Clinical Manifestations, Diagnosis, and Empirical Treatments for Catatonia

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ABSTRACT

Objective: Review the medical literature on the history and clinical features of catatonia so as to provide a contemporary clinical guide for successfully diagnosing and treating the various clinical forms of catatonia.

Design: Results of MEDLINE computerized searches using search terms 'catatonia', 'treatment of catatonia', 'electroconvulsive therapy and catatonia', 'benzodiazepines and catatonia', clinical case reports, and book chapters covering the medical and psychiatric literature relevant to catatonia and its associated treatments were examined.

Setting: Academic medical center.

Participants: None.

Measurements: None.

Results: Catatonia is a common but under-recognized clinical syndrome. No large-scale, controlled studies exist to determine the relative effectiveness of current treatments, including sedative-hypnotic medications (benzodiazepines or barbiturates), and electroconvulsive therapy (ECT).

Conclusion: Despite the lack of large-scale, controlled studies, benzodiazepines appear to be an effective first-line treatment for catatonia. ECT is now often reserved as a second-line treatment despite more than 60 years of documented efficacy and safety. However, ECT should be viewed as a first-line intervention in cases of severe or malignant catatonias.

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INTRODUCTION

Karl Ludwig Kahlbaum (1828–1899) is credited with the original clinical description of catatonia. He described catatonia as a disturbance in motor function representing phases of a progressive illness with periods of mania, depression, and psychosis.[1] Ultimately, if untreated, patients became demented and often died. Catatonia remains a common syndrome seen in a variety of psychiatric and medical illnesses. Nevertheless, it frequently remains undetected in the clinical setting with the consequence that initial treatment is often inappropriate and delayed despite being a potentially fatal condition that is reversible with treatment.

Established and efficacious treatments for catatonia now include benzodiazepines, barbiturates, and electroconvulsive therapy (ECT).[2] The therapeutic role of ECT is based on more than six decades of clinical experience, and ECT is often effective when pharmacotherapy interventions have failed. In fact, the first application of convulsive therapy was more than 70 years ago by Ladislas Meduna (1896–1964) to treat an intractable catatonia syndrome with stupor, which had persisted for four years in a 30-year-old man with an underlying diagnosis of catatonic schizophrenia.[3] A full remission of catatonia was induced by a course of seizures induced chemically (not electrically) with intramuscular camphor oil.[4] This first catatonic patient treated by Meduna with convulsive therapy was able to return to home and work. A few years later in 1938, Ugo Cerletti (1877–1963) and Lucio Bini (1908–1964) electrically induced seizures for the first time in a patient in an excited catatonic delirium. Soon thereafter, ECT became established as a more reliable, tolerable, and efficient method to induce therapeutic seizures.[3]

This article reviews our contemporary understanding of the nature and clinical manifestations of catatonia. Diagnostic considerations and treatment strategies for catatonia in a variety of psychiatric and medical settings, with a particular focus on ECT, are discussed.

TABLE 1. Types of catatonia relevant in psychiatry

DSM-IV Code	Diagnosis	Prognosis with Treatment	Potential Morbidity and Mortality
296.xx	Mood disorder with catatonic features	EXCELLENT	MODERATE
293.89	Catatonic disorder due to...[general medical condition]	GOOD-POOR	HIGH
295.20	Schizophenia, catatonic type	GOOD-FAIR	MODERATE
333.92	Neuroleptic malignant syndrome	FAIR-POOR	HIGH
NONE	Toxic serotonin syndrome	FAIR-POOR	HIGH

The table includes associated DSM-IV codes (if available) ranked in order of types most frequently encountered in practice. Prognosis indicates estimated outcomes with appropriate treatment using benzodiazepines and/or ECT.

RECOGNIZING CATATONIA

Prevalence and psychiatric comorbidity. It is estimated that approximately 90,000 cases of catatonia occur each year in US hospitals.[5] Catatonia has a reported prevalence ranging from 7.6 percent to as high as 38 percent in psychiatric patients and occurs most commonly in the setting of mood disorders.[6] More than half of patients with catatonia have an underlying bipolar affective disorder, and approximately 28 percent of catatonic bipolar patients present in a mixed mood state with features of depression and mania simultaneously.[7] It is estimated that 20 to 30 percent of bipolar affective disorder patients may experience catatonia at some point in time during their illness, most often as a manic manifestation.[5,7] About 10 to 15 percent of catatonic patients meet criteria for an underlying diagnosis of schizophrenia.[5] However, catatonic schizophrenia may be under or over diagnosed due to confusion between catatonia and negative symptoms.

