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

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Introduction

Obsessive-compulsive disorder (OCD) is a heterogeneous psychiatric disorder with a lifetime prevalence in the general population of approximately 2-3% ¹. It is currently classified by the DSM-5 within the chapter of “Obsessive-Compulsive and Related Disorders” (OCRDs), where it is the “nosological organizer”, together with Body Dysmorphic Disorder, Hoarding Disorder, Trichotillomania (Hair-Pulling Disorder) and Excoriation (Skin-Picking) Disorder. ICD-11 will follow the DSM-5 and create an analogue chapter adding Olfactory Reference Disorder and Hypocondriasis (Health Anxiety Disorder) to the other OCRDs ².

The diagnosis of OCD is made by the presence of recurrent or persistent, up-setting thoughts, images, or urges, that are experienced, at some time during the illness, as intrusive and unwanted (obsessions), and that cause anxiety or distress (at least in most individuals, although with time subjects may respond with compulsions before experiencing anxiety); the individual attempts to ignore or suppress the obsessions or to neutralize them by performing a compulsion. Compulsions, which follow obsessions in the vast majority of patients ³, are repetitive behaviors or mental acts performed in response to obsessions. By definition, compulsions are finalized behaviors (aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situations), unlike other repetitive acts like tics which are purposeless. Moreover, compulsions are intentional ⁴. Together with obsessions and compulsions, avoidance behaviors are usually present, and such signs and symptoms interfere with individual functioning and consume time (at least one hour per day for the diagnosis).

Family members are also usually involved in symptoms, as they often directly participate in compulsions and in avoidance behaviors. The term family accommodation has been proposed to refer to family responses specifically related to obsessive-compulsive symptoms: it encompasses behaviors, such as directly participating to compulsions and/or assisting a relative with OCD when he/she is performing a ritual (e.g. controlling that the patient with OCD is “correctly” taking a shower without touching nothing “dirty” or potentially “contaminating”; having to pass towels to the patient taking particular care that they do not touch “contaminated” surfaces) or helping him/her avoiding triggers that may precipitate obsessions and compulsions (the relative has to respect rules that OCD imposes on the patient; e.g. for a patient with contamination obsessions, having to undress before entering home and putting the “dirty” clothes in a specific place at home, avoiding to “contaminate” the house with “dirty clothes” and having to immediately wash themselves before entering “uncontaminated” rooms) ⁵.

OCD has generally an early age at onset, in childhood or early adult life ⁶, with an earlier age at onset in males; the early age at onset may greatly impact on
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The aim of the present paper is to provide an overview of the state-of-the-art treatment of OCD, with a focus on the pharmacological treatment, and a preliminary draft for the development of Italian guidelines for the treatment of patients with OCD.

Evidence-based first-line treatments

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

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

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

OCD patients with comorbid major depression should then receive medication firstly, eventually associated with CBT; for all remaining patients, there is clear evidence from the literature of no additive benefits of combining ab initio CBT and medication. Therefore, the routine use of a combination approach in all adult patients affected by OCD is not supported by the literature. These findings are consistent with the results of a recent network meta-analysis conducted by Skapinakis and colleagues, which stated that there is no sufficient evidence to suggest that combined treatment is better than psychotherapy alone, although combination of medication and CBT seems to be an acceptable treatment, mostly in severe OCD.

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

Pharmacological treatment: which drugs?

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

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

### Which dose?

Fixed-dose studies have been performed for all SRIs except fluvoxamine and clomipramine. The minimal effective dose for fluoxetine and paroxetine (the one that differed statistically from placebo in terms of response) is 40 mg/day, and for escitalopram 20 mg/day; for citalopram and sertraline there is an indication of greater efficacy at higher doses (40-60 for citalopram and 200 for sertraline). A meta-analysis 36 of all placebo-controlled studies in adults with OCD clearly confirmed that medium-to-high doses should be used for the pharmacological treatment of OCD in order to obtain the greatest efficacy. Table I provides minimum target and maximum doses to be used in OCD.

### How to evaluate response and when?

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

When response, defined as above, is evident, continuation treatment, at the same dose, is associated with continued improvement in symptoms until remission is achieved 14. Adherence should be monitored, especially in the first weeks of treatment, when side effects associated with pharmacological treatments may emerge while response is still lacking.

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

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

* Citalopram in Italy is not indicated for the treatment of OCD, although its efficacy is established in placebo-controlled, double-blind studies. * Citalopram is associated with dose-dependent QTc prolongation, thus in Italy the maximum dose recommended for adults is 40 mg/day (20 mg in patients > 65 years-old or with reduced liver function). § Escitalopram is associated with dose-dependent QTc prolongation, thus in Italy the maximum dose recommended for adults is 20 mg/day (10 mg in patients > 65 years-old or with reduced liver function).
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Table II. Definitions of response-remission (Mataix-Cols et al., 2016, modified).

