



AUGMENTATION STRATEGIES IN SELECTIVE SEROTONIN REUPTAKE INHIBITORS RESISTANT OBSESSIVE-COMPULSIVE DISORDER - A SYSTEMATIC LITERATURE REVIEW

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Abstract. The efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of obsessive-compulsive disorder (OCD) has some important limitations, as almost half of these patients are non-responders. Therefore, an increasing number of pharmacological augmentation strategies have been developed in order to cope with SSRIs non-responders: increasing dosages to the maximum tolerated level, antidepressants switch, augmentation with pharmacologic agents or psychotherapy, alternative ways of treatment administration etc. In this systematic review we evaluated studies which focused upon the efficacy of the pharmacologic augmentation strategies in SSRIs resistant cases of OCD. Atypical and typical antipsychotics, antidepressants and other agents such as beta-blockers, psychostimulants or omega 3 fatty acids were detected in clinical studies and included in our review. The most supported strategies are typical antipsychotics (especially haloperidol), atypical antipsychotics (mainly risperidone), antidepressants like clomipramine or trazodone and the beta-blocker pindolol. More research is needed in order to evaluate the efficacy of other pharmacologic agents, such as newer antipsychotics and antidepressants, mood-stabilizers and various serotonergic agents.

Keywords: resistant obsessive-compulsive disorder, antidepressants, antipsychotics, mood-stabilizers, augmentation strategies

1. Introduction

Although clomipramine and selective serotonin reuptake inhibitors (SSRIs) efficacy in obsessive-compulsive disorder (OCD) is sustained by many researches in the literature, this pathology is associated with a notorious tendency to treatment-refractoriness and a rather reserved long-term prognosis. It is estimated that more than 40-60% of the SSRIs treated population have negative results that are associated with serious social disability [1]. This situation is not singular in the anxiety disorders spectrum, as a Cochrane meta-analysis (28 short-term randomized controlled trials-RCTs, 740 participants) showed that a significant proportion of

patients fail to respond to first-line medications [2].

The efficacy of increased antidepressant (mainly SSRIs) dosages for resistant OCD was evaluated in both prospective [3,4] and retrospective trials [5] with favourable results. Doses of sertraline were increased up to 400 mg daily and escitalopram was administered in 33.8 mg mean daily dose. Still, the dangers of adverse events and lowering the quality of patients' life suggest the need for investigating other treatment strategies.

Intravenous administration of clomipramine was evaluated in a small scale RCT in patients refractory to oral clomipramine and the results were superior to placebo [6]. There is a lack of replication studies regarding this specific technique, so its efficacy is still debatable.

Antidepressant switch is an option whenever adverse events are severe or the drug efficacy after 8-10 weeks at the high-end of the therapeutic range is not satisfactory. The duration of a therapeutic trial in OCD is extended by many authors to 12

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weeks, due to the peculiarities of this disorder [7]. Although this recommendation is intuitive and frequently used in clinical practice, there are few studies evaluating long-term efficacy of this strategy. Clinicians could switch to a different antidepressant, cognitive-behavioral therapy or, less frequently, to a drug from a different class.

not respond to treatment. We did not include trials with psychotherapy and pharmacotherapy combos, this decision being based upon the need for a more homogenous group of therapeutic strategies.

We included in our review all the drugs found as augmentation pharmacologic agents, even the dietary supplements or over the counter medicines.

Criteria	Inclusion	Exclusion
Population	Population with age over 18, diagnosed according to DSM IV TR/DSM IV/DSM III R criteria with OCD, who had at least one failed SSRI trial due to non-responsiveness and who are currently in an augmentation phase of the treatment.	Trials with unspecified age of the target population or with pediatric population. Patients who had not previously received SSRIs. Patients that received augmentation pharmacological agents to SSRIs previously.
Intervention	Clinical trials (CTs) which evaluated pharmacological augmentation agents to SSRIs. Open label, RCTs, non-randomized CTs, case series, case control studies, systematic reviews, meta-analyses.	CTs with psychotherapy or combined psychotherapy + pharmacotherapy design.
Site	Hospital, day-care, ambulatory settings	Unspecified place of intervention
Results	Decreasing the severity of OCD as main outcome (evaluated on clinical scales like Y-BICS, CGI or specialists consensus). Secondary outcomes (if any) were increases in the quality of life, general anxiety decrease, global functioning increase etc.	CTs without decreasing the severity of OCD symptoms as main outcome.

