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*REVIEW ARTICLE*

# Are 5-$HT_3$ antagonists effective in obsessive–compulsive disorder? A systematic review of literature

Daniele Serata[1,2], Georgios D. Kotzalidis[1]*, Chiara Rapinesi[1,2], Delfina Janiri[1], Simone Di Pietro[1], Gemma Callovini[1], Daria Piacentino[1], Carlotta Gasperoni[1], Roberto Brugnoli[1], Vittoria Rachele Ferri[1], Nicoletta Girardi[1], Roberto Tatarelli[1], Stefano Ferracuti[1], Gloria Angeletti[1], Paolo Girardi[1,2] and Antonio Del Casale[1,3]

[1]*Neurosciences, Mental Health, and Sensory Organs (NeSMOS) Department, School of Medicine and Psychology, Sapienza University of Rome, UOC Psychiatry, Sant'Andrea Hospital, Roma, Italy*
[2]*Department of Neuropsychiatry, Villa Rosa Suore Ospedaliere of the Sacred Heart of Jesus, Viterbo, Italy*
[3]*Department of Psychiatric Rehabilitation, P. Alberto Mileno Onlus Foundation, San Francesco Institute, Vasto, Chieti, Italy*

**Objective** The purpose of this literature database search-based review was to critically consider and evaluate the findings of literature focusing on efficacy and safety of 5-$HT_3$ antagonists in the treatment of obsessive–compulsive disorder (OCD), so as to test whether preclinical data match clinical therapeutic trials.
**Design** The PubMed database has been searched for papers on 5-$HT_3$ antagonists and OCD in humans and for animal models of OCD and 5-$HT_3$ receptors.
**Results** Of the clinically tested 5-$HT_3$ receptor antagonists, ondansetron has been used to treat OCD in five therapeutic studies, whereas granisetron only in one recent trial. Both showed some efficacy in open studies and superiority to placebo in double-blind studies, along with fair safety. No animal OCD model directly implicated 5-$HT_3$ receptors.
**Conclusions** Overall, results indicate some utility, but the available literature is too scanty to allow for valid conclusions to be drawn. The mismatch between animal models of obsessive–compulsive disorder and clinical data with 5-$HT_3$ antagonists needs more clinical data to ensure that it is not an artefact. 

KEY WORDS—clinical trials as topic; models; animal; obsessive–compulsive disorder; serotonin 5-$HT_3$ receptor antagonists; ondansetron; granisetron

## INTRODUCTION

Obsessive–compulsive disorder (OCD) is severely disabling, with a 2–3% lifetime prevalence in the general population (Ruscio *et al*., 2010). There is evidence for short-term but not long-term (Fineberg *et al*., 2013) efficacy of higher doses than those used for depressive and other anxiety disorders of clomipramine and selective serotonin (5-HT) reuptake inhibitor (SSRI) antidepressants (ADs) (Rabinowitz *et al*., 2008). Treatment resistance ranges from 30% to 57% (Katz *et al*., 1990; Ravizza *et al*., 1995; Newth and Rachman, 2001; Ferrão *et al*., 2007), stressing its pathophysiological complexity. The bulk of OCD treatment data points to drugs acting on serotonin (5-HT) bioavailability (American Psychiatric Association, 2007).

The first studies involving 5-HT in OCD date back to the late 1960s, when clomipramine, the most specific 5-HT transporter inhibitor among tricyclic antidepressants (TCAs) (Fernández de Córdoba and López-Ibor Aliño, 1967; López-Ibor, 1969; Insel *et al*., 1983), showed symptom improvement. With the advent of the SSRIs, fluoxetine, fluvoxamine, paroxetine and sertraline were tested and found to be effective in OCD (Goodman *et al*., 1989; Jenike *et al*., 1989). Studies of peripheral biomarkers of 5-HT metabolism in OCD (Hanna *et al*., 1991, 1995) and SSRI effectiveness support the involvement and dysfunction of 5-HT systems in OCD patients. Despite conflicting results (Lucey *et al*., 1992; Norman *et al*., 1994), acute 5-HT stimulation might lead to OCD symptom worsening

*Correspondence to: G. D. Kotzalidis, Sapienza University of Rome, Italy, School of Medicine and Psychology, Neurosciences, Mental Health and Sensory Organs (NeSMOS) Department Sant'Andrea Hospital, Via di Grottarossa 1035-1039, 00189 Rome, Italy. Tel. 06-33775951; Fax: 06-33775342 E-mail: giorgio.kotzalidis@uniroma1.it

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(Monteleone *et al*., 1997; Broocks *et al*., 1998; Mundo *et al*., 1999). Furthermore, 5-HT$_{2C}$ receptor stimulation with promiscuous serotonin agonists having stronger affinity for this receptor, like *m*-chlorophenylpiperazine (mCPP), worsened anxiety in healthy volunteers and obsessive–compulsive symptomatology in OCD patients (Hollander *et al*., 1992). Terminal 5-HT presynaptic autoreceptor desensitisation following clomipramine/SSRIs might relate to long-term efficacy of 5-HT-enhancing compounds in OCD (Blier and de Montigny, 1998). In fact, compared with depression, longer treatment (10–12 weeks; Dougherty *et al*., 2004) and higher AD doses (El Mansari and Blier, 2006) are needed to obtain symptom improvement in OCD, matching the timeline of 5-HT autoreceptor desensitisation.

Dopaminergic involvement is suggested by D$_2$ dopamine receptor antagonist-induced improvement of compulsive and behavioural Tourette symptoms (Goodman *et al*., 1990), clomipramine's antidopaminergic activity (Austin *et al*., 1991), add-on D$_2$ antagonist effectiveness (McDougle *et al*., 1994, 2000; Ramasubbu *et al*., 2000) and animal findings in the context of the psychostimulant model of OCD (Eilam and Szechtman, 2005). Hence, from the 1990s onward, investigators focused on the role of dopamine (Choi, 2009) as an alternative or complementary neurochemical strategy to address the complex pathophysiology of OCD.

Ineffectiveness of typical antipsychotic monotherapy in OCD (Denys *et al*., 2004) and OCD symptom induction by atypical antipsychotics with combined D$_2$/5-HT$_2$ receptor-blocking properties (Allen and Tejera, 1994; Remington and Adams, 1994) support other pharmacological strategies, based on the interaction between serotonergic and dopaminergic systems. This view is supported by reduced 5-HT transporter density in the midbrain pons area along with increased dopamine transporter availability in OCD patients after citalopram treatment (Pogarell *et al*., 2005).

