.

These findings are consistent with the results of a recent network meta-analysis conducted by Skapinakis and colleagues [13], which stated that there is no sufficient evidence to suggest that combined treatment is better than psychotherapy alone, although combination of medication and CBT seems to be an acceptable treatment, mostly in severe OCD.

Psychological interventions are indicated by some guidelines (NICE guidelines) [33] as first-line treatment for the management of mild to moderate OCD, while for moderate to severe OCD, particularly when other psychiatric disorders are present (not only major depression), pharmacological treatment is indicated as a priority.

Pharmacological treatment: which drugs?

All SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and only clomipramine,

among the tricyclic antidepressants, are considered first-line drugs for adults with OCD. Venlafaxine proved to be as effective as paroxetine or clomipramine in double-blind or single-blind studies in adult patients with OCD; however, the lack of a placebo-controlled study demonstrating its superiority over placebo makes this compound a second choice in the pharmacological treatment of adults with OCD.

Although some meta-analyses indicate that the efficacy of clomipramine is greater as compared to that of SSRIs as a class in terms of standardized mean difference, effect size or NNT (e.g. Hirschtritt et al. [14]), individual head-to-head comparisons between different SRIs did not find statistically significant differences in efficacy. The choice between SSRIs or clomipramine is then conditioned by the higher burden associated with clomipramine in terms of side effects. SSRIs should be then prescribed as first-choice in adults with OCD. Clomipramine may be considered when there is poor response to an SSRI, a previous good response to clomipramine, or patient's preference.

Which dose?

Fixed-dose studies have been performed for all SRIs except fluvoxamine and clomipramine. The minimal effective dose for fluoxetine and paroxetine (the one that differed statistically from placebo in terms of response) is 40 mg/day, and for escitalopram 20 mg/day; for citalopram and sertraline there is an indication of greater efficacy at higher doses (40-60 for citalopram and 200 for sertraline). A meta-analysis [35] of all placebo-controlled studies in adults with OCD clearly confirmed that medium-to-high doses should be used for the pharmacological treatment of OCD in order to obtain the greatest efficacy. Table I provides minimum target and maximum doses to be used in OCD.

How to evaluate response and when

A recent international expert consensus [36] defined response as a ≥ 35% reduction in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score with respect to beginning of treatment (partial response ≥ 25% but < 35% reduction) (Table II); response in OCD is gradual, incremental and requires up to 12 weeks to be evident (usually it takes a minimum of 6-to-8 weeks for *initial* response to be evident). This is a huge difference with respect to response in major depressive disorder, where response is greater in terms of symptoms reduction (>50% on the HAM-D or MADRS usually) and occurs earlier (before weeks 4-8 generally). This difference has to be kept in mind, as it may happen that clinicians not fully aware of this slow response in OCD may be willing to change treatment after only 4 weeks, preventing the drug to be fully effective (the consequence is that patients are mislabeled as resistant).

When response, defined as above, is evident, continuation treatment, at the same dose, is associated with continued improvement in symptoms until remission is achieved [14].

Adherence should be monitored, especially in the first weeks of treatment, when side effects associated with pharmacological treatments may emerge while response is still lacking.

How long should a responder be kept on continuation/maintenance treatment?

Following adequate response, treatment should be kept with the same compound and with the same dose until remission is achieved [37]. Then, treatment should be continued for a further 12 months to prevent the risk of relapses [38-40]. Placebo-controlled, relapse prevention studies lasted up to 12 months, and not all SRIs underwent such trials. Several long-term, naturalistic studies showed that in some cases treatment can be safely continued for several years with maintenance of efficacy and prevention of relapses [41-45]. Severity of illness at baseline, prior duration of untreated illness (which may impact on response rates), number of previous episodes and persistent psychosocial adversities may suggest maintenance of treatment for 2 years or longer [19,20]. Of course, the persistence of residual symptoms as well as a partial response should suggest maintenance treatment and a further assessment of next-step strategies.

Although there is some evidence [41,46] that long-term main-

Table I. Doses of serotonin reuptake inhibitors (SRIs) in the treatment of OCD.