Table 1. Overview of inclusion/exclusion criteria for the systematic literature review

2. Objective and methods

Augmentation in resistant OCD is the mostly researched strategy and the majority of data support the utility of this approach. Therefore, we selected as main objective of our review the augmentation strategies efficacy. For this purpose we selected clinical studies through a search in PubMed, MEDLINE and Cochrane databases, recorded until September 2010 and reference list of articles. We selected studies corresponding to keywords “resistant obsessive compulsive disorder”, “augmentation” and “pharmacological treatment”. All the studies were performed on adult population, using at least two different drugs simultaneously, with the second pharmacologic agent being introduced after at least 8 weeks of mono-therapy with unsatisfactory results (partial or complete non-responsiveness). All patients were diagnosed with DSM IV TR/DSM IV/DSM III R criteria of OCD and presented at least one previous trial with an SSRI during which patients did

3. Results

A number of 67 studies or reviews were found, but only 44 researches satisfied the criteria for inclusion in this review. Since all the studies, meta-analyses and systematic reviews are indexed and could be consulted in the references list, we included in the summary table only the most important researches (table 2).

3.1. Typical antipsychotics

The first double-blind, placebo-controlled antipsychotic augmentation of serotonergic therapy in patients with obsessive-compulsive disorder resistant to treatment, included 34 subjects in the fluvoxamine nonresponders [8]. Patients were randomly assigned to haloperidol (2-10 mg/day, n = 17) or placebo (n = 17) and monitored for four weeks. Of the subjects who received haloperidol group 11 were responders, compared with none in the placebo group. Responsiveness was defined by

Study	Intervention	Design	Population Size=N, (age range)	Outcome indicators	Outcome	L
McDougle CJ et al., 1994 [8]	Fluoxetine nonresponders, haloperidol augmentation (2-10 mg/day) vs. placebo, 4 weeks	Double blind, placebo controlled	N=34, +/-comorbid tic disorder	Y-BOCS score, CGI-I score, clinician consensus Response defined as YBOCS <35%, <16; CGI-I 1.2	Haloperidol superior to placebo in cases with comorbid tics. 11 responders haloperidol vs. 0 in placebo group	4
Keuneman R] et al., 2005 [9]	SRIs and antipsychotics, typical or atypical	Systematic literature review; MEDLINE, EMBASE search (until 2003); medical databases search upon keywords "obsessive-compulsive", "antipsychotic" and "subtypes"	NS	Decreases in OCD symptoms, clinical consensus	Haloperidol and pimoziide are effective as augmenting agents in SRIs non-responsive patients	3
Stein DJ et al., 1997 [12]	Patients were treated with SRIs and risperidone.	Retrospective study, analysis of all OCD patients charts in a specialized clinic.	N=18 (OCD, trichotillomania or Tourette's syndrome)	Decreases in OCD symptoms, NS	Risperidone is efficient as augmenting agent; frequent adverse events, appropriate dose range needs to be further explored	1
McDougle et al., 2000 [14]	Risperidone (2.2 +/-0.7 mg/d) vs. placebo plus SRIs, 12 weeks	Prospective, placebo-controlled, double-blind trial, refractory to SRIs OCD patients	N=70	Y-BOCS score	Risperidone was superior to placebo (p<0.001) in OCD symptoms reduction; good tolerability of risperidone	3
Bystritsky A et al., 2004 [16]	Olanzapine up to 20 mg/day vs. placebo, 6 weeks	Placebo-controlled, double-blind RT	N=26	Y-BOCS score -25%	46% patients had positive results (according to the criteria of the study)	3
Maina G et al., 2008 [20]	Risperidone (1-3 mg/d) vs. olanzapine (2.5-10 mg/d), 16+8 weeks	Single-blind, RT ; 1 st phase-open label prospective to ascertain SRI resistance; 2 nd phase-single blind addition of risperidone vs. olanzapine	N=92 (prospective phase)	Y-BOCS score	No differences between groups at endpoint; significant response to baseline in both groups	3
Metin O et al., 2003 [22]	Amisulpride (mean dose 325+/-106 mg/day) augmentation, 12 weeks	Patients with history of SRIs resistance	N=20	Y-BOCS score, UKU scale for side events	Significant improvements- reduction of Y-BOCS from 26.7+/-6.3 to 12.5+/-2.8 (p=0.0001)	2

