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REVIEW ARTICLE

Placebo Effect in Obsessive-Compulsive Disorder (OCD). Placebo Response and Placebo Responders in OCD: The Trend Over Time

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Abstract: ***Background*:** Placebo response appears to be increasing in antidepressant, antipsychotic and various internal medicine trials. A similar trend has been reported for OCD during 1989-1999. Placebo response is generally considered as the extent to which placebo treatment is associated with core symptom improvement. In this analysis, we used Joinpoint regression to assess the time trend of both placebo response and placebo responder rates according to the year of publication with no time restriction in OCD drug trials.

***Method*:** We included drug and/or psychotherapy trials *vs*. placebo from PubMed, Embase, CINAHL, and PsycINFO retrieved through the search (placebo OR sham) AND (obsessive* OR OCD). We included studies through investigator consensus. We then performed on data of included studies log-linear joinpoint segmented regression models using a $p<0.05$ cutoff.

***Results*:** We included 113 studies from 112 published papers. Placebo mean annual response rates in OCD studies significantly increased from 1991 to 2017 with an annual percent change (APC) of 0.66%, while placebo mean annual responder rates also significantly increased from 2010 to 2017, with an APC of 5.45%. Drug mean annual response rates in OCD studies significantly increased from 1987 to 2012 with an APC of 0.72%, while the corresponding responder rates did not show statistically significant APC changes between 1984 and 2017.

***Conclusion*:** We observed a tendency for placebo to increase both measures of response in OCD clinical drug trials through the years that tend to approximate the responses shown by drugs. Changes in the type of study (moving from classical head to head comparisons to add-on studies in treatment-resistant populations) and countries involved in experimentation may partially account for some portion of these results. It appears that placebo effects are becoming more elusive and out of control.

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1. INTRODUCTION

A common belief lasting until the early nineties was that obsessive-compulsive disorder (OCD) did not respond to placebo [1]. However, this view rapidly changed as reliable scales developed to measure OCD symptoms.

There are two ways to measure the response of a patient or of a group of patients to a given treatment, drug or placebo, *i.e*., to consider improvement with respect to a baseline on a predetermined rating scale in terms of points or percentage, hence providing a measure of the percent response of a group, and to define some criteria for responsiveness and provide the percentage of patients who reached or surpassed a given threshold to qualify as treatment responders. A further specification of the latter is the remitter status, based on even stricter criteria. We will call the former "placebo (or drug) effect" to differentiate it from the ambiguous term "placebo (or drug) response", and term the latter responder rate (to placebo or drug) so to hold the two concepts apart. In OCD, the most commonly used rating scale as a primary outcome measure is the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) [2, 3] and responses to treatments, or treatment effects, as we term them to avoid confusion with number of persons who are considered as treatment responders, are rated as percent variations of scores on the Y-BOCS from baseline at a given time-point. On the other hand, treatment responder rates are considered as the fraction of patients in the sample who are judged on the basis of established criteria, usually an at least 35% (or 25%, according to the study's author choice) drop of Y-BOCS scores from baseline or 1 or 2 (very much or much improved, respectively) on the Clinical Global Impressions scale, improvement version [4].

There is evidence for the growth of placebo effect (and responder rates) in clinical trials across the years for depression [5] and, less consistently, bipolar disorder [6], although some biases may have influenced the conclusions of this second study [7]. Other psychiatric disorders have not been investigated for this year-of-publication effect specifically, but a multivariate meta-analysis carried-out by Ackerman and Greenland [8] found an increase in the effect of placebo through the years, confirming the impressions of others [9]. This could be due to the host of factors, like trends in the type of patient recruited (regarding illness duration, severity, and comorbidity), type of drug used (the side effect profile of a drug like clomipramine increases the likelihood of drug identification by both clinician and patient and may affect outcome), study site characteristics (that may reflect the characteristics of participating physicians and principal investigators and contribute to large across-sites differences which are usually disregarded in most reports), outcome measures employed, publication bias-file drawer effect, and last, but not least, the fact that the more effective the drug in a study, the more effective the placebo [10]. In fact, a publication year effect has been shown for OCD treatment across the years [11]. However, Ackerman and Greenland [8], who used meta-regression to evaluate placebo-controlled drug trials in OCD, did not include in their remarkable paper, drug trials in paediatric populations did not consider surgical procedures *versus* sham surgery or psychotherapies *versus* sham psychological interventions, and failed to consider a considerable number of papers covering a quite long period of time. In fact, they analysed a restricted period of time of placebo-controlled drug trials of three SSRIs and clomipramine in a period spanning from 1989 to 1999 (*i.e*., after the introduction of the Yale-Brown Obsessive Compulsive Scale, Y-BOCS), with a consequent loss of more than ten years of literature.

Systematic investigations of treatment of OCD started at the dawn of the eighties, with the use of clomipramine [12, 13]; clomipramine [14] and imipramine [15, 16] dominated the scene during the mid-eighties, and it was only during the late eighties that SSRIs, primarily fluvoxamine, were introduced [17, 18]. The first two studies comparing sertraline to placebo appeared in 1990 and yielded contrasting results [19, 20]. The first published trials of fluoxetine *versus* placebo appeared in 1992 [21], but regarded data that started being gathered in the late eighties [22-24], therefore simultaneous with, if not preceding those of sertraline. It is noteworthy that fluoxetine had received extensive open trials in OCD since 1985 [25], whereas for sertraline, the two aforementioned double-blind studies were the first studies of sertraline in OCD to be published [19, 20]. This publication lag may create a bias in the attempt to clarify whether the effect of a given treatment increased or decreased with time. Unfortunately, most studies do not provide the period during which they were conducted and render it difficult to correct for this bias. Hence, we will consider publication data as a factor despite realising that it does not exactly reflect the period during which the study has been carried out.

Our aim was to extend Ackerman and Greenland's [8] observations beyond 2002, including also studies that did not use drugs, but other methods as well that could ensure double-blinding. We did not use the same method, but rather a JoinPoint regression.

2. METHODS

We carried-out a general search in the PubMed-MedLine-Index Medicus and Embase-Excerpta Medica and PsycLit-Psychological Abstracts databases using the following strategy: (placebo OR sham) AND (obsessive* OR OCD) with no time, language or any other restriction, but animal studies were subsequently excluded. We did not use the PubMed "Animal studies" function to exclude such studies, because such function often produces unreliable results. Papers were individually searched for adherence to our inclusion criteria. Retrieved relevant papers, comprising reviews and meta-analyses, were searched in their reference lists for providing additional papers with adequate research data. Final inclusion criteria for data analysis comprised: single or double-blind design, clearly stated assessment of response (responder rate or percent response on rating scales), sufficient time of treatment administration for the expected response to be observed, absence or adequate addressing of confounders that could render response not attributable to specific treatments. Specifically, the second part of cross-over studies was discarded if switching from one treatment to another had not a sufficient treatment-free wash-out period to avoid carry-over effects; survival studies were excluded when tapering-off of a combined therapy involved a drug vs. placebo when another drug or treatment

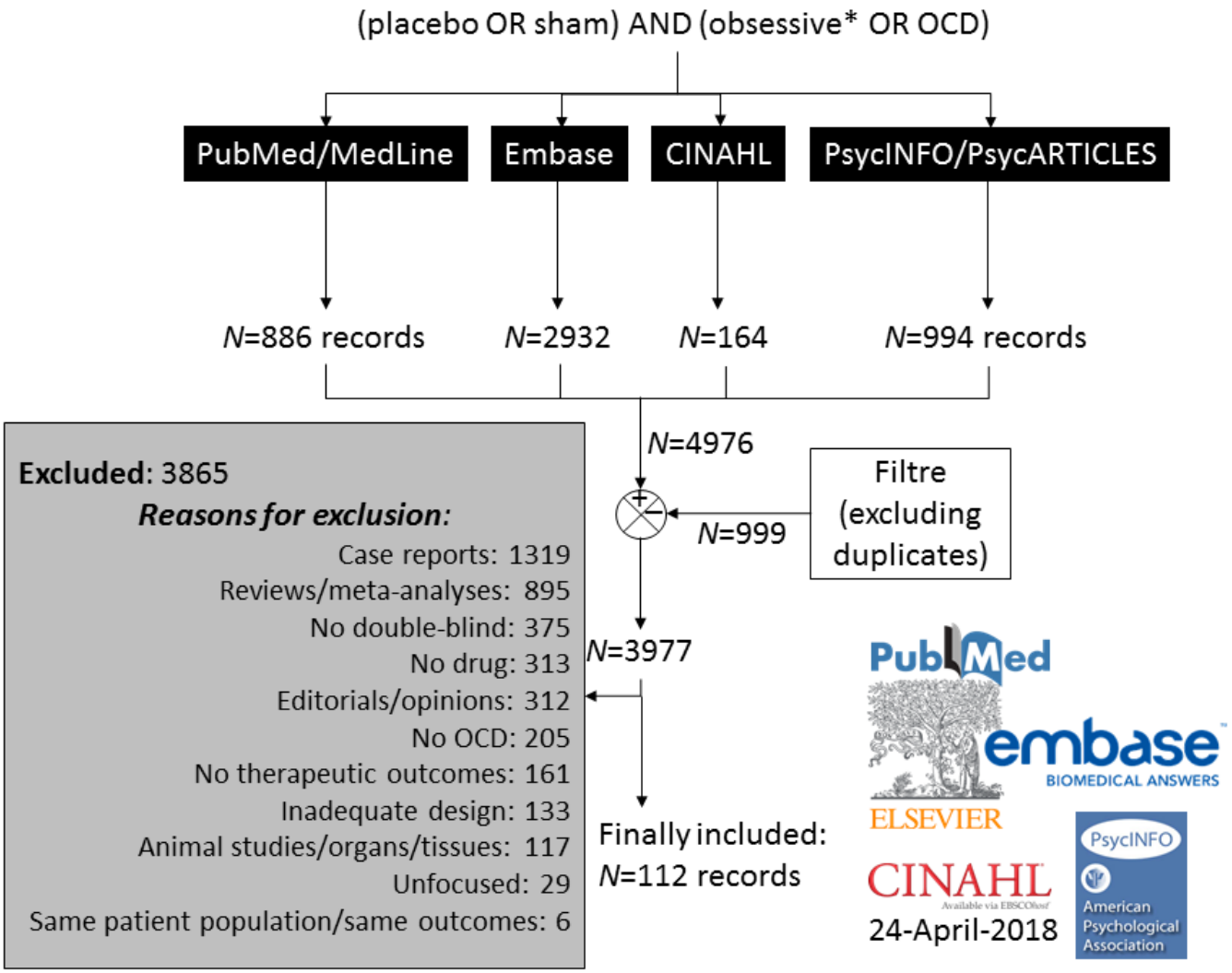

Fig. (1). Algorithm of literature search and article selection.

was continued; add-ons were given not to patients stabilised on a given drug, but on drug-free or drug naïve populations. In this first report on placebo response in OCD we concentrate on double-blind studies using drugs, hence we excluded studies with psychotherapy or comparing mechanical devices with sham, like deep brain stimulation, electroconvulsive therapy, or deep/repetitive transcranial magnetic stimulation, provided they did not have a placebo and a drug arm. Excluded were also studies focusing on other than clinical outcomes, those carried-out on mixed populations (*e.g.*, OCD and Tourette's) without providing results specific for each subpopulation, and those with designs such that a placebo effect could not be calculated.

2.1. Statistical Analysis

We analysed temporal trends of placebo and drug response rates/responder proportions through log-linear joinpoint segmented regression models, which identify points corresponding to statistically significant changes over time in the linear slope of the occurring trend [26]. We used annual mean rates of placebo and drug effect (mean placebo and drug-induced improvements and mean placebo/drug responders) as independent variable assuming constant variance (homoscedasticity) without log transformation. We applied a grid search method to fit regression functions with unknown joinpoints assuming a Poisson distribution and uncorrelated errors. We set the minimum/maximum joinpoint number from 0 to 2, and used a permutation test with overall significance level set at $p<0.05$ and number of randomly permuted datasets of 4,499 to select the best fit. In the final model, each joinpoint indicates a trend change. We reported the estimated annual percent change (APC) for segmented analysis. Joinpoint analyses were performed using the Joinpoint Regression Program, version 3.5, from the US National Cancer Institute (https://surveillance.cancer.gov/joinpoint/).

3. RESULTS

Our PubMed-MedLine-Index Medicus and Embase-Excerpta Medica, CINAHL, and PsycLit-Psychological Abstracts searches yielded 886, 2932, 164, and 994 papers, respectively, as of April 24, 2018. The total output of our research is shown in Fig. **1**, which shows also the reasons for exclusion. All studies were searched for possible further includible papers. Included were 113 studies from 112 papers,

Table1. Placebo and drug responsiveness in OCD studies.

