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REVIEW

# Catatonia: Our current understanding of its diagnosis, treatment and pathophysiology

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## Abstract

Catatonia is a psychomotor syndrome that has been reported to occur in more than 10% of patients with acute psychiatric illnesses. Two subtypes of the syndrome have been identified. Catatonia of the retarded type is characterized by immobility, mutism, staring, rigidity, and a host of other clinical signs. Excited catatonia is a less common presentation in which patients develop prolonged periods of psychomotor agitation. Once thought to be a subtype of schizophrenia, catatonia is now recognized to occur with a broad spectrum of medical and psychiatric illnesses, particularly affective disorders. In many cases, the catatonia must be treated before any underlying conditions can be accurately diagnosed. Most patients with the syndrome respond rapidly to low-dose benzodiazepines, but electroconvulsive therapy is occasionally required. Patients with longstanding catatonia or a diagnosis of schizophrenia may be less likely to respond. The pathobiology of catatonia is poorly understood, although abnormalities in gamma-aminobutyric acid and glutamate signaling have been suggested as causative factors. Because catatonia is common, highly treatable, and associated with significant morbidity and mortality if left untreated, physicians should maintain a high level of suspicion for this complex clinical syndrome. Since 1989, we have systematically assessed patients presenting to our psychiatry service with signs of retarded catatonia. In this paper, we present a review of the current literature on catatonia along with findings from the 220 cases we have assessed and treated.

**Key words:** Catatonia; Schizophrenia; Benzodiazepines; Electroconvulsive therapy; Extrapyramidal disorders



**Core tip:** Catatonia is a complex clinical syndrome occurring in more than 10% of patients with acute psychiatric illnesses, and it is associated with multiple life-threatening complications. In the last several decades, renewed interest in this syndrome has led to a great deal of research and debate regarding its

diagnosis and treatment. In this paper, we present a review of the current literature on catatonia along with findings from the 220 cases we have assessed and treated since 1989. Catatonia itself is readily treated using low-dose lorazepam, and it also has important implications for how other underlying psychiatric conditions should be treated.

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## INTRODUCTION

Catatonia is a clinical syndrome characterized by a distinct constellation of psychomotor disturbances. Two subtypes have been described: Retarded and excited. Catatonia of the retarded type is associated with signs reflecting a paucity of movement, including immobility, staring, mutism, rigidity, withdrawal and refusal to eat, along with more bizarre features such as posturing, grimacing, negativism, waxy flexibility, echolalia or echopraxia, stereotypy, verbigeration, and automatic obedience[1-3]. Excited catatonia, on the other hand, is characterized by severe psychomotor agitation[4], potentially leading to life-threatening complications such as hyperthermia, altered consciousness, and autonomic dysfunction. This so-called "malignant" or "lethal" catatonia can be rapidly fatal if not appropriately treated[5,6]. The relative prevalence and diagnostic significance of catatonic signs differ among studies and patient populations, but there is general agreement that catatonia occurs in 9%-17% of patients with acute psychiatric illnesses[1,2,7] and that retarded catatonia is the more frequently observed subtype[4,8-10].

The catatonic syndrome is associated with other disorders, underscoring the necessity of rapid diagnosis and treatment. In particular, catatonia appears to be a risk factor for the development of neuroleptic malignant syndrome[11-13], which has a mortality rate of approximately 10%[14] and may be clinically indistinguishable from malignant catatonia[15,16]. This has important implications for the treatment of catatonia in the context of psychosis, which will be discussed later in this review. Additionally, the immobility and refusal to eat or drink associated with catatonia can give rise to potentially serious medical complications, including dehydration[17], malnutrition[18,19], deep vein thrombosis and pulmonary embolism[20,21], pneumonia and other infections[17], pressure ulcers[19], and muscle contractures[18,19]. The very nature of catatonia can make it challenging, if not impossible, to carry out patient interviews and examinations, thereby interfering with the recognition of underlying diagnoses. These complications of catatonia highlight the importance of recognizing the syndrome and quickly initiating treatment.