Table 2. Summary table of the results of the systematic literature review
L=level of evidence, consisting of the mean score of the evaluations realized by each researcher (DV, OV, A.G.M, D.G.O), based upon the design of the study and its relevance for the subject (values between 1=low quality and 5=very high quality), NS=not specified

Denys D et al., 2004 [24]	Quetiapine (up to 300 mg/day) vs. placebo, 8 weeks. Resistance to at least 2 SRIs trials	Double blind, placebo-controlled trial	N=40	Y-BOCS>35%, CGI-I	Y-BOCS decrease of 9.0+/-7.0 (31%) in the quetiapine group vs. 1.8+/-3.4 (7%) in the placebo group (F=16.99, df=1.38, p<0.001); 8 responders in the quetiapine group vs. 2 in placebo group (chi ² =4.8, df=1, p=0.28)	3
Bloch MH et al., 2006 [29]	Typical and atypical antipsychotics in resistant OCD	Systematic literature review of double-blind RCT; PubMed, PsychINFO, Embase, Cochrane databases search (until 2005); keywords- "antipsychotic agents", "neuroleptics", "OCD"	N=9 studies, 278 participants	Y-BOCS-35%	Antipsychotic augmentation was considered efficient (ARD=0.22, 95%CI 0.13, 0.31). Antipsychotic augmentation is indicated in patients with at least 3 months of maximal-tolerated SRI therapy. Haloperidol, risperidone-sufficient evidence; quetiapine and olanzapine-inconclusive evidence	4
Pigott TA et al., 1992 [37]	Trazodone (235+/-10 mg/day) vs. placebo, 10 weeks	Double-blind, placebo-controlled study	N=21	Standardized OCD and depression rating scales	Trazodone lacks substantial antiobsessive effect	4
Dannon PN et al., 2000 [40]	At least 2 failed SRIs trials; pindolol (2.5 mg x3/day) as augmentation to paroxetine	Double-blind, placebo controlled trial	N=14	Y-BOCS, HAM-A, MADRS	Significant improvement (p<0.01) in Y-BOCS at 4 weeks; no difference in HAM-A and MADRS between pindolol and placebo	3
Van Ameringen et al., 2006 [49]	Adjunctive topiramate (253.1+/-93.9 mg/day) to consecutive outpatients with OCD, partial or non-responders to SRI monotherapy or SRI combination therapy, 14 weeks	Retrospective, open-label case series	N=16	CGI-I/S	11/16 patients were responders (68.8%) CGI-I scores of much improved; or very much improved; follow-up until 26 weeks had significant CGI improvements (p<0.001)	2

Table 2. Summary table of the results of the systematic literature review (continued)
L=level of evidence, consisting of the mean score of the evaluations realized by each researcher (D.V, O.V, A.G.M, D.G.O), based upon the design of the study and its relevance for the subject (values between 1=low quality and 5=very high quality), NS=not specified

Y-BOCS the score with 35% and score under 16, CGI-I 1.2 and clinician consensus between principal investigator and two other investigators. Patients with comorbid tic disorder responded better to haloperidol, compared to patients without tics.

A literature review [9] showed that early studies of SSRIs augmentation with haloperidol or pimozide in OCD demonstrated favourable response.

3.2. Atypical antipsychotics

Risperidone has been evaluated in terms of efficacy and tolerability as augmentation strategy in four open label RT [10,11,12,13] and two double-blind studies [14,15]. The results were positive for risperidone, this drug proved to be superior to placebo as an augmentation agent in OCD resistant patients with one or more failed SSRIs trials. Patients were monitored using Y-BOCS and clinical consensus. Risperidone decreased OCD symptoms, but also depressive and anxiety symptoms [14].