<table>
<thead>
<tr>
<th>Conceptual</th>
<th>Operational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Response</strong></td>
<td>A clinically meaningful reduction in symptoms relative to baseline severity</td>
</tr>
<tr>
<td><strong>Partial Response</strong></td>
<td>Defined as in treatment response above</td>
</tr>
<tr>
<td><strong>Remission</strong></td>
<td>The patient no longer meets syndromal criteria for the disorder and has no more than minimal symptoms. Residual obsessions, compulsions and avoidance may be present, but are not time consuming and do not interfere with the person’s everyday life</td>
</tr>
<tr>
<td><strong>Recovery</strong></td>
<td>The patient no longer meets syndromal criteria for the disorder and has had no more than minimal symptoms. The clinician may begin to consider discontinuation of treatment or, if the treatment continues, the aim is to prevent relapse</td>
</tr>
</tbody>
</table>

Maintenance therapy for OCD may be provided with lower dosages of the anti-obsessional drug (50-to-66% lower than those used to achieve remission), with clear advantages for tolerability and compliance, all published International guidelines suggest keeping the same medium-to-high dose throughout the maintenance phase in order to prevent relapses. Adherence to treatment is particularly important and should be monitored throughout the whole maintenance phase of the treatment, when remission is achieved (the patient no more suffers from symptoms) and patients may be more prone to forget to take medications as required. Preliminary evidence suggests that relapses due to premature treatment discontinuation or to intermittent adherence respond less well when the same drug at the same dose is reinstated, indicating a possible “toxic” effect of relapses.

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

**Resistant patients**

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

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

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

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

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

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

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

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

**a. Antipsychotic addition to SRIs**

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

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

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

b. CBT addition to medication

The available evidence supports the sequential addition of CBT to SRIs for both OCD patients who respond to medications but still have residual obsessive-compulsive symptoms (1 positive randomized controlled study in adults) (this is a clinically relevant issue since only a minority of subjects accomplish remission using a single treatment modality) 53 and for resistant patients (2 positive randomized controlled studies performed...
versus a placebo psychological comparison – stress management training – and versus risperidone or placebo add on) \(^{54,55}\). Two other RCTs support the effectiveness of switching to medications after non-response to CBT \(^{56,57}\). For severe, treatment-resistant patients, several open-label or retrospective chart reviews support the efficacy of CBT delivered in residential settings or partial hospitalization programs: providing time-intensive treatment, based on delivering higher levels of treatment over a short time period, might be suitable for individuals whose immediate clinical improvement is important \(^{34}\).

c. **Switch to intravenous route of administration**

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

d. **Switch to paroxetine or venlafaxine**

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

e. **Addition of medications other than antipsychotics to SSRIs**

The effectiveness of augmentative compounds other than antipsychotics in resistant OCD has been the subject of several double-blind studies, with promising results for some drugs and negative for others. A list of studies performed is provided in Table IV. All of the compounds that proved to be effective (namely pindolol and topiramate – only 1 positive RCT, memantine – 2 positive RCTs) should be considered as promising add-on strategies, although reserved for patients being refractory to other more evidence-based strategies \(^{60}\). From Table IV clinicians can find out which compounds not to use for resistant OCD patients.

Several controlled studies, moreover, investigated the efficacy of the addition of compounds other than antipsychotics \(ab\ initio\) in moderate to severe non-resistant OCD individuals (Table V). These strategies, although promising for improving the treatment outcome of OCD patients (by shortening response latency or increasing response rates), should be considered at the moment only for research purposes.

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

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

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

Besides pharmacologic, behavioral, and neurosurgical approaches, different brain stimulation methods, including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), and electroconvulsive therapy (ECT), have been investigated in treatment-resistant patients with OCD, revealing positive results for otherwise intractable and treatment-refractory patients. TMS and tDCS represent non-invasive brain stimulation techniques that have been investigated in patients with OCD with mixed results. A recent meta-analysis including 15 RCTs (n = 483), most of which with small-to-modest sample sizes, found that active versus sham TMS stimulation was significantly superior for OCD symptoms. Nonetheless, stimulation targets and degree of treatment resistance show a wide variability across RCTs. There is less evidence in favor of the efficacy of tDCS versus TMS in OCD with a recent systematic review supporting caudal compared to anodal tDCS in treating OCD. With respect to more invasive somatic interventions, traditionally considered for more severe and treatment-resistant cases, ECT does not seem to produce any specific benefit in OC symptoms, being potentially useful only in cases of depressive and/or psychotic comorbidity. On the other hand, levels of evidence for DBS efficacy in treatment-resistant OCD patients are more solid with a recent meta-analysis including 31 studies (n = 116) showing a global percentage of Y-BOCS reduction at 45.1% and global percentage of responders at 60.0%. Stimulation targets were variable with most subjects implanted in striatal areas (anterior limbs of the internal capsule, ventral capsule and ventral striatum, nucleus accumbens and ventral caudate) and the remainders in the subthalamic nucleus and in the inferior thalamic peduncle.

Conflict of interests

The authors declare that there is no conflict of interests.

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

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

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

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