Overall, it is clear that catatonia is a common and serious problem that often remains unrecognized. Despite a renewed interest in the disorder over the last several decades[22], a number of questions remain regarding its causes and treatment. In this paper, we review the current understanding of the diagnosis, treatment, and pathophysiology of catatonia, and we identify several areas of uncertainty where further research is required.

## DIAGNOSIS

### *Clinical features*

While catatonia has long been considered a subtype of schizophrenia or a clinical feature of other medical and psychiatric conditions, the earliest descriptions by Kahlbaum *et al*[23] in fact suggested a unique entity with a distinct clinical course. This proposal was not universally accepted, however, and a great deal of debate has ensued regarding the most appropriate classification of catatonia. Largely due to the influence of Emil Kraepelin, catatonia eventually came to be "officially" seen as a type of schizophrenia[24]. Early descriptions of catatonia in both the diagnostic and statistical manual of mental disorders (DSM) and international classification of diseases included it only under the category of schizophrenia, and this view persisted for many years. Things began to change in the 1970's, when multiple reports indicated that catatonia is more closely associated with affective disorders than schizophrenia[4,25]. More recently, it has been proposed that catatonia is also relatively common in patients diagnosed with autism[26]. In 1994, catatonia was recognized in the DSM-Ⅳ as a disorder that could either complicate general medical conditions or be a specifier in mood disorders. At the same time, there were continued arguments in support of catatonia being its own distinct diagnostic category[7,27].

A number of different criteria have been proposed for the diagnosis of catatonia. In our own ongoing assessment and treatment of consecutively referred patients with catatonia who present to either our acute-care inpatient psychiatric unit or to the consultation-liaison service, we diagnose patients based on the presence of at least four of the catatonic signs originally described by Karl Kahlbaum in 1874[1]. These signs, along with their frequency in our patient series, are presented in Table 1. As we originally reported in 1990[1], immobility and mutism are the most common signs, each present in over 90% of patients. In keeping with this finding, the diagnostic criteria proposed by Taylor *et al*[27] include immobility and mutism (along with stupor) as core criteria for catatonia. A systematic effort to identify the catatonic signs with the best diagnostic performance was conducted by Peralta *et al*[2]. Immobility and mutism were again identified as the most common signs, observed in 90.6% and 84.4% respectively of catatonic patients. Rigidity was also common in their

**Table 1 Frequency of various catatonic signs in our series of 220 consecutive catatonic cases**

| Sign | % of patients |
|---|---|
| Immobility | 97 |
| Mutism | 97 |
| Withdrawal and refusal to eat | 91 |
| Staring | 87 |
| Negativism | 67 |
| Posturing | 58 |
| Rigidity | 54 |
| Waxy flexibility/catalepsy | 27 |
| Stereotypy | 25 |
| Echolalia or echopraxia | 14 |
| Verbigeration | 14 |

sample, observed in 75.0% of catatonic patients. The use of 4 or more catatonic signs as a diagnostic criterion resulted in 100% specificity, but also led to a small number of catatonic patients failing to be identified. As a result, Peralta *et al*[3] suggest the use of three or more catatonic signs as a diagnostic criterion for catatonia, and this recommendation has been supported by more recent work from the same group[3]. The DSM-Ⅴ defines catatonia as the presence of three or more of the following: Catalepsy, waxy flexibility, stupor, agitation, mutism, negativism, posturing, mannerisms, stereotypies, grimacing, echolalia, and echopraxia[28]. A number of scales have been developed to quantify catatonic signs[29]. While these scales may prove useful for research, we have not found them to be necessary for clinical purposes.

The most important step in the diagnosis of catatonia is recognition of the syndrome's characteristic clinical signs. Immobility and mutism are particularly common, and the appearance of either of these signs in the absence of another explanatory condition should raise the clinical suspicion of catatonia, at which point the presence of other catatonic signs can be determined. In our experience, patients are often incontinent, disheveled, and cachectic depending on the duration of illness. The lack of meaningful responses to external stimuli in these patients should not be interpreted as a lack of awareness of their surroundings. Indeed, many of the patients we have treated reported being completely aware and were able to recall their catatonic state in detail after they recovered.

