Systematic review of catatonia treatment

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Objective: To investigate the evidence-based treatment of catatonia in adults. The secondary aim is to develop a treatment protocol.

Materials and methods: A systematic review of published treatment articles (case series, cohort or randomized controlled studies) which examined the effects of particular interventions for catatonia and/or catatonic symptoms in adult populations and used valid outcome measures was performed. The articles for this review were selected by searching the electronic databases of the Cochrane Library, MEDLINE, EMBASE and PSYCHINFO.

Results: Thirty-one articles met the inclusion criteria. Lorazepam and electroconvulsive therapy (ECT) proved to be the most investigated treatment interventions. The response percentages in Western studies varied between 66% and 100% for studies with lorazepam, while in Asian and Indian studies, they were 0% and 100%. For ECT, the response percentages are 59%–100%. There does not seem to be evidence for the use of antipsychotics in catatonic patients without any underlying psychotic disorder.

Conclusion: Lorazepam and ECT are effective treatments for which clinical evidence is found in the literature. It is not possible to develop a treatment protocol because the evidence for catatonia management on the basis of the articles reviewed is limited. Stringent treatment studies on catatonia are warranted.

Keywords: review, catatonia, therapeutics, electroconvulsive therapy, benzodiazepines, lorazepam, ECT

Introduction
Catatonia is a neuropsychiatric syndrome that was originally described by Karl Kahlbaum in 1874, and hence, Kraepelin considered catatonia as a subtype of dementia praecox.¹ ² This conceptualization continued to exist for many years and, consequently, catatonia was classified as a subtype of schizophrenia up to and including Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R. ⁴ Over time, this classification greatly affected recognition and treatment; however, from the late 70s, it became increasingly evident that catatonia is a condition that is associated with a variety of metabolic, neurologic, psychiatric and toxic conditions. ⁵⁻⁷ DSM-IV, therefore, mentioned three entities of catatonia: as a subtype of schizophrenia, as a specification of affective disorders, and due to a medical condition. ⁸ To emphasize the importance of recognizing catatonia, its classification in DSM-5 was altered.⁷ One of the new features of DSM-5 was the inclusion of catatonia under a separate heading in the chapter on Schizophrenia Spectrum and Other Psychotic Disorders.⁹ Catatonia appears in three forms in DSM-5: “catatonia associated with another mental disorder”, “catatonic disorder due to another medical condition” and “unspecified catatonia”.⁹

The pathophysiology and etiology of catatonia remains unclear. One of the hypotheses is that it may be explained by an alteration of the dopaminergic function.¹⁰⁻¹¹ In addition, dysfunction of gamma-aminobutyric acid and glutamate systems may be implicated.¹²
Benzodiazepines and electroconvulsive therapy (ECT) are the most widely studied treatment methods. However, no uniform treatment method has yet been brought forward. To compare the differences in effects between medication, ECT and placebo, and to develop uniform advice, a Cochrane review was performed based on randomized controlled studies (RCTs). However, the conclusion was that none of the studies could be included in this review. A controlled study on the treatment of (chronic) catatonia in people with schizophrenia showed that benzodiazepines have no added value compared to placebo. Until now, no broadly accepted treatment guidelines have been described for catatonia. The purpose of this review of the literature is to establish the evidence-based treatment for catatonia in adults. The secondary aim is to develop a treatment protocol based on the available evidence.

Materials and methods
The study design was based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) method. We searched the databases of the Cochrane Library, MEDLINE, EMBASE and PSYCHINFO in July 2016 using catatonia (and related terms) AND treatment (and related terms) as keywords. We deliberately chose the general term treatment to obtain the broadest possible spectrum of treatment interventions. The main prerequisites were that the articles had been published in either English or Dutch language and that abstracts were available. Articles were selected for inclusion by two authors independent of each other on the basis of predefined inclusion criteria. Treatment manuscripts (irrespective of design) that investigated the effects of particular interventions on catatonia and/or catatonic symptoms in adult populations were included. Case series were included when at least three cases were described. A report was included if response to treatment was measured using a standardized rating instrument or scale. Consequently, all the included full-text articles were analyzed. The results of the included articles are presented in Tables 1–3.

