Glutamatergic Agents as Add-On Medication for the Treatment of Obsessive-Compulsive Disorder:

A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: The aim of the present study was to review the existing literature on clinical trials with glutamatergic agents in adults with obsessive-compulsive disorder (OCD) and to perform a meta-analysis to estimate the overall effect size.

Data Sources: We searched in MEDLINE, Embase, and the Cochrane Library for eligible studies, using the following search terms: (*glutamate* OR *glutaminergic* OR *glutamatergic* OR *NMDA* OR *AMPA* OR *kainate*) AND (*obsessive-compulsive disorder* OR *obsessive* OR *compulsive* OR *OCD*). A separate search was performed for generally known glutamatergic agents. The databases were searched for articles published by May 31, 2015.

Study Selection: Eligible studies were double-blind, randomized controlled trials that tested the efficacy of add-on treatment with a glutamatergic agent in patients with OCD.

Data Extraction: Data were extracted independently by 2 reviewers. We extracted dichotomous data (number of patients with response and remission) to estimate relative risk ratios (RRs), as well as continuous data (scores in Yale-Brown Obsessive Compulsive Scale and Clinical Global Impressions-Severity of Illness and -Improvement scales), which were used to estimate standardized mean differences. Effect sizes were estimated using a random-effects model.

Results: Eight randomized controlled trials were identified. The overall ratio for response was RR = 3.71 (95% CI, 2.35–5.83; $P < .001$). When limited to the studies with treatment-resistant patients, the effect size remained significant (RR = 4.30; 95% CI, 2.19–8.43; $P < .001$). Secondary outcomes, such as the standardized mean differences for continuous data, showed the statistically significant superiority ($P < .001$) of glutamatergic agents over placebo. The risk of dropouts was RR = 1.18 (95% CI, 0.83–1.69; $P = .361$) and the risk of dropouts due to adverse effects was RR = 3.04 (95% CI, 1.57–5.89; $P = .001$).

Conclusions: Glutamatergic agents are effective as add-on treatment for OCD in general and especially for treatment-refractory OCD.

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Obsessive-compulsive disorder (OCD) is a debilitating condition with an estimated lifetime prevalence of about 2.3%.[1] Core features include intrusive thoughts (obsessions) that cause distress and are recognized by the individual as inappropriate. Compulsions are thoughts or acts that are performed in a ritualistic way in order to neutralize the obsessions.[2] According to DSM-IV, OCD belongs to the anxiety disorders, while DSM-5[3] classifies OCD among the obsessive-compulsive and related disorders (also known as obsessive-compulsive spectrum disorders), such as body dysmorphic disorder, hoarding disorder (which was subsumed under OCD in DSM-IV), trichotillomania, and excoriation disorder.

Current evidence-based treatment options include cognitive-behavioral therapy[4] (exposure and response prevention) and medication with antidepressants; serotonin reuptake inhibitors (SRIs) are considered as first-line agents.[5] In contrast to depression or anxiety disorders, where response is defined as a 50% reduction in symptom severity, a 35% reduction is considered to be a response in OCD. Nevertheless, as many as 60% of patients fail to attain even this low-threshold response.[6] These facts are indicative of the urgent need for further alternatives for the treatment of OCD. Thus far, several strategies have been developed to increase treatment efficacy. Augmenting an SRI medication with an additional drug from a different class has shown some promising results. For example, the efficacy of atypical antipsychotics has been tested in several trials.[7]

Apart from the role of serotonin in the pathogenesis of OCD, considerable evidence indicates the importance of glutamate transmission in the pathophysiology of OCD. A number of animal models with transgenic and knockout mice imply a hyperactivity of glutamatergic neurons in the cortico-striatal-thalamic-cortical circuit (CSTC).[8,9] Further, genetic studies indicate that the glutamatergic system plays a role in OCD: for example, genes such as *SLC1A1* (solute carrier family 1 member 1) (which encodes for the excitatory amino acid transporter 3),[10] *GRIN2B* (glutamate ionotropic receptor *NMDA* type subunit 2B) (encodes for the *N*-methyl-D-aspartate [NMDA] receptor 2B subunit),[11] *GRIK2* (glutamate ionotropic receptor kainate type subunit 2),[12] and *DLGAP3* (discs large homolog associated protein 3)[13] have been associated with susceptibility to OCD.

Earlier case reports,[14–16] case series,[17] and open-label studies[18,19] about a decade ago showed some positive results for add-on treatment with glutamatergic agents. Since then, a number of double-blind, randomized controlled trials have been performed. We review here the current literature on

Clinical Points

- Treatment resistance is a common problem among patients with obsessive-compulsive disorder treated with serotonin reuptake inhibitors.
- Add-on treatment with glutamatergic agents is an effective and well-tolerated option and should eventually be preferred to antipsychotics because of the more favorable adverse-effect profile.

augmentation strategies with glutamatergic substances and use meta-analytic techniques to quantify their overall effect size.

METHODS

Search Strategy

The inclusion criteria for the studies were the following: (1) double-blind, randomized controlled trials (either placebo-controlled or head-to-head trials); (2) adult patients diagnosed with OCD; and (3) add-on treatment with an agent with glutamatergic properties. We searched for studies in the electronic databases MEDLINE, Embase, and the Central Register of Controlled Trials of the Cochrane Library. The search terms were (*glutamate* OR *glutaminergic* OR *glutamatergic* OR *NMDA* OR *AMPA* OR *kainate*) AND (*obsessive-compulsive disorder* OR *obsessive* OR *compulsive* OR *OCD*). A separate search was performed for generally known glutamatergic substances: acamprosate, riluzole, memantine, *N*-acetylcysteine, D-cycloserine, lamotrigine, amantadine, and glycine. The applied limits of the search were that the articles should have been published by May 31, 2015. We also searched through the reference lists of reviews and related articles to identify any additional studies.