### *Differential diagnosis*

A number of neurological conditions may appear similar to catatonia, and may even have substantial overlap with respect to pathophysiological mechanisms. The following is a partial list of conditions that, in our experience, have considerable clinical overlap with catatonia and should be carefully considered.

**Extrapyramidal side-effects:** Extrapyramidal side-effects are commonly associated with both typical and atypical antipsychotic drugs[30,31], so they are of special concern in patients with psychiatric illness. Like patients with catatonia, patients with drug-induced parkinsonism may present with immobility, staring, and rigidity. On numerous occasions we have been asked to see a patient with a tentative diagnosis of catatonia who in fact had antipsychotic-induced parkinsonism. This distinction is an important one to make, since the benzodiazepine medication used to treat catatonia may exacerbate the postural instability that is often associated with parkinsonism. One notable difference between the syndromes is that parkinsonian patients are typically cooperative and interactive, in contrast to catatonic patients who are often withdrawn and negativistic. Also, tremor, which is often present in patients with parkinsonism, is not a feature of catatonia. Unusual features like echophenomena and posturing are typically absent in parkinsonism. We have, however, seen parkinsonian patients whose freezing was mistaken for posturing. Additionally, some patients treated with antipsychotic drugs may develop signs consistent with both catatonia and parkinsonism[32]. Other extrapyramidal side-effects may also resemble some aspects of catatonia. For example, the posturing and immobility of catatonic patients can be mistaken for dystonia, while the psychomotor agitation of excited catatonia can appear similar to akathisia. In patients being treated with antipsychotic medication, care must be taken in assessing these clinical features to ensure diagnostic accuracy.

**Neuroleptic malignant syndrome:** Neuroleptic malignant syndrome is a life-threatening reaction to antipsychotic treatment (including treatment with atypical antipsychotics[33]) in which patients develop rigidity, mutism, and delirium accompanied by diaphoresis, hypertension, tachycardia, and fever[34,35]. Autonomic instability helps to distinguish this syndrome from uncomplicated catatonia, but it may sometimes be indistinguishable from malignant catatonia except for the precipitating factor of antipsychotic treatment. Cessation of antipsychotic medication, along with supportive therapy, is often sufficient to treat these patients, but additional pharmacological treatment or electroconvulsive therapy (ECT) may be indicated.

**Nonconvulsive status epilepticus:** Nonconvulsive status epilepticus can be clinically indistinguishable from catatonia. In both cases, patients can be immobile, mute, rigid, and unable to eat, drink, or cooperate with an examination. Although electroencephalogram (EEG) findings in nonconvulsive status epilepticus can be highly variable, these investigations are nonetheless crucial to making the correct diagnosis[36,37].

**Abulia or akinetic mutism:** Disorders of diminished motivation exist on a spectrum including abulia (moderate) and akinetic mutism (severe)[38]. In the extreme case, neurological dysfunction results in a complete lack of spontaneous speech or movement due to a lack of motivation or drive. Patients are fully aware and visual

tracking is preserved. Overt signs of catatonia such as negativism and echophenomena may differentiate the two disorders, but more subtle presentations can make the two conditions difficult to distinguish[39]. In such cases, a trial of lorazepam may be helpful in identifying catatonia.

**Locked-in syndrome:** Locked-in syndrome is usually associated with ventral pontine lesions, and results in near complete paralysis, while blinking and vertical eye movements are spared[40]. Patients are aware and, unlike catatonic patients, generally eager to communicate through blinking. However, it should be noted that some patients with locked-in syndrome are unable to blink or move their eyes. As with catatonic patients, EEG investigations are often normal. Abnormalities identified using magnetic resonance imaging (MRI) or brainstem evoked potentials help to identify patients with the locked-in syndrome.