Drug	Starting dose and incremental dose (mg/day)	Usual target dose (mg/day)	Maximum recommended dose in Italy (mg/day)
Citalopram*	20	40-60	40#
Clomipramine	25	100-250	250
Escitalopram	10	20	20§
Fluoxetine	20	40-60	60
Fluvoxamine	50	200	300
Paroxetine	20	40-60	60
Sertraline	50	200	200

** Citalopram in Italy is not indicated for the treatment of OCD, although its efficacy is established in placebo-controlled, double-blind studies. # Citalopram is associated with dose-dependent QTc prolongation, thus in Italy the maximum dose recommended for adults is 40 mg/day (20 mg in patients > 65 years-old or with reduced liver function). § Escitalopram is associated with dose-dependent QTc prolongation, thus in Italy the maximum dose recommended for adults is 20 mg/day (10 mg in patients > 65 years-old or with reduced liver function).*

Table II. Definitions of response-remission (Mataix-Cols et al., 2016, modified).

	Conceptual	Operational
Treatment Response	A clinically meaningful reduction in symptoms relative to baseline severity	A ≥35% reduction in YBOCS scores plus CGI-I rating of 1 ("very much improved") or 2 ("much improved"), lasting for at least one week
Partial Response	Defined as in treatment response above	A ≥25% but <35% reduction in YBOCS scores plus CGI-I rating of at least 3 ("minimally improved"), lasting for at least one week
Remission	The patient no longer meets syndromal criteria for the disorder and has no more than minimal symptoms. Residual obsessions, compulsions and avoidance may be present, but are not time consuming and do not interfere with the person's everyday life	A score of ≤12 on the YBOCS plus CGI-S rating of 1 ("normal, not at all ill") or 2 ("borderline mentally ill"), lasting for at least one week
Recovery	The patient no longer meets syndromal criteria for the disorder and has had no more than minimal symptoms. The clinician may begin to consider discontinuation of treatment or, if the treatment continues, the aim is to prevent relapse	As above, lasting 1 year

tenance therapy for OCD may be provided with lower dosages of the anti-obsessional drug (50-to-66% lower than those used to achieve remission), with clear advantages for tolerability and compliance, all published International guidelines suggest keeping the same medium-to-high dose throughout the maintenance phase in order to prevent relapses.

Adherence to treatment is particularly important and should be monitored throughout the whole maintenance phase of the treatment, when remission is achieved (the patient no more suffers from symptoms) and patients may be more prone to forget to take medications as required. Preliminary evidence [39] suggests that relapses due to premature treatment discontinuation or to intermittent adherence respond less well when the same drug at the same dose is reinstated, indicating a possible "toxic" effect of relapses.

No clear indications emerge from the literature concerning how to stop medications after the maintenance phase in patients fully remitted: a slow titration regimen is preferable in order to prevent discontinuation symptoms associated with SSRIs (particularly common with drugs with short half-life).

Resistant patients

Treatment-resistant OCD patients are defined as those who undergo adequate trials of first-line therapies without achieving a satisfactory response, usually defined by a reduction in the Y-BOCS total score ≥35% or ≥25% with respect to baseline (see above for the definition of response and partial response) [47].

Practically, before confirming a condition of treatment-resistance, clinicians should follow these steps:

Check the appropriateness of the diagnosis of OCD; particularly, other symptoms should not inappropriately be considered as obsessions or compulsions (obsessive-compulsive personality disorder; ruminations occurring in Major Depressive Disorder or other Anxiety Disorders – e.g. GAD; repetitive stereotyped behaviours encountered in psychoses, in mental retardation, or in organic mental disorders; obsessive concerns about body shape or ritualized eating behaviours in Eating Disorders; patterns of behaviours, interests or restricted and repetitive activities in Autism).

Check that the patient has been exposed to an adequate pharmacological trial (SRIs) in terms of appropriate doses and for at least 12 weeks (see paragraphs above).

Consider potential medical or psychiatric comorbidities that could affect treatment response (e.g., paradigmatic the case of OCD comorbid with Bipolar Disorder, where treatment with high doses of SRIs could worsen both bipolar disorder – mixed episodes, rapid cycling, switch – and OCD).

Consider the possible negative role of family members or caregivers, who might be accommodating OC symptoms, thus counteracting the goal of the treatment and contributing to the maintenance of the disorder. Psychoeducational interventions directed to the families might help to establish a therapeutic alliance, to provide education about the disorder and its treatment, to improve family problem solving skills, and to ameliorate compliance to drug treatments.