Article Selection and Review Strategy

The selection of studies involved an initial screening of title and abstract to find studies fulfilling the inclusion criteria. If it was not clear from title or abstract that a study should be rejected, the full text was obtained. This process was conducted independently by 2 of the authors (Z.G.L. and G.E.L.) to reduce the possibility of rejecting relevant articles.

The data were extracted independently by both authors. In case of disagreement, the senior author (K.T.K.) could be consulted to mediate consensual decisions. Dichotomous data (rates of response and remission) were collected for the primary outcomes of this review. Secondary outcomes were standardized mean differences for continuous data (scores in Y-BOCS, CGI-S, and CGI-I), the risk of dropouts due to any reason, and the risk of dropouts due to adverse effects.

Statistical Methods (meta-analysis)

Meta-analysis was performed whenever more than 1 trial was available in either group of studies (placebo-controlled or head-to-head trials). A random-effects model was applied based on the assumption that the true effect size was not the same in all studies. Relative risk ratios (RRs) were computed for dichotomous data because they have the advantage of being more intuitive than odds ratios (ORs). However, since a significant proportion of meta-analyses use the OR as the main measure of effect size, we also estimated the OR for response, remission, and discontinuation rates to make our results comparable with the results from other studies. We used 2 definitions for response: the first was the response as defined by the authors, the second was the response as defined by Pallanti and Quercioli[6] (full response: ≥ 35% change in Y-BOCS; partial response: change in Y-BOCS between 25%–34%). In estimating RRs for response and remission, we followed the recommendation of the *Cochrane Handbook for Systematic Reviews of Interventions*[20] and performed an intention-to-treat analysis; in the case of unusable data (eg, analysis per protocol), we imputed the missing data by assuming that none of the missing participants experienced a response. We then performed 2 sensitivity analyses: the best-case scenario assumes that all participants with missing outcomes in the experimental intervention group had good outcomes, while all those with missing outcomes in the control intervention group had poor outcomes, and the worst-case scenario assumes the converse.

In the case of zero events trials (in 1 or both arms), the standard continuity correction of 0.5 was applied.[21] If data were not provided in an article or were reported in a nonuseful way, we contacted the corresponding authors. If this approach was unfruitful, we computed an estimated number of responders under the assumption that the changes in scores were normally distributed (this is similar to the procedure described by Furukawa et al[22]).

Calculations were performed using standard formulas[23] in MicroSoft Excel (Excel 2003 Edition, MicroSoft, Redmond, Washington). The forest plot was also created in MicroSoft Excel according to a guide published by Neyeloff et al.[24] Heterogeneity I^2 was computed to assess the percentage of the overall variability attributable to between-studies variability. The risk of bias in individual studies was evaluated using the Cochrane Collaboration's domain-based tool, which assesses allocation concealment, sequence generation, blinding, selective outcome reporting, and other sources of bias. The risk of publication bias was assessed using a funnel plot and Egger regression method.[25]

In Germany, reviews and meta-analyses are not reviewed by an institutional review board.

RESULTS

Search Results

The electronic searches provided 406 references from MEDLINE, 674 from Embase, and 28 references (clinical trials) from the Cochrane Library. Initial scanning of the abstracts left a total of 16 reports, of which another 8 were rejected after further screening and assessment for eligibility. The remaining 8 reports[26–33] fulfilled the inclusion criteria for the review (see flow diagram in eAppendix 1). Six of them included patients with treatment-resistant OCD.[27–30,32,33] Details for each trial are presented in Table 1. The complete