**Vegetative state:** The vegetative state is characterized by a complete lack of awareness of the self or surroundings, often secondary to a severe cerebral injury[41]. The patient makes no voluntary responses to stimuli, and does not visually track objects, but sleep-wake cycles are preserved. Although this definition of the persistent vegetative state is reasonably clear, confidently assessing a lack of awareness can be problematic. EEG and MRI techniques have been used to demonstrate awareness in a disturbing number of patients who otherwise met criteria for a vegetative state[42,43]. Unlike the normal EEG of catatonia, the EEG in vegetative states is almost always abnormal[44].

**Stiff person syndrome:** Stiff person syndrome is an autoimmune disorder frequently presenting with low back and lower extremity stiffness and spasms, as well as exaggerated lumbar lordosis[45], which can be mistaken for posturing. Like catatonia, the condition can render patients immobile. Episodes are typically triggered when patients are startled or experience emotional stress. In contrast with what is observed in patients with catatonia, patients with stiff person syndrome are not mute and will often indicate that they are in great pain as a result of the muscle spasms. Since most patients are GAD65 antibody seropositive[45], antibody testing may be helpful if there is diagnostic uncertainty. The syndrome generally improves in response to benzodiazepine treatment, perhaps supplemented by adjunctive immunotherapy where appropriate.

## INVESTIGATIONS

All patients suspected of having catatonia should have EEG testing as a screen for other neurological conditions. This will typically show epileptiform activity in nonconvulsive status epilepticus and slowing in cases of encephalopathy. The EEG in catatonia is typically normal unless there is a concurrent condition that may be causing the abnormality[1,9,46]. Given that catatonia can develop in the context of a wide array of neurological conditions, brain imaging, preferably by MRI, is recommended[1,47]. In cases of retarded catatonia, immobility generally allows these investigations to be conducted easily. Laboratory investigations should include a complete blood count, blood urea nitrogen, creatinine, muscle and hepatic enzymes, thyroid function tests, electrolytes, blood glucose, and urinalysis to assess for comorbid conditions, causes, or complications of catatonia. Marked dehydration is not uncommon in catatonic patients, and must be attended to. Vital signs should be assessed frequently, as hypertension and fever (often accompanied by elevated creatine phosphokinase, decreased serum iron, and leukocytosis) may herald the onset of malignant catatonia or neuroleptic malignant syndrome if the patient has received antipsychotic agents[35,48-50]. When possible, a careful review of the patient's recent medications and any changes should be conducted. It is important to determine whether or not a patient has been receiving antipsychotic agents or benzodiazepines, as we have reported, and continue to see, the development of catatonia following abrupt discontinuation of benzodiazepines[51,52].

Unfortunately, the nature of catatonia makes some aspects of a physical and neurological exam impossible. Components of the neurological exam that can usually be assessed include the pupillary reaction, ocular movements, corneal reflex, reaction to pain, the presence of drooling, blink response to threat, reaction to light or sound, frontal release signs, assessment of tone, deep tendon reflexes, and the plantar response.

## TREATMENT

A characteristic feature of catatonia is its striking responsiveness to benzodiazepine treatment. We recommend an initial dose of 1-2 mg lorazepam, administered sublingually or intramuscularly. The ability to administer lorazepam intramuscularly is a major advantage, since many catatonic patients refuse to eat or take medication by mouth. A lower lorazepam dose is preferable in patients who are young, elderly, or medically compromised, especially when there is a diagnosis or high likelihood of sleep apnea. If the initial dose is ineffective, it should be repeated in 3 h and again after another 3 h. We have analyzed treatment response in 153 patients treated with lorazepam. In this group, we have observed a response in 132 (85.7%), 90 of whom experienced complete recovery within 3 h. This robust response to low-dose lorazepam has also been reported by others[46,53], but higher doses may be necessary in some cases[54,55]. If a patient responds adequately to benzodiazepine treatment, they should continue on the same dose (provided that this dose is not overly sedating or causing any other problematic side-effects) until treatment of any underlying disorder is underway. Relapse into a catatonic state can occur