Results
Identification
Our search strategy using Ovid database revealed 3,079 potentially relevant manuscripts in the Cochrane Library, MEDLINE, EMBASE and PSYCHINFO. Figure 1 describes the evaluation of these 3,079 publications.

Systematic review results
In total, 31 articles met the inclusion criteria for systematic review. Most of these manuscripts were small scale and four investigations involved cohorts of over 50 people.
### Catatonia treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Study Type</th>
<th>Number of Participants</th>
<th>DSM Version</th>
<th>Disorder Type</th>
<th>Treatment Options</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hung and Huang</td>
<td>Taiwan, 2002–2005</td>
<td>Prospective cohort</td>
<td>7</td>
<td>DSM-IV</td>
<td>Major depressive d</td>
<td>Lorazepam (IM) 2 mg, repeat in case of little effect, diazepam (IV) 10 mg every 8 hours</td>
<td>100%</td>
</tr>
<tr>
<td>Kritzinger and Jordaan</td>
<td>South Africa, not reported</td>
<td>Open prospective</td>
<td>9</td>
<td>DSM-IV</td>
<td>Affective d 44%, psychotic d 33%, organic brain disease 33%</td>
<td>Lorazepam (IM) 2 mg once, Remission 66% within 2 hours, after 48 hours 0%</td>
<td>27%</td>
</tr>
<tr>
<td>Lee et al</td>
<td>Australia, 1996–1997</td>
<td>Prospective cohort</td>
<td>22</td>
<td>DSM-IV, DSM-III-R, DSM-IV, ICD-10, BFCRS, MRS, PASS, SAS, Rosebush, Lohr and Wisniewski</td>
<td>Psychotic d 75%, affective d 17%, other 8%</td>
<td>Lorazepam (PO or iv) or diazepam (IV, IM), 4–8 mg/day during 3 days</td>
<td>73%</td>
</tr>
<tr>
<td>Lin et al</td>
<td>Taiwan, 2002–2011</td>
<td>Prospective cohort</td>
<td>21</td>
<td>DSM-IV, BFCRS</td>
<td>Schizophrenia</td>
<td>Lorazepam (IM) 2 mg, repeat in case of little effect, diazepam (IV) 1 mg every 10 minutes during 48 hours</td>
<td>100%</td>
</tr>
<tr>
<td>Narayanaswamy et al</td>
<td>India, 2004–2005</td>
<td>Retrospective chart</td>
<td>99</td>
<td>DSM-IV, BFCRS</td>
<td>Psychotic d 49%, affective d 44%, unknown 7%</td>
<td>Lorazepam (IV) 2 mg every 6–8 hours during 3 days</td>
<td>32.3%</td>
</tr>
<tr>
<td>Northoff et al</td>
<td>Germany, 1991–1994</td>
<td>Prospective cohort</td>
<td>18</td>
<td>DSM-III-R, Lohr and Wisniewski, Rosebush</td>
<td>Psychotic d 61%, affective d 28%, organic brain disease 11%</td>
<td>Lorazepam (PO or IV) 2–4 times a day 1–2.5 mg</td>
<td>66%</td>
</tr>
<tr>
<td>Rosebush et al</td>
<td>USA, not reported</td>
<td>Prospective open label</td>
<td>15</td>
<td>DSM-III-R</td>
<td>Affective d 47%, psychotic d 40%, other 13%</td>
<td>Lorazepam (PO or IV) 1–2 mg/day</td>
<td>80%, partial remission 6.6%</td>
</tr>
<tr>
<td>Seethalakshmi et al</td>
<td>India, not reported</td>
<td>Prospective cohort</td>
<td>16</td>
<td>DSM-IV, BFCRS</td>
<td>Psychotic d 69%, affective d 6%, organic brain disease 6%, drug induced d 6%, other 12%</td>
<td>Lorazepam (IV) 1 mg every 10 minutes during 48 hours</td>
<td>75.9% partial remission 18%</td>
</tr>
<tr>
<td>Tibrewal et al</td>
<td>India, 2004–2005</td>
<td>Retrospective chart</td>
<td>99</td>
<td>DSM-IV, BFCRS</td>
<td>Psychotic d 49%, affective d 44%, unknown 7%</td>
<td>Lorazepam (IV) 1–2 mg every 6–8 hours during 3 days</td>
<td>32.3% partial remission 68.7%</td>
</tr>
<tr>
<td>Ungvari et al</td>
<td>China, 1992–1993</td>
<td>Prospective open label</td>
<td>18</td>
<td>DSM-III-R, Lohr and Wisniewski, Rosebush, McCall scale</td>
<td>Psychotic d 56%, affective d 28%, other 16%</td>
<td>Lorazepam (PO or IM) 2 mg or diazepam (IM) 10 mg during 48 hours</td>
<td>89%</td>
</tr>
<tr>
<td>Ungvari et al</td>
<td>China, not reported</td>
<td>Randomized controlled trial</td>
<td>20</td>
<td>DSM-IV, BFCRS</td>
<td>Schizophrenia</td>
<td>Lorazepam 2 mg 3 times a day over 6 weeks</td>
<td>Improvement 0%</td>
</tr>
<tr>
<td>Yassa et al</td>
<td>Canada, not reported</td>
<td>Prospective open label</td>
<td>10</td>
<td>Not reported</td>
<td>Affective d 40%, psychotic d 40%, unknown 20%</td>
<td>Lorazepam (PO or IM), 2–3 mg/day, until remission</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Notes:**
- Number of participants at final follow-up.
- Rosebush et al.
- Modified McCall scale (1992).