Evidence-based (at least one positive randomized controlled trial versus placebo) treatment strategies for individuals not responding to a first trial with SRIs are:

- antipsychotic add on to SRIs;
- CBT add on to medications;
- switch to intravenous route of administration (if first-line treatment is clomipramine or citalopram);
- switch to paroxetine or venlafaxine;
- addition of medications other than antipsychotics to SRIs;
- use of brain stimulation techniques.

a. Antipsychotic addition to SRIs

The use of antipsychotic add on to SRIs in resistant OCD is supported by several randomized, double-blind, placebo-controlled studies. Review and meta-analytical studies also confirm that augmentation of SRIs with antipsychotic

Table III. Antipsychotic augmentation in treatment-resistant OCD: double-blind, placebo-controlled studies.

Antipsychotic	Authors	Sample (N)	Trial duration (weeks)	Dose (mg/die)	Mean dose (mg/die)	Minimal length of SRI treatment before enrollment in the study	Results
Aripiprazole	Muscatello et al. 2011	40	16	15 (fixed-dose)	15 (fixed-dose)	12	Aripiprazole > Placebo
	Sayyah et al. 2012	39	12	10 (fixed-dose)	10 (fixed-dose)	12	Aripiprazole > Placebo
Haloperidol	McDougle et al. 1994	34	4	2-10	6.2±3.0	12	Haloperidol > Placebo
Olanzapine	Bystritsky et al. 2004	26	6	5-20	11.2±6.5	12	Olanzapine > Placebo
	Shapira et al. 2004	44	6	5-10	6.1±2.1	8	Olanzapine = Placebo (patients in both arms improved)
Paliperidone	Storch et al. 2013	34	8	3-9	4.94	8	Paliperidone = Placebo (patients in both arms improved)
Quetiapine	Atmaca et al. 2002*	27	8	50-200	91±41	12	Quetiapine > Placebo
	Denys et al. 2004	40	8	100-300	200	8	Quetiapine > Placebo
	Carey et al. 2005	42	6	25-300	168.8±120.8	12	Quetiapine = Placebo
	Fineberg et al. 2005	21	16	50-400	215±124	12	Quetiapine = Placebo
	Kordon et al. 2008	40	12	400-600	-	12	Quetiapine = Placebo
	Diniz et al. 2011#	54	12	50-200	142±65	8	Quetiapine < Placebo
Risperidone	McDougle et al. 2000	36	6	1-6	2.2±0.7	12	Risperidone > Placebo
	Hollander et al. 2003	16	8	0.5-3	2.25±0.86	12	Risperidone > Placebo
	Erzegovesi et al. 2005	20	6	0.5 (fixed-dose)	0.5 (fixed-dose)	12	Risperidone > Placebo
	Simpson et al. 2013	60	8	0.25-4	1.9±1.1	12	Risperidone > Placebo

** Single-blind, placebo-controlled study; # Double-blind placebo and clomipramine controlled study.*

drugs as a class can be considered a valid and first-choice treatment option in resistant OCD patients, especially when a partial response is evident and there is the need of further improving response without waiting for the time (12 weeks) necessary to evaluate the response to another first-line compound (in the case of a switch) (e.g. [47-49]). Not all antipsychotics proved to be effective in treating resistant patients (see Table III for antipsychotics studied, doses used and results versus placebo): aripiprazole and risperidone appeared effective in at least 2 positive RCTs, while only 1 positive study supports the addition of haloperidol and conflicting results are available for olanzapine (1 positive and 1 negative – probably biased – study) and quetiapine (more negative than positive studies). Concerning doses, aripiprazole appeared effective at a dose of 10 and 15 mg/day, olanzapine at a mean dose of 11 mg/day, risperidone at a dose comprised between 0.5 and 2 mg/day. Haloperidol proved effective at a mean final dose of 6 mg/day, but with significant side effects. Approximately 50% of patients are expected to benefit from antipsychotic add on to SRIs [50].

At present, it is uncertain how long adjunctive antipsychotic treatment should be maintained once response is achieved: the discontinuation of the antipsychotic leads to an exacerbation of obsessive-compulsive symptoms in the vast majority of patients (83.3% within the 24-week follow-up)[51], suggesting the need to continue with the augmentation strategies in order to achieve remission and prevent relapses over the long-term. However, if such a treatment is carried out over the long term, patients are exposed to the common and serious adverse effects associated with long-term antipsychotic administration, especially the metabolic ones [52].