Serotonin 5-HT$_3$ receptors affect 5-HT, dopamine, noradrenaline, acetylcholine, gamma-aminobutyric acid (GABA) and neuromodulator functions in the central and peripheral nervous systems (Barnes *et al*., 1990; Martin *et al*., 1992; Huang *et al*., 2004; Choi *et al*., 2007; Fukushima *et al*., 2009; Ortega *et al*., 2012).

5-HT$_3$ receptors in rodents are highest in the area postrema, solitary tract nucleus (Tecott *et al*., 1993; Morales and Wang, 2002), neocortex, anterior olfactory complex, hippocampus, amygdala, striatum and nucleus accumbens (Morales *et al*., 1998). The 5-HT$_{3A}$ subunit was supposedly the prevalent subtype, but recently, all neurons expressing it in the hippocampal CA1 area and scattered cortical areas were found to express also the 5-HT$_{3B}$ subunit (Doucet *et al*., 2007).

5-HT$_3$ receptors are co-localised with GABA interneurons in the ventral tegmental area (VTA), indirectly inhibiting cortical–mesolimbic dopamine release (Bloom and Morales, 1998; Chen *et al*., 2001). Localisation in accumbal and amygdalar dopaminergic terminals (Morales *et al*., 1998) prompts us to consider them as part of the cortico-striatal-thalamo-cortical OCD circuitry (Del Casale *et al*., 2011).

Although much preclinical evidence points to a role of the 5-HT$_3$ receptor in psychiatric disorders, 5-HT$_3$ antagonists have been little used in their treatment. Serotonin 5-HT$_3$ antagonists, like ondansetron and granisetron, are worldwide prescribed, safe and effective antiemetic agents, mainly used in postsurgical and antineoplastic drug-induced nausea and emesis. Both selectively inhibit 5-HT$_3$ receptors (Butler *et al*., 1988). However, they also antagonise weakly 5-HT$_4$ receptors (Miyata *et al*., 1995; Hasler, 2009), whereas ondansetron probably inhibits also other 5-HT receptor subtypes (Tonini, 2005) and granisetron appears to be more 5-HT$_3$ selective (Blower, 1995). Having no appreciable affinity for the GABA/benzodiazepine receptor complex, they have no sedative effects (Costall *et al*., 1990; Goodin and Cunningham, 2002) or potential for abuse, dependence, tolerance or withdrawal following abrupt discontinuation (Costall and Naylor, 1992). A role for 5-HT$_3$ receptor antagonists in psychiatric disorder treatment has been advanced since the early 1990s (Stefański *et al*., 1992).

5-HT$_3$ receptor activation has been found to increase, and 5-HT$_3$ receptor antagonists to reduce, anxiety-like behaviour in animals (Costall and Naylor, 1992). The zacopride derivative (*S*)-des-4amino-3-iodozacopride, which different from other benzoamides has a 200-fold preference for these receptors over the 5-HT$_4$ receptors (Hewlett *et al*., 1999), showed anxiolytic activity in the mouse elevated plus-maze model of anxiety (Zhang *et al*., 2001). 5-HT$_3$ antagonism may reduce threat perception, whose aberrant levels are a core feature of OCD (Zhang *et al*., 2001). Postsynaptic 5-HT$_3$ inhibition decreases 5-HT turnover rate (Edwards *et al*., 1996) and may relate to SSRI effectiveness in OCD.

Regarding the 5-HT–dopamine interplay in OCD, 5-HT$_3$ stimulation enhances dopaminergic activity when dopaminergic neurons are already hyperactive (Costall *et al*., 1987, 1990); however, other indirect interactions between the 5-HT$_3$ receptor and the dopaminergic system are possible, and one of these involves nicotinic acetylcholine receptor (nAChR) antagonism. In fact, nAChRs modulate dopaminergic transmission (Exley and Cragg, 2008), and antagonists may cross-react with 5-HT$_3$ receptors because of 5-HT$_3$/nAChR structural similarity (Drisdel *et al*., 2008).



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Preclinical evidence suggests a role for 5-$HT_3$ inhibition in OCD treatment, mostly based on data of OCD animal models, which vary in their conception of OCD and cover only partial aspects of human OCD-related behaviour (Fineberg *et al*., 2011; Hoffman, 2011; Albelda and Joel, 2012a, 2012b). In summary, the main pharmacological models are quinpirole-induced and stimulant-induced stereotypies, 8-hydroxy-2-diisopropylaminotetralin (8-OH-DPAT)-induced and mCPP-induced reduction in spontaneous or reinforced alternation and SSRI-induced reduction of rodent marble-burying behaviour (Albelda and Joel, 2012a). All these models encounter either face/content, construct or predictive validity problems (Fineberg *et al*., 2011; Albelda and Joel, 2012a, 2012b); furthermore, they do not consider the 5-$HT_3$ receptor. However, ondansetron reversed anticholinergic-induced impairment in spontaneous alternation in the marmoset in one study (Barnes *et al*., 1990) and attenuated stimulant-induced stereotypy in the rat (Shankar *et al*., 2000), whereas the 5-$HT_3$ receptor has not been heretofore tested in the marble-burying paradigm. Combining these data, we may consider 5-$HT_3$ receptor involvement in OCD as possible.

Our aim was to review systematically the efficacy and safety of ondansetron and granisetron, the only 5-$HT_3$ receptor antagonists that have received trials in the treatment of OCD, either in monotherapy or as add-on/augmentation and at any dose, and to evaluate how these results match preclinical data.

### *Design*

We conducted a PubMed search with no language or date limit with the following search strategy: (ondansetron OR Zofran OR granisetron OR Kytril OR serotonin3 antagonist* OR 5-HT3 receptor* OR 5ht3* OR 5-ht3*) AND (obsessive* OR compulsive* OR hoarding* OR washing OR ritual* OR OCD* OR anxiety disorders OR tic disorder* OR Tourette*). The last three keywords were included because OCD belongs to anxiety disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, whereas tic disorders and Tourette's disorder often co-occur with OCD; however, we did not include any human study not specifically focusing on OCD. All authors carried out searches under the guidance of the corresponding author; all authors regularly met to discuss and compare their findings and to decide which papers to include in the review; all interpretation was subjected to rounds of criticism and approval; consensus was obtained when all members agreed.