Table 1. Overview of the Reviewed Studies

Study	Year	Groups	N	Duration	Evaluation	Inclusion Criteria	Response, Remission	Results
Greenberg et al[26]	2009	Placebo, glycine 60 mg/d	24	12 wk	Y-BOCS, CGI-S, CGI-I, SDS, QLS, NIMH-OC	Outpatients ≥18 Y-BOCS ≥12 wk unchanged medication regimen	Response: ≥35% reduction in Y-BOCS, ≤16 Y-BOCS Remission: no definition	Enrolled: glycine, n=12; PLC, n=12 Completers: glycine, n=3; PLC, n=5 Analyzed: glycine, n=5; PLC, n=9 (available case analysis) Response: glycine, n=2; PLC, n=0 Remission: NR Dropouts: glycine, n=9; PLC, n=7 Dropouts due to AE: glycine, n=8; PLC, n=1 Y-BOCS end point, mean (SD): glycine, 18.40 (4.80); PLC, 23.70 (7.10) CGI-S end point, mean (SD): glycine, 4.00 (0.70); PLC, 4.1 (1.1) CGI-I end point, mean (SD): glycine, 2.8 (0.8); PLC, 3.7 (1.1)
Mowla et al[27]	2010	Placebo, topiramate (100–200 mg)	49	12 wk	Y-BOCS, $HDRS_{17}$, CGI-I	≥18 Y-BOCS ≥12 wk treatment with antidepressants	Response: ≥25% reduction in Y-BOCS Remission: no definition	Enrolled: TPM, n=24; PLC, n=25 Completers: TPM, n=20; PLC, n=21 Analyzed: TPM, n=20; PLC, n=21 Response: TPM, n=12; PLC, n=0 Remission: NR Dropouts: TPM, n=4; PLC, n=4 Dropouts due to AE: TPM, n=4; PLC, n=2 Y-BOCS end point, mean (SD): TPM, 17.90 (4.30); PLC, 27.6 (5.4) CGI-S end point: NR CGI-I end point, mean (SD): TPM, 2.10 (0.47); PLC, 3.80 (0.45)
Berlin et al[28]	2011	Placebo, topiramate (up to 400 mg/d)	48	12 wk	Y-BOCS, MADRS, CGI, Patient Global Impressions Scale, SDS	≥18 Y-BOCS or ≥10 in questions 1–5 of the obsession scale ≥12 wk treatment with antidepressants	Response: no definition Remission: no definition	Enrolled: TPM, n=24; PLC, n=24 Completers: TPM, n=13; PLC, n=14 Analyzed: TPM, n=19; PLC, n=20 (available case analysis) Response: NR Remission: NR Dropouts: TPM, n=5; PLC, n=4 Dropouts due to AE: TPM, n=5; PLC, n=0 Y-BOCS end point: NR CGI-S end point: NR CGI-I end point: NR
Afshar et al[29]	2012	Placebo, NAC (2,400 mg/d)	48	12 wk	Y-BOCS, CGI-S, CGI-I, CGI-E	≥16 Y-BOCS ≥12 wk treatment with antidepressants	Partial response: ≥25%–34% reduction in Y-BOCS Full response: ≥35% reduction in Y-BOCS Remission: no definition	Enrolled: NAC, n=24; PLC, n=24 Completers: NAC, n=19; PLC, n=20 Analyzed: NAC, n=19; PLC, n=20 (available case analysis) Response 35%: NAC, n=10; PLC, n=3 Remission: NR Dropouts: NAC, n=5; PLC, n=4 Dropouts due to AE: NAC, n=3; PLC, n=0 Y-BOCS end point, mean (SD): NAC, 16.83 (5.52); PLC, 21.89 (3.95) CGI-S end point, mean (SD): NAC, 3.31 (0.88); PLC, 3.88 (1.00) CGI-I end point, mean (SD): NAC, 2.50 (0.80); PLC, 2.81 (0.70)
Bruno et al[30]	2012	Placebo, lamotrigine (100 mg/d)	40	16 wk	Y-BOCS, HDRS, CGI-S	≥18 Y-BOCS ≥12 wk treatment with antidepressants	Partial response: ≥25%–34% reduction in Y-BOCS Full response: ≥35% reduction in Y-BOCS Remission: no definition	Enrolled: LMT, n=20; PLC, n=20 Completers: LMT, n=17; PLC, n=16 Analyzed: LMT, n=20; PLC, n=20 Partial response: LMT, n=10; PLC, n=0 Full response: LMT, n=7; PLC, n=0 Remission: NR Dropouts: LMT, n=3; PLC, n=4 Dropouts due to AE: LMT, n=1; PLC, n=0 Y-BOCS end point, mean (SD): LMT, 17.65 (9.70); PLC, 25.95 (5.10) CGI-S end point, mean (SD): LMT, 3.41 (0.51); PLC, 4.75 (0.68) CGI-I end point: NR

(continued)

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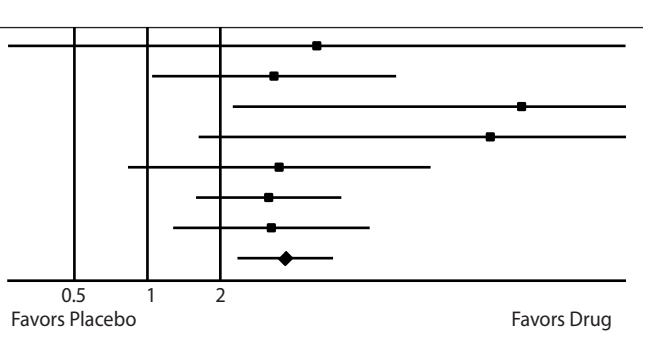
Table 1 (continued). Overview of the Reviewed Studies