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Thorén *et al*. [13]	1980	Karolinska Universitetssjukhuset, Karolinska Institutet, Stockholm, Sweden	24; 8 placebo *vs*. 8 clomi *vs*. 8 nortriptyline	Clomi *vs*. nortriptyline *vs*. placebo × 5 wk	↓ from BL of OCD Scale derived from the CPRS Responders classified according to clinicians' ratings	7% OCD Scale	Not given	Clomi 50→150 mg/day Nortriptyline 50→150 mg/day	42%; 21% OCD Scale	54.54% including open clomi trial; Nortriptyline: Not given
Flament *et al*. [27]	1985	Child Psychiatry Branch, National Institute of Mental Health, Bethesda, MD, USA	19 paediatric patients; 10 received placebo first, 9 clomi	11-wk Randomised Cross-over (at wk 5) Trial; Clomi *vs*. placebo	↓O-C Rating Scale; no response criteria	10.37% OCR Scale		Chlomi 50→max200 mg/day	32.6% OCR Scale	
Mavissakalian *et al*. [14]	1985	Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA	12; 5 placebo *vs*. 7 clomi	RCT clomi *vs*. placebo ×12 wk	Response: ↓Obsessive-Compulsive Neurotic Scale; Responders: Clinician Rating for OCD (5 points; score 1 on at least 3 points)	43% O-C Neurotic Scale	15.53% Clinician Rating for OCD	Clomi 50→max300 mg/day	35.13% O-C Neurotic Scale	43% Clinician Rating for OCD
Foa *et al*. [15]	1987	Department of Psychiatry, Medical College of Pennsylvania, Philadelphia, PA, USA	37, 18 (7 scoring high [≥21] on the BDI) placebo *vs*. 19 (9 scoring high on the BDI) imipramine	DB RCT imipramine *vs*. placebo × 6 wk	Effect: ↓MOCI from BL	3.67% MOCI		Imipramine 25→max250 mg/day	7.42% MOCI	
Perse *et al*. [17]	1987	Anxiety Disorders Center, Department of Psychiatry, University of Wisconsin, Madison, WI, USA	20 randomised to placebo *vs*. flexible fluvoxamine doses; 4 drop-outs for various reasons left 16 patients available for the analysis; 8 placebo first, 8 fluvoxamine first	Fluvoxamine *vs*. placebo DB cross-over trial; placebo run-in × 2 wk → DB fluvoxamine *vs*. placebo × 8 wk → × 2 wk placebo → × 8 wk DB cross-over	↓from BL of Maudsley OC Inventory scores for treatment effect; Responder rate: Clinician's judgement for response	-7% (Maudsley scores ↑)	19%	Fluvoxamine 50 → max 150 mg/day	14.54%	81%
Pato *et al*. [28]	1988	Laboratory of Clinical Science, NIMH, Bethesda, MD, USA	21 responders to clomi ×4 months; 71.42% had significant depression; all received placebo substitution	Clomi substituted by placebo in four days, then placebo ×7 wk; survival study (relapse rates)	Substitution effect: ↑Y-BOCS; ↑CPRS O-C; ↑NIMH-OC; Response: lack of relapse/recurrence; evidence of recurrence: development of "significant symptoms"	43.7% ↑Y-BOCS; 52.78% ↑CPRS O-C; 43.87% NIMH-OC	9.52% (OCD symptoms)	Clomi tapering-off (four days, half the dosage first, than all drug substituted with placebo)		

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Goodman *et al*. [18]	1989	Department of Psychiatry, Yale University School of Medicine and Connecticut Mental Health Center, Ribicoff Research Facilities, New Haven, CT, USA	42; 21 placebo *vs.* 21 fluvoxamine	Multicentre (2 sites), DB RCT fluvoxamine *vs*. placebo ×6-8 wk	Effect: ↓Y-BOCS score from BL; Response: CGIi 1-2 (used different scale, but rating is similar)	0% Y-BOCS	0%	Fluvoxamine started at 50 mg/day → max 300 mg/day	22.4% Y-BOCS	42.8%
Jenike *et al*. [29]	1989	Harvard Medical School and Massachusetts General Hospital, Boston, MA, USA	27: 14 placebo *vs.* 13 clomi	Multicentre (? sites), DB clomi *vs.* placebo × 10 wk	↓Y-BOCS scores from BL as treatment effect; no criterion for response, but stratification according to percentages of ↓Y-BOCS	8.46% ↓Y-BOCS	20-39% ↓Y-BOCS: 21.42%; ≥40% ↓Y-BOCS: 0%	Clomi 50→200 mg/day →max300 mg/day	36.93% ↓Y-BOCS	20-39% ↓Y-BOCS: 76.92%; ≥40% ↓Y-BOCS: 46.15%
Chouinard *et al*. [20]	1990	McGill University, Montréal, Québec, Canada	87, 44 placebo *vs.* 43 sertraline	Multicentre RCT DB sertraline, flexible doses *vs*. placebo × 10 wk	Treatment effect: % ↓Y-BOCS score from BL; % ↓NIMH-OC Scale score from BL; Response: CGIi 1-2	6.55% Y-BOCS; 6.13% NIMH-OC	11.364% CGIi	Sertraline 50→200 mg/day	16.2% Y-BOCS; 15.2% NIMH-OC	25.581% CGIi
Greist *et al*. [30]	1990	Department of Psychiatry, University of Wisconsin, Madison, WI, USA	31; 16 placebo *vs*. 15 clomi	Single site part of multicentre (21 sites) study, DB parallel RCT of clomi fixed→ flexible dose *vs*. placebo ×10 wk	Effect: ↓NIMH-OC and ↓Y-BOCS scores from BL; Response: Patient and Physician Global Evaluation (conceptually similar to CGIi 1-2)	6.97% ↓Y-BOCS; 8.64% ↓NIMH-OC	5% "CGIi"	Clomi 25→200 max 300 mg/day	34.883% ↓Y-BOCS 27.912% ↓NIMH-OC	45% CGIi
Jenike *et al*. [31]	1990	Harvard Medical School, Boston, and the OCD Clinic and Research Unit, the Department of Molecular Biology, and the Inpatient Psychiatric Service, Massachusetts General Hospital, Boston, MA, USA	38; 20 placebo *vs.* 18 fluvoxamine	DB fluvoxamine *vs.* placebo × 10 wk	↓Y-BOCS scores from BL as treatment effect; no criterion for response	4% ↓Y-BOCS		Fluvoxamine 50→max300 mg/day	16.81% ↓Y-BOCS	

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Katz *et al*. [32]	1990	New Drug Development Department-CNS Section, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, NJ, USA	266 with Ham-D <17; 129 placebo *vs*. 134 clomi	Multicentre (12 sites), DB RCT clomi *vs*. placebo in pts. with DSM-III OCD and Ham-D <17 or Ham-D 17-21 (subsequently excluded from the analysis due to small sample size) ×10 wk →responders (CGIi ≤3) with treatment confirmed (placebo, N=12, clomi, N=101) ×42 wk	Effect: ↓NIMH-OC scores from BL; response: CGIi 1-2	1.96% at week 10; 21.56% at week 52; 24.71% at end-point; NIMH-OC	9.3% 10 wk; 2.4% wk 52; 16.7% at end-point (wk 70) CGIi	Clomi 20→min 100, target 250, max 300 mg/day	34.69% at week 10; 55.1% at week 52; 46.94% at end-point, NIMH-OC	75.37% 10 weeks; 61.2% week 52; 72.2% at end-point (week 70) CGIi
Mavissakalian *et al*. [33]	1990	Department of Psychiatry, Ohio State University, Columbus, OH, USA	25; 12 placebo *vs*. 13 clomi	DB RCT clomi *vs*. placebo ×10 wk	Effect: ↓CY-BOCS from BL; response: much improved	1.11% Y-BOCS	0% Much improved	Clomi 50→2-weeks 200 mg/day →flexible	54.19% Y-BOCS	35% Much improved
Montgomery *et al*. [34]	1990	Imperial College London, St Mary's Hospital Medical School, London UK	14; 7 placebo first, 7 clomi first	4-wk DB clomi *vs*. placebo→cross-over ×4 wk	Criteria for effect or response not specified; assessment with 6-item obsessional scale extracted from CPRS and MADRS	5.2% (↓from BL of CPRS Obs Scale scores)		Clomi 75 mg/day	64.5% (↓from BL of CPRS Obs Scale scores)	
McDougle *et al*. [35]	1991	Connecticut Mental Health Center, New Haven, CT, USA	30 DR (failure to reach ≥35% ↓ from BL Y-BOCS scores and CGIi>2 and clinician consensus after fluvoxamine × 8 wk) at flexible doses up to 300 mg/day; 9 placebo *vs*. 11 add-on lithium [study 1]; 5 *vs*. 5 add-on lithium	DB RCT to add-on lithium *vs*. placebo ×2 wk to unchanged fluvoxamine (up to 300 mg/day) [study 1, 20 patients]; 4 wk blind placebo followed by 4 wk open lithium [study 2, 10 inpatients]	Y-BOCS (response: ↓≥35% drop from BL and Y-BOCS<16); CGIi 1-2; clinician consensus: all three=marked, 2 of 3=partial, <2 no response)	Study 1: -5.09% (Y-BOCS scores↑) Study 2: 5.83% (Y-BOCS)	Studies 1 & 2: 0% marked and partial (Y-BOCS, CGIi, clinician cons.)	Clomi 200-300 mg/day + lithium 900 mg/day →0.5-1.2 mEq in plasma	Study 1: 10.52% (Y-BOCS); Study 2: -10.66% (Y-BOCS scores↑)	Study 1: 9.091% marked, 9.091% partial (Y-BOCS, CGIi, clinician's consensus); Study 2: 0% marked and partial

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
The Clomi Collaborative Study Group [36]	1991	Clinical Neuropharmacology, Glaxo Inc, Research Triangle Park, NC, USA	520; 120 placebo *vs.* 118 clomi (study 1) 129 placebo *vs.* 134 clomi (study 2)	Multicentre (9 centres study 1; 12 centres, study 2), clomi *vs.* placebo × 10 wk; two identical studies	Effect: ↓CY-BOCS from BL; Response ↓≥35% from BL	3% Y-BOCS study 1 5% Y-BOCS study 2	7.5% Y-BOCS study 1 7% Y-BOCS study 2	Clomi 25→max300 mg/day	38% Y-BOCS study 1 44% Y-BOCS study 2	51% Y-BOCS study 1 60% Y-BOCS study 2
DeVeaugh-Geiss *et al.* [37]	1992	Clinical Neuropharmacology, Glaxo Inc, Research Triangle Park, NC, USA	60 children or adolescents 10-17 years, 29 placebo *vs.* 31 clomi	Multicentre (5 sites) DB RCT clomi *vs.* placebo × 8 wk	Effect: ↓Y-BOCS from BL; Response: CGIi 1-2	8% Y-BOCS	17% CGIi	Clomi 25→100, max 200 mg/day	37% Y-BOCS	59.8% CGIi
Mallya *et al.* [38]	1992	McLean Hospital, Harvard Medical School, Belmont, MA, USA	28 with HAM-D<20; 14 placebo *vs.* 14 fluvoxamine	RCT fluvoxamine *vs.* placebo ×10 wk	Effect: ↓Y-BOCS from BL; Response: ≥35%↓Y-BOCS from BL	5% ↓Y-BOCS	7% Y-BOCS	Fluvoxamine 50→300 mg/day	33% ↓Y-BOCS	43% Y-BOCS
Pigott *et al.* [39]	1992	NIH Clinical Center, Rockville Pike, Bethesda, MD, USA	17 drug-free; 6 placebo *vs.* 11 trazodone	DB RCT trazodone *vs.* placebo ×10 wk	Effect: ↓Y-BOCS scores from BL	10.3% Y-BOCS		Trazodone 50→ 300 mg/day	12.98%; Y-BOCS	
Riddle *et al.* [21]	1992	Yale Child Study Center, Yale University, New Haven, CT, USA	14 (8.5-16 years); 6 placebo first *vs.* 7 fluoxetine first	Cross-over randomised study fluoxetine *vs.* placebo ×20 wk (first 8 wk to one and 12 to the other in random order)	Effect: ↓CY-BOCS scores from BL	26.72% (week 8) CY-BOCS		Fluoxetine 20 mg/day	44.03% (week 8) CY-BOCS	
Stein *et al.* [40]	1992	Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York State Psychiatric Institute, New York, NY, USA	35 with ≥56 on SRON and SROC; comorbidity with depression only if OCD primary and dominating; 21 placebo *vs.* 14 clomi	Multicentre (2 sites) DB RCT to clomi *vs.* placebo ×10 wk	Effect: Score ↓OCS, SRON, SROC; Response: CGIi 1-2	12% OCS; 33.33% SRON; 31.63% SROC	19% CGIi	clomi 25→100- 300 mg/day	29.49% OCS; 40.49% SRON; 29.11% SROC	50% CGIi
Grady *et al.* [41]	1993	Department of Psychiatry, Duke, University Medical Center; Durham, NC, USA	13 DR (fluoxetine) OCD 80 mg/day ×10 wks; order of administration not specified	DB cross-over to add-on buspirone *vs.* placebo ×8 wk to unchanged fluoxetine (80 mg/day)	Effect: ↓Y-BOCS score from BL; Response: Y-BOCS ↓≥25% from BL and other unusual criteria	-2.9% (↑Y-BOCS scores)	0% (Y-BOCS)	Buspirone → 60 mg/day added on fluoxetine, 80 mg/die	3.91% (Y-BOCS)	7.7% (Y-BOCS)

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Hoehn-Saric *et al*. [42]	1993	Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA	21 with NIMH-OC≥9, Y-BOCS≥16; Ham-D≤21; 10 placebo *vs*. 11 clomi	DB CRT clomi *vs*. placebo ×10 wk	Effect: ↓NIMH-OC and ↓Y-BOCS scores from BL; Response: not investigated	2.083% NIMH-OC; 5.714% Y-BOCS		Clomi 25→200 mg/day; min 100 max 300 mg/day	31.521% NIMH-OC; 39.534% Y-BOCS	
McDougle *et al*. [43]	1993	Clinical Neuroscience Research Unit, Yale University School of Medicine, Connecticut Mental Health Center, New Haven, CT, USA	33 DR (failure to reach ↓≥35% drop from BL Y-BOCS scores after fluvoxamine × 8 wk) at flexible doses up to 300 mg/day; 14 placebo *vs*. 19 add-on buspirone	RCT to add-on buspirone *vs*. placebo ×8 wk to unchanged fluvoxamine (up to 300 mg/day)	Y-BOCS (response: ↓≥35% from BL); CGIi 1-2; clinician consensus	9.09% (Y-BOCS)	14.29% (Y-BOCS, CGIi, clinician consensus)	Buspirone 15→60 mg/day added on fluvoxamine at the same dose of BL	4.96% (Y-BOCS)	10.52% (Y-BOCS, CGIi, clinician's consensus)
Montgomery *et al*. [22]	1993	Imperial College London, Paterson Wing, St Mary's Hospital Medical School, London UK	214; 56 placebo *vs*. 52 fluoxetine, 20 mg/day *vs*. 52 fluoxetine, 40 mg/day *vs*. 54 fluoxetine, 60 mg/day	Multicentre (13 sites) 8-wk DB fluoxetine 20, 40 or 60 mg *vs*. placebo	Treatment effect: ↓Y-BOCS scores Response: ≥↓25% from BL and CGIi 1-2	17.5% Y-BOCS	26%	Fluoxetine 20, 40 and 60 mg/day	21.6% 20.5% 28.6% Y-BOCS	36% 48% 47%
McDougle *et al*. [44]	1994	Department of Psychiatry, Yale University School of Medicine, Yale Child Study Center, New Haven, CT, USA	34 (failure to reach ↓≥35% drop from BL Y-BOCS scores after fluvoxamine × 7 wk) with or without tics; 17 add-on placebo *vs*. 17 add-on haloperidol	Double-blind DR to fluvoxamine since 7 wk randomised ×4 wk to add-on haloperidol or placebo	Response: Y-BOCS ↓≥35% from BL and final Y-BOCS≤16; CGIi 1-2; and consensus of clinician. Two criteria met: partial responder; all three met: marked responder	7.63%	0%	Fluvoxamine up to 300 mg/day; dose unaltered during trial; add-on haloperidol 2→max10 mg/die (mean, 6.2 mg)	27.17%	65%
Tollefson *et al*. [23]	1994	Psychopharmacology Division, Eli Lilly & Co., Indianapolis, Ind, USA	355; 89 placebo *vs*. 87 fluoxetine 20 mg, *vs*. 89 fluoxetine 40 mg *vs*. 90 fluoxetine 60 mg	Multicentre (8 sites), DB fluoxetine at fixed doses *vs*. placebo × 13 wk	Y-BOCS ↓ from initial score for effect; Y-BOCS ↓≥35% for response	-1.2% (mean Y-BOCS scores ↑)	8.5%	Fluoxetine 20 mg/day 40 mg/day 60 mg day	15.24% 20.26% 25.99%	32.1% 32.4% 35.1%
Tollefson *et al*.* [24]	1994	Psychopharmacology Division, Lilly Research Laboratories, Eli Lilly & Co., Indianapolis, Indiana, USA	76 responders of the previous study with their treatment confirmed; 6 placebo *vs*. 23 fluoxetine 20 mg, *vs*. 21 fluoxetine 40 mg *vs*. 26 fluoxetine 60 mg	Multicentre (8 sites), DB fluoxetine at fixed doses *vs*. placebo × 6 months (extension)	Y-BOCS ↓ from initial score for effect; Y-BOCS ↓≥35% for response	-6.25% (mean Y-BOCS scores ↑), but at BL patients were not OCD	50% Y-BOCS	Fluoxetine 20 mg/day 40 mg/day 60 mg day	10.09% 11.32% 23.91% Y-BOCS, but at BL patients were not OCD	47% Y-BOCS