**Abbreviations:** BFCRS, Bush–Francis Catatonia Rating Scale; d, disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; IM, intramuscular; IV, intravenous; MRS, Modified Rogers Scale; PASS, positive symptoms subscale; PO, per os, oral administration; SAS, Simpson–Angus Scale; SCID, structured clinical interview for DSM disorders.
Table 2 Characteristics of studies which investigated treatment of catatonia with electroconvulsive therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Country, period</th>
<th>Study type</th>
<th>n</th>
<th>Diagnosis of catatonia and measurement of treatment effect</th>
<th>Underlying diagnosis</th>
<th>Treatment and co-medication</th>
<th>Treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bush et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>USA, not reported</td>
<td>Prospective cohort study</td>
<td>4</td>
<td>DSM-III-R, BFCRS</td>
<td>Affective d 75%, other 25%</td>
<td>ECT 3 times/week, bilaterally Medication: methohexital and succinylcholine. Neuroleptic drugs discontinued until the end of the treatment phase</td>
<td>Remission 100%</td>
</tr>
<tr>
<td>Cristancho et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>USA, not reported</td>
<td>Case series</td>
<td>5</td>
<td>Not reported</td>
<td>Affective d 40%, psychotic d 40%, systemic disease (lupus) 20%</td>
<td>ECT unilaterally right, 8–12 sessions Medication: methohexital or etomidate added to succinylcholine</td>
<td>Remission 80%, partial response 20%</td>
</tr>
<tr>
<td>Dutt et al&lt;sup&gt;16&lt;/sup&gt;</td>
<td>India, 2004–2008</td>
<td>Retrospective chart</td>
<td>42</td>
<td>BFCRS, ICD-10</td>
<td>Not specified (see Table 1)</td>
<td>ECT Medication: additionally most patients treated with antipsychotics. Some used antidepressants and mood stabilizers. Not clear if this was during ECT</td>
<td>Response 100%</td>
</tr>
<tr>
<td>England et al&lt;sup&gt;17&lt;/sup&gt;</td>
<td>USA, 2004–2009</td>
<td>Retrospective chart</td>
<td>12</td>
<td>BFCRS, SCID</td>
<td>Not specified (see Table 1)</td>
<td>ECT Medication: majority required lorazepam through ECT course. Other co-medication not clear</td>
<td>Definitely beneficial response 83%, likely beneficial response 17%</td>
</tr>
<tr>
<td>Girish and Gill&lt;sup&gt;18&lt;/sup&gt;</td>
<td>India, not reported</td>
<td>Double-blind, randomized controlled trial</td>
<td>14</td>
<td>BFCRS, ICD-10, Positive and Negative Syndrome Scale, Columbia side effect checklist, Simpson–Angus rating scale</td>
<td>Schizophrenia 64%, psychosis NOS 36%</td>
<td>ECT bilaterally 3 times/week plus placebo in ECT group. Sham ECT plus risperidone 4–6 mg/day in risperidone group. Medication: lorazepam was stopped. ECT group: thiopeptone, succinylcholine, atropine. Risperidone group: thiopeptone</td>
<td>Catatonia scores reduced significantly in the ECT group. 50% continued to receive ECT beyond a 3-week period. ECT patients did not obtain total recovery&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hatta et al&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Japan, 2003–2005</td>
<td>Prospective cohort study</td>
<td>17</td>
<td>DSM-IV</td>
<td>Not specified (see Table 1)</td>
<td>ECT 3 times per week bilaterally Medication: atropine sulfate, thiopeptone and suxamethonium. Psychotropic medication discontinued during ECT</td>
<td>Remission 100%</td>
</tr>
<tr>
<td>Kugler et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>USA, not specifically reported (last 3 years)</td>
<td>Retrospective chart Case series</td>
<td>13</td>
<td>DSM-5, CGI-I</td>
<td>Described per case (see Table 1)</td>
<td>ECT ultrabrief right unilateral, 3 times weekly. 3 cases switched to bilateral ECT 3 times weekly. 1 case started bilaterally Medication: methohexital and succinylcholine Other co-medication: described per case (see Table 1)</td>
<td>85% treatment responders; 76% complete remission, all treated with ultrabrief right unilateral ECT</td>
</tr>
<tr>
<td>Medda et al&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Italy, 2008–2014</td>
<td>Prospective, observational study</td>
<td>26</td>
<td>DSM-IV, BFCRS, CGI</td>
<td>Bipolar d</td>
<td>Bitemporal ECT 3 times weekly Medication: thiopeptone, rocuronium, sugammadex. Lorazepam was continued; last dose at least 12 hours prior to ECT. Other co-medication specified in Table 2</td>
<td>80.8% responders</td>
</tr>
</tbody>
</table>
Electroconvulsive therapy