Study	Year	Groups	N	Duration	Evaluation	Inclusion Criteria	Response, Remission	Results
Ghaleiha et al[31]	2013	Placebo, memantine (20 mg/d)	41	8 wk	Y-BOCS	≥21 Y-BOCS	Partial response: ≥25%–34% reduction in Y-BOCS Full response: ≥35% reduction in Y-BOCS Remission: ≤16 Y-BOCS	Enrolled: MMN, n=20; PLC, n=20 Completers: MMN, n=14; PLC, n=15 Analyzed: MMN, n=14; PLC, n=15 Partial and full response: MMN, n=19; PLC, n=6 Remission: MMN, n=17; PLC, n=6 Dropouts: MMN, n=2; PLC, n=2 Dropouts due to AE: n=0 Y-BOCS end point: NR CGI-S end point: NR CGI-I end point: NR
Haghighi et al[32]	2013	Placebo, memantine (5–10 mg/d)	40	12 wk	Y-BOCS, CGI-S, CGI-I	≥21 Y-BOCS ≥12 wk treatment with antidepressants	Partial response: ≥25%–34% reduction in Y-BOCS Full response: ≥35% reduction in Y-BOCS Remission: no definition	Enrolled: MMN, n=20; PLC, n=20 Completers: MMN, n=14; PLC, n=15 Analyzed: MMN, n=14; PLC, n=15 Partial response: MMN, n=4; PLC, n=4 Full response: MMN, n=9; PLC, n=0 Remission: NR Dropouts: MMN, n=6; PLC, n=5 Dropouts due to AE: NR Y-BOCS end point, mean (SD): MMN, 19.57 (3.76); PLC, 23.67 (3.56) CGI-S end point, mean (SD): MMN, 3.29 (0.61); PLC, 3.87 (0.64) CGI-I end point, mean (SD): MMN, 2.50 (0.65); PLC, 2.80 (0.56)
Afshar et al[33]	2014	Topiramate (≤200 mg/d), placebo	38	12 wk	Y-BOCS, CGI-S, CGI-I	≥16 Y-BOCS ≥12 wk treatment with antidepressants	Response: ≥25% reduction in Y-BOCS Remission: no definition	Enrolled: TPM, n=19; PLC, n=19 Completers: TPM, n=13; PLC, n=14 Analyzed: TPM, n=13; PLC, n=14 Response: TPM, n=7; PLC, n=2 Remission: NR Dropouts: TPM, n=6; PLC, n=5 Dropouts due to AE: TPM, n=3; PLC, n=1 Y-BOCS end point, mean (SD): TPM, 21.45 (3.44); PLC, 24.32 (4.50) CGI-S end point, mean (SD): TPM, 4.38 (1.15); PLC, 5.21 (1.20) CGI-I end point, mean (SD): TPM, 2.31 (1.49); PLC, 3.60 (1.10)

Abbreviations: AE = adverse events, CGI-E = Clinical Global Impressions-Efficacy Index, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HDRS = Hamilton Depression Rating Scale, $HDRS_{17}$ = 17-item HDRS, LMT = lamotrigine, MADRS = Montgomery-Asberg Depression Rating Scale, MMN = memantine, NAC = *N*-acetylcysteine, NIMH-OC = National Institute of Mental Health Obsessive Compulsive scale, NR = not reported, QLS = Quality of Life Scale, PLC = placebo, SDS = Sheehan Disability Scale, TPM = topiramate, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Figure 1. Forest Plot of Relative Risk (RR) for Response to Glutamatergic Agents in Patients With OCD

Study	Drug	RR	95% CI	*P*
Greenberg,[26] 2009	Glycine	5.00	0.27–93.96	.282
Afshar,[29] 2012	NAC	3.33	1.05–10.63	.042
Bruno,[30] 2012	Lamotrigine	35.00	2.25–544.06	.011
Mowla,[27] 2010	Topiramate	26.02	1.63–416.01	.021
Afshar,[33] 2014	Topiramate	3.50	0.83–14.73	.088
Ghaleiha,[31] 2013	Memantine	3.17	1.59–6.32	.001
Haghighi,[32] 2013	Memantine	3.25	1.28–8.27	.013
Total		3.71	2.35–5.83	<.001



Abbreviations: NAC = *N*-acetylcysteine, OCD = obsessive-compulsive disorder.

Table 2. Main Analysis and Sensitivity Analyses for Efficacy of Glutamatergic Agents in Patients With OCD

Analysis	No. of Trials	Effect Size (95% CI)	*P*
All studies			
Main analysis	7	RR = 3.71 (2.35 to 5.83)	<.001
		OR = 11.29 (4.77 to 26.71)	<.001
Worst-case scenario	7	RR = 1.83 (1.24 to 2.71)	.003
Best-case scenario	7	RR = 4.99 (3.22 to 7.72)	<.001
Sensitivity analysis-1 (≥ 25% response)	7	RR = 3.21 (1.74 to 5.91)	<.001
Sensitivity analysis-2 (≥ 35% response)	5	RR = 4.57 (2.19 to 9.54)	<.001
Y-BOCS	6	SMD = −1.12 (−1.47 to −0.77)	<.001
CGI-S	5	SMD = −0.91 (−1.56 to −0.26)	.006
CGI-I	5	SMD = −1.23 (−2.26 to −0.20)	.020
NNT, LL–UL	7	2–6	…
Refractory OCD			
Main analysis	5	RR = 4.30 (2.19 to 8.43)	<.001
		OR = 11.01 (3.56 to 34.09)	<.001
Worst-case scenario	5	RR = 1.83 (1.13 to 2.99)	.015
Best-case scenario	5	RR = 6.12 (3.41 to 10.98)	<.001
Sensitivity analysis-1 (≥ 25% response)	5	RR = 3.74 (1.45 to 9.64)	.006
Sensitivity analysis-2 (≥ 35% response)	4	RR = 5.13 (2.02 to 13.04)	.001
Y-BOCS	5	SMD = −1.16 (−1.55 to −0.77)	<.001
CGI-S	4	SMD = −1.07 (−1.78 to −0.37)	.003
CGI-I	4	SMD = −1.32 (−2.58 to −0.07)	.038
NNT, LL–UL	5	2–5	…

Abbreviations: LL = lower limit, NNT = number needed to treat, OCD = obsessive-compulsive disorder, OR = odds ratio, RR = risk ratio, SMD = standardized mean difference, UL = upper limit.