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Greist *et al*. [45]	1995	Dean Foundation for Health, Research, and Education, Madison, Wisconsin, USA	325; 84 placebo *vs*. 241 sertraline: 80 sertraline 50 mg/day; 81 sertraline 100 mg/day; 80 sertraline 200 mg/day	Multicentre (11 sites), DB parallel comparison of three dosages of sertraline *vs*. placebo ×12 wk	Effect: ↓Y-BOCS score from BL; Response: Y-BOCS ↓≥25% from BL CGIi 1-2	14.6% ↓Y-BOCS	30% CGIi	Sertraline, pooled 50, 100, and 200 mg/day	23.4% 27.37% 22.83% 33.02% ↓Y-BOCS	38.9% CGIi
Fux *et al*. [46]	1996	Ministry of Health Mental Health Center, Faculty of Health Sciences, Ben Gunion University of the Negev, Beersheva, Israel	13 partial or complete non-responders to clomi/SSRIs or with severe side effects; 6 placebo first, 7 inositol first	Cross-over RCT inositol *vs*. placebo ×6 wk; cross-over ×6 wk without washout	Response criteria not specifically stated, but data given so that we extrapolated % ↓Y-BOCS scores for response and calculated % of patients who achieved ↓Y-BOCS≥35% (or 25%) from BL for response	1.55% Y-BOCS; Placebo first at 6 wk: 12.4%	0% ↓Y-BOCS≥ 35% Placebo first at 6 wk: 0% ↓Y-BOCS≥ 25%	Oral inositol 18 g/day	21.104% Y-BOCS; Inositol first at 6 wk: 25.01%	30.77% ↓Y-BOCS≥ 35%; Inositol first at 6 wk: 28.57% (57.14% ↓Y-BOCS≥ 25%)
Goodman *et al*. [47]	1996	Department of Psychiatry, University of Florida College of Medicine, Gainsville, FL, USA	156; 78 placebo *vs*. 78 fluvoxamine	Multicentre (4 sites), DB RCT fluvoxamine *vs*. placebo ×10 wk	Effect: ↓Y-BOCS score from BL; ↓NIMH-OC score from BL; Response: CGIi 1-2	5.42% Y-BOCS; 3.89% NIMH-OC	8.6%	Fluvoxamine started at 50 mg/day → max 300 mg/day	21.14% Y-BOCS; 19.101% NIMH-OC	43.4%
Nakajima *et al*. [48]	1996	Department of Neuropsychiatry, Kyoto Perfectural University of Medicine, Kawaramachi-Hirokoji, Kamigyoku, Kyoto, Japan	27 fluvoxamine 300 mg/die *vs*. 34 fluvoxamine 150 mg/die *vs*. 33 placebo	DSM-III-R OCD patients assigned to one of three groups: high-dose fluvoxamine *vs*. low-dose fluvoxamine *vs*. placebo × 8 wk	Y-BOCS scores (%↓Y-BOCS from BL; response ↓≥35% from BL)	7.25%	36.36%	Fluvoxamine 150 mg/day 300 mg/day	28.33%; 29.96%	79%; 77.8%
Zohar *et al*. [49]	1996	Chaim Sheba Medical Centre, Tel-Hashomer, Israel, and Sackler Medical School, Tel Aviv University, Israel	399; 99 placebo *vs*. 201 paroxetine *vs*. 99 clomi	Multicentre-multinational (? sites), DB paroxetine *vs*. clomi *vs*. placebo × 12 wk	Y-BOCS ↓≥25%	18.87%	35.4%	Paroxetine 20-60 mg/day; Clomi 50-250 mg/day	30.77%; 32%	55.1%; 55.3%
Jenike *et al*. [50]	1997	Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA	64; 21 placebo *vs*. 20 phenelzine *vs*. 23 fluoxetine	10-wk fluoxetine *vs*. phenelzine *vs*. placebo	↓Y-BOCS scores from BL as treatment effect	1%		Phenelzine 60 mg/day, Fluoxetine 80 mg/day	9.4%; 14.7%	

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Lindsay *et al*. [51]	1997	Clinical Research Unit for Anxiety Disorders, School of Psychiatry, University of New South Wales at St Vincent's Hospital, Sydney, NSW, Australia	18 (13 drug-free, 5 unresponsive to clomi or fluoxetine); 9 placebo (anxiety management) *vs*. 9 CBT	Parallel assignment to CBT (ERP) *vs*. anxiety management assumed as the placebo (5 1-h sessions per wk × 3 wk); control group also did homework	Treatment effect: ↓Y-BOCS from BL; ↓MOCI from BL; ↓PADUA scores from BL; Response criteria: not provided	-5.93% (↑Y-BOCS); 12.002% MOCI; 15.201% PADUA		CBT in 15 sessions divided in three weeks, about 1 hour per session, for both ERP and anxiety management (hyperventilation and respiration and relaxation control with no cognitive restructuring and exercise at home)	61.67% Y-BOCS; 43.76% MOCI; 50.99% PADUA	
Ushijima *et al*. [52]	1997	Department of Psychiatry, Jikei University School of Medicine, Nishishinbashi, Minato-ku, Tokyo, Japan	33 150 mg/die fluvoxamine *vs*. 29 300 mg/die fluvoxamine *vs*. 42 placebo	Multicentre, DB fluoxetine at fixed doses *vs*. placebo × 8 wk	Y-BOCS ↓ from initial score for effect; Y-BOCS ↓≥35% for response	11.66% (mean Y-BOCS ↓)	38.1% Y-BOCS	Fluvoxamine 150 mg/day 300 mg/day	23.9% 24.05% (mean Y-BOCS ↓)	55.17% 51.51% Y-BOCS
Fallon *et al*. [53]	1998	Department of Psychiatry, Columbia University, Division of the New York State Psychiatric Institute, New York, NY, USA	54, 29 DR placebo *vs*. 25 DR i.v. clomi	DR to oral clomi, randomised to i.v. clomi *vs*. placebo × 14 days	Effect: %↓Y-BOCS from BL; %↓CGIs from BL; %↓NIMH-OC from BL; response ↓≥25% from BL; CGIi 1-2	3.3% Y-BOCS; 0% CGIs; 0% NIMH-OC	0% CGI; 0% Y-BOCS	Intravenous (i.v.) Clomi 250 mg/day	11.8% Y-BOCS; 10.1% CGIs; 9.565% NIMH-OC	20.7% CGIi 21.4% Y-BOCS
Li, J. *et al*. [54]	1998	Mental Health Center of Sichuan province, Mianyang, China	42; 12 placebo *vs*. 15 clomi *vs*. 15 paroxetine	DB CCMD-2 OCD paroxetine 20→80 mg/day *vs*. 50→300 mg/day *vs*. placebo ×4 wk	Effect: ↓Y-BOCS from BL; unclear response criteria	10.06%		20-80 mg/day paroxetine, 50-300 mg/day clomi	51.32% 48.71%	
March *et al*. [55]	1998	Departments of Psychiatry and Psychology, Duke University Medical Center, Durham, NC, USA	189 children and adolescents; 95 placebo *vs*. 92 sertraline	Multicentre (12 sites), RCT Sertraline flexible doses *vs*. placebo ×12 wk	Effect: ↓CY-BOCS from BL; Response: ≥25%↓CY-BOCS from BL	15.31% ↓CY-BOCS	37% ≥25%↓CY-BOCS	Sertraline 25-50→max200 mg/day	29.05% ↓CY-BOCS	53% ≥25%↓CY-BOCS
Kronig *et al*. [56]	1999	Department of Psychiatry, Hillside Hospital of LIJMC, Glen Oaks, New York, NY, USA	167; 81 placebo *vs*. 86 sertraline	Multicentre (10 sites), Double-blind sertraline 50-200 mg/die randomised *vs*. PLC ×12 wk	CGIi 1-2 (response), ↓Y-BOCS from BL; ↓NIMH from BL (primary outcome)	17.16% Y-BOCS	23.45% CGIi	Sertraline 50-200 mg/day	38.08%	41.8%

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Dannon *et al*. [57]	2000	Psychiatry Department, Chaim Sheba Medical Center, Tel Hashomer, Israel	14 DR to 60 mg/day paroxetine ×≥15 wks (Y-BOCS ↓<25%), 6 placebo *vs*. 8 pindolol	DB RCT of DR, ×6 wk to add-on pindolol or placebo	Unresponsiveness: Y-BOCS ↓<25% from BL; Effect of treatment: ↓Y-BOCS scores from BL	7.69%		Paroxetine 60 mg/day; add-on pindolol 7.5 mg/die	25.69%	
McDougle *et al*. [58]	2000	Department of Psychiatry, Section of Child and Adolescent Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA	36 SSRI-refractory; 16 placebo *vs*. 20 add-on risperidone	Double-blind refractory to clomi, fluvoxamine, sertraline, fluoxetine, and paroxetine (failure to reach ↓≥35% drop from BL Y-BOCS scores), randomised ×6 wk to add-on risperidone or placebo	Response: Y-BOCS ↓≥35% from BL and final Y-BOCS≤16; CGIi 1-2; and consensus of clinician. Two criteria met: partial responder; all three met: marked responder	9.42%	0	Clomi, fluvoxamine, sertraline, fluoxetine, or paroxetine at fixed dose; add-on risperidone 1-6 mg/die (mean, 2.2 mg)	31.8%	50%
Geller *et al*. [59]	2001	Pediatric OCD Clinic, McLean Hospital, Belmont, MA, USA	103 with ≥4 on the CGIs and ≥16 on the CY-BOCS (7-18 years); 32 placebo *vs*. 71 fluoxetine	Multicentre (21 sites), 13-wk, DB RCT 2:1. Fluoxetine *vs*. placebo	CY-BOCS scores (response ↓≥40% from BL)	19.7%	25%	Fluoxetine, mean 24.6 mg/day	38.7%	49%
Montgomery *et al*. [60]	2001	Imperial College of Science, Technology and Medicine, London, UK	401; 101 placebo *vs*. 102 20 mg citalopram, *vs*. 98 40 mg citalopram, *vs*. 100 60 mg citalopram	Multicentre (53 sites), multinational (12 countries); randomisation to citalopram *vs*. placebo ×12 wk	Treatment effect: ↓Y-BOCS scores Response: ≥↓25% from BL	22.05%	36.6%	Citalopram 20 mg/day 40 mg/day or 60 mg/day	33.47% 34.23% 40.15%	57.4%; 52%; 65%;
Riddle *et al*. [61]	2001	Division of Child and Adolescent Psychiatry, Johns Hopkins Hospital, Baltimore, MD, USA	120 (8-17 years); 63 placebo *vs*. 57 fluvoxamine	Multicentre (17 sites) DB RCT fluoxetine *vs*. placebo × 10 wk	Effect: ↓CY-BOCS scores from BL; Response: CY-BOCS ↓≥25% from BL	13.63% CY-BOCS	26%	Fluvoxamine 25→ 50-max 200 mg/day	24.79% CY-BOCS	42.1%
Romano *et al*. [62]	2001	Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN, USA	71 responders (out of 130) to 20-wk 20, 40 or 60 mg fluoxetine with ↓≥25% drop from BL; 35 placebo *vs*. 36 fluoxetine	Multicentre (11 sites), randomisation to fluoxetine as before *vs*. placebo × 52 wk	No relapse	62%		Fluoxetine 20, 40 or 60 mg/day	82.5%; only 60 mg/die fluoxetine different from placebo	

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Atmaca *et al*. [63]	2002	Fırat Üniversitesi Hastanesi, Fırat Tıp Merkezi, Psikiyatri Anabilim Dalı, Elazig, Turkey	27 DR (one 3-month trial of 25→300 mg/day clomi or 50→300 mg/day fluvoxamine or 20→80 mg/day fluoxetine yielded CGIi ≥3 and Y-BOCS ≥18 and clinician consensus) to SSRIs or clomi ×2 months), 13 placebo *vs*. 14 DR to quetiapine add-on	Single-blind randomisation of DR patients with stabilised SSRI or clomi to add-on quetiapine or placebo × 8 wk	Treatment effect: ↓Y-BOCS score from BL; ↓CGIs from BL; response: significant improvement, ≥60% ↓Y-BOCS score from BL; partial improvement, ≥30-59% ↓Y-BOCS score from BL plus clinician consensus	10.08% (↓Y-BOCS); 15.88% (↓CGIs)	0%	Stable SSRI or clomi; add-on quetiapine flexible, *i.e*., 50 mg/day → ↑25 mg/day when Y-BOCS did not ↓ by 2 from previous evaluation	44.4% (↓Y-BOCS); 47.161% (↓CGIs)	71.4%
Greist *et al*. [64]	2002	Healthcare Technology Systems, University of Wisconsin, Madison, WI, USA	218 (age 15-80), Y-BOCS≥16, not comorbid with psychoses and Tourette's; 75 placebo (relaxation) *vs*.74 computer-guided *vs*. 69 therapist-guided	Multicentre (8 sites), parallel comparison of three psychotherapies, computer-assisted CBT, therapist-conducted CBT *vs*. relaxation assumed as the placebo × 10 wk (therapists not raters)	Effect: ↓Self-rated Y-BOCS score from BL; Response: Y-BOCS ↓≥25% from BL CGIi 1-2; PGIi 1-2	6.6% ↓Self-rated Y-BOCS Relaxation, 1-h/day ×10 weeks	15% PGIi; 14 % CGIi	Computer-guided CBT , 9 steps: 1-3 education and assessment; 4-9 self ERP ×1 h or more; Clinician-guided CBT, one 1-hour weekly session ×11 weeks ERP + homework	22.77% 30.16% ↓Self-rated Y-BOCS	38% PGIi; 38% CGIi 58% PGIi 60% CGIi
Koran *et al*. [65]	2002	Department of Psychiatry, Stanford, CA, USA	223 responders to 16 or 52-wk 50-200 mg/day sertraline with Y-BOCS ↓≥25% from BL *and* CGIi ≤3; 114 placebo *vs*. 109 sertraline	Multicentre (21 sites), DB randomisation to flexible sertraline or to placebo × 28 wk	No relapse, defined as either ↑Y-BOCS scores ≥5 from randomisation and total score of ≥20 and ↑CGIi score of ≥1; Insufficient clinical response	76%		Sertraline flexible doses 50-200 mg/day	91%	
Liebowitz *et al*. [66]	2002	New York State Psychiatric Institute and Department of Psychiatry at Columbia University, New York, NY, USA	43 (children 6-18 years); 22 placebo *vs*. 21 fluoxetine (acute); 7 placebo *vs*. 11 fluoxetine (extension)	Multicentre (2 sites), RCT fluoxetine *vs*. placebo ×8 wk (acute phase) → responders extension ×8 wk	CGIi 1 or 2 (response), ↓CY-BOCS from BL (primary outcome)	22.12% acute; 54.6% extension	31.81% (CGIi)	Fluoxetine 60-80 mg/die	34.62% acute; 74.36% extension	57.14% CGIi