The search yielded 152 papers as of [24 November 2014], most of which were loosely dealing with the role and the pharmacological rationale of 5-$HT_3$ receptor inhibitor treatment in OCD and related disorders. These papers were localised and obtained, and their references searched for possible other useful material. We then selected only those papers that used 5-$HT_3$ receptor antagonists to evaluate OCD symptoms in healthy controls or to treat patients with OCD for the clinical part of our review. Concerning the evaluation of the role of the 5-$HT_3$ receptor in animal models of OCD, we selected papers mentioning this receptor in their text. Papers were selected on the basis of their appropriateness, that is, publication in peer-reviewed journals; adequate description of aims and methods, the latter being appropriate for reaching the aims; use of sound models in animals and adequate diagnostic systems for population inclusion in human studies (e.g. DSM-IV/IV-TR or International Classification of Diseases (ICD)-9/10); sufficiently long follow-up for effects of treatment to appear; the use of standardised scales to assess treatment effects (or behavioural measures in animal paradigms); and the clear description of results. We did not refer to the DSM-5 (American Psychiatric Association, 2013; Discussion), as studies with 5-$HT_3$ antagonists focusing on the new conceptualisation of an OCD spectrum have still to appear in literature. Of all considered studies, only six were therapeutic trials (five with ondansetron and one with granisetron), and one was a one-dose behavioural study with ondansetron (Table 1). Additional searches were focused on each of the main animal models of OCD (marble burying, acral lick dermatitis, spontaneous alternation, quinpirole-induced checking behaviour, stimulant-induced stereotypies, 8-OH-DPAT-induced and mCPP-induced reduction in spontaneous or reinforced alternation) and the role of 5-$HT_3$ receptors, using simple wording and uniting the models in one set through OR in PubMed (e.g. marble* OR quinpirole* OR acral* OR checking* OR spontaneous alternation OR (stimulant* AND stereotyp*) OR DPAT OR 8-hydroxy-diisopropyl amino tetralin* OR mCPP OR meta-chlorophenylpiperazine* OR reinforced alternation), thereafter combining it with the 5-$HT_3$ receptor to find the intersection through AND (5-HT3* OR 5HT3* OR 5-hydroxytryptamine3* OR serotonin3*). This search yielded 294 items, the relevance of which was decided through repeated meetings of all authors.

## RESULTS

Animal models of OCD foresee no role for 5-$HT_3$ receptor antagonists (only one study was found to be interesting among the 294 papers of the search string output but focused on the 5-$HT_{1A}$ receptor; Alkhatib *et al*., 2013); however, evidence points to compatibility



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Table 1. Summary of pharmacological trials of 5-HT$_3$ receptor antagonists in OCD

| Drug | Investigators, year (location) | Experimental design | Number, age (years) and gender of patients receiving 5-HT$_3$ antagonists | Co-morbidities | Doses | Psychometric tools | Results | Side effects |
|---|---|---|---|---|---|---|---|---|
| Ondansetron | Broocks *et al.*, 1998 (NIMH, Bethesda, Maryland, USA) | Double-blind single i.v. ondansetron versus placebo pretreatment followed by i.v. mCPP, to test role of 5-HT$_3$ receptors in OCD | 11 DSM-III-R OCD patients, adults, 6 men and 5 women, mean age 39.1 ± 14.4, range 22–58 | Mild–moderate depression (BDI ≥ 12 ≤ 26) | 0.15 mg/kg ondansetron once | CPRS-OC, NOC, BDI | Ondansetron did not counteract mCPP-induced OCD symptoms | mCPP → anxiety, sweating, nausea, drowsiness, tremor, yawning, and warm-skin sensation unaffected by ondansetron |
| Ondansetron | Hewlett *et al.*, 2003 (Nashville, Tennessee, USA) | 8-week open-label ondansetron administration to drug-free OCD patients | 8 DSM-IV OCD patients, mean age 36.5 ± 5.9, 5 men and 3 women, ≥16 Y-BOCS | 4 GAD, 6 PD, 3 tic-like mannerisms, 1 dysthymic disorder | 3 mg/day ondansetron, 3 divided doses | Y-BOCS, HAM-D, HAM-A | Ondansetron followed by 28% drop of Y-BOCS scores from baseline (55% in remitters) and remission (at least 35% drop of Y-BOCS scores from baseline) in 3 OCD patients (37% of total sample, 50% of completers); tic-like mannerisms = positive predictor for response | Most frequent: 5 constipation, 3 dry mouth, and 2 headache; 2 dropouts at the 7th week for unspecified reasons |
| Ondansetron | Pallanti *et al.*, 2009 (Florence, | 12-week 'single-blind' (using blind | 14 treatment-resistant (at least | Mild depression (MADRS ≥ 9 ≤ 17) | Add-on ondansetron 0.50 mg/day for | Y-BOCS, MADRS, CGI | Ondansetron augmentation → treatment | Mild–moderately decreased appetite, headache; no |
| | | ondansetron to treatment-resistant OCD patients already treated with antidepressants (possibly antipsychotics) | adequately dosed SSRIs or clomipramine) DSM-IV OCD patients, mean age 42.2 ± 11.3, 8 men and 6 women | | antipsychotics unchanged) | | remission (≥35% drop) in 7.14% | |
| Ondansetron | Soltani *et al.*, 2010 (Ahwaz, Iran) | 8-week double-blind ondansetron–fluoxetine versus placebo–fluoxetine | 20 DSM-IV-TR OCD patients, mean age 26 ± 2.76, 11 men and 9 women, ≥21 Y-BOCS | Exclusion of psychiatric disorders, substance abuse, major physical disease | Ondansetron 4 mg/day–fluoxetine 20 mg/day combination | Y-BOCS | Ondansetron–fluoxetine combination associated with 81.43% drop in Y-BOCS scores, compared with 55.55% with fluoxetine–placebo | No significant differences between ondansetron and placebo; one dropout for severe headache with ondansetron |
| Granisetron | Askari *et al.*, 2012 (Tehran, Iran) | 8-week double-blind granisetron–fluvoxamine versus placebo–fluvoxamine | 20 DSM-IV-TR OCD patients, mean age 35.2 ± 6.8, 6 men and 14 women, ≥21 Y-BOCS | Exclusion of axis I disorders, substance abuse and major physical disease | Granisetron 1 mg q12h–fluvoxamine 100 mg/day combination for first 4 weeks, increased to 200 mg/day thereafter, with granisetron dose remaining unaltered | Y-BOCS | Granisetron–fluvoxamine combination associated with 60% drop in Y-BOCS, compared with 35.36% of placebo–fluvoxamine; furthermore, 100% complete response (≥35% drop from baseline) and 90% remission (≤16 on Y-BOCS) in OCD, compared | No significant differences between granisetron and placebo |