Olanzapine was also assessed in subjects with OCD refractory to treatment with SSRIs. A placebo-controlled trial, double blind, [16] included 26 subjects with 6 weeks of augmentation with olanzapine (up to 20 mg/day) versus placebo. Y-BOCS covariance analysis scores was used to determine effective strategies for augmentation, and responsiveness was defined as a decrease of at least 25% of scores on this scale. Among patients treated with olanzapine, a total of six (46%) showed improvement over 25% of Y-BOCS score, compared with no cases in the group who received placebo.

Another double-blind, placebo-controlled study of 6-week duration, included the addition of lower doses of olanzapine (5-10 mg/day) with fluoxetine therapy in cases resistant obsessive-compulsive disorder [17]. Patients had followed an open-label phase, lasting eight weeks, which received fluoxetine, the response was partial or absent. The group receiving olanzapine and fluoxetine, and one that was treated with fluoxetine plus placebo had significant improvements during the 6 weeks ($F = 11.64$, $p < 0.0001$).

An open-label study [18] included 10 participants diagnosed with OCD for at least one year, with a minimum Y-BOCS value of 18. Patients were nonresponders to fluoxetine (at least 60 mg/day, minimum 10 weeks) and had failed 1-5 trials focused only on SSRIs. These subjects received as augmentation strategy olanzapine, in doses increasing from 2.5 mg/day to 10 mg/day, during 4 weeks.

A long term study, open label, included 26 subjects with obsessive-compulsive disorder, diagnosed for at least two years, resistant to SSRIs therapy, who received olanzapine and were monitored for at least one year [19]. After 12 weeks of combination therapy, most patients ($n = 17$) had reduced

symptoms of the obsessive-compulsive disorder, as the Y-BOCS lower total score, and this tendency to decrease was maintained throughout the 12 months of the study.

Comparison of **olanzapine and risperidone** augmentation regarding the augmentation of the SSRI effect in OCD patients who responded by not more than 35% decrease in Y-BOCS score after 16 weeks was achieved in a single blind study [20], lasting 8 weeks. Patients receiving augmentation therapy had significant response to the baseline without recording differences in the efficacy of the two antipsychotics.

A case report on **aripiprazole** augmentation of SSRI therapy at high doses involved a patient with limited insight OCD who had a favourable evolution [21].

Amisulpride, in a flexible dose of 200-600 mg/day (mean dose 325 ± 106 mg/day), was evaluated as an augmentation strategy in 20 patients with refractory OCD to SSRIs in an open study [22]. The difference between the baseline and endpoint Y-BOCS score (26.7 ± 6.3 to 12.5 ± 2.8) was statistically significant ($p = 0.0001$).

Quetiapine was administered in a double-blind, randomized, placebo-controlled augmentation of SSRI therapy for obsessive-compulsive disorder refractory to SSRIs [23]. This study used flexible doses of quetiapine in patients who had not responded adequately to a period of 12 weeks SSRI open-label. The double-blind phase included 42 patients who were randomized to placebo or quetiapine for 6 weeks. There were significant improvements in the recorded scores Y-BOCS, both among those treated with quetiapine (40% responders, $n = 8$) and in patients treated with placebo (47.6% responders, $n = 10$). Thus, quetiapine did not demonstrate significant benefit compared with placebo at the end of six weeks of treatment ($p = 0.636$).

Another double-blind, randomized, placebo-controlled trial [24] included 40 elderly patients diagnosed with primary OCD, who were assessed during 8 weeks therapy with quetiapine 300 mg/day or placebo. All patients were non-responsive to at least two different antidepressants in the SSRI class, administered at the maximum tolerated doses for 8 weeks. Responders were defined by subtracting Y-BOCS score at least 35%. The final results showed mean reductions of Y-BOCS score by 9.0 ± 7.0 (31%) in subjects treated with quetiapine and 1.8 ± 3.4 (7%) in the placebo group ($p < 0.001$), 8 patients who received active substance (40%) and 2 (10%) of those receiving placebo were responders ($p = 0.028$).