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Geller *et al.* [67]	2003	Obsessive Compulsive Disorder Program and Pediatric Psychopharmacology Research Program, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA	8-17 yr-old children who responded to 16-wk 10-60 mg/day paroxetine; 98 placebo *vs*. 95 paroxetine	Multicentre (? sites); paroxetine-responder children aged 8-17 randomised to paroxetine as before *vs*. placebo ×16 wk	CY-BOCS (response ↓≥25% from BL and CGIi 1 or 2); No relapse; relapse defined as ↑CGI by 1 in two follow-up visits or ↑CGI by 2 at any time or CGI≥5 at any time		56.1%	Paroxetine flexible doses (10-60 mg/die)	65.3%	
Hollander *et al*. [68]	2003	Department of Psychiatry, The Mount Sinai School of Medicine, New York, NY, USA	27, 10 placebo *vs*. 17 clonz	Multicentre (2 sites), DR + drug- naïve patients randomised 2:1 to clonz or placebo × 10 wk	CGIi 1-2	2.6%Y-BOCS	22% CGIi	Clonz 3-6 mg/day	7% Y-BOCS	6.2% CGIi
Hollander *et al*. [69]	2003	Department of Psychiatry, The Mount Sinai School of Medicine, New York, NY, USA	16 DR (CGIi≥3 after at least two trials of SSRIs, clomi or venlafaxine for 12 wks), 6 placebo *vs*. 10 add-on risperidone	DB RCT of DR patients to risperidone *vs*. placebo × 8 wk added on stable previous SSRI, venlafaxine or clomi	Effect: ↓Y-BOCS score from BL Response: Y-BOCS ↓≥25% and CGIs ↓≥2 points from BL	4.53% Y-BOCS	0% Y-BOCS and CGIi	Risperidone 0.5→max 3 mg/day add-on to minimum mg/day: 200 clomi, 60 fluoxetine, 150 fluvoxamine, 150 sertraline, 60 citalopram or 325 venlafaxine	20.89% Y-BOCS	40% Y-BOCS *and* CGIi
Hollander *et al*. [70]	2003	Department of Psychiatry, The Mount Sinai School of Medicine, New York, NY, USA	89 placebo *vs.* 88 paroxetine, 20 mg/day, *vs.* 86 paroxetine, 40 mg/day, *vs.* 85 paroxetine, 60 mg/day	Multicentre (15 sites), paroxetine, three fixed doses with an about 1:1:1:1 randomisation DB *vs.* placebo × 12 wk	Effect: ↓Y-BOCS score from BL Response: Y-BOCS ↓≥25% and CGIs ↓≥2 points from BL	13% Y-BOCS	Not provided	Paroxetine 20, 40, 60 mg/day	16% 25% 29% Y-BOCS	Not provided
Hollander *et al*. [70]	2003	Department of Psychiatry, The Mount Sinai School of Medicine, New York, NY, USA	105 responders to paroxetine randomised to placebo (*N*=52) or to paroxetine (*N*=53) 20-60 mg/day	Multicentre (15 sites), Paroxetine responders to flexible paroxetine doses (20-60 mg/day) or placebo × 6 months	Non-relapse: relapse defined as return of Y-BOCS to BL values or ≥1↑CGI at any time-point		41.2% Y-BOCS/ CGIi	Paroxetine 20, 40 or 60 mg/day		62.3% Y-BOCS/ CGIi
Hollander *et al*. [71]	2003	Department of Psychiatry, The Mount Sinai School of Medicine, New York, NY, USA	253; 126 placebo *vs.* 127 fluvoxamine controlled-release	Multicentre (5? sites) RCT Fluvoxamine controlled-release 100-300. placebo × 12 wk	Effect: ↓Y-BOCS score from BL Response: CGIi 1 or 2	19.01% Y-BOCS	23% CGIi	Fluvoxamine 100 → 100-300 mg/day	34.56% Y-BOCS	44% CGIi

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Bystritsky *et al*. [72]	2004	Department of Psychiatry and Biobehavioral Sciences, Anxiety Disorders Program, University of California at Los Angeles (UCLA) School of Medicine, Los Angeles, CA, USA	26 DR (unchanged after two adequate antidepressant trials and a course of behavioural psychotherapy), 13 placebo *vs*. 13 risperidone	DR to clomi or SSRIs with dose unchanged randomised × 6 wk to add-on olanzapine or placebo	Effect: % ↓Y-BOCS; Response: Y-BOCS ↓≥25% from BL	-1.99% (↑Y-BOCS from BL)	0% (↓≥25% Y-BOCS)	Full-dose clomi, fluoxetine, sertraline, paroxetine; add-on olanzapine 2.5 → 5-20 mg/day	17.36% (↓Y-BOCS from BL)	46% (↓≥25% Y-BOCS)
Denys *et al*. [73]	2004	Rudolf Magnus Institute of Neuroscience (DD), Department of Psychiatry, University Medical Center Utrecht, Utrecht, The Netherlands	20 DR to SSRIs to add-on placebo; 20 to add-on quetiapine	DR to SSRIs (failure to achieve ↓≥25% of Y-BOCS scores from BL) randomised to add-on quetiapine *vs*. placebo × 8 wk	Y-BOCS (response ↓≥35% drop from BL); CGIi 1-2	6.8% Y-BOCS; 7,5% CGIi	10% CGIi	Various SSRIs at various doses plus quietapine (B) 200-300 mg/day	31.9% Y-BOCS 27,5% CGIi	40% CGIi
Fux *et al*. [74]	2004	BeerSheva Mental Health Center, Ben Gurion University of the Negev, Beer-Sheva, Israel	11 with unsatisfactory response to SSRI during last 2 months: 5 placebo add-on *vs*. 6 EPA add-on	Cross-over RCT, EPA *vs*. placebo added-on highest tolerated SSRI dose	Response criteria not specified; assessment performed with Y-BOCS	32.3%		Various SSRIs at various doses; EPA 2g/day	28.8%	
Geller *et al*. [75]	2004	Pediatric OCD Clinic, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA	203 (7-17 years); 105 placebo *vs*. 98 paroxetine	Multicentre (34 sites); paroxetine *vs*. placebo × 10 wk	Effect: ↓CY-BOCS score from BL; Response: ↓≥25% CY-BOCS from BL	21.1%	41.2%	Paroxetine 10-50 mg/die	36%	64.9%
Kamijima *et al*. [76]	2004	Showa University School of Medicine, Shinagawa-ku, Tokyo, Japan	188; 94 placebo *vs*. 94 paroxetine	Multicentre (? sites), DB paroxetine *vs*. placebo × 12 wk	Effect: ↓Y-BOCS scores from BL; response: ↓≥25% Y-BOCS from BL; CGIi 1-2	14.8% Y-BOCS	23.7% CGIi	Paroxetine 20-50 mg/day	33.4% Y-BOCS	50% CGIi
Shapira *et al*. [77]	2004	Department of Psychiatry, University of Florida, College of Medicine, Gainesville, FL, USA	44 partial/non responders to fluoxetine, 22 placebo *vs*. 22 add-on olanzapine	DR (partial/non-responders, *i.e*., <↓25% Y-BOCS score from BL or <16 total Y-BOCS or symptomatic) to 8-wk double-blind fluoxetine randomised × 6 wk to add-on olanzapine or placebo	Treatment effect: % ↓Y-BOCS scores from BL; Response: Y-BOCS ↓≥25% from BL	3.8%	41% ↓≥25% from BL; (18% ↓≥35% Y-BOCS from BL)	Fluoxetine 40 mg/day; Olanzapine 5-10 mg/day	5.1%	41% ↓≥25% from BL; (23% ↓≥35% Y-BOCS from BL)

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
The Pediatric OCD Treatment Study (POTS) Team [78]	2004	Department of Psychiatry, Duke University Medical College, Durham, NC, USA	112 children and adolescents (7-17 yrs.) CY-BOCS≥16; 28 placebo *vs*. 28 sertraline *vs*. 28 CBT *vs*. 28 sertraline + CBT placebo	Multicentre (3 sites), balanced, masked RCT (biased by patient preference) of sertraline *vs*. CBT *vs*. sertraline + CBT *vs*. placebo × 12 wk	Effect: ↓CY-BOCS from BL; Response: CY-BOCS≥10	14.68%	3.6%	Sertraline 25→max200 mg/day; 14 CBT sessions with psychoeducation, cognitive training mapping OCD target symptoms and ERP; Sertraline + CBT	29.79% 46.15% 52.84%	21.4% 39.3% 53.6%
Carey *et al*. [79]	2005	MRC Research Unit on Anxiety Disorders, University of Stellenbosch, Cape Town, South Africa	42 SSRI-resistant patients defined as not responding to at least two adequate trials (12 wks); 21 SSRI+placebo, 20 SSRI+ quetiapine	Multicentre RCT (5 sites); DR (CGI≥3 or ↓Y-BOCS ≤25% from before treatment) to SSRI randomised to add-on quetiapine *vs*. placebo × 6 wk	Treatment effect: % ↓Y-BOCS score from BL Response: ↓Y-BOCS ≥25% from BL *and* CGIi 1-2	26% Y-BOCS 22.6% CGIi	47.6%	Various SSRIs at various doses; Add-on quetiapine, ≈200 mg/day	26.9% Y-BOCS 21,1% CGIi	40%
Erzegovesi *et al*. [80]	2005	Department of Neurosciences, San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy	39 patients stabilised on fluvoxamine 150-300 mg/day; 19 placebo *vs*. 20 add-on risperidone; 20 DR (10 placebo; 10 risperidone) and 19 responders (9 placebo; 10 risperidone)	DR to fluvoxamine (failure to reach ↓≥35% drop from BL Y-BOCS score) and responders to open fluvoxamine randomised × 6 wk to add-on risperidone or placebo	Y-BOCS scores (response ↓≥35% drop from BL); (Responders and non-responders here refer to open fluvoxamine and *not* to the add-on)	13.89%; Responders 27.63%; Non-responders: 6.82% Y-BOCS	Non-resp 20% Y-BOCS	Fluvoxamine 150-300 mg/die; risperidone 0.5 mg/die	18.24%; Responders, 3.82%; non-responders, 25.57%	Non-responders, 50%
Fineberg *et al*. [81]	2005	Department of Psychiatry, Queen Elizabeth II Hospital, Hertfordshire, Welwyn Garden City, Department of Psychology, University of Hertfordshire, Hatfield, UK	21 DR (Y-BOCS ≥18 and ↓≥25% Y-BOCS after ≥12 wks SSRI at max tolerated dose); 10 placebo, 11 quetiapine add-on	Add-on of quetiapine *vs*. placebo × 16 wk on stable SSRI at max tolerated dose	Effect: %↓Y-BOCS from BL; response ↓≥25% from BL	6%	10%	Quetiapine 25→max 400 mg/die + SSRI (citalopram, sertraline, paroxetine)	14%	27.27%
Foa *et al*. [82]	2005	Center for the Treatment and Study of Anxiety, University of Pennsylvania, Philadelphia, PA, USA	122, 26 placebo *vs*. 36 clomi, *vs*. 29 ERP, *vs*. 31 clomi + ERP	Multicentre (3 centres), 12-wk RCT; Clomi *vs*. placebo *vs*. ERP *vs*. clomi + ERP	Effect: ↓Y-BOCS from BL Response: CGIi <3	11.2% Y-BOCS 6% CGIi	8%	Clomi 200 mg/day ERP: 2h exposure sessions, 5 times a week + daily exposure and ritual prevention homework max 2h Combined Clomi + ERP	30.7% Y-BOCS; 19.6% CGIi 55.28% Y-BOCS; 43.75% CGI 58.66% Y-BOCS; 40.82 CGIi	41.67% 62.07% 67.74%

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Kobak *et al*. [83]	2005	Dean Foundation For Health, Research and Education, Middleton, WI, USA	60 with Ham-D <16; 30 placebo *vs*. 30 St. John's wort *(Hypericum perforatum)*	Multicentre (4 sites), DB CRT of flexible *Hypericum* or placebo × 12 wk	Effect: ↓Y-BOCS scores from BL; response: CGIi 1-2	20.665 % Y-BOCS	16.7% CGIi	Hypericum perforatum (Saint John's wort) flexible doses 600→1800 mg/day	23.306 % Y-BOCS	17.9% CGIi
Koran *et al*. [84]	2005	Department of Psychiatry and Behavioral Sciences, Stanford University Medical Center, Stanford, CA, USA	23 DR with OCD since at least 3 years, with Y-BOCS ≥20 and poor response to at least two SSRI trials (≥8 wks at full dose); 32 placebo	Add-on to stable antidepressant therapy of morphine, lorazepam or placebo × 7 wk: 2 wk of each in random order; cross-over, but only first part considered (prior to cross-over)	Effect: ↓Y-BOCS score Response: Y-BOCS (response ↓≥25% from BL)	7%	0%	Morphine 30 mg/week 1 →15-45 mg/week adjustment Lorazepam 1 mg →0.5-2 mg/week	27% 6%	30.43% 17.4%
Li, X. *et al*. [85]	2005	Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, Birmingham, AL, USA	13 DR to ≥12-wk SSRIs (symptomatic; ≥10 score on Y-BOCS items 1-5; ≥16 total Y-BOCS score); 5 placebo first, 5 haloperidol first, 3 risperidone first	DB cross-over of DR on stable antidepressant, randomised × 9 wk to add-on risperidone, haloperidol or placebo (1 wk placebo→2 wk placebo or haloperidol or risperidone→1 wk placebo→2 wk cross-over→ 1wk placebo→ 2 wk cross-over)	Effect: ↓Y-BOCS from BL; no criteria for response	23.96%		≥40 mg fluoxetine, ≥200 mg fluvoxamine, ≥100 mg sertraline; dose unaltered during trial; add-on haloperidol 2 mg/day risperidone 1 mg/day	48.62% 36.29%	
Nakatani *et al*. [86]	2005	Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan	28 DR; 8 placebo + autogenic training *vs*. 10 behaviour therapy + placebo *vs*. 10 fluvoxamine + autogenic training	DR patients assigned to one of three groups: behavioural therapy + placebo; fluvoxamine + autogenic training; autogenic training + placebo ×12 wk	Y-BOCS scores (response ↓≥35% from BL), CGIi 1-2; responsiveness to placebo was taken as the response of Y-BOCS scores and the CGIi criterion of the placebo + autogenic training group	6.88%	0%	Fluvoxamine 150-200 mg/day	28.87%	30%
Buchsbaum *et al*. [87]	2006	Mount Sinai School of Medicine, New York, NY, USA	16 DR, 6 placebo *vs*. 10 risperidone	DR to clomi, fluvoxamine, sertraline, fluoxetine, paroxetine, citalopram, and venlafaxine randomised double-blind ×8 wk to add-on risperidone or placebo	Response: Y-BOCS ↓≥25% from BL; CGIi 1-2	4.53%	0% (CGIi) 0% (Y-BOCS)	Actual minimum daily doses: 200 mg clomi, 60 fluoxetine, 150 fluvoxamine, 150 sertraline, 60 citalopram, 325 venlafaxine; add-on risperidone 0.5 → 3 mg/day	20.89%	40% (CGIi) 40% (Y-BOCS)

