REVIEW



Adult catatonia: etiopathogenesis, diagnosis and treatment

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Practice points

- Catatonia is common in psychiatric inpatients.
- A catatonic patient is more likely to be suffering from a bipolar disorder than any other disorder.
- Prompt recognition and treatment with benzodiazepines or electroconvulsive therapy decreases the lethality of the catatonic syndrome.
- Specific catatonic signs should be elicited during a neuropsychiatric clinical examination.
- The use of a screening instrument improves the detection of catatonia.
- The lorazepam test validates the diagnosis of catatonia.
- Lorazepam 2–16 mg/day is the first treatment of choice.
- Should lorazepam fail, electroconvulsive therapy should be started without delay.

SUMMARY Catatonia is common, and has an incidence in psychiatric inpatients from the USA, UK and other western countries of 10%. Half of the patients with catatonia suffer from bipolar disorder and approximately 10% have a diagnosis of schizophrenia. With multiple possible etiologies, a unifying pathogenesis of catatonia that explains all motor and autonomic symptoms remains elusive. Early recognition is of utmost importance in order to provide optimal treatment and to decrease morbidity and mortality. Benzodiazepines are the first treatment of choice and yield high response rates, especially in the context of mood disorders. Should a treatment with benzodiazepines fail, electroconvulsive therapy should be started without delay.

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The evolution of a diagnosis

Catatonia is common in psychiatric inpatients. Prospective studies report an incidence of the catatonia syndrome among hospitalized psychiatric patients of approximately 10% [1]. Kahlbaum, in 1874, described it as a set of motor symptoms that were not tied to a specific disease, but was seen both in psychotic and in mood disturbed patients [2]; however, years later, Kraepelin classified it as a form of dementia praecox [1,3]. In the first four editions of DSM, catatonia is classified as a subtype of schizophrenia. This historical decision partly explains the neglect of the catatonic syndrome and its dramatic underdiagnosis [4]. It has become clear, however, that most patients with catatonic symptoms probably have medical and neurological disorders [5]. These insights have led to the addition of 'catatonia secondary to a general medical condition' in DSM-IV. Catatonic symptoms are observable in most patients diagnosed with anti-NMDAR encephalitis [6,7], after surgical procedures [5,8], during drug intoxication and withdrawal, and in patients with epilepsy and abnormal metabolic states [9]. Patients developing catatonia from a psychiatric disorder will probably suffer from a mood disorder, but practically any kind of psychiatric disorder can be associated with catatonia, including schizophrenia, obsessive-compulsive disorder, post-traumatic stress disorder and autism [10-12]. Since catatonia is easily recognizable and distinguishable from other conditions, pleas to the DSM-5 Work Groups for its classification as an independent, distinct syndrome have been published [1]. Catatonia has a characteristic course, as already described by Kahlbaum [2], and an effective treatment response [13,14]. In DSM-5, the divorce between catatonia and schizophrenia is finalized with the deletion of catatonia as a schizophrenia subtype. Catatonia can now be classified either as a coded specifier 'with catatonia' for all psychotic disorders and mood disorders, or as 'unspecified catatonia'. The latter diagnosis means that catatonia can be classified as an independent syndrome, which will hopefully "foster recognition of the catatonia syndrome and permit research on nosology, treatment and outcome" [1].

Catatonia in mood disorders

Half of the patients with catatonia suffer from bipolar disorder [9,15]. It is not uncommon that a catatonic attack is a first episode of a bipolar disorder [16]. This preferential link between