(*Continues*)




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| Drug | Investigators, year (location) | Experimental design | of patients receiving 5-$HT_3$ antagonists | Co-morbidities | Doses | Psychometric tools | Results | Side effects |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | with 35% of placebo–fluvoxamine | |
| Ondansetron | Pallanti *et al*., 2014 (Florence, Italy) | 12-week 'single-blind' (using blind rater to assess patient status) administration of ondansetron to treatment-resistant OCD patients already treated with antidepressants; another 4 weeks of ondansetron discontinuation | 21 treatment-resistant (at least 24 on the Y-BOCS and 4 on the CGIs after ≥12-week treatment with adequately dosed SSRIs) DSM-IV OCD patients, mean age 36.43 ± 10.37, 10 men and 11 women | Exclusion of current axis I disorders or past depressive episode prior to onset of OCD, substance abuse, treatment with other psychotropic drugs, behavioural psychotherapy and major physical disease | Add-on 0.50 mg/day ondansetron for the first 2 weeks to 1 mg/day until the 12th week (SSRIs unchanged) | Y-BOCS, CGI, Drug Effect Scale | Ondansetron augmentation → treatment response (≥25% Y-BOCS drop from baseline and CGIi 1 or 2) in 57.14% of OCD patients; during discontinuation, relapse (≥25% Y-BOCS increase from previous visit [last 2 weeks] and/or CGIi 6 or 7) occurred in 66.667% of responders | Mild side effects, no discontinuation due to adverse events |
| Ondansetron | Heidari *et al*., 2014 (Tehran, Iran) | 8-week double-blind ondansetron–fluvoxamine versus placebo–fluvoxamine | 23 DSM-IV-TR OCD patients, mean age 36.2 ± 6.9, 10 men and 13 women, ≥21 Y-BOCS | Exclusion of axis I disorders, substance abuse in the last 6 months, psychotherapy, lactation, pregnancy and major medical condition | Ondansetron 4 mg q12h–fluvoxamine 100 mg/day combination for first 4 weeks, increased to 200 mg/day thereafter | Y-BOCS | Ondansetron–fluvoxamine combination associated with 48.48% drop in Y-BOCS, compared with 30.27% of placebo–fluvoxamine; furthermore, 86.37% complete response (≥35% drop from baseline) versus 31.8% placebo and 63.64% remission (≤16 on Y-BOCS) in OCD, compared with 27.28% of placebo–fluvoxamine. Greater improvement with ondansetron–fluvoxamine versus placebo–fluvoxamine significant at weeks 4–6 on the Y-BOCS, mainly due to the obsessive subscale | No significant differences between ondansetron and placebo |

*Abbreviations*. BDI, Beck Depression Inventory (Beck *et al*., 1961); CGI, Clinical Global Impressions scale (Guy, 1976); CPRS-OC, Comprehensive Psychiatric Rating Scale, obsessive–compulsive subscale (Thorén *et al*., 1980); GAD, Generalised Anxiety Disorder; HAM-A, Hamilton Rating Scale for Anxiety (Hamilton, 1959); HAM-D, Hamilton Rating Scale for Depression (Hamilton, 1960); i.v., intravenous; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Scale (Montgomery and Åsberg, 1979); NOC, National Institute of Mental Health, Obsessive–Compulsive Rating Scale (Insel *et al*., 1983); OCD, obsessive–compulsive disorder; PD, personality disorder; Y-BOCS, Yale–Brown Obsessive–Compulsive Scale (Goodman *et al*., 1989).




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between some models and possible utility in OCD. Despite preclinical and pharmacological rationale for 5-HT$_3$ antagonists in OCD treatment, only six clinical studies focused on this topic.

Ondansetron was first tested in healthy volunteers to assess the role of 5-HT$_3$ receptors in anxiety behaviour triggered by mCPP. In single-dose administration, 0.15 mg/kg intravenous (i.v.) ondansetron pretreatment did not prevent the elicitation of anxiety by 0.08 mg/kg i.v. mCPP but shortened the time needed for self-rated anxiety to return to its baseline levels, compared with double-blind placebo (Broocks *et al*., 1997). In a subsequent study, the same randomised design and dosages were used in OCD patients, enriched by the addition of ondansetron–placebo and placebo–placebo conditions (Broocks *et al*., 1998). Ondansetron did not affect anxiety ratings on its own and did not reverse the anxiogenic effect of mCPP, pointing to a difference in 5-HT$_3$ receptor function between healthy volunteers and OCD patients. The overall indication for the clinical use of 5-HT$_3$ receptor antagonists in OCD emerging from these pilot studies was not strong; however, after about 5 years, an open-label trial followed (Hewlett *et al*., 2003). In another trial, ondansetron has been administered to treatment-resistant OCD patients as an open-label add-on to SSRIs and antipsychotics (however, the trial was reported to be 'single-blind' because the rater was blinded as to patients' treatment condition; Pallanti *et al*., 2009), whereas another study by the same group used the same single-blind design on another set of patients, who were not taking antipsychotics and who were observed longer, after withdrawing the add-on ondansetron (Pallanti *et al*., 2014). The other three recent trials that were carried out on Iranian patients tested a combination of a 5-HT$_3$ receptor antagonist with an SSRI antidepressant, that is, ondansetron and fluoxetine (Soltani *et al*., 2010), ondansetron and fluvoxamine (Heidari *et al*., 2014) and granisetron and fluvoxamine (Askari *et al*., 2012). Duration of open monotherapy and combination studies was 8 weeks, whereas the most extended study was the one involving add-on in treatment-resistant OCD and the follow-up involving drug discontinuation. Trial results are summarised in Table 1.