Signs and subtypes. No laboratory or radiological tests directly assist the clinician in making a specific diagnosis of catatonia, and little is known about its pathophysiology. The diagnosis of catatonia is made on clinical signs and symptoms that manifest as a syndrome comorbid with psychiatric and/or medical illnesses. Catatonia due to psychiatric conditions tend to occur in one of two forms: A retarded-stuporous or an excited-delirious type.[5] Both can be chronic and may include as many as 40 recognized signs of catatonia. The most common signs include mutism, negativism, posturing, staring, catalepsy, and echo-like behavior (e.g., echolalia and echopraxia). Scales can be useful to screen for catatonia and include the Bräunig-Catatonia Rating Scale, Bush-Francis Catatonia Screening Instrument,

Bush-Francis Catatonia Rating Scale, Rogers Scale, Northroff Scale, and Catatonia Rating Scale.

The DSM-IV definition and diagnostic classifications of catatonia remain debated and need clearer definition.[5] The DSM-IV provides limited descriptions of a few of the various catatonia syndromes encountered in psychiatry and are outlined in Table 1.[6]

The most common type of catatonia occurs with mood disorders, yet the DSM-IV does not code separately for this unique condition with its specific and effective treatments. Instead, catatonia is construed simply as a specifier for the current or most recent mood disorder episode (unipolar or bipolar), in the same way that melancholic or atypical features might be part of the clinical picture. Catatonia is also recognized as a mental disorder that may occur due to a general medical condition (e.g., brain neoplasm or hepatic encephalopathy). In this instance the catatonia must be a direct physiological consequence of a general medical condition. Only one sign of catatonia is required in this instance with no minimal duration specified. Schizophrenia, catatonic type, as defined in the DSM-IV, is relatively uncommon and can be easily missed in the setting of prominent negative symptoms (e.g., mutism).

Limitations of the current DSM-IV classification include its failure to recognize other varieties of catatonia, such as permanent and periodic catatonia, and offering no guidance for the clinician in distinguishing benign from malignant catatonias.[8] Based on the recent literature, recommended future criteria for subtypes of catatonia include nonmalignant, delirious, and malignant subtypes.[9] Proposed specifiers include catatonia secondary to general medical conditions, toxic states; or mood, neurological, or psychotic disorders.[9] When catatonia persists for at least 24 hours, in the setting of clear functional impairment, then treatment with benzodiazepines and/or ECT should commence. If catatonia is left unrecognized and untreated it becomes chronic, and patients may die from complications of malnutrition, immobility, and/or dangerous behavior.

The DSM-IV does recognize that catatonia is frequently associated with medical illnesses and carries a significant morbidity and mortality. In fact, all physicians should screen for malignant catatonia in medically and psychiatrically compromised patients. Malignant catatonia is characterized by the triad of severe rigidity, autonomic nervous system instability, and altered mental status. The presence of a febrile catatonia is especially important to recognize clinically as it may be a harbinger of malignant catatonia. Until the more widespread use of ECT, most patients with malignant catatonia died.[10]

Of particular relevance in psychiatric practice with respect to the above are the neuroleptic malignant syndrome (NMS) and the toxic serotonin syndrome (TSS).[11] Both can be considered iatrogenic types of malignant catatonias secondary to the use of psychiatric medications. NMS is defined in the DSM-IV simply as a medication-induced movement disorder although it can perhaps be better construed as an iatrogenic form of malignant catatonia that is responsive to ECT.[12] Finally, missing a diagnosis of schizophrenia, catatonic type by overlooking catatonic features in the clinical picture and then treating only with typical neuroleptics may place the patient at increased risk of progressing to a malignant catatonia in the form of NMS.

Differential diagnosis. Careful consideration should be given to the differential diagnosis of catatonia as listed in Table 2.[8]

Catatonia can be confused with other conditions, such as nonpsychiatric stupor, encephalopathy, stroke, stiff-person syndrome, Parkinson's disease, locked-in syndrome, malignant hyperthermia, nonconvulsive status epilepticus, or autism. Treatment of the underlying condition usually resolves the catatonia symptoms and also portends outcome. Any suspicion of an occult medical cause of catatonia should be screened for with a focus on history, vital signs, and the neurological exam. Measurement of serum electrolytes and toxicology screens may be useful to rule out metabolic or toxic causes. If non-convulsive status epilepticus is suspected, it can be detected by EEG and treated appropriately in ways similar to treatments for catatonia. In some cases, neuroimaging may be useful.