Eleven studies described the effects of ECT as a treatment method for catatonia. The characteristics of these studies are described in Table 2. In six studies, ECT was administered as a secondary therapy when there was no response or insufficient response to benzodiazepines. In three studies, ECT was initiated after ineffective pharmacotherapy, but also as primary therapy, for example, in life-threatening situations. ECT was not only initiated after ineffective pharmacotherapy, but also as primary therapy, for example, in life-threatening situations. ECT was administered in doses varying from 2 to 16 mg/day. Three studies investigated a Lorazepam/diazoepam protocol, with the study characterized and is reported in 17 studies of which the study characteristics are described in Table 1. Lorazepam is the most widely studied medication, which is administered in doses varying from 2 to 16 mg/day. The reported bilateral ECT frequency was 3 times per week bilaterally. Medication: methohexital, succinylcholine, glycopyrrolate, atropine (less frequent) and caffeine sodium benzoate.

Notes: 

1. Number of participants at final follow-up. 
2. ECT is superior over neuroleptics in catatonia. 
3. Rosebush et al. 
4. BFCRS, Bush–Francis Catatonia Rating Scale; CGI-I, Clinical Global Impression for improvement; d, disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECT, electroconvulsive therapy; ICD, International Classification of Diseases; IV, intravenous; SCID, structured clinical interview for DSM disorders.

Abbreviations:

BFCRS, Bush–Francis Catatonia Rating Scale; CGI-I, Clinical Global Impression for improvement; d, disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECT, electroconvulsive therapy; ICD, International Classification of Diseases; IV, intravenous; SCID, structured clinical interview for DSM disorders.