There are also open label studies which show positive results for quetiapine as an augmenting agent in OCD SSRIs non-responders [25,26,27].

Ziprasidone and quetiapine were compared in a retrospective study in 24 patients, as augmentation strategies with high doses of SSRIs [28]. Global clinical improvement was obtained in 80% of the patients treated with quetiapine and 44.4% of those treated with ziprasidone, the overall improvement on Y-BOCS being 66.7%. Y-BOCS and CGI scores were higher at 2, 3 and 6 months follow-up for patients in the ziprasidone group, compared with the quetiapine group.

Comparative analysis of antipsychotics

A systematic review of the SSRI therapy antipsychotic augmentation effect in refractory OCD [29] included double-blind, randomized studies contained in the PubMed (1967-2005), Embase (1974-2000) and Cochrane Central Register of Controlled Trials databases. Patients considered responsive were those with more than 35% reduction in Y-BOCS scale during augmentation with antipsychotics. Nine studies involving 278 participants were obtained from the search in the mentioned databases. The meta-analysis of these studies supported the effectiveness of antipsychotic augmentation (absolute risk difference was significant at values of 0.22, confidence interval 0.13-0.31). Another finding of this meta-analysis was that patients with OCD should be treated with SSRIs for at least three months at maximum dose before initiation of antipsychotic augmentation. Only one third of patients with resistant OCD had a significant response to antipsychotic augmentation. Data from the literature supports the effectiveness of haloperidol, risperidone and less of quetiapine or olanzapine.

Augmentation with atypical antipsychotics has been studied in SSRIs non-responders (n=44) after 12 weeks that were subsequently assigned to combination therapy with SSRIs and olanzapine, quetiapine or risperidone, in parallel with cognitive-behavioral therapy [30]. The duration of this study was one year and, in terms of results, it was found that the Y-BOCS total score decreased from 29.3 +/-9.9 (baseline) to 19.3 +/-6.8 (one year).

Another meta-analysis focused upon the effectiveness of antipsychotic augmentation in SRIs refractory OCD included 10 RTs with the following active substances: haloperidol (n = 1), risperidone (n = 3), olanzapine (n = 2) and quetiapine (n = 4) [31]. The total number of subjects included in this meta-analysis was 305, out of which 157 were randomized on pharmacologically active agent and 148 on placebo. The response was more frequently observed in patients receiving antipsychotics and the combined weighted rate of responsiveness was 3.31 (95%, confidence interval 1.40-7.84).

3.4. Antidepressants

Citalopram administered intravenously (iv) was evaluated in an open study on a group comprising 39 outpatients diagnosed with OCD, monitored for over 3 weeks [32]. Patients included in this study had moderate to severe OCD symptoms, persisting for at least one year, a Y-BOCS original score of at least 25 and they had not responded to at least two oral SSRIs trials, except for citalopram. Drug administration was performed iv, starting from 20 mg/day, up to 40-80 mg/day, depending on individual tolerability, during the first 21 days and orally thereafter, until day 84. Study results show that the substance was well tolerated even at high doses (2.6% discontinuation rate). In terms of effectiveness, the Y-BOCS score decreased by 35% in 39 patients, of whom 4 had reductions of more than 35%. Some of the patients had reductions in the Y-BOCS total score of over 20% (n = 27) and additional improvements were obtained by day 84.

Clomipramine added to SSRIs or vice versa, adding an SSRI to clomipramine, as augmentation therapy is an option supported by several open studies and expert consensus. Another open-label, comparison RT, involved citalopram vs. citalopram plus clomipramine in patients with resistant to treatment OCD [33]. This trial evaluated 16 adult outpatients (aged between 18 and 45 years) for 90 days with moderate to severe forms of OCD, the minimum initial Y-BOCS score 25, without comorbid axis I, who had not responded to therapy with clomipramine or citalopram, administered separately. Patients treated with citalopram and clomipramine (n=9) had a Y-BOCS score decreasing significantly compared with patients Y-BOCS treated only with citalopram (n=7) at day 90. The average improvement of the Y-BOCS score was 35% in patients who received antidepressants combination.