Table 3. Reported Adverse Effects

Drug	Reported Adverse Effects
Glycine	Nausea, unpleasant taste
Topiramate	Fatigue, influenza-like symptoms, paresthesia, headache, dizziness, toothache, anxiety, memory problems, insomnia, somnolence, taste perversion
N-acetylcysteine	Nausea/vomiting
Lamotrigine	Sedation, fatigue, headache, skin rash
Memantine	Drowsiness, headache, constipation, dizziness, fatigue, nausea, decreased appetite, itching, nervousness, rash

list of the assessed trials and the reasons for rejection appear in eAppendix 1.

Meta-Analysis

Effect size for efficacy. Seven studies provided usable data for the estimation of RR, and 6 provided data for the estimation of standardized mean differences. In the main analysis, the mean RR for response was 3.71 (95% CI, 2.35–5.83; $P < .001$; see also forest plot in Figure 1). Only 1 study[31] provided the number of patients with remission so that we did not perform a meta-analysis for remission. In our worst-case and best-case scenario analyses, the RRs for response were 1.83 (95% CI, 1.24–2.71; $P = .003$) and 4.99 (95% CI, 3.22–7.72; $P < .001$), respectively. Analyses were repeated for trials with refractory OCD (defined as nonresponse, ie, reduction in the Y-BOCS score of less than 25%,[6] after treatment with an SRI agent at a therapeutic dose for at least 12 weeks), and the results remained significantly in favor of glutamatergic drugs. The results are presented in Table 2.

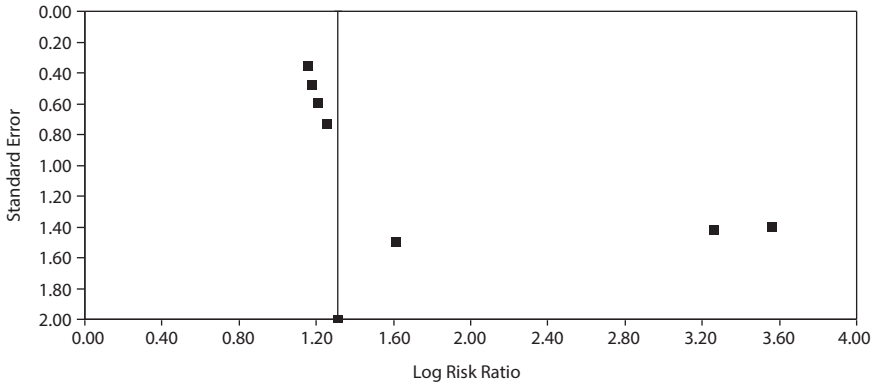
Tolerability. All 8 trials were considered in the estimation of tolerability parameters. The overall RR for discontinuation was 1.18 (95% CI, 0.83–1.69; $P = .361$). The RR for discontinuation due to adverse effects was 3.04 (95% CI, 1.57–5.89; $P = .001$). The estimated odds ratios were 1.22 (95% CI, 0.70–2.12; $P = .474$) and 4.31 (95% CI, 1.93–9.62; $P < .001$), respectively. Reported adverse effects for each agent are presented in Table 3.

Heterogeneity. The computed heterogeneity I^2 was 0% in the main analysis for response (95% CI, 0%–64%) and 10% in the main analysis for refractory OCD (95% CI, 0%–82%). Heterogeneity under 40% is considered low.

Risk of Bias and Publication Bias

The risk of bias for each study can be determined by assessing the following 6 domains: (1) sequence generation, (2) allocation concealment, (3) blinding, (4) missing data, (5) selective outcome reporting, and (6) other sources of bias. The overall risk of bias could be described as low (see the risk of bias graph in eAppendix 2). The results for the individual trials are presented in eAppendix 2. Finally, visual inspection of the funnel plot gives some indication of publication bias (Figure 2); in particular, there is a gap on the bottom left side that could indicate unpublished studies with small to moderate effects. Egger regression method also indicates a degree of publication bias, since the intercept of the fitted

Figure 2. Publication Bias: Funnel Plot[a]



[a]The gap on the bottom left portion of the graph could be indicative of publication bias. However, the small number of trials limits the robustness of the results.

line was not near zero (eAppendix 3). However, the small number of studies limits the robustness of these 2 methods (some authors suggest that a funnel plot is not meaningful if the number of studies is fewer than 10).

DISCUSSION

Results

To our knowledge, this is the first meta-analysis to estimate the effect of agents with glutamatergic properties as augmentative medication for the treatment of OCD. The mean effect sizes were RR = 3.71 (95% CI, 2.35–5.83; $P < .0001$) for OCD in general and RR = 4.30 (95% CI, 2.19–8.43; $P < .001$) for refractory OCD, which indicate a very substantial drug efficacy. There were no significant differences between drug and placebo groups as far as dropouts are considered, while the risk for dropouts due to adverse effects was significantly higher in the active drug group than in the placebo group. Because of the small number of trials, it is not possible to draw conclusions about differences in efficacy among the 5 agents used (ie, *N*-acetylcysteine, memantine, topiramate, glycine, and lamotrigine) with any assurance. Based on the present studies, the highest RR for response was observed for lamotrigine, while the lowest RR for dropouts due to adverse effects was observed for the 2 studies with memantine (RR = 1 in the study by Ghaleiha et al,[31] and RR = 2.25 in the study by Haghighi et al[32]).