TREATING CATATONIA

Once catatonia is recognized, appropriate interventions, such as medications and ECT, can be rapidly used. Despite effective interventions, no large-scale, controlled studies or meta-analyses of standard treatments applied to patients with catatonia exist largely due to the acute and often clinically severe nature of the disorder. However, historically after the introduction of ECT into psychiatric treatment, mortality from catatonia and associated psychiatric illnesses significantly declined. Despite the empirical success of ECT for treatment of acute catatonia, little is known about the longitudinal course of chronic catatonia treatment with ECT.

Despite a limited understanding of the neurophysiological abberations responsible for catatonia, decades of clinical experience has shown that ECT and/or benzodiazepines are our best current treatments for catatonia. Other interventions, such as dantrolene, bromocriptine, amantadine, and anticonvulsants (e.g., carbamazepine) may have some utility, but it remains to be seen whether these treatments will furnish an efficacy and safety profile comparable to that of ECT and benzodiazepines.[13,14]

The 2005 UK Health Technology Assessment Programme's stringent report of the clinical and cost-effectiveness of ECT found two "good-quality" systematic reviews of the efficacy and safety of ECT in catatonia but no conclusive evidence

TABLE 2. Differential diagnosis of conditions mimicking catatonia with a list of signs similar to catatonia and clinical features distinguishing these conditions from catatonia. Keep in mind, these conditions may be comorbid with catatonia of any etiology.

Diagnosis	Features Similar to Catatonia	Distinguishing Features
Non-catatonic stupor	Immobility, unresponsiveness, mutism, altered mental status	Clear precipitating cause (e.g., head trauma, anoxia, drug intoxication)
Encephalopathy	Acute onset, bizarre behavior, altered mental status	Typically occurs in the context of medical illness, reversible with treatment of underlying medical condition
Stroke	Acute onset, may present with immobility, mutism, and/or altered mental status	History of cerebrovacular disease, focal neurological signs, CT/MRI findings
Stiff-Person syndrome	Immobility, posturing	Stiffness and spasms precipitated by surprise
Parkinson's disease	Immobility, altered mental status, comorbid affective disorder	Symptoms improved with dopamine agonists and anticholingerics, cogwheel rigidity
Locked-in syndrome	Immobility, mutism	Complete paralysis with preserved vertical eye movements and blinking, associated with lesions in pons and cerebral peduncles
Malignant hyperthermia	Immobility, mutism, altered mental status, autonomic nervous system instability	Hyperthermia secondary to inhalation anesthetics, autosomal dominant, diagnosed with muscle biopsy
Status epilepticus	Immobility, mutism, altered mental status, bizarre behavior	Epileptiform activity in EEG
Autistic disorder	Mutism, immobility, echo-like behavior	Chronic with onset in childhood
Severe obsessive-compulsive disorder	Repetitive echo-like behavior, comorbid affective disorder	Anxiety, awareness of compulsive behavior
Elective mutism	Mutism	Possible underlying personality disorder or paranoia

for its cost-effectiveness in this disorder.[14] Despite this viewpoint, there have been many clinical reports of effectiveness of benzodiazepines, ECT, or both to alleviate the symptoms of catatonia regardless of severity or etiology.[16,17]

Benzodiazepines. In current clinical practice, benzodiazepines are most utilized as first-line treatment for catatonia. One retrospective review examined treatments in 270 episodes of catatonia in 178 patients.[18] The most common intervention was the use of a variety of benzodiazepines with a reported 70 percent response rate. Lorazepam treatment specifically demonstrated 79-percent complete remission of catatonia. ECT use occurred less frequently but led to resolution of catatonic symptoms in 85 percent of patients treated and had a better response in treating malignant catatonias. Overall, it appears that 50 to 70 percent of patients with catatonia respond to lorazepam 2mg every 3 to 8 hours (6–16 mg/day) over a period of 3 to 5 days.[19] Patients with acute catatonia typically start to improve rapidly with lorazepam when administered within 24 hours of onset of symptoms.

Electroconvulsive therapy. Benzodiazepines are not uniformly effective when treating catatonia.