Benzodiazepines

Treatment with benzodiazepines is the most extensively studied method and is reported in 17 studies of which the study characteristics are described in Table 1. Benzodiazepines are the most extensively studied medication, which is administered in doses varying from 2 to 16 mg/day. Three studies investigated a Lorazepam/diazepam protocol, with the study characterized and is reported in 17 studies of which the study characteristics are described in Table 1. Lorazepam is the most widely studied medication, which is administered in doses varying from 2 to 16 mg/day. The reported bilateral ECT frequency was 3 times per week bilaterally. Medication: methohexital, succinylcholine, glycopyrrolate, atropine (less frequent) and caffeine sodium benzoate.

Notes: 

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Abbreviations:

BFCRS, Bush–Francis Catatonia Rating Scale; CGI-I, Clinical Global Impression for improvement; d, disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECT, electroconvulsive therapy; ICD, International Classification of Diseases; IV, intravenous; SCID, structured clinical interview for DSM disorders.
Table 3 Characteristics of studies which investigated treatment of catatonia with antipsychotics

<table>
<thead>
<tr>
<th>Author</th>
<th>Country, period</th>
<th>Study type</th>
<th>n*</th>
<th>Diagnosis of catatonia and measurement of treatment effect</th>
<th>Underlying diagnosis</th>
<th>Treatment</th>
<th>Treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>England et al</td>
<td>USA, 2004–2009</td>
<td>Retrospective chart</td>
<td>7</td>
<td>BFCRS, SCID</td>
<td>Not specified</td>
<td>Clozapine</td>
<td>Definitely beneficial response 85%, likely beneficial response 17%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(see Table 1)</td>
<td></td>
<td>Olanzapine and quetiapine</td>
<td>Varying results</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Risperidone and aripiprazole</td>
<td>Negative effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cholorpromazine</td>
<td>Remission 68%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Risperidone</td>
<td>Remission 25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Haloperidol</td>
<td>Remission 16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Olanzapine</td>
<td>PANSS after 1 week (−13.1; p&lt;0.001), after 6 weeks (−5.0; p&lt;0.001)</td>
</tr>
<tr>
<td>Hatta et al</td>
<td>Japan, 2003–2005</td>
<td>Prospective cohort</td>
<td>28</td>
<td>DSM-IV</td>
<td>Not specified</td>
<td>Schizophrenia</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19</td>
<td>(see Table 1)</td>
<td></td>
<td>Risperidone</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19</td>
<td></td>
<td></td>
<td>Haloperidol</td>
<td>16%</td>
</tr>
<tr>
<td>Martenyi et al</td>
<td>Austria, not</td>
<td>Open-label double-blind trials</td>
<td>35</td>
<td>DSM-IV, PANSS</td>
<td>Schizophrenia</td>
<td>Olanzapine</td>
<td>Used more in recovery and discharge compared to admission</td>
</tr>
<tr>
<td>Yoshimura et al</td>
<td>Japan, 2008–2010</td>
<td>Retrospective chart</td>
<td>39</td>
<td>DSM-IV, BFCRS, CGI-I</td>
<td>Schizophrenia</td>
<td>Quetiapine</td>
<td></td>
</tr>
</tbody>
</table>

Note: *Number of participants at final follow-up.

Abbreviations: BFCRS, Bush–Francis Catatonia Rating Scale; CGI-I, Clinical Global Impression for improvement; DSM, Diagnostic and Statistical Manual of Mental Disorders; IV, intravenous; PANSS, Positive and Negative Syndrome Scale; SCID, structured clinical interview for DSM disorders.

In two studies, ECT was administered unilaterally, the hypothesis being that this would reduce the risk of cognitive side effects. Because of the small cohort involved in both studies, this hypothesis could not be confirmed. The total number of ECT sessions in the included studies varied from two to 13.

The percentages, represented in terms of response and remission (Table 2), ranged from 59% to 100%. Most articles were based on chart reviews and case studies and, consequently, lacked any form of randomization, control group, uniform treatment and crucial information on medication or co-medication. Of the 11 studies which investigated ECT, six studies actively reported about side effects. Cristancho et al describe that all patients tolerated ECT well without major adverse effects or cognitive impairment. However, in other studies, patients treated with ECT were observed to have cognitive/memory impairment or complained of headache during treatment. The risk of cognitive adverse effects may be related to higher ECT frequency and must be balanced against the risk of morbidity and mortality due to catatonia.