catatonia and mood disorders was already observed by Kahlbaum, who wrote that in most cases catatonia manifests itself in the first stages with an easily recognizable clinical picture of melancholia, often preceded by mania [2]. According to Fink and Taylor, recovery occurred most often in Kraepelin's catatonic patients in whom the episode started with a depressive phase [9]. A similar favorable outcome of a "benign stupor", a "new manic-depressive reaction type", was observed by August Hoch in 1921 [17]. Bleuler wrote that catatonic symptoms were, as a rule, intertwined with manic and melancholic conditions, and that they often dominate the clinical picture, in which case he spoke of a manic or melancholic catatonia [18]. Kirby observed that a catatonic phase "may replace the depression in what appears to be a circular attack" [16]. In more recent studies [19], it was shown that in patients presenting with catatonic symptoms, schizophrenia is overdiagnosed. A quarter of the patients diagnosed with the catatonic subtype of schizophrenia fulfill research criteria for an affective disorder. This overdiagnosis probably results from a failure to recognize mania and from a belief that catatonic symptoms occur only in schizophrenia [20]. In an early prospective trial of 55 consecutive admissions exhibiting one or more catatonic signs, only four (7%) had a diagnosis of schizophrenia, five (9%) had depression, whereas 34 (62%) fulfilled research criteria of mania [21]. Approximately a third of patients presenting with manic or mixed episodes will exhibit a range of catatonic symptoms, as assessed with the Bräunig Catatonia Rating Scale [22]. Whether or not a subset of catatonic symptoms is more frequently observed in mood disorders than in other conditions remains debatable [23]; although it has been suggested that catatonia in manic patients is typically associated with excitement [24], whereas depressed catatonic patients present with profound motor retardation and catatonic inhibition, automatic obedience, and, less frequently, waxy flexibility [9]. The prognosis of catatonia is good, regardless of the underlying cause and the number or pattern of catatonic features, but it is even better in mood disorders [9]. Conversely, the presence of catatonic symptoms may indicate a more severe course of the bipolar disorder as catatonia is associated with longer hospital stays, more comorbidities and more suicide attempts in manic patients [22].

Catatonia in schizophrenia

Approximately 10-20% of patients with catatonia meet the criteria for schizophrenia [9,15]. In a Croatian sample of 402 schizophrenic patients, 15% had a diagnosis of schizophrenia, catatonic type [25]. In a random sample of 225 Chinese patients with chronic schizophrenia, a third met stringent criteria for catatonia [26], and 80% of patients exhibited at least one catatonic symptom [27]. Some authors suggest that abnormal movements, mannerisms, stereotypes, catalepsy, negativism, automatic obedience and waxy flexibility are, more than other catatonic signs and symptoms, associated with schizophrenia [24], but conflicting results show that there is no clear and distinct catatonic picture accompanying schizophrenia [26,28]. Catatonic features indicate a generally poor prognosis in the chronic phase of schizophrenia [26]. Catatonic subjects have a significantly earlier age of onset [25,26], more negative symptoms [26], exhibit more aggressive behavior and are more often hospitalized [25]. Moreover, the catatonic type of schizophrenia seems to be more genetically determined than other subtypes [25,26]. Huang and colleagues have postulated the existence of an acute and chronic type of catatonia [29]. The acute form is linked to mood disorders, and has a mean duration of less than 2 weeks; whereas the chronic form lasts longer than 3 weeks and suggests an underlying schizophrenic condition.

Malignant catatonia

The most severe form of catatonia is malignant catatonia [30]. Although already observed in the first half of the 19th century [31,32], the first widely known description of the syndrome originates from Stauder in 1934, who deemed it to be always fatal, calling it 'lethal catatonia' [33]. Although malignant catatonia is a serious medical condition, mortality is reduced with adequate treatment. Malignant catatonia is a heterogeneous syndrome. Psychomotor excitement, fever, altered consciousness, muscle rigidity and disturbance of autonomic regulation are the most characteristic symptoms. The excited phase usually results in exhaustion, stupor, cardiovascular collapse and death. In some cases psychomotor excitement alternates with stuporous episodes. This was the typical course of malignant catatonia described in reports from the preantipsychotic era [34]. Less frequently, in approximately 10% of reported cases, the course is primarily stuporous, without a preceding phase

of motor excitement. This form is very close to what is observed in neuroleptic malignant syndrome, which is considered by several experts to be a drug-induced form of catatonia [35]. The widespread use of antipsychotics from the 1950s seemed to have decreased the frequency of malignant catatonia in general, but gave birth to a new subtype, an antipsychotic drug-induced stuporous form of malignant catatonia [36]. An extensive review of all published cases revealed that malignant catatonia can appear in association with diverse psychiatric, neurological and medical conditions, such as paraneoplastic conditions and autoimmune diseases [37]. The syndrome is, however, most frequently associated with schizophrenia and bipolar disorder. The mortality rate of malignant catatonia, which was above 75% in the preantipsychotic era [38], has decreased to 14% in the last 25 years. The most important step in decreasing the lethality of the syndrome is its prompt recognition and early effective treatment of the severe autonomic imbalance, as well as the frequent medical complications.