ECT has the potential to be more broadly effective than benzodiazepines since it may also treat an underlying affective disorder, which will be present in most cases of catatonia. The clearest indication for early intervention with ECT is when treating malignant or excited-delirious forms of catatonia.[19] In contrast, those with chronic catatonia do not respond as quickly or as completely to ECT, making early diagnosis and appropriate intervention essential. Reports suggest that ECT administered early in the treatment of catatonia results in more optimal outcomes.[17] ECT may salvage cases of prolonged catatonia unresponsive to anticonvulsants, but more ECT sessions may be necessary.[20]

One review examined whether the first-line use of ECT was more effective than medications alone in patients with affective disorders.[21] Half the patients in this retrospective study demonstrated signs of catatonia (*N*=13), and nine of these received a diagnosis of bipolar affective disorder. Successful outcome with few side effects was reported with use of ECT alone suggesting that first-line use of ECT in patients with affective disorders and catatonia can be an effective yet is an underutilized treatment option.

Patients with both schizophrenia and catatonia present unique treatment challenges. Little is known about the long-term use of ECT in catatonic schizophrenia, yet one study suggests that those with catatonic schizophrenia who receive ECT had fewer relapses of catatonia and were discharged from the hospital earlier than those who received sham-ECT.[14] Trials that reported successful use of ECT in catatonic schizophrenia also reported benefits in patients with positive symptoms of psychosis.[22] However, the use of ECT in catatonic schizophrenia is left out of many treatment algorithms, and hence not prescribed. Patients with catatonic schizophrenia treated with antipsychotics may develop a worsening catatonia or NMS, overlooked as negative symptoms.

ECT technique in catatonia. The basic ECT method for treating catatonia is no different than that used for treating any other psychiatric illnesses. The majority of reports have used bilateral ECT when treating catatonic patients. One protocol recommends five days of bitemporal ECT at stimulation energies set to half the patient's age.[23] Successful treatment response is predicted by the duration and quality of ECT-induced seizures.[24] Induction of as little as two to three seizures with ECT will sometimes be an effective initial treatment for catatonia,[19] with fuller alleviation of symptoms generally occurring with a course of about five seizures.[18] More severe forms of malignant and excited-delirious catatonia may require daily bilateral ECT. The long-term and neurophysiologic effects of ECT when treating catatonia remain unclear. Limited SPECT neuroimaging studies suggest a course of ECT results in increased cerebral perfusion.[25]

Combination treatment with benzodiazepines and ECT. Benzodiazepines and ECT both affect GABA neurotransmission[26,27] resulting in an increased seizure threshold and decreased cortical excitability. This suggests a common pathway for inhibitory GABA neurotransmission in the treatment of catatonia and that a combination of both treatments might be clinically advantageous.

How these treatments can be best combined remains uncertain. There are reports of ECT-refractory catatonia successfully treated with lorazepam[28] and vice-versa.[29] Some advocate that ECT should be used within the first few days of a severe catatonia if not relieved by lorazepam.[30]

NMS and catatonia. When the diagnosis of catatonia has been made, the use of antipsychotic and/or antidepressant medications should generally be avoided. Atypical and typical antipsychotics are broadly used in psychiatry, and particularly with the use of a typical agent, such as haloperidol in the acute setting, they carry risks of exacerbating catatonia and inducing NMS. In contrast, atypical antipsychotic usage may be associated with reduced mortality in some cases of NMS.[31]

Some investigators describe NMS as a specific iatrogenic subtype of malignant catatonia; whereas, others (including the DSM-IV) consider catatonia to be a differential diagnosis of NMS.[6] While the distinction between NMS and pure catatonia is important to make, both catatonia and NMS share clinical features that likely reflect a shared pathophysiology resulting in a syndrome of catatonia. If a simple case of catatonia becomes complicated by the features of NMS (fever, rigidity, autonomic disturbance, and elevated serum CPK in response to a neuroleptic) consideration should be given to ECT as an urgent treatment for both conditions. A retrospective analysis of 665 cases of NMS found better outcomes in patients treated with dopamine agonists and ECT as compared to other interventions.[32] In the series, 21 percent of the untreated patients died compared to 9.7 percent of those treated with dopamine agonists and 10.3 percent of those receiving ECT. A more recent study reported 73-percent effectiveness when using ECT to treat 40 cases of NMS.[33] Complete recovery occurred in 63 percent of cases. In cases of suspected NMS and severe muscle rigidity, repeated serum CPK levels may provide a guide to assess treatment response.