Mechanism of Action

All of the drugs studied share a common property, the modulation of the glutamatergic system. Glycine is a coagonist of the NMDA receptor and is necessary for the efficient opening of the ion channel.[34] Memantine is a voltage-dependent noncompetitive NMDA-receptor antagonist that inhibits prolonged calcium influx while allowing a baseline activity.[35] Topiramate inhibits AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate receptors and thus can influence the activity of NMDA receptors indirectly.[36,37] Lamotrigine interferes with second-messenger signaling by blocking the arachidonic acid cascade.[38] Finally, *N*-acetylcysteine restores extracellular glutamate, thus modulating glutamate transmission.[39]

Although current models of OCD assume that glutamate is overactive, NMDA agonists nevertheless seem to have a beneficial effect on OCD. For example, D-cycloserine, an NMDA agonist at the glycine site, seems to enhance the results of exposure and response prevention by accelerating fear extinction.[40] Like the monoamine hypothesis for depression or schizophrenia, glutamate overactivity may be an oversimplified theory.[41] Glutamate transmission might not be hypoactive or hyperactive but "out of tune," and medication is presumed to stabilize it.

Treatment Strategies for Refractory OCD

Refractory OCD, defined as an unsatisfactory response to a 12-week trial with an SRI, constitutes a major problem for the clinician. Several strategies have been developed to deal with this situation. Combining initial SRI treatment with cognitive-behavioral therapy or switching to another agent should be the first option according to existing guidelines (eg, American Psychiatric Association guidelines; http://www.guideline.gov/content.aspx?id=11078). If the response still remains poor, combination of 2 agents could be considered (eg, SRI with an antipsychotic or buspirone, or clomipramine with a selective serotonin reuptake inhibitor). Taking the results of the present meta-analysis into consideration, adding a glutamatergic agent to an SRI presents a further option. Positive results have further been reported for other classes of drugs, such as 5-HT_3 antagonists (eg, ondansetron)[42] and pindolol.[43] Nonmedication treatments include TMS (transcranial magnetic stimulation) and more invasive procedures such as deep brain stimulation, with neurosurgical operations reserved as a last resort.[44,45]

CONCLUSIONS

We show that glutamatergic agents are effective as add-on treatment for OCD. Lamotrigine had the highest RR for response; however, since its efficacy was tested in

only 1 trial,[30] its superiority over the other agents cannot be concluded with assurance. All substances were well tolerated and the reported adverse effects were mild and benign, which is a major advantage in comparison to antipsychotics, the main class of drugs used as augmentation in the treatment of OCD.

Limitations and Strengths

One of the limitations of this study is the small number of trials and the small number of patients included. However, the results were statistically significant, which can be attributed to the clear and substantial effect of the drugs under study. Another limitation is the heterogeneity of the substances included. Although all of them affect the glutamatergic system in one way or another, one cannot preclude the possibility that their efficacy may be due to other pharmacodynamic properties of the individual substances. However, this objection could theoretically be raised for every group of drugs, even for common ones, such as the antipsychotics or the anticonvulsants.

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Drug names: acamprosate (Campral and others), *N*-acetylcysteine (Acetadote and others), clomipramine (Anafranil and others), cycloserine (Seromycin), glycine (Aminoacetic Acid and others), lamotrigine (Lamictal and others), memantine (Namenda and others), ondansetron (Zofran and others), riluzole (Rilutek and others), topiramate (Topamax and others).

Author contributions: Dr Laoutidis conceived and designed the study, participated in data collection and evaluation, performed the statistical analysis, and drafted the manuscript. Dr Lekka participated in study design, data collection and evaluation, performed statistical analysis, and drafted the manuscript. Dr Kioulos participated in designing the study, supervised collection and analysis of data, and helped draft the manuscript. All authors have read and approved the manuscript.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Glutamatergic Agents as Add-On Medication for the Treatment of Obsessive-Compulsive Disorder: A Systematic Review and Meta-Analysis

Authors: Zacharias G. Laoutidis, MD; Georgia E. Lekka, MD; and Kanellos T. Kioulos, MD

DOI Number: 10.4088/JCP.15r10164

List of Supplementary Material for the article

1. **eAppendix 1** Rejected studies
2. **eAppendix 2** Assessment of bias
3. **eAppendix 3** Egger's test