**Table 2 Rates of response to lorazepam treatment in catatonic patients with various underlying diagnoses**

| Diagnosis | Patients responding (%) |
|---|---|
| Bipolar disorder ($n$ = 31) | 97 |
| Unipolar depression ($n$ = 30) | 93 |
| Other psychoses ($n$ = 24) | 92 |
| Medical/neurological condition ($n$ = 11) | 82 |
| Schizophrenia ($n$ = 22) | 59 |

if benzodiazepines are discontinued before this. In our experience, a subset of patients may develop catatonia whenever attempts are made to discontinue lorazepam, and these patients may require long-term maintenance treatment[56]. This phenomenon has also been reported by others[57].

It should be noted that patients with long-standing catatonia may not respond as robustly or as rapidly to benzodiazepine treatment as those with acute catatonia[54,58]. We have reported the cases of two brothers, one of whom had been catatonic for 2 wk prior to treatment, while the other had been hospitalized with catatonia for 5 years[59]. The first brother recovered completely in 2 wk on a lorazepam dose of 3 mg/d. The second brother, on the other hand, showed only gradual improvement on lorazepam 4 mg/d before being discharged from hospital a year after treatment initiation.

An underlying diagnosis of schizophrenia may be associated with a less robust response to benzodiazepine treatment[53]. We have observed a response rate of only 59.1% in patients with schizophrenia, compared with a response rate of over 90% in patients with other psychiatric diagnoses (Table 2). The poorer treatment response in patients with schizophrenia may be related to the chronicity of symptomatology, or it may suggest a distinct underlying pathophysiology, perhaps reflecting the prominence of psychosis affecting their motor behaviour. Nevertheless, benzodiazepines can be effective for treating catatonia in many patients with schizophrenia, and a therapeutic trial is warranted. This is especially the case given the overall safety of benzodiazepine medication.

ECT is another highly effective option for the treatment of catatonia[9,60], and even patients who do not respond to benzodiazepines are likely to respond to ECT[61,62]. Despite its effectiveness, ECT has an important drawback: It requires clear consent. Catatonic patients are unable to discuss ECT or consent to its administration, and consent from a substitute decision maker is often difficult to obtain. Because of these problems, and because benzodiazepines are easily administered and have a high margin of safety, we recommend that benzodiazepines be used as the first line of treatment. ECT should be considered in patients who fail to respond to benzodiazepines after several days and surrogate consent should be sought. The exception to this strategy is the patient with malignant catatonia, for whom ECT should be administered early, since the condition has a high rate of mortality if it is not rapidly and effectively treated[6,49].

Of the catatonic patients we have assessed, 77.7% later reported having experienced psychotic symptoms during the catatonic episode. This raises a difficult problem in treatment, since antipsychotic medications may be associated with an increased risk of neuroleptic malignant syndrome in patients with catatonia. White *et al*[12] identified 17 consecutive patients with neuroleptic malignant syndrome, all of whom exhibited catatonic signs prior to antipsychotic exposure. In our own patients, we have observed that 3.6% of catatonic patients treated with antipsychotic medications developed neuroleptic malignant syndrome[63]. This is in contrast to an incidence of 0.07%-1.8% in all patients treated with antipsychotic drugs[64,65]. Raja *et al*[11] identified 3 cases of neuroleptic malignant syndrome in a series of consecutive patients presenting to the psychiatric emergency service, all 3 of whom demonstrated catatonic signs and low serum iron prior to the onset of neuroleptic malignant syndrome. The relationship between catatonia and neuroleptic malignant syndrome is not limited to patients treated with typical antipsychotics, as clozapine has also been reported to be a precipitating factor[13]. Although more research is required in order to identify which patients are most susceptible to neuroleptic malignant syndrome, we feel that the existing evidence is sufficient to recommend the avoidance of antipsychotic drugs in acutely catatonic patients. In our experience, once catatonic symptoms have been treated by benzodiazepines or ECT and patients are eating, drinking, and walking, antipsychotic treatment can be initiated safely.