All patients received OCD DSM diagnoses. The early mCPP challenge study used the DSM-III-R (American Psychiatric Association, 1987), whereas the clinical studies used either the DSM-IV (American Psychiatric Association, 1994) or the DSM-IV-TR (American Psychiatric Association, 2000). Cut-off for inclusion was 16 on the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) (Goodman *et al*., 1989a, 1989b) in the open study (Hewlett *et al*., 2003) and 21 in the three combination studies (Soltani *et al*., 2010; Askari *et al*., 2012; Heidari *et al*., 2014; Table 1). Although not specified as an inclusion cut-off, the single-blind studies carried out in treatment-resistant patients used a definition of treatment resistance of at least 20 Y-BOCS score after 12 weeks of adequate dosing of drugs that have proven anti-OCD efficacy; hence, all patients in that study had scored at least 20 at baseline in the first of these studies (Pallanti *et al*., 2009), whereas in the second, the criterion was even more restrictive, requiring both 24 on the Y-BOCS and 4 on the Clinical Global Impressions scale (moderately ill) (Pallanti *et al*., 2014).

Daily ondansetron doses ranged from 0.5 titrated to 1 mg in two studies (Pallanti *et al*., 2009, 2014), to 3 mg in the open study (Hewlett *et al*., 2003), to 4 mg in one of the combination studies (Soltani *et al*., 2010) and 8 mg in the other (Heidari *et al*., 2014), whereas 2 mg/day granisetron was used in the other combination study (Askari *et al*., 2012). The range of ondansetron doses used in these studies (1–8 mg/day) was lower than the one used in schizophrenia (4–16 mg/day; Bennett and Vila, 2010). Because the antiemetic equivalence of the oral formulations of the two drugs is 1 mg granisetron to 32 mg ondansetron (Fox-Geiman *et al*., 2001), the dose of granisetron used by Askari *et al*. (2012) is rather high. The ondansetron dose is related to side effect appearance, as there were none (Pallanti *et al*., 2009) or very few in the lowest-dose studies (Pallanti *et al*., 2014), whereas open administration of 3 mg/day ondansetron (Hewlett *et al*., 2003) was associated with 18 adverse events in eight patients (ratio = 2.25), with constipation dominating the scene (Table 2). Constipation was not among the adverse events emerging with the ondansetron–fluoxetine combination but did appear with the granisetron–fluvoxamine combination (Table 2); however, some adverse events in these three studies could be partly attributed to the respective SSRI. The study that used the highest ondansetron dose in this series (Heidari *et al*., 2014) reported the highest number of side effects among ondansetron-using studies, that is, 31, with nausea and headache as the most frequent. The granisetron–fluvoxamine study (Askari *et al*., 2012) reported 45 adverse events in 20 patients (ratio = 2.25), compared with 12 in 20 patients in the ondansetron–fluoxetine study (ratio = 0.6, i.e. the most favourable, but again dose equivalences and SSRI co-administration should be considered; Soltani *et al*., 2010). Among side effects, constipation, headache and dry mouth predominated, whereas sexual disorders/dysfunctions were found in the two combination studies involving co-administration of SSRIs; this was an expected effect for this class of antidepressants, so we believe that it is unlikely that they would represent a side effect of



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Table 2. Reported adverse events with 5-$HT_3$ antagonist treatment: a summary of published studies

| Study | Drug, dose × duration (number of patients) | Adverse event | Number of reported events |
|---|---|---|---|
| Pallanti *et al*., 2009 | Ondansetron 0.5 → 1 mg/day added on antidepressants and/or antipsychotics × 12 weeks ($N = 14$) | None | 0 |
| Hewlett *et al*., 2003 | Ondansetron 3 mg/day × 8 weeks ($N = 8$) | Constipation | 5 |
| | | Dry mouth | 4 |
| | | Headache | 2 |
| | | Worsened premenstrual dysphoria | 1 |
| | | Gastrointestinal upset | 1 |
| | | Chest discomfort | 1 |
| | | Urinary urgency | 1 |
| | | Dizziness | 1 |
| | | Agitated depression | 1 |
| | | Bacterial cholecystitis | 1 |
| Soltani *et al*., 2010 | Ondansetron 4 mg/day + fluoxetine 20 mg/day × 8 weeks ($N = 20$) | Sweating | 3 |
| | | Headache | 2 |
| | | Anxiety | 2 |
| | | Sexual dysfunction | 2 |
| | | Insomnia | 1 |
| | | Decreased appetite | 1 |
| | | Tremor | 1 |
| Askari *et al*., 2012 | Granisetron 2 mg/day + fluvoxamine 100 → 200 mg/day × 8 weeks ($N = 20$) | Drowsiness | 5 |
| | | Dry mouth | 5 |
| | | Constipation | 5 |
| | | Nausea | 5 |
| | | Dizziness | 4 |
| | | Nervousness | 4 |
| | | Decreased appetite | 3 |
| | | Sweating | 3 |
| | | Fatigue | 3 |
| | | Diarrhoea | 3 |
| | | Itching | 2 |
| | | Sexual dysfunction | 2 |
| | | Muscle tension | 1 |
| Pallanti *et al*., 2014 | Ondansetron 0.5 → 1 mg/day added on SSRI antidepressants × 12 weeks ($N = 21$) | Constipation | 3 |
| | | Headache | 2 |
| | | Dizziness | 1 |
| Heidari *et al*., 2014 | Ondansetron 8 mg/day + fluvoxamine 100 → 200 mg/day × 8 weeks ($N = 23$) | Dizziness | 6 |
| | | Headache | 5 |
| | | Constipation | 4 |
| | | Muscle cramp | 4 |
| | | Nervousness | 4 |
| | | Dry mouth | 3 |
| | | Insomnia | 3 |
| | | Diarrhoea | 2 |

In the lowest-dose study, no adverse events were reported. Intake of 2 mg daily granisetron was associated with the emergence of more adverse events than 4 mg daily ondansetron; however, these differences may reflect differences in SSRI-associated adverse events. In fact, differences between ondansetron and placebo in these studies were not significant.

5-$HT_3$ receptor antagonists, although interactions are possible; in fact, ondansetron and other 5-$HT_3$ receptor antagonists were shown to interfere with animal erectile activity in conjunction with other serotonergic and dopaminergic mechanisms (Maeda *et al*., 1994, 1995; Lau *et al*., 2007). Overall, the adverse symptom pattern mimicked the one described for patients with neoplastic diseases treated for chemotherapy-induced nausea, except for headache being less common than constipation (Goodin and Cunningham, 2002). The event/patient ratios found in oncological studies were 0.85 for 32 mg/day i.v. ondansetron and 0.77 for 2 mg/day oral granisetron (Perez *et al*., 1998). Generally, symptoms were not severe. A side effect constituted the reason for study discontinuation only in one case of a patient treated with ondansetron + fluoxetine and dropped out for severe headache (Soltani *et al*., 2010). Despite the high rate of side effect occurrence, ondansetron and granisetron appear to be safe and well tolerated.

