Update on Catatonia

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Since its initial description by Kahlbaum (1828-1899) over a century ago, catatonia has been associated with psychiatric, neurologic, and medical disorders. Contemporary authors view catatonia as a syndrome of motor signs in association with disorders of mood, behavior, or thought. Some motor features are classic but infrequent (eg, echopraxia, waxy flexibility) while others are common in psychiatric patients (eg, agitation, withdrawal), becoming significant because of their duration and severity.

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Nosology

After Kahlbaum, catatonia was associated with schizophrenia by Kraepelin (1855-1925) and Bleuler (1857-1939). This notion continued in the DSM series, despite reports linking catatonia to affective disorders[3,4] or systemic/toxic reactions.[5,6] DSM-IV now recognizes catatonic schizophrenia (295.3x), catatonia due to a general medical condition (293.89), and catatonia secondary to mania or major depression (these lack specific diagnostic codes).

Some authors have advocated a separate nosology for catatonia.[7,8] This argument is based on the provisional nature of a diagnosis of catatonia, since it can be associated with metabolic, toxic, neurologic, or psychiatric conditions while appearing similar in features. In addition, the treatment of catatonia is different from that of other major psychiatric disorders. It typically responds well to lorazepam and related benzodiazepines as well as electroconvulsive therapy (ECT), and it may be precipitated or worsened by antipsychotic medications.

A related difficulty of the DSM-IV nosology is that “catatonia due to a general medical condition” (293.89) is disallowed for an episode that occurs exclusively during the course of a delirium. The DSM requisite of assessing consciousness/attention and cognition is problematic in the usually mute catatonic patient.

Another nosologic debate is whether neuroleptic malignant syndrome (NMS) and serotonin syndrome are forms of malignant catatonia.[9,10] These syndromes share many clinical features with catatonia, and recent reports show autonomic disturbances in catatonia, highlighting the clinical overlap. A systematic review of defined NMS cases showed 15 of 16 with catatonia, and severity ratings of NMS correlated with the number of catatonic signs.[11] In addition, lorazepam[12,13] and ECT[14] may treat both catatonia and NMS. The advent of specific rating scales for NMS should allow for systematic research as to its treatment and clinical similarity with catatonia.[15,16]

The relationship of catatonia to other motor disorders, particularly Parkinson disease, has also been addressed. Two reports found catatonia could be separately identified by divergent scores on parallel ratings of Parkinson disease and catatonia scales in elderly patients with either schizophrenia[17] or depression.[18] Of note in the latter study, apomorphine improved symptoms of Parkinson disease without affecting catatonic symptoms.

Diagnosis and rating scales

In routine practice, the diagnosis of catatonia can be difficult. Operational definitions for catatonic phenomena have not been well described. In addition, there is debate in the research literature...
about the number of signs necessary and sufficient to diagnose catatonia, with a range of 1 to 4 signs. In *DSM-IV*, the number of motor signs required to meet criteria for catatonia varies with the primary diagnosis. For catatonia secondary to a general medical condition, only 1 motor sign is needed; for the other diagnoses, 2 signs are required. *DSM-IV* does not define these signs well, lacks guidelines about the severity required, and offers a probably incomplete list of signs (only 12 signs are given in the criteria for catatonic schizophrenia). Our group developed a 23-item rating scale (Bush-Francis Catatonia Rating Scale [BFCRS]) that operationally defines each catatonic sign, rates its severity, and provides a standardized schema for clinical examination. A case is defined by the presence of at least 2 of the first 14 items from this scale as shown in the Table.

**TABLE**

<table>
<thead>
<tr>
<th>Screening items from the Bush-Francis Catatonia Scale</th>
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<td>(Presence of at least 2 of these 14 signs defines a case)</td>
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Reliability of the BFCRS depends on the use of its companion standardized examination procedure. This protocol allows rapid and systematic examination, which facilitates monitoring treatment response, which may occur within hours or less. This scale has been confirmed as highly reliable and sensitive to clinical change. Other catatonia rating scales have been published and generally correlate well. Although the BFCRS has proved useful and practical for clinical and research purposes, the comparative clinical use of these scales is not well established.