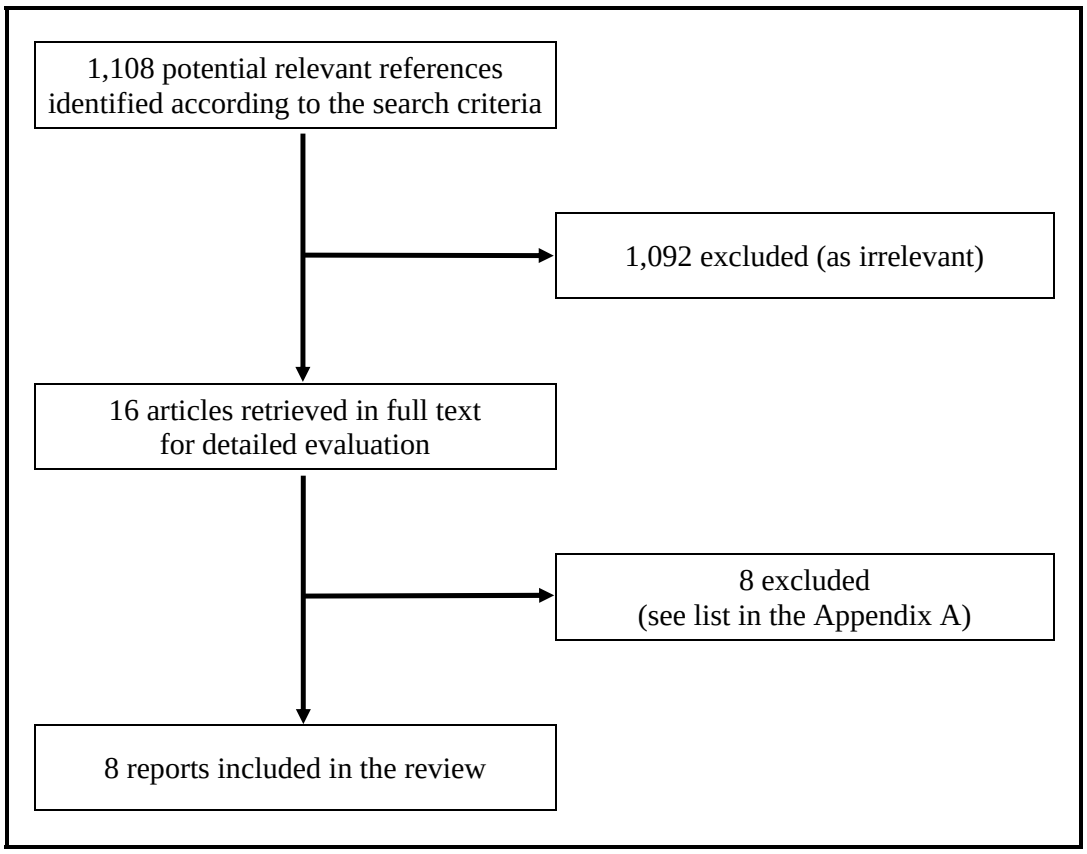
Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

eAppendix 1.
I. Rejected studies

Article	Reason for rejection
Bloch MH, Wasylink S, Landeros-Weisenberger A, Panza KE, Billingslea E, Leckman JF, Krystal JH, Bhagwagar Z, Sanacora G, Pittenger C. Effects of ketamine in treatment-refractory obsessive-compulsive disorder. Biol Psychiatry. 2012 Dec 1;72(11):964-70.	No RCT.
Hussain A, Dar MA, Wani RA, Shah MS, Jan MM, Malik YA, Chandel RK, Margoob MA. Role of lamotrigine augmentation in treatment-resistant obsessive compulsive disorder: a retrospective case review from South Asia. Indian J Psychol Med. 2015 Apr-Jun;37(2):154-8	No RCT.
Koran LM, Aboujaoude E, Bullock KD, Franz B, Gamel N, Elliott M. Double-blind treatment with oral morphine in treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry. 2005 Mar;66(3):353-9.	Monotherapy.
Kumar TC, Khanna S. Lamotrigine augmentation of serotonin re-uptake inhibitors in obsessive-compulsive disorder. Aust N Z J Psychiatry. 2000 Jun;34(3):527-8.	No RCT.
Lafleur DL, Pittenger C, Kelmendi B, Gardner T, Wasylink S, Malison RT, Sanacora G, Krystal JH, Coric V. N-acetylcysteine augmentation in serotonin reuptake inhibitor refractory obsessive-compulsive disorder. Psychopharmacology (Berl). 2006 Jan;184(2):254-6	No RCT.
Pasquini M, Biondi M. Memantine augmentation for refractory obsessive-compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2006 Aug 30;30(6):1173-5	No RCT.
Poyurovsky M, Weizman R, Weizman A, Koran L.Memantine for treatment-resistant OCD. Am J Psychiatry. 2005 Nov;162(11):2191-2.	No RCT.
Rodriguez CI, Kegeles LS, Levinson A, Feng T, Marcus SM, Vermes D, Flood P, Simpson HB. Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. Neuropsychopharmacology. 2013 Nov;38(12):2475-83	Monotherapy.

II. Flow diagram of the study



eAppendix 2. Assessment of bias

We used the Cochrane Collaboration's tool for assessing the risk of bias. These criteria may be considered sufficiently strict. This included extracting of six domains and judging them. The consensual authors' judgment were either "Yes", indicating low risk of bias, "No" indicating high risk of bias, or "Unclear" indicating unknown risk of bias. The criteria to assess the studies were:

Domain	Description	Review Author's Judgement
Sequence generation	Describe the method used to generate the allocation sequence	Was the allocation sequence adequately generated? (Yes, No, Unclear)
Allocation concealment	Describe the method used to conceal the allocation sequence	Was allocation adequately concealed? (Yes, No, Unclear)
Blinding of participants, personnel, and outcome	Describe all measures used to blind participants and personnel	Was knowledge of the allocated intervention adequately prevented during the study? (Yes, No, Unclear)
Incomplete outcome data	Describe the completeness of outcome data for each main outcome including attrition and exclusions from the analysis.	Were incomplete outcome data adequately addressed? (Yes, No, Unclear)
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors and what was found.	Are reports of the study free of suggestion of selective outcome reporting? (Yes, No, Unclear)
Other sources of bias	State any important concerns about bias not addressed in the other domains.	Was the study apparently free of other problems that could put it at high risk of bias?