Antipsychotics are the mainstay of long-term schizophrenia treatment, yet may worsen catatonia and precipitate NMS. When treating co-morbid schizophrenia and catatonia, one author suggests using high-dose benzodiazepines for 1 to 2 weeks, followed by a course of ECT, and as a last resort, clozapine with ECT.[18] Clozapine has low dopamine receptor affinity and is known to facilitate seizure activity. One open-label treatment study reported that more than a third of patients successfully treated for catatonia with benzodiazepines and ECT no longer demonstrated psychosis,[29] providing clinical evidence that militates against

aggressive use of antipsychotics in catatonic patients, until at least the etiology of the catatonic syndrome has been clarified.

Serotonergic antidepressant drugs confer some risk of the development of a TSS.[11] The TSS is due to excessive stimulation of central and peripheral serotonin receptors and manifests as a change in mental status with motor and autonomic nervous system abnormalities. It can present as a malignant form of catatonia. One report suggests benzodiazepines and ECT may be useful treatments in the TSS.[11]

Barriers to ECT use in catatonia. Perhaps the biggest barrier to more frequent and appropriate use of ECT in the setting of catatonia, as well as in other clinical situations, is the social stigma against ECT. Society's wary stance regarding ECT stems from a combination of claims of overuse in its early history, claims of misuse, cultural fears regarding accidental electrocution, and the capital punishment and electrocution of state-sanctioned criminals.[34] Furthermore, local laws on ECT often complicate the process of obtaining ethical consent in the severe and acutely catatonic patient.

Modern ECT can also be delayed or not pursued by physicians, patients, and families due to excessive concern regarding potential for retrograde amnesia.[35] However, amnesia may also occur secondary to high-dose benzodiazepine use and manifest in untreated psychiatric disorders. Clinicians need to carefully weigh the risks and benefits of a trial of ECT in the setting of acute catatonia. In a patient with a severe or chronic catatonia, concerns regarding effects of ECT on memory are relatively minor compared to the potentially life-saving benefit of ECT.

PROGNOSIS

If untreated, catatonia is associated with significant morbidity and mortality.[36] After four days of persistent catatonia, evidence indicates that the risk of permanent disability increases.[5] The long-term course of catatonia is also determined by the etiology of the syndrome. Little is known about the long-term treatment outcomes following administration of ECT for catatonia. However, it is clear that fatality rates from catatonia significantly decreased after the introduction and adoption of ECT as standard treatment in psychiatry.[37] One small retrospective study suggested that patients with catatonic depression who were treated with ECT in addition to a tricyclic antidepressant, lithium, bupropion, or high-dose venlafaxine had better long-term outcomes over the course of four years compared to patients who received ECT and selective serotonin reuptake inhibitors.[38] In the rare familial (genetic) form of catatonia, the prognosis is poor, and benzodiazepines and ECT fail to treat this type of catatonia.[39] Cerebral pathology may also predict a less favorable treatment outcome with ECT.[40]

Application of ECT in special patient populations. Several reports describe the use of ECT for treatment of catatonia in special patient populations. ECT is reported as a safe and effective treatment for catatonia during pregnancy to minimize fetal exposure to teratogenic medications.[21] There are cases reports of the effectiveness of ECT for treating catatonia in patients with comorbid medical illnesses such as lupus cerebritis[41] and breast cancer.[42] ECT can be effective in treating children with catatonia, and it is estimated that half of children who receive ECT do so because of a diagnosis of catatonia.[43] In one report, ECT successfully treated catatonic stupor in a 14-year old boy with autism.[44]

SUMMARY

History provides compelling evidence for ECT as one of the most effective treatments in psychiatry. In this respect, catatonia is a particularly striking example of its enduring efficacy more than 70 years after Meduna's first administration of convulsive therapy. ECT often produces remission of catatonia despite being called upon as a last resort and despite our limited understanding of its neurobiological effects. Catatonia is a relatively common syndrome in hospitalized psychiatric patients for which all clinicians need to be vigilant. The long-term prognosis of catatonia depends on its etiology. It is a frequently observed syndrome complicating both acute medical and psychiatric disorders. In either scenario, ECT is a safe and effective intervention that complements use of benzodiazepines. Future technological advances in convulsive therapy such as magnetic seizure therapy (MST) or focal electrically-administered seizure therapy (FEAST) may provide novel future treatments for catatonia.

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