**Differential diagnosis**

Once catatonia is recognized, the clinician should consider psychiatric catatonia as a matter of exclusion, especially with unfamiliar patients or new onset. A variety of systemic, neurologic, and toxic conditions may produce a catatonic syndrome. Catatonia arising from psychiatric illness and
that secondary to general medical conditions or toxicities shows a similar pattern and severity of catatonic signs.\textsuperscript{25,26}

The laboratory workup should vary based on clinical factors. Brain imaging is encouraged, since strokes, hematomas, and space-occupying lesions can all present with new-onset catatonia\textsuperscript{25,27,28} and such patients may worsen if exposed to prolonged treatment with benzodiazepines. Other tests to consider include blood chemistries, hematology, electroencephalography, toxicology, and possibly lumbar puncture. The scope of investigation will depend on the age of the patient, psychiatric history, severity and duration of the catatonic state, and the promptness of response to initial treatment.

**Neurobiology**

No specific genetic, pathologic, neurochemical, or structural mechanisms have been elucidated in catatonia, although promising information is becoming available. Familial clustering of catatonia suggests a genetic component that lacks classic Mendelian inheritance. For example, in a study of 25 catatonia patients, Barnes and colleagues\textsuperscript{4} found familial clustering in probands with overt psychiatric disorders as well as in patients whose catatonia appeared idiopathic or associated with a general medical condition. Molecular studies of periodic catatonia show familial aggregation and initial evidence for genetic linkage to chromosome 15.\textsuperscript{29}

Neurochemical studies in catatonia have focussed primarily on dopamine and \textit{\alpha}-aminobutyric acid (GABA).\textsuperscript{30} Attention has been directed to these systems because of clinical similarities between catatonia and basal ganglia disorders in which these transmitters are implicated. In addition, effective biologic treatments, such as amobarbital, benzodiazepines, and ECT, have direct or indirect actions on these neurochemical systems. Northoff\textsuperscript{30} found elevated levels of the dopamine metabolite homovanillic acid in a series of inpatients with catatonia, and higher levels predicted a positive initial response to lorazepam during the first 24-hour period of treatment. Anecdotal reports of a positive treatment response to zolpidem, which shares strong GABA-A agonism with lorazepam, led Carroll\textsuperscript{31} to hypothesize a role for GABA-A receptor dysfunction in catatonia.

**Treatment**

The treatment response in catatonia is typically one of complete resolution. Benzodiazepines and ECT are the most recommended modalities in current usage. Amobarbital has a longer history of clinical use, dating from the early 1930s. Only 1 randomized placebo-controlled double blind trial for initial treatment has been published.\textsuperscript{32} This study of 20 mute patients compared intravenous amobarbital with saline infusions in a crossover design. There was no change among 14 saline trials, but 10 of 20 patients responded to amobarbital (scores on a 5-point arousal scale improved 56% within 10 minutes).

In an open trial with 13 acute catatonic patients, Bush and colleagues\textsuperscript{20} reported that 2 mg of intravenous lorazepam reduced catatonia scores on the BFCRS by 60% within 10 minutes. Numerous case series and prospective open trials over the past 20 years with parenteral or oral benzodiazepines such as lorazepam show a response rate of 60% to 80% within hours or days, but there are no published randomized controlled trials for acute catatonia.\textsuperscript{33} Despite this, the consistent response in these studies along with extensive clinical experience has led to a consensus favoring benzodiazepines as initial treatment. A parenteral benzodiazepine challenge has been encouraged as initial treatment for catatonia.\textsuperscript{20,33}