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
O'Connor *et al*. [88]	2006	Fernand-Seguin Research Centre, Louis-H. Lafontaine Hospital, Montreal, QC, Canada	21 with Y-BOCS >16; 10 placebo *vs.* 11 fluvoxamine (first protocol); thereafter, 43 (comprising the first 21) received CBT *vs*. 10 CBT alone, *vs.* 12 CBT + stabilised on antidepressant	DB, random allocation to fluvoxamine *vs*. placebo ×5 months (first protocol); after conclusion or stabilisation (on or off-drug) of another population, all receive CBT; CBT to drug naïve patients, CBT + stabilised on drug, CBT to previous placebo group, CBT to previous fluvoxamine group × 5 months (20 sessions) (second protocol)	Treatment effect: ↓Y-BOCS scores Response: >↓35% Y-BOCS from BL	6.96% Y-BOCS	0%	Fluvoxamine 100 → max 300 mg/day; CBT – ERP 1 weekly session for a total of 20 over 5 months; CBT + fluvoxamine	15.19% 53.33% (not used in analyses) 42.69% Y-BOCS (not used in analyses)	9%
Fineberg *et al*. [89]	2007	Postgraduate Medical School, University of Hertfordshire, Hatfield, UK	320 responders to 16-wk 10 or 20 mg escitalopram with Y-BOCS ↓≥25% from BL; 157 placebo *vs.* 163 escitalopram 10 or 20 mg/day	Multicentre (62 sites), multi-national (14 countries), DB RCT escitalopram 10 *vs*. 20 *vs*. placebo × 24 wk	No relapse, defined as either an increase in Y-BOCS scores ≥5 from randomisation or as unsatisfactory treatment effect (lack of efficacy) judged by investigator; Responders: Y-BOCS ↓≥25% from BL	48% no relapse	72% Y-BOCS	Escitalopram fixed dose 10mg/die or 20mg/die	77% no relapse	90% Y-BOCS
Stein *et al*. [90]	2007	University of Cape Town, Department of Psychiatry, Groote Schuur Hospital, Cape Town, South Africa	458; 114 placebo *vs*. 113 escitalopram 10, 114 escitalopram 20, 117 paroxetine	Double-blind randomized fixed-dose escitalopram × 24 wk to paroxetine or placebo	Primary outcome: ↓Y-BOCS from BL at week 12; secondary: mean Y-BOCS change from BL at week 24; Remission: Y-BOCS ≤10 Response: CGIi 1 or 2; Y-BOCS ↓≥25% from BL	wk12: 30.54% wk24: 38.51% Y-BOCS	wk12 38.5%; wk24 38% (CGIi); wk12 52%; wk24 50% (Y-BOCS)	Escitalopram 10 mg/die or Escitalopram 20 mg/die or Paroxetine 40 mg/die	wk12: 42.97% wk24: 51.77% wk12: 45.64 wk24: 51.84% wk12: 42.75 wk24: 54.62%	wk12 50% wk24 58% (CGIi) wk12 66% wk24 63% (Y-BOCS) wk12 56% wk24 58.5% (CGIi) wk12 70.5% wk24 70.5% (Y-BOCS) wk12 54% wk24 58% (CGIi) wk12 65% wk24 67% (CGIi)
Amiaz *et al*. [91]	2008	Division of Psychiatry, Chaim Sheba Medical Center, Tel-Hashomer, Israel	10 DR to SSRIs or clomi ×2 months; 5 placebo first, 5 naltrexone first	DB cross-over of DR patients to ≥2-month clomi or 2 SSRIs × 5 wk to add-on naltrexone or placebo, × 1 wk to add-on placebo only × 5 wk to cross-over add-on naltrexone or placebo	Treatment effect: ↓Y-BOCS score from BL; ↓CGIs from BL; no response criteria provided	5.46% (↓Y-BOCS); 18.42% (↓CGIs)		Stable SSRI or clomi; add-on naltrexone 50 → 100 mg/die	-16.07% (↑Y-BOCS scores); -10.7% (↑CGIs scores)	

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Kordon *et al*. [92]	2008	Department of Psychiatry and Psychotherapy, University of Luebeck, Luebeck, Germany	40 DR; 20 placebo *vs*.20 add-on quetiapine	Multicentre (2 sites), DR to SSRI or clomi × 12 wk (failure to reach ↓≥25% drop from BL Y-BOCS scores) randomised to add-on quetiapine or placebo	Y-BOCS (response ↓≥35% drop from BL); CGIi 1-2	15.1% Y-BOCS	30% CGIi	SSRI or clomi at fixed dose; Quietiapine 400-600 mg/day	21.6% Y-BOCS	22% CGIi
Greenberg *et al*. [93]	2009	New York University School of Medicine, Department of Psychiatry, New York, NY, USA	13 DR (drugs or psychotherapy), with treatment stabilised ×≥12wks, 9 placebo *vs*. 5 glycine add-on	DB RCT 1:1 of DR to add-on glycine *vs*. placebo × 12 wk to unchanged regimen (drugs and/or psychotherapy)	Effect: ↓Y-BOCS score from BL; ↓NIMH-OC score from BL;↓CGIs score from BL; Response: Y-BOCS ↓≥35% from BL *and* CGIi 1-2	4.04% (Y-BOCS); 2.44% NIMH-OC; 2.36% (CGIs)	0% (Y-BOCS plus CGIi)	Glycine powder dissolved in water plus flavour enhancer → 60 g/day added on stabilised treatment (drug and/or psychotherapy)	24.59% (Y-BOCS); 22.22% NIMH-OC; 13.04% (CGIs)	40% (Y-BOCS plus CGI)
Sayyah *et al*. [94]	2009	Department of Psychiatry, Joondi Shapoor University of Medical Sciences, Ahwaz, Iran	44 with Y-BOCS≥21; 20 placebo *vs*. 24 aqueous extract of *Echium amoenum*	DB, RCT of 500 mg aqueous extract of *Echium amœnum* × 6 wk	Effect: ↓Y-BOCS scores from BL Response: not provided	11.31% Y-BOCS		125 mg aqueous extract of *Echium amoenum* capsules: 1 morning; 1 afternoon, 2 night	25.55% Y-BOCS	
Mowla *et al*. [95]	2010	Department of Psychiatry, Bushehr University of Medical Sciences, Bushehr, Iran	41 Y-BOCS≥18 to: -*N*=20 Topiramate; or -*N*=21 placebo; × 12 wks	12-wk, double-blind, placebo-controlled, randomized trial of 200 mg/day topiramate *vs*. placebo	Treatment effects: ↓Y-BOCS from BL; response: Y-BOCS ↓≥25% from BL (after 12 weeks)	2.4% (↓Y-BOCS)	0% (Y-BOCS ↓≥25% from BL)	Topiramate (initially 25 mg/day, increased in 25-mg increments weekly to a target dose of 200 mg/day	32% (↓Y-BOCS);	60% (Y-BOCS ↓≥25% from BL)
Storch *et al*. [96]	2010	Department of Pediatrics, Rothman Center for Neuropsychiatry, University of South Florida, St. Petersburg, FL, USA	30 children and adolescents with OCD (Range 8-17 years); 15 placebo, 15 D-cycloSer	DB RCT of CBT + D-cycloSer *vs*. CBT + Placebo × 8 wk (10 sessions). 1:1 randomisation	Effect: % ↓ CGI-S, CYBOCS, and ADIS-CSR from BL. no criterion for response	41% (↓CGI-S), 58% (↓ CY-BOCS), 53% (↓ADIS-CSR)		25 or 50 mg of D-cycloSer (depending on patient weight) 1 h before psychotherapy, sessions 4-10	57%(↓CGI-S) 72% (↓ CYBOCS) 71% (↓ADIS-CSR)	
Sayyah *et al*. [97]	2011	Education Development Center (EDC), Jundishapur University of Medical Sciences, Ahwaz, Iran	52 drug naïve OCD patients randomised to celecoxib (*N*=27) or placebo (*N*=25)	DB RCT of fluoxetine 20 mg/day + celecoxib 400 mg/day *vs*. fluoxetine 20 mg/day + placebo × 8 wk	Effect: % ↓Y-BOCS score from BL; no criterion for response	46.7% (↓Y-BOCS)		Fluoxetine 20 mg/day + Celecoxib 400 mg/day	66.2% (↓Y-BOCS)	

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Muscatello *et al*. [98]	2011	Section of Psychiatry, Department of Neurosciences, Psychiatric and Anaesthesiological Sciences, Section of Pharmacology, Department of Clinical and Experimental Medicine and Pharmacology, IRCCS Centro Neurolesi "Bonino-Pulejo" University of Messina, Messina, Italy	30 Y-BOCS≥18 to N=16 aripripazole (15 mg/day) N=14 Placebo	16-wk, open-label. flexible-dose (up to 30 mg/day), pilot trial	Treatment effects: ↓Y-BOCS score from BL; partial response (pr): Y-BOCS ↓≥25% from BL; complete response (cr): Y-BOCS ↓≥35% from BL; remission (r) (Y-BOCS ≤16 after 16 weeks)	-2.54% (↓Y-BOCS)	0% (pr); 0% (cr)	Aripiprazole 15 mg/day added to SSRI	28.5% (↓Y-BOCS);	43.7% (pr); 25% (cr)
Berlin *et al*. [99]	2011	Department of Psychiatry, The Mount Sinai School of Medicine, New York, NY, USA	36 OCD patients with Y-BOCS ≥ 18; 18 randomised to placebo and 18 to topiramate	DB RCT of add-on topiramate (up to 400 mg/d) over continuing SSRI vs. placebo plus SSRIs × 12 wk	Effect: % ↓Y-BOCS score from BL after 12 weeks. No response criteria	16% (↓Y-BOCS from BL to 12 weeks)		Add-on topiramate titrated over 8 weeks up to 400 mg/day or maximum tolerated dose	38% (↓Y-BOCS)	
Pakseresht *et al*. [100]	2011	Jundishapur University of Medical Sciences, Ahwaz, Iran	31 (18-60 y) to -N=15 extract of *Valeriana Officinalis L*. (765 mg/day) or -N=16 placebo (30 mg/day) × 8 wks (Y-BOCS≥21)	8-wk double-blind, parallel-group, randomised trial	Treatment effect: ↓Y-BOCS from BL after 8 weeks; no response criteria provided	23.3% (↓Y-BOCS);		Valeriana Root (Valeriana Officinalis L.) 750 mg/day in three divided doses	43.3% (↓Y-BOCS)	
Sayyah *et al*. [101]	2012	Jundishapur University of Medical Sciences, Ahwaz, Iran	23 drug naïve OCD patients; add-on to fluoxetine, 12 $ZnSO_4$, 11 placebo	DB RCT of 20 mg/day fluoxetine + 440 mg/day $ZnSO_4$ *vs*. 20 mg/day fluoxetine + placebo × 8 wk	Effect: % ↓Y-BOCS score from BL. no criterion for response	46.84% (↓Y-BOCS)		20 mg/day Fluoxetine + 440 $ZnSO_4$ mg/day	54.54% (↓Y-BOCS)	
Sayyah *et al*. [102]	2012	Imam General Hospital, Jundishapur University of Medical Sciences, Ahwaz, Iran	32 adult outpatients: N=15 10 mg/day aripiprazole N=17 placebo	12-wk, double-blind RCT	Treatment effects: ↓Y-BOCS score from BL; response: Y-BOCS ↓≥25% after 12 weeks	17.6% (↓Y-BOCS);	8.3% (Y-BOCS ↓≥25% after 12 weeks)	Aripiprazole 10 mg/day	29.5% (↓Y-BOCS);	53% (Y-BOCS ↓≥25% after 12 weeks)
Afshar *et al*. [103]	2012	Nour Hoospital, Psychosomatic Research Center, Department of Psychiatry, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran	48 DR OCD patients (SSRI/clomi non-responders); 19 *N*AC, 20 placebo	DB RCT of add-on →2400 mg/day *N*AC *vs*. placebo ×12 wk	Effect: % ↓Y-BOCS score from BL. % ↓ CGI-S from BL Partial response: Y-BOCS ↓≥25% from BL; Response: Y-BOCS ↓≥35% from BL	20.7% (↓Y-BOCS) 10.4% (↓CGIs)	Response: 15%; No data on partial response	Initial dosage of 600 mg/d of *N*AC, which doubled weekly to a maximum dose of 2400 mg/d	39.2% (↓Y-BOCS); 24.9% (↓CGIs)	Response: 52.6% No data on partial response given