The two 5-$HT_3$ receptor antagonists employed in clinical studies of OCD were administered to a total of 62 patients; no study involved more than 22 patients to expose to ondansetron or granisetron, and no study used exactly the same design as others. When designs were similar (i.e. SSRI + 5-$HT_3$ receptor antagonist), as in the case of Soltani *et al*. (2010), Askari *et al*. (2012),



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the drugs were different and doses were not comparable (Table 1). Because of small sample sizes and study design heterogeneity, these findings should be interpreted with caution.

In all five ondansetron studies and in the granisetron study, treatment for 8 or 12 weeks was associated with important Y-BOCS score reductions. In the open study, a 28% drop from baseline was observed after 8 weeks (Hewlett *et al*., 2003), whereas in the resistant OCD studies, mean Y-BOCS drop was 21.29% (Pallanti *et al*., 2009) and 27.2% (Pallanti *et al*., 2014) after the addition of oral ondansetron solution. In the three placebo-controlled SSRI + 5-HT$_3$ receptor antagonist combination studies, Y-BOCS score reduction ranged from slightly less than 50% (Heidari *et al*., 2014) to more than 80% (Soltani *et al*., 2010) for ondansetron and 60% for granisetron (Askari *et al*., 2012), but the possible effect of co-administered SSRI should be taken into account also when considering improvement. However, the combination of an SSRI with a 5-HT$_3$ receptor antagonist was paralleled by significantly greater drops in Y-BOCS scores than the combination with a placebo (Table 1; Soltani *et al*., 2010; Askari *et al*., 2012; Heidari *et al*., 2014).

The only positive response predictor identified by these studies was the patient having tic-like mannerisms, reported only by the initial open study (Hewlett *et al*., 2003). This has not been replicated by others.

## DISCUSSION

### *What do preclinical data suggest about OCD and 5-HT$_3$ receptor antagonists and is this matched by animal OCD models?*

The main animal OCD models do not imply a role for 5-HT$_3$ receptor antagonists (Fineberg *et al*., 2011; Albelda and Joel, 2012a, 2012b). However, some of these models are compatible with a role of the 5-HT$_3$ receptor in the pathophysiology of OCD (Barnes *et al*., 1990; Shankar *et al*., 2000).

Drug treatment of OCD currently involves administering SSRIs or TCAs with high affinity for the serotonin transporter. The first reports of efficacy of such a drug in OCD regarded clomipramine and appeared during the late 1960s to early 1970s; they were lacking any neurochemical pathophysiological connection (cf. Marshall, 1971), and the rationale was purely empirical. Despite progress in the development of animal models and neurochemistry-based drug design, the approach of drug treatment of OCD remained largely empirical and did not follow the indications stemming from animal studies. For example, one of the first successful animal models of OCD, the spontaneous alternation paradigm, appeared in the medical literature in 1991, suggesting that 5-HT$_{1A}$ receptor stimulation could be related to increased obsessive-like behaviour (Yadin *et al*., 1991). This would allow speculating that by decreasing 5-HT$_{1A}$ receptor activity, OCD symptoms may improve. However, the year before, it was reported that buspirone, a partial 5-HT$_{1A}$ receptor *agonist*, benefitted patients with OCD when given as an add-on to fluoxetine (Markovitz *et al*., 1990); this study had a pharmacological rationale that was generally based on animal studies of anxiety disorders, but *not* of OCD; hence, it preceded the implementation of the animal OCD model, and in fact, it went the opposite way. About the same time the OCD model was proposed, a study of OCD patients suggested that the SSRI fluoxetine induced a downregulation of 5-HT$_3$-related responses in the long term (Lesch *et al*., 1991), pointing to the same direction of the model.

The spontaneous alternation behaviour may be differently affected by drugs depending on the substance used to impair it. For example, if impaired alternation is elicited through the 5-HT$_{1A}$ agonist 8-OH-DPAT, 5-HT$_{1A}$ inhibitors or long-term downregulators may counteract it, whereas in the mCPP setting, it is 5-HT$_{2C}$ inhibitors that restore it (Papakosta *et al*., 2013). Again, all this receptor specificity identified in the laboratory found little correspondence in terms of new drug development and clinical trial application.

The subsequently developed canine acral lick dermatitis model of OCD was based on the observation that a drug class (serotonin transporter inhibitors) with proven effectiveness in OCD reduced the licking behaviour that was responsible for triggering dermatitis (Rapoport *et al*., 1992). This model, which was pharmacologically based, has been used little thereafter and did not lead to the development of drugs to use as anti-OCD.

The quinpirole-induced checking behaviour model of OCD (Szechtman *et al*., 1998) pointed to the involvement of dopamine activation in the elicitation of OCD-related behaviour in the rat. This would suggest that interventions aiming at reducing dopaminergic activity mediated through D$_2$ receptors could be useful in OCD. However, subsequent experimentation in the context of this model suggested only the possible utility of kappa-opioid receptor manipulation (Perreault *et al*., 2007) and helped in realising the fact that behavioural and environmental changes may modify the quinpirole-related response (Zadicario *et al*., 2007) but did not lead to the development of new drugs. Furthermore, the quinpirole-induced OCD-like behaviour was reversed in deer mice by serotonin transporter



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inhibitors (Korff *et al*., 2008). Moreover, clomipramine *in vitro* inhibited dopamine receptor binding (Austin *et al*., 1991), which validates the model, inasmuch as clomipramine has shown superior anti-OCD activity than other antidepressants (Ackerman and Greenland, 2002). One could argue that the rat psychostimulant (amphetamine) model fits to schizophrenia or mania and would not be suitable for OCD. On the other hand, in the quinpirole-induced water contra-freeloading rat model of OCD, clomipramine, but not $D_2$-binding antipsychotics, reduced this behaviour (De Carolis *et al*., 2011). This speaks in favour of the aptness of the model for OCD but also reveals the complexity of animal behaviour and neurotransmitter–neuromodulator interactions. A chemical is bound to induce certain changes that may be of interest to facets of multiple disorders, but the challenge then is to dissect those changes and attribute them correctly to their appropriate frame/condition.