Etiopathogenesis of catatonia

The occurrence of catatonia in such a wide variety of conditions and its unique response to benzodiazepines and electroconvulsive therapy (ECT) supports the theory that catatonia may have unique biological correlates separate from other syndromes and disorders [39,40]. With multiple possible etiologies, a unifying pathogenesis of catatonia that explains all motor and autonomic symptoms remains elusive; although there are several models of catatonia [39,41] that should be used and expanded in future research to assess possible biomarkers of catatonia and predictors of treatment response and outcome.

Motor circuitry model

Dysfunction of the motor system involving frontal lobe basal ganglia circuitry or interference with this system (through thalamic, parietal lobe, cerebellar or limbic abnormalities) has been described as a possible mechanism of catatonia [9,42].

Epilepsy model

The symptom overlap between psychomotor seizures and catatonia and the high prevalence of seizures in patients with catatonia lend strong face validity to the model in which seizure-like activities manifest clinically as catatonia. The



frontal lobes and anterior limbic systems are likely sites of abnormal electrical discharges in this model that also provide a rationale for the efficacy of anticonvulsants, benzodiazepines and ECT through their common mechanism of increased seizure threshold.

Neurotransmitter model

The often dramatic response to treatment with benzodiazepines, positive modulators of the benzodiazepine/GABA_A receptor complex, is a crucial observation supporting the role of GABA dysfunction in catatonia [43,44]. Tolerance of high doses of benzodiazepines in catatonic patients without ensuing sedation is another clue pointing to alterations in GABA_A receptor function. Several authors have discussed the role of neurotransmitters and synaptic transmission in catatonia usually involving GABA [45,46], glutamate (the biological antagonist of GABA) [47,48] and dopamine (hypoactivity) [49,50].

Genetic model

Studies show an increased familial transmission in first-degree relatives for periodic catatonia [51,52], a type of psychomotor psychosis in the classification system of endogenous psychoses of Leonard [53,54]. These findings await replication.

Endocrine model

Several lines of evidence suggest the importance of neuroendocrine abnormalities in catatonia. The early studies of periodic catatonia by Gjessing suggested thyroid abnormalities [55] and hypothalamic dysfunction [56]. Case reports associate catatonia and endocrinopathies such as hypoparathyroidism, thyrotoxicosis and pheochromocytoma [57,58].

Immune model

Catatonia has been reported in patients with infections of the CNS, as in herpes [59], HIV [60], cerebral malaria [61] and typhoid fever [62]. In these examples, catatonia is probably caused by neuroinvasion of the infectious agent or parasite. Aseptic or autoimmune encephalitides such as antiphospholipid syndrome [63], lupus cerebritis [64], pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections [65] and anti-NMDAR encephalitis have also been associated with catatonia [66–68], supporting involvement of autoimmunity and cerebral antibodies in the mechanism of catatonia.

Fear model

The finding that severe trauma and anxiety may precipitate catatonia [69,70] raises questions about mechanisms by which trauma leads to catatonia or other disorders. The biological pathways of trauma leading to psychiatric and medical disorders are thought to encompass endocrine, immune, electrophysiological and neuropsychological factors, as well structural changes in the brain [71–73].

Autonomic nervous system model

Although catatonia is considered to be primarily a motor syndrome, 40% of catatonic patients show autonomic symptoms including abnormalities of temperature, blood pressure, pulse rate, respiratory rate and perspiration [74]. Autonomic dysfunction is the hallmark of malignant catatonia [75], its drug-induced variant neuroleptic malignant syndrome [76] and aseptic encephalitis with catatonic symptoms, including the recently coined anti-NMDAR encephalitis [40,66]. Early studies support that there is autonomic dysfunction in catatonia [77]. Autonomic dysfunction in catatonia implies involvement of the autonomous nervous system that consists of the parasympathetic subsystem, mediated by the vagus nerve, and the sympathetic subsystem, medicated by sympathetio-adrenal circuits in the spinal cord [78].