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Bruno *et al*. [104]	2012	Section of Psychiatry, Department of Neurosciences, Psychiatric and Anaesthesiological Sciences, University of Messina, Messina, Italy	33 DR OCD patients (persistent obsessive-compulsive symptoms: despite adequate SSRI trial(s) → Y-BOCS ≥16); 17 lamotrigine, 16 placebo	DB RCT of add-on lamotrigine 100 mg/day vs placebo for 16 wk	Effect: % ↓Y-BOCS score from BL; Partial response: Y-BOCS ↓≥25% from BL; Response: Y-BOCS ↓≥35% from BL	-1.2% (↓Y-BOCS)	Response: 0%	Add-on lamotrigine increased from 25 mg/day to 100 mg/day at week 4, in increments of 25 mg/week Maximum dose of 100 mg maintained until the end of the trial	33.8% (↓Y-BOCS)	Partial response: 50% Complete response: 35%
Askari *et al*. [105]	2012	Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran	39 drug naïve OCD patients (Y-BOCS ≥21) randomised to placebo (*N*=20) or granisetron (*N*=19)	Multicentre DB RCT of fluvoxamine 100-200 mg/day + granisetron 2 mg/day *vs*. fluvoxamine 100 - 200 mg/day + placebo × 8 wk	Effect: % ↓Y-BOCS score from BL Partial response: Y-BOCS ↓≥25% from BL Response: Y-BOCS ↓≥35% from BL Remission: Y-BOCS ≤ 16	34.7% (↓Y-BOCS)	Partial response: 35%; Complete response: 35%; Remission: 35%	Fluvoxamine 100 mg/day × first 4 weeks, 200 mg/day × next 4 weeks + granisetron 2 mg/day	59.1% (↓Y-BOCS)	Partial response: 100% Complete response: 100% Remission: 90%
Ghaleiha *et al*. [106]	2013	Research Center for Behavioral Disorders and Substance Abuse, Hamadan University of Medical Sciences, Hamadan, Iran	38 patients with diagnosis of OCD and Y-BOCS score ≥21 randomised to add-on placebo (*N*=19) or memantine (*N*=19)	DB RCT of fluvoxamine + memantine *vs*. fluvoxamine + placebo × 8 wk	Effect: % ↓Y-BOCS score from BL Partial response: Y-BOCS ↓≥25% from BL Response: Y-BOCS ↓≥35% from BL Remission: Y-BOCS ≤16	36.9% (↓Y-BOCS)	Partial or complete response: 32% Remission: 32%	Memantine 10 mg/day for the first week of the trial, then 20 mg/day	57,9% (↓Y-BOCS)	Partial or complete response: 100% Remission: 89%
Storch *et al*. [107]	2013	Department of Pediatrics, University of South Florida, St. Petersburg, FL, USA	47 children and adolescents with OCD (Range 7-17 years) randomised to RegSert (*N*=14), SloSert (*N*=17) or placebo (*N*=16) + CBT for all	DB RCT of sertraline at standard dosing + CBT or sertraline titrated slowly + CBT or placebo + CBT × 18 wk. Patients randomized in a 1:1:1 fashion.	Effect: % ↓CY-BOCS score from BL. Response: CY-BOCS ↓≥30% from BL Remission: CY-BOCS score <10	37.9% (↓Y-BOCS)	Response: 62.5% (CY-BOCS ↓≥30% from BL) Remission: 18.8% (CY-BOCS score below 10)	RegSert: upward titration from 25 mg/day to 200 mg/day in 5 wk. SloSert: upward titration from 25 mg/day to 200 mg/day in 9 wk	RegSert: 34.7% (↓Y-BOCS) SloSert: 35.5% (↓Y-BOCS)	Response: 57.1% for RegSert + CBT; 64.7% for SloSert + CBT; Remission: 42.9% for RegSert + CBT; 23.5% for SloSert + CBT
Haghighi *et al*. [108]	2013	Research Center for Behavioral Disorders and Substances Abuse, Hamadan University of Medical Sciences, Hamadan, Iran	29 inpatients with diagnosis of OCD and Y-BOCS score ≥21 despite treatment with SSRI or clomi to: memantine (*N*=14) or placebo (*N*=15)	DB RCT of add-on memantine 5–10 mg/day *vs*. placebo × 12 wk	Effect: % ↓Y-BOCS score from BL. % ↓ CGI-S from 4th week; Partial response: Y-BOCS ↓≥25% from BL; Response: Y-BOCS ↓≥35% from BL	15.8% (↓Y-BOCS) 13.4% (↓CGIs)	Partial or complete response: 26.6%	Add-on memantine 5–10 mg/day	32.2% (↓Y-BOCS) 30.2% (↓CGIs)	Partial or complete response: 92.8%

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Storch *et al*. [109]	2013	Department of Pediatrics, Rothman Center for Neuropsychiatry, University of South Florida, St. Petersburg, FL, USA	34 DR OCD patients (Y-BOCS≥ 19 despite at least 2 adequate SSRI trials) randomised to placebo (*N*=17) or paliperidone (*N*=17)	DB RCT of add-on Paliperidone (up to 9 mg/d) *vs*. placebo × 8 wk	Effect: % ↓Y-BOCS score from BL. %↓CGI-S from BL Response: Y-BOCS ↓≥35% from BL CGI-i = 1 - 2	15.7% (↓Y-BOCS) 18.7% (↓CGI-S)	Response: 29% (Y-BOCS ↓≥35%) 18% (CGIi =1/2)	Add-on Paliperidone starting from 3 mg/day and titrated up to 9 mg/day by week 6 unless not tolerated	29.4% (↓Y-BOCS) 20.1% (↓CGI-S)	Response: 35% (Y-BOCS ↓≥35%) 35% (CGIi=1/2)
Rodriguez *et al*. [110]	2013	New York State Psychiatric Institute, New York, NY, USA; Department of Psychiatry, Columbia University, College of Physicians and Surgeons, New York, NY, USA	15 drug free OCD patients with Y-BOCS ≥ 16 who had failed at least one prior SSRI trial and/or CBT: 8 to ketamine and 7 to placebo	DB Crossover RCT of iv ketamine (0.5 mg/kg) *vs*. iv saline spaced at least 1-wk apart	Effect: ↓OCD-VAS Response: Y-BOCS ↓≥35% from BL	7.2% (↓OCD-VAS)	Response: 0%	Intravenous infusion of ketamine (0.5 mg/kg) over 40 min	45.4% (↓OCD-VAS)	Response: 50%
Simpson *et al*. [111]	2013	Department of Psychiatry, Columbia University, New York State Psychiatric Institute, New York, NY, USA	100 patients on SSRI with still clinically significant OCD (Y-BOCS ≥ 16); 97 patients to *N*=38 Risperidone (up to 4 mg/d) *N*=40 EX/RP (17 session, 2 wkly) *N*=19 placebo	RCT comparing SSRI augmentation with either EX/RP therapy, risperidone (→ max 4.0 mg/d), or pill placebo × 8 wk in two centres	Effect: % ↓Y-BOCS score from BL Response: Y-BOCS ↓≥25% from BL	10.81% (↓Y-BOCS)	Responders: 15% (Y-BOCS ↓≥25%)	Add-on risperidone (up to 4 mg/day) EX/RP (17, 2×week, 90 min-sessions)	EX/RP: 52.2% (↓Y-BOCS). Risperidone: 13.4% (↓Y-BOCS)	EX/RP response: 80% Risperidone response: 22.5%
Park *et al*. [112]	2014	Department of Psychology, University of South Florida, Tampa, FL, USA	30 children and adolescents with OCD (CY-BOCS≥16) stable on psychotropic medication × ≥ 12 wks: 15 to D-cycloSer; 15 to placebo	DB RCT of ERP + D-cycloSer (25-50 mg) after last 7 sessions *vs*. ERP + placebo × 10 wk	Effect: %↑ Homework compliance (rated with a 7-point Likert scale ranging from 0 ("did not complete any assigned homework") to 6 ("completed all homework and made efforts above and beyond assignments"); no criterion for response	4.7% (↑ homework compliance)		Exposure and response prevention therapy (ERP) + D-cycloSer (25-50 mg depending on weight) after last 7 session	-6% (↑ homework compliance)	
Grant *et al*. [113]	2014	Pediatrics and Developmental Neuroscience Branch, NIMH, National Institutes of Health, Bethesda, MD, USA	60 treatment-resistant children and adolescents (7-17 years, CY-BOCS≥20); 30 to riluzole, 30 to placebo	DB RCT of add-on riluzole (up to 100 mg/day) *vs*. placebo × 12 wk	Effect: % ↓CY-BOCS score from BL. %↓CGI-S from BL %↑ CGAS from BL Response: CY-BOCS ↓≥30% from BL	22.9% (↓CY-BOCS) 10.7% (↓CGI-S) 18,8% (↑CGAS)	Response: 18%	Add-on riluzole starting from 10 mg/day and increased daily up to 100 mg/day	20.1% (↓CY-BOCS) 9.8% (↓CGI-S) 12.8% (↑ CGAS)	Response: 16%

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Mataix-Cols *et al*. [114]	2014	King's College London, Institute of Psychiatry, London, UK	27 children and adolescents with OCD (CY-BOCS≥16); 13 to D-cycloSer, 14 to placebo	DB RCT of Exposure and response prevention therapy (ERP) + D-cycloSer 50 mg after each session *vs*. ERP + placebo × 17 wk	Effect: % ↓CY-BOCS score from BL. Response: CY-BOCS ↓≥35% from BL Remission: CY-BOCS score ≤ 10	59.3% (↓CY-BOCS)	Response: 64.2% (CY-BOCS ↓≥35% from BL); Remission: 42.8% (CY-BOCS ≤10)	Exposure and response prevention therapy (ERP) + D-cycloSer 50 mg after each session	60% (↓CY-BOCS)	Response: 61.5% (CY-BOCS ↓≥35% from BL); Remission: 53.8% (CY-BOCS score ≤10)
Afshar *et al*. [115]	2014	Isfahan Psychosomatic Research Center, Isfahan University of Medical Sciences, Isfahan, Iran	31 Y-BOCS≥16 to -*N*=16 Topiramate (mean dose: 137.5 mg/day) -*N*=15 Placebo Add-on on current SSRIs	12-wk, double-blind, placebo-controlled	Treatment effects: ↓Y-BOCS score from BL; response (r): Y-BOCS ↓≥25% from BL after 12 weeks	8.33% (↓Y-BOCS) after 12 weeks	14.28% (Y-BOCS ↓≥25% from BL after 12 weeks)	Topiramate (range 100-200, mean dose: 137.5 mg/day), initial dose of 25 mg/day increased by 25 mg weekly to a maximum 200 mg/day	19.81% (↓Y-BOCS) after 12 weeks	53.84% (Y-BOCS ↓≥25% from BL to 12 weeks)
Sarris *et al*. [116]	2015	Department of Psychiatry, The Melbourne Clinic, The University of Melbourne, Melbourne, VIC, Australia	34 to: *N*=18 3g/day *N*AC or *N*=16 Placebo (Y-BOCS≥16)	16-wk, double-blind, placebo-controlled, randomised trial	Treatment effects: ↓Y-BOCS score from BL; response: Y-BOCS ↓≥35% after 16 weeks	19.5% (↓Y-BOCS);	27% (Y-BOCS ↓≥35% from BL)	*N*AC (1.5 g q 12 h)	21% (↓Y-BOCS)	20% (Y-BOCS ↓≥35% from BL)
Pittenger *et al*. [117]	2015	Departments of Psychiatry and Psychology, Yale Child Study Center, Interdepartmental Neuroscience Program, Yale University School of Medicine, New Haven, CT, USA	40 DR OCD patients (SSRI/Clomi non-responders): 20 to riluzole, 18 to placebo	DB RCT of add-on riluzole (50 mg/day) *vs*. placebo × 12 wk	Effect: % ↓Y-BOCS score from BL; Partial response: Y-BOCS ↓≥25% from BL; Response: Y-BOCS ↓≥35% from BL	11% (↓Y-BOCS)	Partial or complete response: 11%	Add-on riluzole 50 mg/day after 2-week placebo lead-in phase	15% (↓Y-BOCS)	Partial or complete response: 26,3%
Jahanbakhsh *et al*. [118]	2016	Pharmaceutical Research Center, Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran	30 OCD patients currently treated with SSRI; 15 to *W. somnifera*, 15 to placebo	DB RCT of add-on *W. somnifera* extract 120 mg/day *vs*. placebo × 6 wk	Effect: % ↓Y-BOCS score from BL no criterion for response	11.1% (↓Y-BOCS)		W. somnifera extract 120 mg/day	46.2% (↓Y-BOCS)	
Paydary *et al*. [119]	2016	Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, Tehran, Iran	44 drug naïve OCD patients (Y-BOCS ≥21); 22 to *N*AC add-on, 22 to placebo add-on	Multicentre DB RCT of fluvoxamine 200 mg/day + *N*AC 2000 mg/day *vs*. fluvoxamine 200 mg/day + placebo × 10 wk	Effect: % ↓Y-BOCS score from BL Response: Y-BOCS ↓≥35% from BL Remission: Y-BOCS ≤ 16	30.3 (↓Y-BOCS)	Response: 22.7%	Fluvoxamine 100 mg/day for × first 4 weeks → 200 mg/day; + *N*AC 1000 mg/day × 1st week → 2000 mg/day	39% (↓Y-BOCS)	Response: 54.5%

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Khalkhali *et al*. [120]	2016	Department of Psychiatry, Guilan University of Medical Sciences, Rasht, Iran	53 DR to: -N=26 Lamotrigine -N=27 placebo Y-BOCS≥21 with stable SRIs dosages × at least 3 months before the study	12-wk, double blind, placebo-controlled RCT of 100 mg/day add-on lamotrigine to SSRIs in DR OCD-patients	Treatment effects: ↓Y-BOCS score from BL; response: Y-BOCS ↓>25% from BL (at week 12)	17.7% (↓Y-BOCS);		Adjunctive lamotrigine - doses (fixed 100 mg/day) (25→100 mg/day during the first 4 weeks, increments of 25 mg/week)	32.5% (↓Y-BOCS);	
Rutrick *et al*. [121]	2016	Adams Clinical Trials, Watertown, MA, USA	50 DR to N=24 placebo or 7N=26 Mavoglurant (augmentation to SSRIs) (Y-BOCS≥16)	Multicentre, randomised, DB, add-on phase 2 study × 16 wk	Treatment effects: ↓Y-BOCS from BL; Response (Y-BOCS ↓≥25% from BL) at week 17	32.06% (↓Y-BOCS)	50% (Y-BOCS ↓≥25% from BL)	(4 week up-titration period → 12-weeks fixed-dose 200 mg Mavoglurant q 12 h → 3-weeks tapering-off	26.59% (↓Y-BOCS)	34.5% (Y-BOCS ↓≥25% from BL)
Feng *et al*. [122]	2016	Department of Psychiatry, Tongde Hospital of Zhejiang Province, Hangzhou, Zhejiang, China	360 OCD patients with Y-BOCS ≥ 16 randomised to GROUP A (*N*=120) GROUP B (*N*=120) or GROUP C (*N*=120)	SB RCT of TEAS with CBT + clomi (GROUP A) *vs*. TEAS with CBT + placebo (GROUP B) *vs*. sham TEAS with CBT + clomi (GROUP C) × 12 wk	Effect: % ↓Y-BOCS score from BL, Response: Y-BOCS ↓≥35% from BL, Remission: CY-BOCS score ≤ 12	GROUP B: 45% (↓Y-BOCS) GROUP C: 38.2% (↓Y-BOCS)	GROUP B: Response: 82.5% Remission: 22.5% GROUP C: Response: 67.5% Remission: 9.2%	GROUP A: Transcutaneous electrical acupoint stimulation combined with CBT + clomi	GROUP A: 59.3% (↓Y-BOCS)	GROUP A: Response: 89.2% Remission: 29.2%
de Leeuw *et al*. [123]	2017	Altrecht Academic Anxiety Center, Utrecht, The Netherlands	39 patients with OCD randomised to D-cycloSer (*N*=19) or placebo (*N*=20) in add-on	DB RCT of Exposure and response prevention therapy (ERP) + D-cycloSer 125 mg/day *vs*. ERP + placebo × 8 wk	Effect: % ↓Y-BOCS score from BL. Partial response: Y-BOCS ↓≥25% from BL Response: Y-BOCS ↓≥30% from BL	17% (↓Y-BOCS)	Partial or complete response: 35%	Exposure and response prevention therapy (ERP) + D-cycloSer 125 mg/day	25.2% (↓Y-BOCS)	Partial or complete response: 90%
Asnaani *et al*. [124]	2017	Department of Psychiatry, Center for the Treatment and Study of Anxiety, University of Pennsylvania, Philadelphia, PA, USA	100 patients on SRI with Y-BOCS ≥ 16 randomised to risperidone (*N*=40), EX/PR (*N*=40) or placebo (*N*=20)	RCT comparing EX/RP therapy + SSRI, risperidone (0.25 mg/day × 3 days, 0.5 mg/day × 4 days, → ↑0.5 mg/wk to max4.0 mg/day +SSRI *vs*. pill placebo + SSRI × 8 wk	Effect: ↑ QLESQ-SF score from BL; ↓SAS-SR and ↓SDS score from BL. No response criteria	11.6% (↑ QLESQ-SF); 5.5% (↓ SAS-SR); 19% (↓ SDS)		SSRI augmentation with either EX/RP therapy (17 twice-weekly, 90-min sessions) or risperidone (0.25 mg/d × 3 days, 0.5 mg/d × 4 days, → ↑0.5 mg/week to max 4.0 mg/day)	EX/RP therapy: 20.6% (↑ QLESQ-SF); 14.8% (↓ SAS-SR); 51.5% (↓ SDS) Risperidone: 5.7% (↑ QLESQ-SF) 4.5% (↓ SAS-SR) 20.6% (↓ SDS)	

(Table 1) contd….