Infused clomipramine was evaluated in 56 subjects diagnosed as refractory to oral clomipramine OCD [34]. Clomipramine was administered to these patients as 14 infusion doses and the follow-up period ranged from 4 to 11 years. Of the 44 subjects interviewed on re-evaluation, 70.5% had OCD and obsessive-compulsive symptoms, while 29.5% were below the clinical level. Nearly 50% reported large and very large improvements compared to their previous status with clomipramine infusion.

In patients with inadequate response to 6 months of clomipramine 150 mg/day the addition of 50 mg/day sertraline was considered better than when the dose of clomipramine was increased to 250 mg/day [35].

Trazodone as a strategy for augmentation of SSRI therapy was evaluated in a series of case

reports and small scale studies. Thus, in some cases ($n = 5$), augmentation of SSRI therapy with trazodone 300-600 mg/day has helped to reduce symptoms of OCD, anxiety and sleeplessness, sexual dysfunction and gastrointestinal discomfort [36]. A double-blind, placebo-controlled RT that included 11 subjects treated with trazodone (235 mg/day mean dose) and 6 patients who received placebo, found no significant differences between the two groups [37]. However, this study was short term (6 weeks) and included too few subjects to be relevant.

3.5. Others

A placebo-controlled cross-over trial used **eicosapentaenoic acid (EPA)** as adjunctive agent in SSRI treated obsessive-compulsive disorder [38]. This study included 11 patients on stable maximally tolerated dose of SSRI with no improvement in the last 2 months. These patients were randomly allocated on placebo (6 weeks), followed by 2 g of EPA, or EPA followed by placebo, while they continued the SSRI treatment. The mean scores declined from 26.0 +/-5 to 17.6 +/-6 by week 6 on placebo and to 18.5 +/-4 on EPA. The negative results suggest that adjunctive EPA is not recommended as adjunctive agent to SSRI in resistant obsessive-compulsive disorder.

Dextroamphetamine proved itself efficient versus placebo in severe chronic OCD in a double-blind cross-over study [39].

Pindolol is a beta-blocker and serotonin 1A presynaptic receptor antagonist that increases serotonergic transmission and has mixed results as augmentation agent in resistant obsessive-compulsive disorder. Pindolol up to 2.5 mg x 3/day was associated to paroxetine (60 mg daily) in a double-blind, placebo-controlled study, in resistant obsessive compulsive disorder [40]. This augmentation strategy was efficient vs. placebo after 4 weeks ($p < 0.006$) on Y-BOCS scores. An 8-week, double-blind, placebo-controlled study examined the efficacy of pindolol added to fluvoxamine [41] and found no differences between active drug and placebo. Two open-label studies found either a modest effect of pindolol augmentation (one responsive patient out of 8) or response only after tryptophan was also added to a serotonergic agent, in a triple combination [42,43].

Buspirone in doses up to 60 mg/day was evaluated in small and methodologically limited studies that could not find certain effectiveness in resistant OCD. A 10 weeks, double blind, placebo-controlled RT evaluated buspirone augmentation but did not find significant differences versus placebo, also 29% of buspirone patients responded, as the YBOCS scores showed [44]. Another 6-week, double-blind, placebo controlled study that evaluated the efficacy

of 60 mg/day buspirone as augmentation strategy to fluvoxamine showed negative results [45].

Inositol has been studied in double-blind, placebo-controlled studies as an augmentation strategy and the data suggest a mild effect of this drug in a minority of resistant obsessive-compulsive disorder patients. One double-blind, placebo-controlled study, with 13 subjects, evaluated the effect of adding inositol to SSRIs and concluded that there was a small but significant decrease in the active drug group [46]. Another double-blind, placebo-controlled study showed no difference between groups, but there were only 10 patients included in this trial [47].

Memantine is another drug evaluated for the treatment of resistant obsessive-compulsive disorder in a 2009 clinical trial due to the genetics, neuroimaging, animal studies and case reports that support involvement of glutamatergic mechanisms in the pathophysiology of this pathology [48]. In an open-label trial 15 adult subjects who had not responded to SSRIs treatment for at least 12 weeks received 20 mg/day memantine for 12 weeks. At endpoint, 6 patients were responders (42.9%) as Y-BOCS scores reflected.