In conclusion, we recommend prioritizing aripiprazole or risperidone add on to SRIs over other antipsychotics (olanzapine augmentation may also be effective, but only when the other two have failed), when such a strategy is used.

b. CBT addition to medication

The available evidence supports the sequential addition of CBT to SRIs for both OCD patients who respond to medications but still have residual obsessive-compulsive symptoms (1 positive randomized controlled study in adults) (this is a clinically relevant issue since only a minority of subjects accomplishes remission using a single treatment modality) [53] and for resistant patients (2 positive randomized controlled studies performed

versus a placebo psychological comparison – stress management training – and versus risperidone or placebo add on) [54,55]. Two other RCTs support the effectiveness of switching to medications after non-response to CBT [56,57].
For severe, treatment-resistant patients, several open-label or retrospective chart reviews support the efficacy of CBT delivered in residential settings or partial hospitalization programs: providing time-intensive treatment, based on delivering higher levels of treatment over a short time period, might be suitable for individuals whose immediate clinical improvement is important [34].

c. Switch to intravenous route of administration

A further approach in resistant OCD consists in changing route of administration, switching to intravenous therapy: this option is available only for clomipramine or citalopram. To date, only one study [58] investigated with appropriate methodology (randomized placebo-controlled study) whether IV clomipramine was efficacious for patients with OCD refractory to oral clomipramine. This controlled study demonstrated the significant superiority of IV clomipramine over IV placebo, indicating that IV clomipramine is an effective treatment for patients with OCD who have a history of an inadequate response or intolerance to oral clomipramine. Although no study specifically examined the efficacy of IV citalopram in non-responders to oral citalopram, clinicians might consider the use of intravenous therapy when patients failed oral SSRIs and hepatic first-pass metabolic effect is considered to contribute to resistance.

d. Switch to paroxetine or venlafaxine

Switching from clomipramine to SSRIs, or vice versa, or from SSRI to another SSRI, is a common strategy in clinical practice [28,59]. Only one controlled trial, however, supports the efficacy of this strategy: non-responders to prospectively administered venlafaxine or paroxetine responded to the switch to the other compound, with paroxetine being more effective than venlafaxine. The switch strategy is then recommended, to our opinion, only after the failure of antipsychotic or CBT augmentation, or when a first-choice compound showed no improvement, not even minimal.

e. Addition of medications other than antipsychotics to SRIs

The effectiveness of augmentative compounds other than antipsychotics in resistant OCD has been the subject of several double-blind studies, with promising results for some drugs and negative for others. A list of studies performed is provided in Table IV. All of the compounds that proved to be effective (namely pindolol and topiramate – only 1 positive RCT, memantine – 2 positive RCTs) should be considered as promising add-on strategies, although reserved for patients being refractory to other more evidence-based strategies [60]. From Table IV clinicians can find out which compounds not to use for resistant OCD patients.
Several controlled studies, moreover, investigated the efficacy of the addition of compounds other than antipsychotics *ab initio* in moderate to severe non-resistant OCD individuals (Table V). These strategies, although promising for improving the treatment outcome of OCD patients (by shortening response latency or increasing response rates), should be considered at the moment only for research purposes.

Table IV. Efficacy of augmentation with compounds other than antipsychotics in treatment-resistant OCD: double-blind, placebo-controlled studies.

Compound	Authors	Dose (mg/die)	Results
Lithium	McDougle et al. 1991 Pigott et al.1991	In range	Lithium = Placebo
Buspirone	Pigott et al.1992 McDougle et al. 1993 Grady et al. 1993	30-60	Buspirone = Placebo
Desipramine	Barr et al. 1997	125 ng/ml (plasma level)	Desipramine = Placebo
Inositol	Fux et al. 1999	1800	Inositol = Placebo
Pindolol	Dannon et al. 2000	7.5	Pindolol > Placebo
Gabapentin	Corà-Locatelli et al. 2001	Up to 3600	Gabapentin = Placebo
Clonazepam	Crockett et al. 2004		Clonazepam = Placebo
Naltrexone	Amiaz et al. 2008	100	Naltrexone = Placebo
Topiramate	Mowla et al. 2010 Berlin et al. 2011 Afshar et al. 2014	100-200 50-400 100-200	Topiramate > Placebo Topiramate = Placebo (> on compulsions only) Topiramate = Placebo
Lamotrigine	Bruno et al. 2012	100	Lamotrigine > Placebo
Memantine	Haghighi et al. 2013 Modarresi et al. 2018	5-10 20	Memantine > Placebo Memantine > Placebo
Riluzole	(Grant et al. 2014)* Pittenger et al. 2015	100 100	Riluzole = Placebo