Although amobarbital has not been directly compared with benzodiazepines for initial treatment of catatonia, arguments favoring benzodiazepines include familiarity in contemporary psychiatric practice, a favorable therapeutic index, and the availability of flumazenil, a specific antagonist for benzodiazepines. (Of note, the salutary effect of lorazepam was reversed by flumazenil in a case of catatonic stupor and mutism.\textsuperscript{34}) Recent prospective open trials show that marked improvement or complete resolution of catatonia will occur in 60% to 80% of cases within hours or a few days with lorazepam and related benzodiazepines. Initial dosages of 2 to 6 mg of lorazepam per day are recommended by any route of administration, but some patients may require titration to higher doses ranging from 12 to 16 mg daily. Prolonged trials of benzodiazepines are not advised for severe catatonia, since complications such as dehydration, decubitus ulcers, and embolic events have been reported in this situation. Benzodiazepines appear effective for catatonia attributed to psychiatric illness, neuroleptic toxicity, and a variety of other conditions. Age, sex, and severity of catatonia do not appear to predict treatment response,\textsuperscript{20,35} but comorbid schizophrenia may predict a less robust effect.\textsuperscript{35,36} Since these
comorbid disorders cannot be reliably assessed in mute catatonic patients, specific treatment may be delayed until resolution of the catatonic state. Chronic catatonia associated with schizophrenia may be poorly responsive to lorazepam added to antipsychotics. Convulsive therapy has both a historical tradition and modern support as a treatment for catatonia. In the 1930s, the use of both chemically induced and electroconvulsive seizures was described. Since then, clinical experience and case series have shown that ECT produces remission of catatonia even when other treatments such as amobarbital or lorazepam have failed. An additional advantage of ECT is its effectiveness for both the catatonic syndrome and the frequently associated affective or psychotic disorders. Clinical reports suggest that ECT and lorazepam are synergistic in the treatment of catatonia.

The available literature on antipsychotics in the treatment of catatonia is inconsistent and suggests caution. Several clinical reports show that the older highpotency agents, such as haloperidol or second-generation antipsychotics, failed to improve catatonia, induced or worsened catatonia, or led to progression from catatonia to NMS. In contrast, other case reports suggest risperidone or other second-generation antipsychotics may be beneficial. One report reanalyzed data from clinical trials of schizophrenia, using 3 items from the Positive and Negative Symptom Scale as a retrospective proxy for catatonia, and suggested modest treatment benefit of olanzapine after 6 weeks.

Only 1 randomized double-blind study involving antipsychotics in catatonia has been published. In this study, 14 of 68 nonaffective catatonic patients in whom a trial of lorazepam failed were randomized to receive risperidone plus sham ECT (n = 6) or bilateral ECT plus placebo (n = 8). Scores on the BFCRS declined more than 90% with ECT and approximately 50% with risperidone after 3 weeks.

The inconclusive literature on antipsychotics has led to an expert consensus favoring initial treatment with lorazepam and consideration of ECT for refractory or severely compromised cases if lorazepam fails after a period of days. Unfortunately, ECT may not be available, leading the clinician to consider use of second-generation antipsychotics. In this situation, Rosebush and Mazurek envision a cautious trial of these agents with continued benzodiazepines and careful monitoring for worsening catatonia or signs of NMS.

Use of antipsychotic agents in the treatment of malignant catatonia (an uncommon severe variant characterized by extreme agitation, fever, and other autonomic disturbances) is also not recommended because of the risk of exacerbation. In this setting, prompt use of ECT has been advocated.

**Summary**

Catatonia is a distinct neuropsychiatric syndrome that is becoming more recognized clinically and in ongoing research. It occurs with psychiatric, metabolic, or neurologic conditions. It may occur in many forms, including NMS. Treatment with benzodiazepines or ECT usually leads to a dramatic and rapid response, although systematic randomized trials are lacking. An important unresolved question is the role of antipsychotic agents in treatment and their potential adverse effects.

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**Drugs mentioned in this article**

- Amobarbital (Amytal)
- Apomorphine (Apokyn)
- Flumazenil (Romazicon)
- Haloperidol (Haldol)
- Lorazepam (Ativan)
- Olanzapine (Zyprexa)
- Risperidone (Risperdal)
- Zolpidem (Ambien)

**References:**

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