Topiramate is another glutamatergic drug investigated as an augmentation agent in SSRIs monotherapy partial or nonresponsive patients for a minimum of 14 weeks [49]. The mean dose of topiramate was 253.1 +/-93.9 mg/day and the mean time to response was 9.2 +/- 4.5 weeks. CGI-S scores decreased significantly from initiation of topiramate until 26 weeks ($p < 0.001$). This case series suggests the addition of topiramate may be useful in treatment-resistant obsessive-compulsive disorder.

Gabapentin (mean dose 2520 mg/day) augmentation was evaluated in a 6 weeks open-label study in 5 patients who responded partially to fluoxetine [50]. This trial showed a partial response to gabapentin augmentation.

A double-blind, placebo-controlled study [51] showed a response (Y-BOCS decrease with 25%) to 30-45 mg once-weekly oral **morphine sulphate** in the treatment resistant OCD.

Ondansetron 1 mg x 3 times daily was associated with significant decrease in Y-BOCS scores in an 8 weeks, small, open-label study [52].

Conclusions

The synthesis of clinical data extracted from the systematic review is presented in table 3, accompanied by the level of evidence for each augmentation therapeutic strategy.

The most convincing data at this moment support augmentation of SSRIs resistant OCD with antipsychotics (level of evidence B). There are significant differences between individual antipsychot-

Class of drugs	Studies	References	Level of evidence
Typical antipsychotics (haloperidol, pimozide)	1RT DB PC; 1SLR	8,9	A
Atypical antipsychotics			
Risperidone	4 OL RT; 2 RT DB PC; 1 CT SB	10-15, 20	A
Olanzapine	2 OL RT; 2 RT DB PC; 1 CT SB		
	1 CS	16-19, 20	B
	1 RT OL		
Aripiprazol	2 RT DB, 1 CT R	21	D
Amisulpride	1 CT R	22	D
Quetiapine	1 RT, 1 SLR, 1 MA	23-27, 28	C
Ziprasidone		28	D
Antipsychotics overall efficacy (typical, atypical)		29-31	B
Antidepressants			
Citalopram	1 RT OL	32	C
Clomipramine	3 RT OL	33-35	B
Trazodone	1 RT DB PC, 1 CS	36,37	B
EPA	1 RT DB	38	D
Dextroamphetamine	1 RT DB	39	D
Pindolol	2 RT DB PC, 2 RT OL	40-43	B
Buspirone	2 RT DB PC	44,45	D
Inositol	2 RT DB PC	46,47	C
Memantine	1 RT OL	48	D
Morphine sulphate	1 RT DB PC	51	C
Ondansetron	1 OL trial	52	C
Topiramate	1 OL trial	49	C
Gabapentin	1 OL trial	50	C

Table 3. Level of evidence for augmentation strategies in SSRIs resistant OCD

Legend:

RT=randomized trial

DB=double-blind, SB=single-blind

PC=placebo controlled, OL=open label

SLR=systematic literature review

CT=comparative head-to-head trial

R=retrospective

CS= case series

MA=meta-analysis

GRADE A High quality— Further research is very unlikely to change our confidence in the estimate of effect,

GRADE B Moderate quality— Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate,

GRADE C Low quality— Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate,

GRADE D Very low quality— Any estimate of effect is very uncertain.

ics regarding their efficacy in the treatment of OCD symptoms. Risperidone and typical antipsychotics (haloperidol and pimozide) are associated with the most evidence and are recommendations of level A, followed by olanzapine and quetiapine.

Clomipramine and trazodone could be used as augmentation strategy in this population (level of evidence B), although the risk for developing a serotonergic syndrome should be taken into consideration.

Adding pindolol to an SSRI and, in a less supported manner, inositol, topiramate, gabapentin, ondansetron and morphine sulphate could be recommended as third line approach, in order to increase the efficacy of the antidepressant. EPA,

dextroamphetamine and buspirone have been associated until now with unsatisfactory or negative results.

More research is needed in order to formulate clear recommendation, especially for newer atypical antipsychotics and antidepressants or other serotonergic agents.

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