** Children.*

Table V. Add-on treatment (ab initio) in moderate to severe OCD: double-blind, placebo-controlled studies

Compound	Authors	Mechanism	Dose (mg/die)	Results
Quetiapine	Vulink et al. 2009	antipsychotic	300-450	Quetiapine > Placebo
Granisetron	Askari et al 2012	5-HT3 receptor antagonist	1	Granisetron > Placebo
Ondansetron	Heidari et al. 2014	5-HT3 receptor antagonist	8	Ondansetron > Placebo
Celecoxib	Shalbafan et al. 2015	NSAID	200 x 2	Celecoxib > Placebo
Memantine	Ghaleiha et al. 2013 Farnia et al. 2018	NMDA receptor antagonist	20 10	Memantine > Placebo Memantine = Placebo
Riluzole	Emamzadehfard et al. 2016	Glutamate-modulating agent	50 x 2	Riluzole > Placebo
N-acetylcysteine	Paydary et al. 2016	Glutamate-modulating agent	2000	NAC > Placebo on YBOCS (not on response and remission)
L-carnosine	Arabzadeh et al. 2017	Glutamate-modulating agent	500 x 2	L-carnosine > Placebo
Gabapentin	Farnia et al. 2018	Glutamate-modulating agent	300	Gabapentin = Placebo

NSAID: nonsteroidal anti-inflammatory drug; NDMA: N-methyl-D-aspartate; NAC: N-acetylcysteine.

f. Use of brain stimulation techniques for treatment-resistant patients

Besides pharmacologic, behavioral, and neurosurgical approaches, different brain stimulation methods, including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), and electroconvulsive therapy (ECT), have been investigated in treatment-resistant patients with OCD [61,62], revealing positive results for otherwise intractable and treatment-refractory patients.

TMS and tDCS represent non-invasive brain stimulation techniques that have been investigated in patients with OCD with mixed results. A recent meta-analysis [63] including 15 RCTs (n = 483), most of which with small-to-modest sample sizes, found that active versus sham TMS stimulation was significantly superior for OCD symptoms. Nonetheless, stimulation targets and degree of treatment resistance show a wide variability across RCTs. There is less evidence in favour of the efficacy of tDCS versus TMS in OCD with a recent systematic review supporting cathodal compared to anodal tDCS in treating OCD [64].

With respect to more invasive somatic interventions, traditionally considered for more severe and treatment-resistant cases, ECT does not seem to produce any specific benefit in OC symptoms, being potentially useful only in cases of depressive and/or psychotic comorbidity [28]. On the other hand, levels of evidence for DBS efficacy in treatment-resistant OCD patients are more solid with a recent meta-analysis [65] including 31 studies (n = 116) showing a global percentage of Y-BOCS reduction at 45.1% and global percentage of responders at 60.0%. Stimulation targets were variable with most subjects implanted in striatal areas (anterior limbs of the internal capsule, ventral capsule and ventral striatum, nucleus accumbens and ventral caudate) and the remainders in the subthalamic nucleus and in the inferior thalamic peduncle.

Conflict of interests

The authors declare that there is no conflict of interests.

References

1 Ruscio AM, Stein DJ, Chiu WT, et al. *The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication*. Mol Psychiatry 2010;15:53-63.

2 Stein DJ, Kogan CS, Atmaca M, et al. *The classification of Obsessive-Compulsive and Related Disorders in the ICD-11.* J Affect Disord 2016;190:663-74.

3 Leonard RC, Riemann BC. *The co-occurrence of obsessions and compulsions in OCD.* J Obsessive Compuls Relat Disord 2012;1: 211-5.

4 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th ed*. Washington, DC: American Psychiatric Press 2013.

5 Albert U, Baffa A, Maina G. *Family accommodation in adult obsessive-compulsive disorder: clinical perspectives.* Psychol Res Behav Manag. 2017;10:293-304.

6 Dell'Osso B, Benatti B, Hollander E, et al. *Childhood, adolescent and adult age at onset and related clinical correlates in obsessive-compulsive disorder: a report from the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS).* Int J Psychiatry Clin Pract 2016;20:210-7.