Although lorazepam and ECT have long been recognized as effective treatments for patients with catatonia, other options have been suggested. Several case reports have described patients effectively treated with zolpidem[66,67], which, like typical benzodiazepines, may treat catatonia through interactions with GABA-A receptors[68]. As well, amantadine and memantine, which act as NMDA antagonists but also interact with a number of other neurotransmitter systems, have shown efficacy in a small number of patients[69,70]. It is not yet clear whether these options are likely to be helpful in the small fraction of patients who do not respond to either lorazepam or ECT.

## PATHOPHYSIOLOGY

While the pathophysiology of catatonia is still unclear, several theories have been proposed based on the available data. One possible interpretation of catatonia is that the syndrome is an outward manifestation of intense anxiety[22,71]. The majority of catatonic patients we have treated reported feeling extremely anxious before and during their catatonic episode, to the extent that some believed they were about to die, had already died, or that they needed to remain immobile

in order to avoid threats from others. Benzodiazepines reduce anxiety by enhancing chloride conductance through GABA-A receptor ion channels, and may treat catatonia through this mechanism. However, a number of our patients - particularly those with schizophrenia - reported little anxiety during their catatonic episode. This observation does not exclude the possibility that anxiety is an important component of catatonia, but suggests that it is not an essential component for all patients with the syndrome.

A second interpretation of catatonia is that it is essentially a movement disorder similar to parkinsonism. As noted previously, the clinical features of catatonia overlap with those of parkinsonism, which is understood to be caused by dysfunction of the basal ganglia. Since most projection neurons in the basal ganglia are GABAergic, it is plausible that benzodiazepines could treat catatonia by influencing GABA signaling in the basal ganglia. Functional imaging studies have shown that catatonia is associated with altered activity in orbitofrontal, prefrontal, parietal, and motor cortical regions[72], suggesting that these cortical structures may also play a role in the pathophysiology of catatonia. This interpretation is reinforced by observations that GABA-A binding is reduced in cortical regions of catatonic patients, motor and affective symptoms are correlated with these abnormalities in GABA-A binding, and cortical abnormalities in catatonic patients are normalized following exposure to lorazepam[72].

Whatever the pathophysiology of catatonia may be, it is clear that a wide variety of underlying disorders can be associated with the emergence of catatonic signs. These include mood disorders, nonaffective psychotic disorders, a number of medical and neurological conditions, and genetic disorders[73]. How - or if - these diverse etiologies converge upon a final common pathway causing catatonia is unknown, and it is possible that variations in the clinical presentation of catatonia represent distinct underlying mechanisms that would respond preferentially to different treatments. For instance, future research may allow physicians to identify patients who are unlikely to respond to lorazepam treatment and should receive ECT or another pharmacological treatment as a first line option.

## CONCLUSION

The syndrome of catatonia encompasses a wide range of psychomotor abnormalities, none of which are present in all patients. Immobility and mutism are especially common, and the presence of these signs should prompt physicians to actively assess other markers of catatonia. The differential diagnosis of catatonia is complex, and catatonia itself can arise from a diverse array of psychiatric and medical etiologies, complicating the investigation of these patients. Affective disorders are the most common underlying psychiatric diagnoses. Fortunately, most catatonic patients rapidly respond to low-dose lorazepam. Some patients, particularly those with long-standing catatonia or schizophrenia, may respond more gradually or not at all to lorazepam, and may require ECT or other pharmacological treatments. We feel that the use of antipsychotics should generally be avoided until the acute catatonic episode has resolved in order to avoid precipitating neuroleptic malignant syndrome. The pathophysiology of catatonia is still poorly understood, and it is unclear whether different constellations of clinical signs might represent distinct underlying mechanisms. Recognizing and treating catatonia usually results in rapid resolution of the syndrome, whereas failing to recognize it may lead to potentially fatal complications including infection, neuroleptic malignant syndrome, and pulmonary embolism. Because of this, physicians should maintain a high level of suspicion for the catatonic syndrome, especially in patients experiencing an acute psychiatric illness.

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