**Antipsychotics**

Four studies (Table 3) examined the role of antipsychotics in treating catatonia. It should be noted that the examined cohorts largely consisted of patients with an underlying psychotic disorder. England et al concluded that clozapine has a beneficial effect on catatonic symptoms. On the other hand, classic antipsychotics may result in clinical deterioration and appear to be associated with the development of lethal catatonia or malignant neuroleptic syndrome.
Hatta et al observed that patients responded better to an antipsychotic drug with low affinity for dopamine receptors (clozapine) than to an antipsychotic drug with high affinity (haloperidol). The main disadvantage of this study is that the effect cannot be attributed to any of the used antipsychotics due to the use of co-medication.

Treatment with olanzapine demonstrated mixed results. It was concluded that treatment with olanzapine decreased symptoms measured by the Positive and Negative Syndrome Scale score. However, another study did not include the use of an instrument for measuring catatonia, so no specific effect could be attributed to this treatment. Yoshimura et al observed that quetiapine was more significantly used around the time of recovery and discharge, compared to other antipsychotics. However, after 30 months, in most patients, this antipsychotic drug had been replaced with another due to lack of effect. Here too, the effect of co-medication is not entirely clear. Adverse effects such as worsening of catatonic symptoms, increasing confusion, agitation and restlessness in patients treated with typical antipsychotics have been mentioned. Others reported that tremor and rigidity occurred in most of the cases. Yoshimura et al observed that three patients on first-generation antipsychotics and risperidone developed a neuroleptic malignant syndrome.

Other treatment methods

The use of carbamazepine in the acute phase of catatonia was examined in an open prospective study involving nine patients. Carbamazepine was administered when patients did not sufficiently respond to lorazepam. This study revealed that lorazepam initially produces good results, but its effect wears off after a few hours. Eventually, all patients were given carbamazepine, whereupon four patients recovered and one patient showed partial recovery. It should be noted that this study involved a small study group without adequate information about co-medication.

Packing therapy involves wrapping the catatonic patient in cold wet towels in order to reinforce, inter alia, sensory integration. The researchers concluded that it could be used as a co-intervention, but not as primary treatment. McDaniel et al described the effect of topiramate on catatonic symptoms in four cases unresponsive to benzodiazepines and antipsychotics. After treatment with topiramate, the patients showed recovery or improvement, but it is not clear whether this improvement was the result of the use of topiramate.

The effect of aminopetine in patients with schizophrenia and chronic catatonia was examined in an RCT conducted by Ungvari. The author concluded that aminopetine has no effect on catatonic symptomatology.

Therapeutic efficacy of the N-methyl-D-aspartate (NMDA) antagonist amantadine has been reported by Northoff et al and Freitas de Lucena et al. Northoff et al reported three cases with acute akinetic catatonia, in which IV infusion of 500 mg amantadine (if necessary, repeated after 24 hours) led to resolution of catatonic symptoms. Considerable reduction of scores in various motor scales was seen with most pronounced effects 4–6 hours after administration. Patients were not taking antipsychotic or any other psychotropic drugs. It should be mentioned that amantadine might exacerbate psychotic symptoms. Therefore, Northoff et al excluded cases of paranoid schizophrenia. Freitas de Lucena et al evaluated the use of amantadine for 4 weeks in five cases of acute catatonia in schizophrenia of schizoaffective disorder. Doses were increased up to 600 mg/day over a period of 4 weeks. Patients were medication free for at least 72 hours. Antipsychotic medication was reintroduced in the third week. In all five patients, amantadine led to considerable reduction in catatonic symptoms. The best response was observed between 10 and 21 days.

Discussion

There are currently no broadly accepted guidelines for the treatment of catatonia. The articles included in our review all have a level of evidence not exceeding 1b (individual RCT), of which most do not exceed 2b (individual cohort study). In addition, the diversity of methods and outcome measures used makes unambiguous interpretation of these studies impossible, and therefore, it was not feasible to develop an evidence-based treatment protocol. However, the investigated articles clearly show similarities in terms of design and results, which may prove useful in clinical practice and are a starting point for further research.