Greenberg et al., 2009

Domain	Description	Review Author's Judgement
Sequence generation	Randomized trial. Block design.	**Yes.**
Allocation concealment	Assignment envelopes are not described. Drug containers of identical appearance.	**Unclear.**
Blinding of participants, personnel, and outcome	Double blind trial.	**Yes.**
Incomplete outcome data	Available data analysis.	**Yes.**
Selective outcome reporting	All prespecified outcomes of interest are reported in the pre-specified way.	**Yes.**
Other sources of bias	High attrition rates and small sample size.	**No.**

Mowla et al., 2010

Domain	Description	Review Author's Judgement
Sequence generation	Standard randomization procedure generated by computer.	**Yes.**
Allocation concealment	Assignment envelopes not described. Tablets of same color and shape.	**Unclear.**
Blinding of participants, personnel, and outcome	Double blind trial.	**Yes.**
Incomplete outcome data	Completers' analysis.	**No.**
Selective outcome reporting	All prespecified outcomes of interest are reported in the pre-specified way.	**Yes.**
Other sources of bias	The study appears to be free of other sources of bias.	**Yes.**

Berlin et al., 2011

Domain	Description	Review Author's Judgement
Sequence generation	Randomized trial, use of permuted blocks.	**Yes.**
Allocation concealment	Assignment envelopes not described. Identical tablets and drug containers.	**Unclear.**
Blinding of participants, personnel, and outcome	Double blind trial.	**Yes.**
Incomplete outcome data	Intention-to-treat analysis.	**Yes.**
Selective outcome reporting	All prespecified outcomes of interest are reported only in graphs.	**No.**
Other sources of bias	The study appears to be free of other sources of bias.	**Yes.**

Afshar et al., 2012

Domain	Description	Review Author's Judgement
Sequence generation	Randomized trial. Random-list generator software.	**Yes.**
Allocation concealment	Assignment envelopes and drug containers are not described.	**Unclear.**
Blinding of participants, personnel, and outcome	Double blind trial.	**Yes.**
Incomplete outcome data	The analysis is described as ITT, however it is actually an available case analysis.	**Yes.**
Selective outcome reporting	Rates of partial response are not reported.	**No.**
Other sources of bias	The study appears to be free of other sources of bias.	**Yes.**

Bruno et al., 2012

Domain	Description	Review Author's Judgement
Sequence generation	Randomized trial. Randomized codes generated by computer.	**Yes.**
Allocation concealment	Assignment envelopes are not described. Identical appearing capsules.	**Unclear.**
Blinding of participants, personnel, and outcome	Double blind trial.	**Yes.**
Incomplete outcome data	Intention-to-treat analysis.	**Yes.**
Selective outcome reporting	All prespecified outcomes of interest are reported in the pre-specified way.	**Yes.**
Other sources of bias	The study appears to be free of other sources of bias.	**Yes.**

Ghaleiha et al., 2013

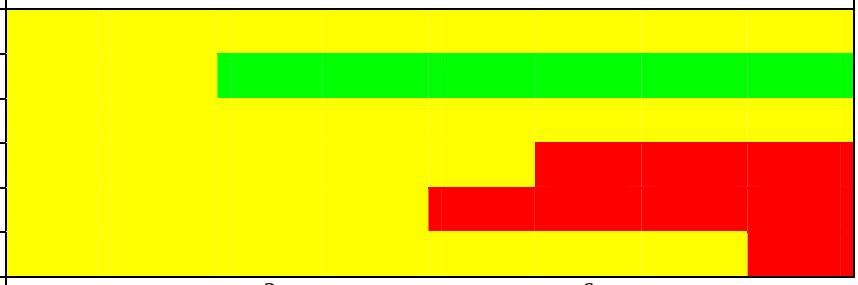
Domain	Description	Review Author's Judgement
Sequence generation	Computerized random number generator.	**Yes.**
Allocation concealment	Opaque and sealed assignment envelopes. Placebo with the same taste and shape.	**Yes.**
Blinding of participants, personnel, and outcome	Double blind trial.	**Yes.**
Incomplete outcome data	The analysis is described as ITT, however it is actually an available case analysis.	**Yes.**
Selective outcome reporting	Unclear report of response rates. Endpoint scores in YBOCS are not reported.	**No.**
Other sources of bias	The study appears to be free of other sources of bias.	**Yes.**

Haghighi et al., 2013

Domain	Description	Review Author's Judgement
Sequence generation	Randomized trial. Computerized random number generator.	**Yes.**
Allocation concealment	Patients drew raffle tickets from a ballot box. Tablets and drug containers of identical appearance.	**Yes.**
Blinding of participants, personnel, and outcome	Double blind trial.	**Yes.**
Incomplete outcome data	Completers' analysis.	**No.**
Selective outcome reporting	All prespecified outcomes of interest are reported in the pre-specified way.	**Yes.**
Other sources of bias	The study appears to be free of other sources of bias.	**Yes.**

Afshar et al., 2014

Domain	Description	Review Author's Judgement
Sequence generation	Randomized trial. Random number generator software.	**Yes.**
Allocation concealment	Assignment envelopes are not described. Identical appearing tablets.	**Unclear.**
Blinding of participants, personnel, and outcome	Double blind study.	**Yes.**
Incomplete outcome data	Completers' analysis	**No.**
Selective outcome reporting	All prespecified outcomes of interest are reported in the pre-specified way.	**Yes.**
Other sources of bias	The study appears to be free of other sources of bias.	**Yes.**

Domain	Assessment
Sequence generation	
Allocation concealment	
Blinding	
Missing Data	
Selective Reporting	
Other Bias	
	3 6

Yes	Unclear	No

Risk of bias graph. The semaphore colors provide a visual impression of the quality of the study reports for meta-analysis; green: condition is fulfilled; yellow: condition is questionable, and red: condition is not fulfilled and risk of bias is present. The allover risk for bias is low.

eAppendix 3. Egger's test