The identified dopaminergic component of OCD prompted people to try dopamine antagonists as add-ons in OCD. The use of neuroleptics in OCD dates back to the mid-1950s, but results were not 'impressive' (Trethowan and Scott, 1955). Add-on/augmentation strategies with atypical antipsychotics were adopted since the first decade of this century (D'Amico *et al*., 2003). A meta-analysis of randomised controlled trials found a modest increase in efficacy for risperidone and quetiapine as add-on treatments, in the face of scanty available data (Komossa *et al*., 2010), but other analyses found risperidone and haloperidol, but not quetiapine or olanzapine (Bloch *et al*., 2006; Skapinakis *et al*., 2007), to be effective, although the latter was more positive for olanzapine and quetiapine than the former (Skapinakis *et al*., 2007).

The first genetic study of 5-$HT_3$ involvement in the pathophysiology of OCD indicated a lack of involvement of this receptor in early-onset OCD (Mössner *et al*., 2007), but another study showed an association between the c.256G-allele of the HTR3E variant rs7627615 and the washing phenotype and another between the HTR3E c.256G/c.256G-genotype and impaired performance on neuropsychological tasks pertaining to visual organisation (Lennertz *et al*., 2014). Animal models of psychiatric disorders do not propose the 5-$HT_3$ receptor as a putative mediator of OCD-like behaviours but rather advance its possible involvement in anxiety, psychosis and mood regulation; their possible indication in OCD stems from indirect evidence. For example, 5-$HT_3$ receptors in the posterior VTA mediate reinforcing properties of alcohol (Rodd *et al*., 2007, 2008), which eventually leads to compulsion (Everitt and Robbins, 2005), so it is possible that 5-$HT_3$ receptor antagonists reduce the reinforcing properties of compulsions, which make part of the clinical picture of OCD. Microinfusion in this area of quinpirole blocked the 5-$HT_3$ receptor agonist-induced reinforcing effect of alcohols in the preceding experiments similarly to 5-$HT_3$ receptor antagonists, hence pointing to an effect of these drugs on the activity of dopaminergic neurons in the posterior VTA, which would mediate reinforcement with increased firing and would be slowed down by 5-$HT_3$ receptor antagonists and presynaptic, somatodendritic $D_2$ autoreceptors. The quinpirole model of OCD would be at odds with the aforementioned effect, but it should be underlined that the area where effects are obtained matters and that the same substances may have opposite effects when administered in different areas. So quinpirole may enhance reinforcement when delivered to the nucleus accumbens and reduce it when given in the VTA. Another example of the importance of the area that regards the effects of 5-$HT_3$ receptors is that their activation in the accumbens potentiates terminal dopaminergic activation, whereas in the dorsolateral prefrontal cortex, both dopamine and serotonin act synergistically to inhibit cortical neurons (Gobbi and Janiri, 1999). More recently, an integrated dopamine-5-HT interactive model has been proposed, according to which quinpirole enhances compulsive checking by acting on dopaminergic behavioural drive, whereas 8-OH-DPAT maintains such checking by inhibiting the serotonergic setting off of this control circuit (Alkhatib *et al*., 2013).

A simple 5-$HT_3$ inhibition model of the therapeutic effect of drugs soothing the symptoms of OCD cannot account for what is observed in the clinical setting; for example, clozapine, despite its recognised competitive antagonism of 5-$HT_3$ receptors (Rammes *et al*., 2004, 2009), may induce obsessive symptoms or trigger a full-blown OCD picture in about one-fifth to one-fourth of patients with schizophrenia (Mukhopadhaya *et al*., 2009; Sa *et al*., 2009), but has shown anti-OCD activity in one patient with schizophrenia and co-morbid OCD when added on aripiprazole (Peters and de Haan, 2009). The obsessive symptom triggering by clozapine has been attributed to its ability to block 5-$HT_{2A/2C}$ receptors (Schirmbeck and Zink, 2012) as well as to its ability to interfere with 5-$HT_{1A}$ receptors (Ichikawa *et al*., 2001; Kayahan *et al*., 2005), whereas it is possible that its anti-OCD effect could be due in part to 5-$HT_3$ receptor blockade. It should also be recalled that clozapine is an antagonist of muscarinic M1 and M3 receptors, but with high concentrations, it shifts to partial agonism (Olianas *et al*., 1999); should something similar occur to serotonergic receptors, it could explain why OCD symptoms in clozapine-treated people occurred with high blood concentrations of the drug (Schirmbeck and



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Zink, 2012). The clue to interpret findings is the specific localisation of receptors in the various areas and the timing of administration of the various drugs, but also patient biological variability.

Alternative mechanisms involve the glutamate system in OCD. Most data involve the medial prefrontal cortex (Fan *et al*., 2010; Aoki *et al*., 2012), pointing to impaired glutamatergic transmission there (Aoki *et al*., 2012) and in the cortico-striatal-thalamo-cortical circuit in OCD patients (Ting and Feng, 2008). This could be reflected in an increased glutamate wasting in the cerebrospinal fluid of OCD patients (Chakrabarty *et al*., 2005). Animal data point to the possible utility of *N*-methyl-D-aspartate (NMDA) glutamate receptor enhancement in OCD (Albelda *et al*., 2010), and interestingly, 5-HT$_3$ antagonists attenuate and granisetron enhances rat medial prefrontal NMDA responses (Liang *et al*., 1998).

In summary, despite recent progress, animal models currently mimic insufficiently human conditions and are currently unlikely to address the increasingly reported heterogeneity of OCD (Starcevic and Brakoulias, 2008; Nedeljkovic *et al*., 2009; Taylor, 2011; Brakoulias, 2013). The evidence for using 5-HT$_3$ receptor antagonists in OCD is piecemeal and does not adhere to indications derived from animal models of OCD. So, how is it that investigators decided to try 5-HT$_3$ antagonists in OCD?

### *What do clinical 5-HT$_3$ receptor antagonist studies say about their utility in OCD?*

The idea to use serotonin 5-HT$_3$ receptor inhibitors in OCD could have been justified after the report that ondansetron pretreatment enhanced the return of mCPP-induced anxiety behaviour back to normal in healthy human volunteers (Broocks *et al*., 1997), but scarcely so after the report that OCD patients were not responsive at all to ondansetron pretreatment before mCPP challenge (Broocks *et al*., 1998). The rationale that serotonin 5-HT$_3$ receptor inhibitors could lower mesolimbic dopaminergic hyperactivity led some investigators to use it in Tourette's disorder (Toren *et al*., 1999, 2005), a neuroleptic-responsive disorder sharing high co-morbidity with OCD and some of its pathogenic mechanisms (McDougle *et al*., 1993). Ondansetron 8 mg titrated to 16–24 mg/day monotherapy was accompanied by improved tics in four out of six Tourette patients with a trend towards improvement also on the Y-BOCS in those three who were co-morbid with OCD in one open study (Toren *et al*., 1999). However, a double-blind study versus placebo that followed 6 years later showed tic improvement on only one of the two scales used and no improvement on the Y-BOCS (Toren *et al*., 2005). These results point to 5-HT$_3$ receptor antagonists being active against tics, but not compulsions, in Tourette's disorder, thus questioning their utility in OCD if used alone.