The response rate to benzodiazepines in Western studies lies between 66% and 100%. Non-Western studies reported the lowest response rates. A possible explanation for this is that these studies involved chronic, untreated catatonia. In addition, response seems to depend on dosage and frequency of administration. Studies which involved doses of 2–2.5 mg and more frequent administration (several times a day) showed higher response and remission. No evident side effects have been described for these dosages. The maximum daily dose used was 12–16 mg. As benzodiazepines can easily be administered in various settings, they are the therapy of first choice. Lorazepam is the most widely studied compound within this treatment.
framework. Some studies also examined the effect of diazepam,\textsuperscript{20–22} but there are no studies that explicitly measured the differences in effects between different types of benzodiazepines. The studies also varied in terms of manner of administration (PO, IM or IV). There are no indications that there is any preference based on efficacy in this respect. How long therapy should be continued was not really examined. There are, though, indications that prolonged treatment is required to obtain a lasting effect.\textsuperscript{23,27,28} When treatment with lorazepam proves beneficial, this effect is noticeable within several hours to a few days.\textsuperscript{19–22,24,27,28,30,33} No maximum term for treatment with lorazepam was mentioned, but if it does not entirely produce the desired effect within 4–5 days, it is recommended to consider ECT.\textsuperscript{16,30} ECT appeared to be a very effective treatment for patients who do not respond to benzodiazepines.\textsuperscript{16,18,25,30,32,34,36}

In severe catatonia involving potentially life-threatening situations such as severe dehydration, autonomic dysregulation, thrombosis or decubitus, ECT may be a good alternative to pharmacotherapy. If treatment with lorazepam is nonetheless the preferred option, it is recommended to provide this therapy in this category of patients at a psychiatric department of a general hospital where the patient’s condition can be better monitored and appropriate measures can be taken (infusion, heparin). Chronic catatonic symptoms constitute another possible reason for opting for ECT in an earlier phase. Various studies described chronic catatonia as a significant patient characteristic of nonresponders to lorazepam.\textsuperscript{14,17,19} A possible explanation for this is that acute and chronic catatonia have different neurobiologic bases.\textsuperscript{14} There is no specific cut-off value between acute and chronic catatonia, but generally chronic catatonic symptoms are described as lasting for at least tens of days.\textsuperscript{17,19}

ECT is a very effective therapy for catatonia, also when benzodiazepine (lorazepam) trials have failed.\textsuperscript{16,18,25,30,35,36} The response percentages vary between 59% and 100%.\textsuperscript{18,25,30,34,39} The reason why this therapy is a secondary treatment option (in most cases) is that ECT cannot be administered in all settings and because of the potential side effects.

The role of antipsychotics in treating catatonia is not entirely clear. They do seem to be an appropriate therapy when a psychotic disorder is considered to be the underlying cause of catatonia. In these cases, the results of the articles suggest to select an atypical instead of a typical antipsychotic to avoid the risk of deterioration of catatonic symptoms and induction of extrapyramidal movement disorders.

There is insufficient evidence to confirm the therapeutic effects of carbamazepine, topiramate and amineptine. Studies about NMDA antagonists do stress the importance of the potential involvement of glutamatergic dysfunction. However, double-blind control trials are needed to elaborate further on this hypothesis.

**Conclusion**

In summary, the results clearly showed that benzodiazepines and ECT are the only treatments for which there is clinical evidence. Identifying and treating the underlying disorder is essential in the treatment of catatonia. Moreover, the role of antipsychotics is not yet entirely clear. However, there does not seem to be evidence for the use of antipsychotics as therapy for catatonic patients without any underlying psychotic disorder. Typical antipsychotics can worsen the clinical picture. On the basis of the investigated articles, we were not able to develop a treatment protocol because the evidence for catatonia management is limited. Therefore, an urgent need is warranted for more stringent intervention studies in people with catatonia.

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