7 Albert U, Manchia M, Tortorella A, et al. *Admixture analysis of age at symptom onset and age at disorder onset in a large sample of patients with obsessive-compulsive disorder.* J Affect Disord 2015;187:188-96.

8 Ravizza L, Maina G, Bogetto F. *Episodic and chronic obsessive-compulsive disorder.* Depress Anxiety 1997;6:154-8.

9 Dell'Osso B, Buoli M, Hollander E, Altamura AC. *Duration of untreated illness as a predictor of treatment response and remission in obsessive-compulsive disorder.* World J Biol Psychiatry 2010;11:59-65.

10 Mataix-Cols D, Boman M, Monzani B, et al. *Population-based, multigenerational family clustering study of obsessive-compulsive disorder.* JAMA Psychiatry 2013;70709-17.

11 Albert U, Barcaccia B, Aguglia A, et al. *Obsessive beliefs in first-degree relatives of probands with obsessive-compulsive disorder: is the cognitive vulnerability in relatives specific to* OCD? Pers Individ Dif 2015;87:141-6.

12 Dell'Osso B, Marazziti D, Albert U, et al. *Parsing the phenotype of obsessive-compulsive tic disorder (OCTD): a multidisciplinary consensus.* Int J Psychiatry Clin Pract 2017;2):156-9.

13 Skapinakis P, Caldwell D, Hollingworth W, et al. *Pharmacological and psychotherapeutic interventions for management of*

obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. Lancet Psychiatry 2016;3:730-9.
14 Hirschtritt ME, Bloch MH, Mathews CA. *Obsessive-Compulsive Disorder: Advances in Diagnosis and Treatment*. JAMA 2017;317:1358-67.
15 Kohn R, Saxena S, Levav I, et al. *The treatment gap in mental health care.* Bull World Health Organ 2004;82:858-66.
16 García-Soriano G, Rufer M, Delsignore A, et al. *Factors associated with non-treatment or delayed treatment seeking in OCD sufferers: a review of the literature.* Psychiatry Res 2014;220:1-10.
17 Altamura AC, Buoli M, Albano A, et al. *Age at onset and latency to treatment (duration of untreated illness) in patients with mood and anxiety disorders: a naturalistic study.* Int Clin Psychopharmacol 2010;25:172-9.
18 Stengler K, Olbrich S, Heider D, et al. *Mental health treatment seeking among patients with OCD: impact of age of onset.* Soc Psychiatry Psychiatr Epidemiol 2013;48:813-9.
19 Albert U, Barbaro F, Bramante S, et al. *Duration of untreated illness and response to SRI treatment in Obsessive-Compulsive Disorder*. Eur Psychiatry 2019;58:19-26.
20 Fineberg NA, Dell'Osso B, Albert U, et al. *Early intervention for obsessive-compulsive disorder: an expert consensus statement.* Eur Neuropsychopharmacol 2019;29:549-65.
21 Dell'Osso B, Camuri G, Benatti B, et al. *Differences in latency to first pharmacological treatment (duration of untreated illness) in anxiety disorders: a study on patients with panic disorder, generalized anxiety disorder and obsessive-compulsive disorder.* Early Interv Psychiatry 2013;7:374-80.
22 Poyraz CA, Turan Ş, Sağlam NG, et al. *Factors associated with the duration of untreated illness among patients with obsessive compulsive disorder*. Compr Psychiatry 2015;58:88-93.
23 Benatti B, Camuri G, Dell'Osso B, et al. *Which factors influence onset and latency to treatment in generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder?* Int Clin Psychopharmacol 2016;31:347-52.
24 March J, Frances A, Carpenter D, et al. *The Expert Consensus Guidelines Series. Treatment of obsessive-compulsive disorder.* J Clin Psychiatry 1997;58:2-72.
25 Baldwin DS, Anderson IM, Nutt DJ, et al. *Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology.* J Psychopharmacol 2005;19:567-96.
26 Baldwin DS, Anderson IM, Nutt DJ, et al. *Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology*. J Psychopharmacol 2014;28:403-39.
27 Canadian Psychiatric Association. *Clinical practice guidelines. Management of anxiety disorders*. Can J.Psychiatry 2006;51(8 Suppl 2):9S-91.
28 Koran LM, Hanna GL, Hollander E, et al. American Psychiatric Association. *Practice Guideline for the treatment of patients with obsessive-compulsive disorder.* Arlington, VA: American Psychiatric Association 2007.
29 American Psychiatric Association. *Guideline Watch (March 2013): Practice Guideline for the treatment of patients with obsessive-compulsive disorder*. Arlington, VA: American Psychiatric Association 2013.
30 Bandelow B, Zohar J, Hollander E, et al. WFSBP Task Force on Treatment Guidelines for Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disoders. *World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders-first revision*. World J Biol Psychiatry 2008;9: 248-312.
31 Bandelow B, Sher L, Bunevicius R, et al. WFSBP Task Force on Mental Disorders in Primary Care; WFSBP Task Force on Anxiety Disorders, OCD and PTSD. *Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder in primary care*. Int J Psychiatry Clin Pract 2012;16:77-84.
32 Katzman MA, Bleau P, Blier P, et al. Canadian Anxiety Guidelines Initiative Group on behalf of the Anxiety Disorders Association of Canada/Association Canadienne des troubles anxieux. *Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders.* BMC Psychiatry 2014;14(Suppl 1):S1.
33 National Institute for Health and Clinical Excellence*. Obsessive-compulsive disorder: core interventions in the treatment of obsessive-compulsive disorder and body dysmorphic disorder CG3*1. London: National Institute for Health and Clinical Excellence 2005.
34 Ibert U, Di Salvo G, Solia F, et al. *Combining drug and psychological treatments for obsessive-compulsive disorder: what is the evidence, when and for whom*. Curr Med Chem 2018;25:5632-46.
35 Bloch MH, McGuire J, Landeros-Weisenberger A, et al. *Meta-analysis of the dose-response relationship of SSRI in obsessive-compulsive disorder.* Mol Psychiatry 2010;15:850-5.
36 Mataix-Cols D, Fernández de la Cruz L, Nordsletten AE, et al. *Towards an international expert consensus for defining treatment response, remission, recovery and relapse in obsessive-compulsive disorder.* World Psychiatry 2016;15:80-1.
37 Fineberg NA, Brown A, Reghunandanan S, et al. *Evidence-based pharmacotherapy of obsessive-compulsive disorder*. Int J Neuropsychopharmacol 2012;15:1173-91.
38 Fineberg NA, Tonnoir B, Lemming O, et al. *Escitalopram prevents relapse of obsessive- compulsive disorder*. Eur Neuropsychopharmacol 2007;17:430-9.
39 Maina G, Albert U, Bogetto F. *Relapses after discontinuation of drug associated with increased resistance to treatment in obsessive-compulsive disorder.* Int Clin Psychopharmacol 2001;16:33-8.
40 Batelaan NM, Bosman RC, Muntingh A, et al. *Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials.* BMJ 2017;358:j3927.
41 Ravizza L, Barzega G, Bellino S, et al. *Drug treatment of obsessive-compulsive disorder (OCD): long-term trial with clomipramine and selective serotonin reuptake inhibitors (SSRIs).* Psychopharmacol Bull 1996;32:167-73.
42 Cherian AV, Math SB, Kandavel T, et al. *A 5-year prospective follow-up study of patients with obsessive-compulsive disorder treated with serotonin reuptake inhibitors.* J Affect Disord 2014;152-154:387-94.
43 Eisen JL, Sibrava NJ, Boisseau CL, et al. *Five-year course of obsessive-compulsive disorder: predictors of remission and relapse*. J Clin Psychiatry 2013;74:233-9.
44 Catapano F, Perris F, Masella M, et al. *Obsessive-compulsive disorder: a 3-year prospective follow-up study of patients treated with serotonin reuptake inhibitors OCD follow-up study*. J Psychiatr Res 2006;40:502-10.
45 Nakajima A, Matsuura N, Mukai K, et al. *Ten-year follow-up study of Japanese patients with obsessive-compulsive disorder.* Psychiatry Clin Neurosci 2018;72:502-12.
46 Mundo E, Bareggi SR, Pirola R, et al. *Long-term pharmacotherapy of obsessive-compulsive disorder: a double-blind controlled study*. J Clin Psychopharmacol 1997;17:4-10.
47 Albert U, Marazziti D, Di Salvo G, et al. *A systematic review of evidence-based treatment strategies for obsessive- com-*

pulsive disorder resistant to first-line pharmacotherapy. Curr Med Chem 2018;25:5647-61.