The 5-HT$_3$ antagonist properties of olanzapine and mirtazapine, which induced improvement in nausea induced by inappropriately high doses of fluoxetine in one case of poor insight OCD (Fornaro and Martino, 2010), hardly constitute an indication for OCD. However, specific 5-HT$_3$ antagonists may nonspecifically increase treatment adherence to SSRIs, which have as their principal side effects nausea and vomiting; this could indirectly facilitate the therapeutic effects of SSRIs. It should be noted that in one of the studies considered here (Askari *et al*., 2012), nausea was one of the observed side effects; however, patients were also taking 100–200 mg/day fluvoxamine, which might have caused the side effect.

The first published paper on 5-HT$_3$ antagonists in OCD (Hewlett *et al*., 2003) had as a rationale the fact that increased serotonin in the synapse may benefit OCD and that 5-HT$_3$ antagonists were found to have anxiolytic properties, which is distant from the view that OCD is not a typical anxiety disorder. The second paper published was that of an add-on trial of ondansetron in OCD and had a sound rationale, not bound to any animal model of OCD, but integrating the serotonergic and dopaminergic models and incorporating data from animal studies and human neuronal activation patterns of the prefrontal cortex, providing a rationale not limited to the mesolimbic–mesostriatal transmissions, but extending to the frontal cortex and exploiting the cutting off of the reinforcing potential of the disorder (Pallanti *et al*., 2009). The rationale offered by the ondansetron–SSRI combination study was that ondansetron had worked as an add-on in the previous study and based on considerations of the localisation of the 5-HT$_3$ receptors and their actions, not attributing the possible anti-OCD activity to central or peripheral actions (Soltani *et al*., 2010). Finally, the granisetron–SSRI combination study used as a rationale the 5-HT$_3$ antagonist-induced reduction of reinforcement as well as clinical considerations, focusing on the VTA, which is the origin of both mesolimbic and mesocortical dopaminergic projections (Askari *et al*., 2012). All these studies were consistent in their finding some benefit for patients who were treated with 5-HT$_3$ antagonists. Despite these effects not being impressive, some benefit was obtained, and the two randomised, placebo-controlled trials showed an advantage of 5-HT$_3$ antagonists over placebo in



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obtained rating scale-documented improvement. However, safety data (Table 2) are favourable.

In summary, the studies heretofore reporting clinical utility of 5-$HT_3$ receptor antagonists in OCD are insufficient to document their efficacy either as monotherapy or as add-on or in combination with other drugs. However, data collected to date are not inconsistent, as they all point to the same direction. The possible usefulness of an add-on administration is suggested by the fact that 5-$HT_3$ antagonists and SSRIs have a synergistic anxiolytic/antidepressant effect in neuro behavioural rodent models (Gupta *et al*., 2014). Interestingly, recently developed antidepressants with anti-5-$HT_{3A}$ properties like vortioxetine, which was active in a spontaneous alternation rodent paradigm (whereas ondansetron was inactive; Gaarn du Jardin *et al*., 2014), are currently being proposed as possible treatment for OCD (Pizarro *et al*., 2014).

### *Limitations of currently available studies*

Beyond the already underlined limitations of study heterogeneity and small sample size, the heretofore conducted trials did not classify their OCD patients according to subtypes (Lochner *et al*., 2008), dimensions (Storch *et al*., 2010) or proposed specifiers (Leckman *et al*., 2010). In the DSM-5, hoarding disorder is not put inside OCD, but along body dysmorphic disorder, hair pulling, skin picking and other clinical entities; it is put aside as one of the obsessive–compulsive and related disorders (American Psychiatric Association, 2013). As clinical studies performed to date have been conducted without distinction between hoarding disorder and OCD, it is possible that some OCD results could be ascribed to hoarding disorder. It should be stressed that OCD and hoarding disorder appear to be biologically distinct (Tolin *et al*., 2014). There was a lack of randomised controlled trials, and the possible year-of-publication bias (Ackerman and Greenland, 2002) cannot be set off, since similar time intervals were involved in the Ackerman and Greenland (2002) regression analysis and in this review. Furthermore, the trials conducted with 5-$HT_3$ receptor antagonists in OCD as previously conceptualised are too few to allow for clear-cut conclusions to be drawn. Despite results heretofore being scanty, because the American Psychiatric Association (2007) considers it as a third-line treatment for OCD, this class of drugs is worth considering for further studies to clarify its possible utility in the treatment of OCD.

## CONCLUSION

The few clinical studies of 5-$HT_3$ antagonists in the treatment of OCD support a role of these drugs in inducing improvement, but the relatively small sample sizes do not allow drawing of straightforward conclusions. Their effects were claimed to occur also in monotherapy, but we feel that in the presence of drug resistance, their use would be best exploited in add-ons. Clinical studies suggest that the question should be more focused upon by animal studies, whose indications have not been tested adequately in clinical studies as of now and did not lead to date to the development of new medications for OCD. Animal research and human clinical research need to keep pace of one another and to reciprocally incorporate the issues arising from each one. Future studies should be able to distinguish between OCD proper and hoarding disorder, which is currently being investigated autonomously in clinical trials (e.g. Rodriguez *et al*., 2013; Saxena and Sumner, 2014).

## FINANCIAL AND COMPETING INTERESTS DISCLOSURE

In the past 3 years, Stefano Ferracuti has participated in advisory boards for Pfizer and Lilly and received honoraria from Lilly, Bristol-Myers, Sigma Tau, Schering and Pfizer; Paolo Girardi has received research support from Lilly and Janssen, has participated in Advisory Boards for Lilly, Organon, Pfizer and Schering and received honoraria from Lilly and Organon; Roberto Tatarelli has participated in Advisory Boards for Schering, Servier and Pfizer and received honoraria from Schering, Servier and Pfizer. Georgios D. Kotzalidis is the recipient of a Research Grant of the Italian Ministry of Education and University.

All other authors of this paper 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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