Author(s)	Year	Affiliation/ Country	Population (N)	Design	Outcome Measures (Response Criteria)	Placebo Effect (%)	Placebo Responders (%)	Drug(s) or other Treatment than Placebo	Drug Effect (%)	Drug Responders (%)
Ahmadpanah *et al*.[125]	2017	Hamadan University of Medical Sciences (HUMS), Behavioral Disorders and Substance Abuse Research Center, Hamadan, Iran	43 DR OCD patients (not responding to SSRI or Clomi) to buprenorphine (*N*=23) or placebo (*N*=20)	DB RCT of DR patients with stabilised SSRI or clomi to add-on buprenorphine or placebo × 12 wk	Effect: % ↓Y-BOCS score from BL. Partial response: Y-BOCS ↓≥25% from BL Response: Y-BOCS ↓≥35% from BL	7% (↓Y-BOCS)	Partial or complete response: 25%	Buprenorphine tablets (2-4 g; sublingual) daily	17,5% (↓Y-BOCS)	Partial or complete response: 39%
Modarresi *et al*. [126]	2017	Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran	32 DR OCD patients (failing at least 3 adequate trials of antidepressant, including clomi) and Y-BOCS ≥ 24 randomised to memantine (*N*=16) or placebo (*N*=16)	DB RCT of add-on memantine 20 mg/day *vs*. placebo × 12 wk	Effect: % ↓Y-BOCS score from BL; Response: Y-BOCS ↓≥35% from BL	-0.2% (↓Y-BOCS)	Response: 0%	Add-on memantine 20 mg/day	31% (↓Y-BOCS)	Response: 73.3%
Costa *et al*. [127]	2017	Department & Institute of Psychiatry, University of São Paulo Medical School, São Paulo-SP, Brazil	40 DR OCD patients (not responding to SSRI or clomi) randomised to *N*AC (*N*=18) or placebo (*N*=22)	DB RCT of add-on *N*AC (up to 3000 mg/day) *vs*. placebo × 16 wk	Effect: % ↓Y-BOCS score from BL Response: Y-BOCS ↓≥25% from BL	12.1% (↓Y-BOCS)	Response: 26.3%	Add-on *N*AC, 1,200 mg/day for the first week, 2,400 mg in the second week, 3,000 mg/day from the third week on	16.8% (↓Y-BOCS)	Response: 37.5%
Arabzadeh *et al*. [128]	2017	Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran	44 drug naïve OCD patients (Y-BOCS ≥21) randomised to L-carnosine (*N*=22) or placebo (*N*=22)	DB RCT of fluvoxamine 100 - 200 mg/day + L-carnosine 1000 mg/day *vs*. fluvoxamine 100 - 200 mg/day + placebo × 10 wk	Effect: % ↓Y-BOCS score from BL Partial response: Y-BOCS ↓≥25% from BL; Response: Y-BOCS ↓≥35% from BL Remission: Y-BOCS ≤ 14	24.3 (↓Y-BOCS)	Partial: 45.5%; Complete: 9.1%; Remission: 9.1%	Fluvoxamine 100 mg/day × 4 wk→200 mg/day × 6 wk + L-carnosine 1000 mg/day	35.3 (↓Y-BOCS)	Partial: 45.5% Complete: 36.4% Remission: 27.3%

Abbreviations used: BDI=Beck Depression Inventory; BDZs=benzodiazepines; BL=baseline; BT= Behaviour Therapy; CBT=Cognitive-Behavioural Therapy; CGI=Clinical Global Impressions scale-i=improvement, s=severity; clomi=clomipramine; clonz=clonazepam; CCMD-2=Chinese Criteria of Mental Disorders, 2nd edition; CPRS=Comprehensive Psychopathological Rating Scale, Karolinska institutet; DB=double-blind; DLPFC=dorsolateral prefrontal cortex; DR=drug-resistant/treatment-resistant; D-cycloSer=D-cycloserine; EPA=eicosapentaenoic acid; ERP=exposure and ritual (response) prevention; GAF=Global Assessment of Functioning; GVC=gamma ventral capsulotomy; halo=haloperidol; Ham-D=Hamilton Depression Rating Scale; MOCI=Maudsley Obsessional Compulsive Inventory; MT=motor threshold; *N*AC=*N*-Acetylcysteine; NIMH= National Institute of Mental Health Global Obsessive-Compulsive Scale; OCS= Obsessive Compulsive Scale; PGI=Patient's Global Impressions; RegSert=Standard sertraline dose; SloSert=slowly titrated sertraline; SROC=Self-Rating Obsessive-Compulsive Personality Inventory; SRON=Self-Rating Obsessional Neurotic Scale; wk=weeks; Y-BOCS=Yale-Brown Obsessive-Compulsive Scale; YGTSS, Yale Global Tick Severity Scale; $ZnSO_4$=zinc sulfate; ↑=increase; ↓=reduction; *Patients were not DSM-IV OCD at inclusion, because they had responded to previous trial; hence, actual baseline was factitious and the differences observed were modest for all groups, meaning that treatment continued to work.

which met criteria for inclusion. The results of the included studies [13-15, 17, 18, 20-24, 28-128] are summarised in Table **1**.

Joinpoint regression analyses of the period 1979-2017 showed that placebo mean annual effect rates in OCD studies significantly increased (APC value significantly differing from zero to $\alpha = 0.05$ level) from 1991 to 2017 with an APC of 0.66% (p=0.04) following a period without statistically significant APC changes (Fig. **2**). Placebo mean annual responder rates also significantly increased from 2010 to 2017 with an APC of 5.45% (p=0.02) following a period without statistically significant APC changes (Fig. **3**). Drug mean annual effect rates in OCD studies significantly increased from 1987 to 2012 with an APC of 0.72% (p=0.04) between two periods without statistically significant APC changes (Fig. **4**). Drug mean annual responder rates did not

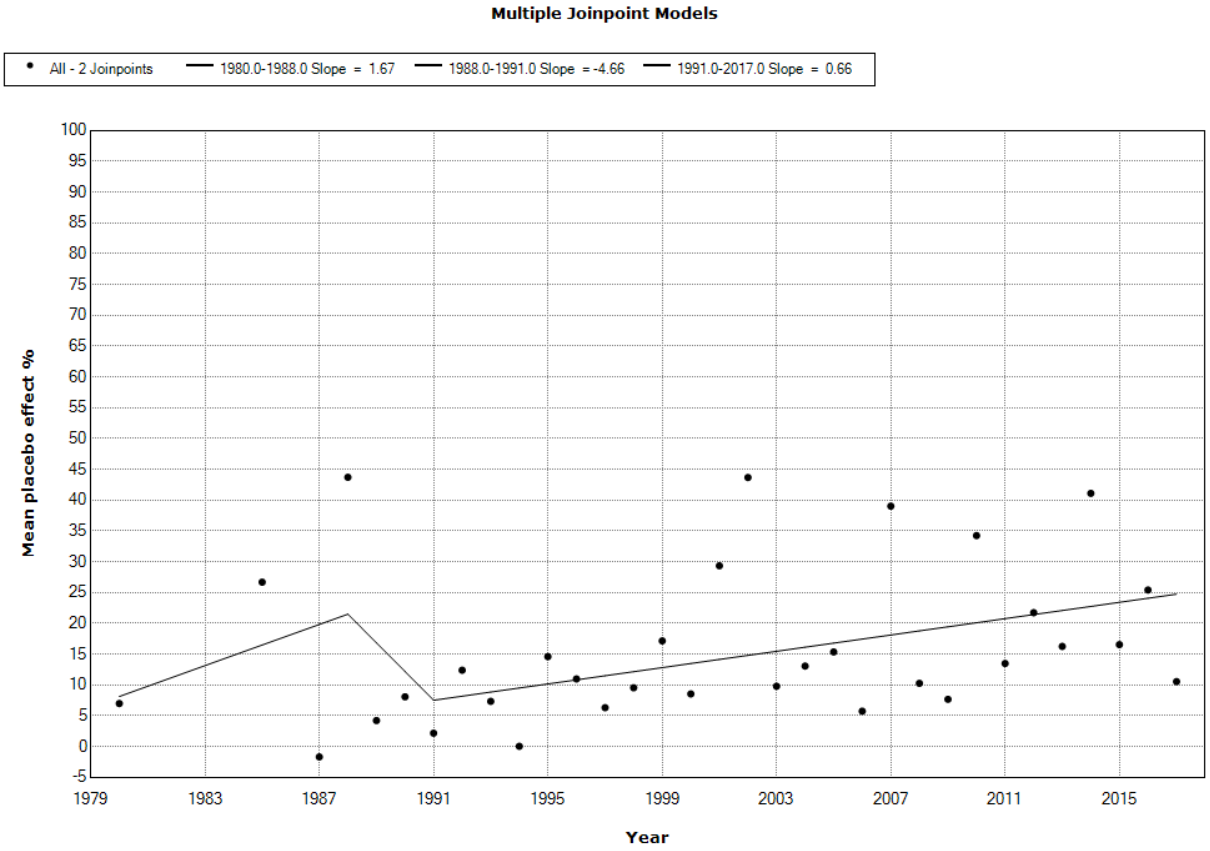

Fig. (2). Multiple Join-Point model of the time (year of publication) trend of placebo effect in OCD double-blind trials.

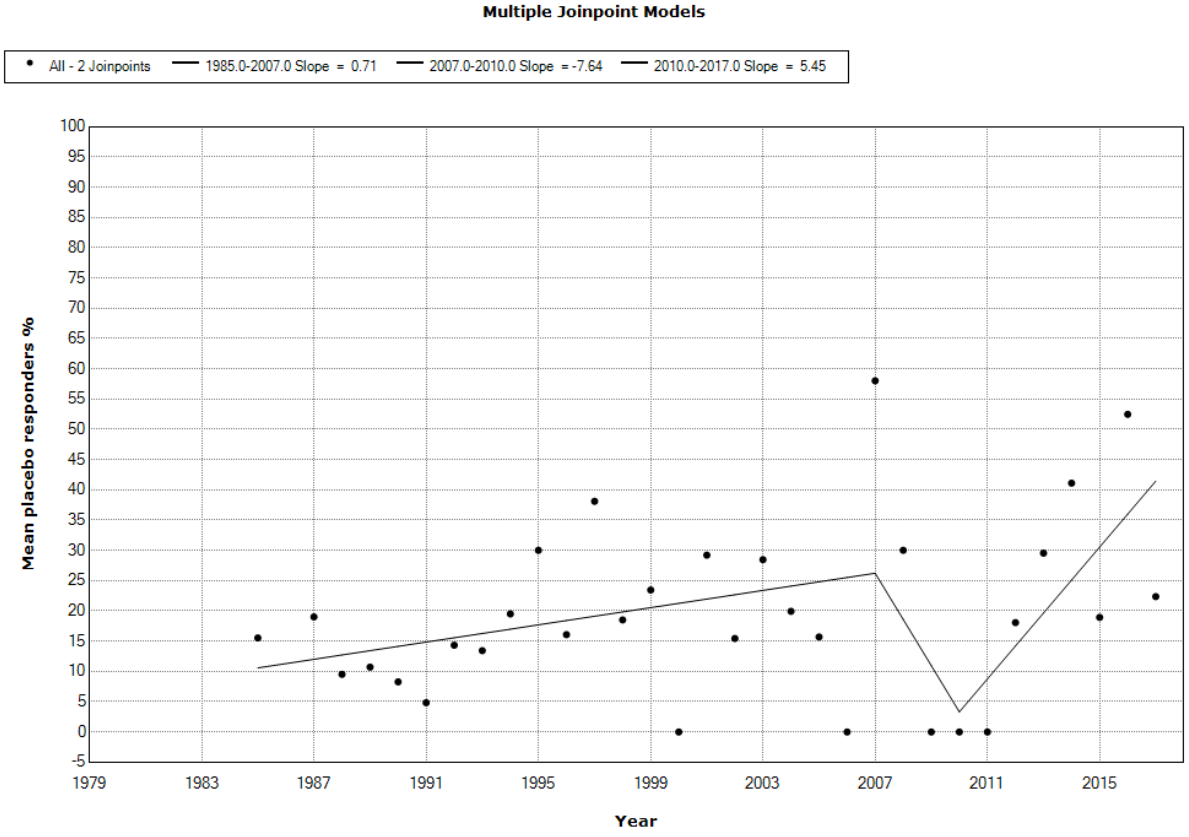

Fig. (3). Multiple Join-Point model of the time (year of publication) trend of placebo responder rates in OCD double-blind trials.