[48] Dold M, Aigner M, Lanzenberger R, et al. *Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: an update meta-analysis of double-blind, randomized, placebo-controlled trials.* Int J Neuropsychopharmacol 2015;18(9). pii: pyv047.

[49] Zhou DD, Zhou XX, Lv Z, et al. *Comparative efficacy and tolerability of antipsychotics as augmentations in adults with treatment-resistant obsessive-compulsive disorder: a network meta-analysis.* J Psychiatr Res 2019;111:51-8.

[50] Albert U, Carmassi C, Cosci F, et al. *Role and clinical implications of atypical antipsychotics in anxiety disorders, obsessive-compulsive disorder, trauma-related, and somatic symptom disorders: a systematized review.* Int Clin Psychopharmacol 2016;31:249-58.

[51] Maina G, Albert U, Ziero S, Bogetto F. *Antipsychotic augmentation for the treatment-resistant obsessive-compulsive disorder: what if antipsychotic is discontinued?* Int Clin Psychopharmachol 2003;18:23-8.

[52] Albert U, Aguglia A, Chiarle A, etal. *Metabolic syndrome and obsessive-compulsive disorder: a naturalistic Italian study.* Gen Hosp Psychiatry 2013;35:154-9.

[53] Tenneij NH, van Megen HJGM, Denys DA, et al. *Behavior therapy augments response of patients with obsessive-compulsive disorder responding to drug treatment.* J Clin Psychiatry 2005;66:1169-75.

[54] Simpson HB, Foa EB, Liebowitz MR, et al. *A randomized, controlled trial of cognitive-behavioral therapy for augmenting pharmachoterapy in obsessive-compulsive disorder.* Am J Psychiatry 2008;165:621-30.

[55] Simpson HB, Foa EB, Liebowitz MR, et al. *Cognitive-behavioral therapy vs risperidone for augmenting serotonin reuptake inhibitors in obsessive-compulsive disorder: a randomized clinical trial.* JAMA 2013;70:1190-9.

[56] Van Balkom AJ, Emmelkamp PM, Eikelenboom M, et al. *Cognitive therapy versus fluvoxamine as a second-step treatment in obsessive-compulsive disorder nonresponsive to first-step behavior therapy.* Psychother Psychosom 2012;81:366-74.

[57] Skarphedinsson G, Weidle B, Thomsen PH, et al. *Continued cognitive-behavior therapy versus sertraline for children and adolescents with obsessive-compulsive disorder that were non-responders to cognitive-behavior therapy: a randomized controlled trial.* Eur Child Adolesc Psychiatry 2015;24:591-602.

[58] Fallon BA, Liebowitz MR, Campeas R, et al. *Intravenous clomipramine for OCD refractory to oral clomipramine: a controlled study.* Arch Gen Psychiatry 1998;55:918-24.

[59] Dell'Osso B, Altamura AC, Mundo E, et al. *Diagnosis and treatment of obsessive-compulsive disorder and related disorders.* Int J Clin Pract 2007;61:98-104.

[60] Zhou DD, Zhou XX, Li Y, et al. *Augmentation agents to serotonin reuptake inhibitors for treatment-resistant obsessive-compulsive disorder: A network meta-analysis.* Prog Neuropsychopharmacol Biol Psychiatry 2019;90:277-87.

[61] Dell'Osso B, Altamura AC, Allen A, et al. *Brain stimulation techniques in the treatment of obsessive-compulsive disorder: current and future directions.* CNS Spectr 2005;10:966-79, 983.

[62] Dell'Osso B, Cremaschi L, Oldani L, et al. *New directions in the use of brain stimulation interventions in patients with obsessive-compulsive disorder.* Curr Med Chem 2018;25:5712-21.

[63] Trevizol AP, Shiozawa P, Cook IA, et al. *Transcranial magnetic stimulation for obsessive-compulsive disorder: an updated systematic review and meta-analysis.* J ECT 2016;32:262-6.

[64] Rapinesi C, Kotzalidis GD, Ferracuti S, et al. *Brain stimulation in obsessive-compulsive disorder (OCD): a systematic review.* Curr Neuropharmacol 2019, in press.

[65] Alonso P, Cuadras D, Gabriëls L, et al. *Deep brain stimulation for obsessive-compulsive disorder: a meta-analysis of treatment outcome and predictors of response.* PLoS One 2015;10:e0133591.