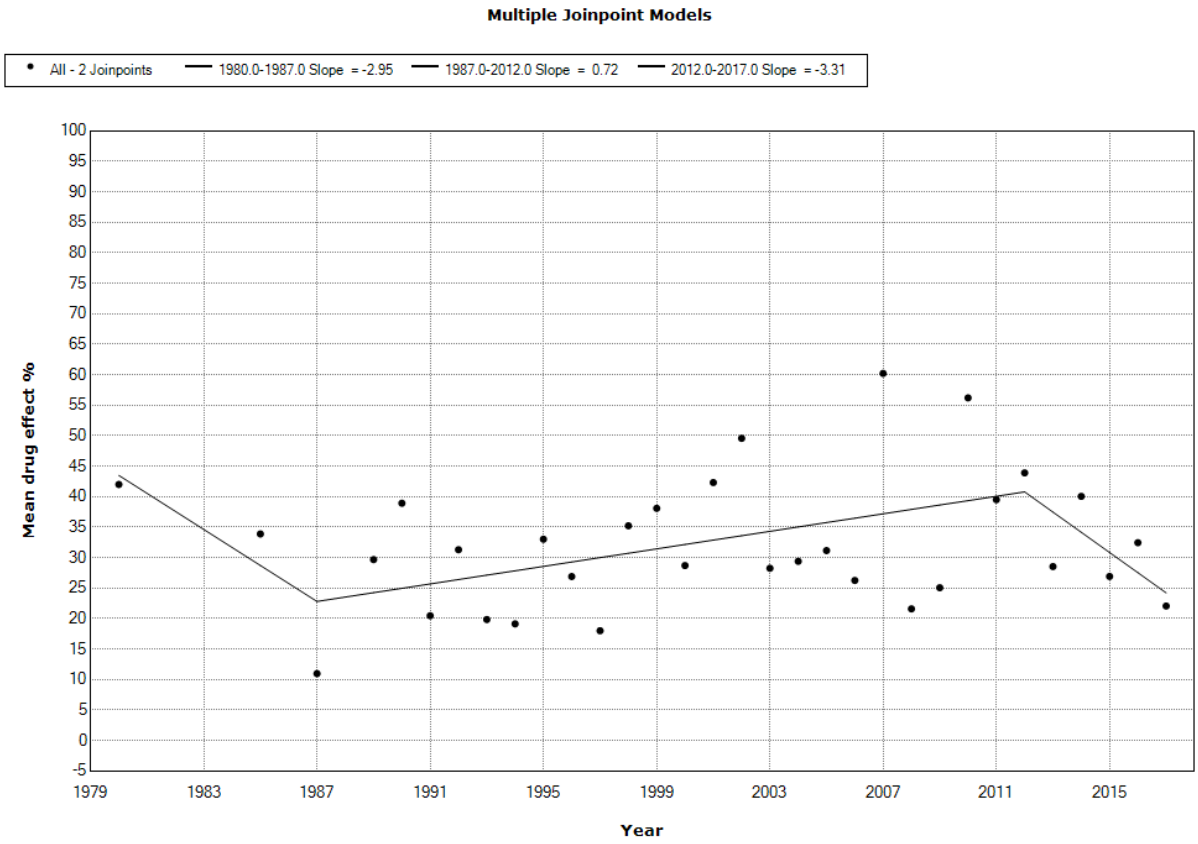

Fig. (4). Multiple Join-Point model of the time (year of publication) trend of drug effect in OCD double-blind trials.

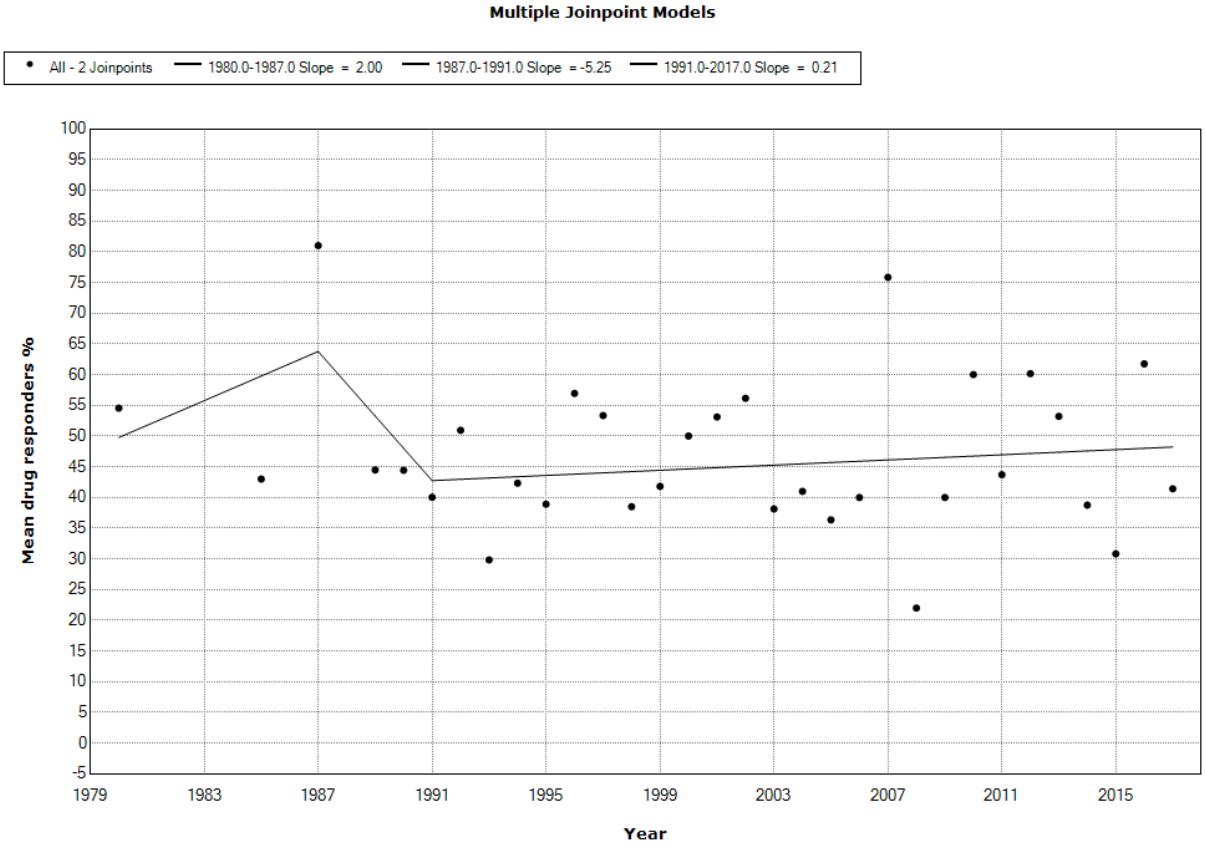

Fig. (5). Multiple Join-Point model of the time (year of publication) trend of drug responder rates in OCD double-blind trials.

show statistically significant APC changes between 1984 and 2017 (Fig. **5**).

4. DISCUSSION

In this study, using Joinpoint regression analyses, we found significant increases in the net effect of placebo from 1991 to 2017 and in placebo responder rates from 2010 to 2017. The effects of drug treatment of OCD increased from 1987 to 2012, between two periods of no significant changes (1979-1987 and 2012-2017), while responder rates to drug treatment showed no statistically significant annual changes between 1984 and 2017. We confirmed the finding of a trend towards an increase of placebo effects in OCD drug treatment studies, previously reported by Ackerman and Greenland for the decade 1989 to 1999 in their 2002 meta-regression [8]. Surprisingly, we did not find drugs to increase their effect of responder rates in parallel with placebo. In fact, the increasing placebo effect that was found for other psychiatric (*e.g*., schizophrenia [129] and depression [130]) and non-psychiatric disorders (*e.g*., hypertension [131]), and placebo efficacy dragged drug efficacy to higher levels [130]. Here we found a trend towards increased placebo effects and responder rate, with a decrease in the difference between drug and placebo, to the point that the most recent response rates (effects) between placebo and drugs nearly overlap (Figs. **2** and **4**), while responder rates differ little (Figs. **3** and **5**); something similar has been described for schizophrenia [132], but not for depression [130]. Furthermore, we also found that effect/responder rates for OCD to both placebo and drugs are low compared to other psychiatric disorders, as recently reported using effect sizes as outcome measures [133]. Why OCD should be stiffer than other psychiatric disorders in responding to treatment may have a response to the pathophysiology of the disorder and to its related personality characteristics. That you can't teach an old dog new tricks may well apply to this disorder. A therapeutic response may be hampered by too often controlling one's health state, that prevents a patient from establishing an adequate clinical progress, and people with OCD often display pathological doubt, that prompts them to control for any change all too often and then to doubt for results.

It is not easy to explain the increase with time of placebo effects and responder rates we found here. One explanation that has been offered for similar results in depression is the "baseline inflation" [134], *i.e*., the tendency to inflate baseline scores of the scale chosen for subject inclusion in a randomised clinical trial (RCT) so to ensure more participants to the sponsor. This, combined with patient expectation and the Hawthorne-like effect of being closely observed, yields better results for drug and placebo alike. However, there has been no increase in baseline Y-BOCS scores of included samples.

Other possible explanations may involve historical factors. In fact, most early studies involved testing the efficacy of clomipramine and SSRIs in patients with OCD, or were survival studies focusing on Kaplan-Meyer curves after switching patients with a benefit on an antidepressant agent to placebo, measuring recurrence/relapse rates. In contrast, later studies increasingly focused on treatment-resistant populations and add-on drugs *vs*. placebo. It is highly probable that such populations are more resistant to the effects of both drugs and placebo. However, this should have been followed by a decrease in overall responsiveness, which we did not find; on the contrary, both effect and responder rates increased in later years, more so regarding placebo (Figs. **2**-**5**).

Another issue may regard the principal sites involved in the various studies. In antipsychotic drug trials, the increase in placebo response has been observed for North America-based studies, but not for those conducted in the rest of the world or for international studies including US sites [135], and the same phenomenon has been observed for painkiller trials, with sample size and study duration driving the placebo response increase [136]. Sample size in US studies correlated weakly with placebo response in our study (Pearson's r=0.21). However, treatment duration did correlate strongly (Pearson's r=0.54). Here we observed a curious phenomenon, *i.e*., that in studies 1980-2008, US-based studies prevailed over the rest of the world (N=52 *vs*. N=24), whereas in studies conducted from 2009 on, the rest of the world studies reversed the ratio (N=13, USA *vs*. N=24, rest of the world). The reversal was driven by Iran (N=17), a country that was not present during the 1980-2009 period. In Iranian studies, the correlation between sample size was much weaker than in US-based studies (r=0.093), perhaps a consequence of the fact that sample sizes in these studies were about 20 each with a much lower standard deviation than in US studies (Table **1**). In contrast with US studies, there was a strong *negative* correlation between treatment duration and response to placebo (r=-0.471). Despite the entity of placebo effect did not differ between US-based and Iran-based studies (Student's t=1.145; p=0.256, not significant), we feel that the recent upsurge of placebo responder rates and the constant increase of placebo response are linked to the results of Iranian studies. The samples in American studies varied widely, as did the number of sites, while the Iranian studies recruited middle samples and tended to be single-center (Table **1**). It has been suggested in antidepressant trials for major depression that two factors that may be linked to reduced ability to detect a signal for an antidepressant are constituted by extremely large and extremely small samples and by multicentricity [137]; a reduced signal is usually linked to increasing placebo response that dampens the drug-placebo difference.

A possibility with longer-term treatment to associate with placebo response could reside in the exacerbating-remitting course that often characterizes OCD [138], especially in paediatric cases [139]. If the interpretation of the placebo effect as a regression to the mean holds true [140], it would ensure that by treating people for more time, there will be an increased probability of spontaneous remission of the disorder, that would be subsequently attributed to placebo. This matches the results of American studies, but is opposite to what Iranian studies tell us.

Still another possibility is a change in the characteristics of included patients. It has been speculated that RCTs tend to include patients repeatedly the same persons who

participated in prior antidepressant trials, and this is usually addressed with excluding patients having participated recently in another RCT or having received psychotherapy in recent times. In fact, it was shown that patients with low income may be eager to participate in more than one antidepressant drug trial [141]. These patients would be expected to display a rather uniform behaviour in responding to treatment, thus favouring placebo response and their data tend to be increasingly included in databases, thus affecting results. In OCD, we do not have data at this regard, but the recent change in the classification of OCD spectrum disorders in the DSM-5 [142], which were previously classified amidst the anxiety disorders and included hoarding disorder [143], may have impacted the response of OCD to placebo. However, in this case, we should have expected a join point to occur about 2013, the year of introduction of DSM-5 [142]. In placebo effect, there was no such join point. Placebo effect showed a continuous growth from 1991 onwards, while placebo responder rate had a joinpoint at 2010, when the shift from DSM-IV-TR™ had still to occur. It should be said that DSM-IV-TR™ diagnoses in drug trials continued to be adopted along with DSM-5 diagnoses for some time. At any rate, it appears that in OCD, as in other mental and non-mental disorders, placebo effect and responder rates are puzzlingly increasing and appear to be out of control, and this depends on multiple factors [137, 144], pointing to changing populations included in RCTs (independently from initial severity) and prompting to a revision of the RCT model. Given that this trend is not specifically bound to a single condition, it is possible that it reflects continuing human evolution.

4.1. Limitations and Strengths

Our study is not a meta-analysis and the overall placebo effect and placebo-responder rates are not weighted for sample size. Furthermore, we did not include studies not using drugs, *i.e*., somatic treatments *vs*. sham, and did not distinguish between adult and paediatric studies. Moreover, we did not select our studies based on their quality nor did we address possible sponsor bias. However, our study is the first considering such a wide time period and the first to consider both net placebo effects and responder rates based on clear-cut criteria. Future studies will have to address the above concerns. It has been suggested that mechanical devices [145] and surgery [146] are endowed with a superior placebo effect than drugs, although the evidence is still inconclusive [147], and placebo, despite displaying large effects in depression, was not superior in non-pharmacological than in pharmacological studies in a meta-analysis [148]. Comparison between drug and somatic treatment of OCD will show whether in this disorder there is a strong mechanical device component in placebo response and whether there is an increase of response with the year of publication with these treatments similar to what occurs with drugs.

The fact that the curves of effect and responder rates did not reciprocally correspond for both placebo and drugs may be explained by the fact that some studies did not report one of them (Table **1**). Investigators need to report their data more clearly in the future, so to allow other investigators to perform meta-analyses on their data.

The current situation with OCD treatment is that this disorder is either treated with drugs having the ability to block the reuptake of serotonin or with cognitive-behavioral therapy or both, or with attempts to add-on ongoing pharmacotherapy other pharmacological agents having antidopaminergic or antiglutamatergic properties or somatic treatments like deep brain stimulation or transcranial magnetic stimulation. The first studies focused on the efficacy of drugs used classical designs and were carried-out by prestigious institutions. Once the concept that first line treatments were represented by SSRIs/clomipramine, the treatment paradigms shifted towards add-on and somatic treatments, and this may have affected the figures we obtained. The closing gap between placebo and drug treatment must prompt investigators to formulate new hypotheses to test and industries to produce alternatively working drugs.

CONCLUSION

In this Joinpoint regression analysis, we observed an increase of the response to placebo (placebo effect) as well as an increase in responder rates in OCD studies with the year of publication. Changes in study types and sites are apparently related to the results obtained. The gap between response to drug and response to placebo appears to be reducing to an extent that current therapeutic approaches to OCD are becoming questionable and should prompt to seek newer approaches in facing this stubborn disorder.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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