Diagnosis of catatonia

Early diagnosis is of utmost importance in order to provide optimal treatment. Delaying diagnosis, and thus treatment, puts the patient at considerable risk for major adverse events, including mortality [5,79]. There is no consensus on what constitutes a diagnosis of catatonia, nor is there an agreed threshold for the number or the duration of symptoms that should be present to justify a diagnosis of catatonia [80,81]. Several authors have suggested various diagnostic criteria. Barnes and coworkers define catatonia as the presence of the combination of at least one motor symptom and at least one symptom of psychosocial withdrawal, excitement and/or bizarre repetitive movements [82]. Rosebush and coworkers [83], and Peralta and Cuesta [84] require the presence of at least four out of 12, or three out of 11 criteria, respectively. Fink and Taylor suggest that in the presence of immobility, mutism or stupor lasting for at least 1 h, patients have to exhibit only one secondary criterium (catalepsy, automatic obedience and posturing) observed

or elicited on two or more occasions [9]. In the absence of immobility, mutism or stupor, a diagnosis can be confirmed when at least two other symptoms are present. In DSM-5, the presence of any combination of at least three symptoms out of a set of 12 (Table 1) defines the diagnosis of catatonia.

In rating scales, a total of 42 different symptoms are examined. What the scientific basis is for the selection of 12 in DSM is not entirely clear. The DSM-criteria narrow the definition of catatonia, placing an unreasonable emphasis on symptoms such as echophenomena (two of 12 symptoms), stupor and mutism (if stupor is present, it is highly likely that mutism will also be present), and postural immobility (three symptoms), while omitting important and frequent symptoms such as automatic obedience and ambitendency (Table 2).

Given the fact that the 12 DSM-5 symptoms are all included in, and comprise ten of the 14-items of, the screening instrument of the Bush–Francis Catatonia Rating Scale (BFCRS) [85] (posturing and catalepsy are separate symptoms in DSM-5, while seen as one in BFCRS, as are echolalia and echopraxia; and the BFCRS items staring, rigidity, verbigeration and withdrawal are not in DSM-5 criteria), DSM-5 criteria are probably a useful screening tool and can indeed help to detect catatonia. One might argue that it is advantageous that the catatonic symptoms in DSM-5, apart from waxy flexibility and catalepsy, are all obvious on observation and do not necessitate a clinical examination. Nevertheless, observation and psychiatric interview will not suffice to detect the catatonic syndrome, since the most striking symptoms, such as posturing, are present only in a minority of the cases. It is of importance to elicit specific catatonic signs during a neuropsychiatric examination. A rating scale or checklist can guide the clinician and improve detection. A number of catatonia rating scales have been published, and have recently been extensively reviewed [80]. The systematic use of these rating scales has been found to improve rates of identification of the catatonic syndrome [4,85]. Of 139 patients screened, clinicians diagnosed catatonia in 2%, whereas a systematic screening using the Bush-Francis Catatonia Screening Instrument diagnosed catatonia in 18% [85]. It is important to note that the choice of including certain symptoms in the definition of catatonia, and excluding others, can emphasize overlaps of symptoms between catatonia and other disorders, such as Tourette's syndrome. The presence of isolated catatonic symptoms, such as echophenomena in Tourette's disorder, does not imply the presence of a catatonic syndrome but should alert the clinician to the presence of other catatonic symptoms that should be verified through a focused exam, use of a comprehensive rating scale and implementation of a lorazepam test.

| Table 1. Definition of DSM-5 symptoms of catatonia. | |
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| DSM-5 symptom | Symptom definition |
| Catalepsy | Maintains posture(s), including mundane (e.g., sitting or standing for hours without reacting) |
| Waxy flexibility | During reposturing, patient offers initial resistance before allowing him-/her-self to be repositioned (similar to that of bending a warm candle) |
| Stupor | Extreme hypoactivity and immobility. Minimally responsive to stimuli |
| Agitation, not influenced by external stimuli | Extreme hyperactivity, constant motor unrest that is apparently nonpurposeful |
| Mutism | Verbally unresponsive or minimally responsive |
| Negativism | Apparently motiveless resistance to instructions or to attempts to move/examine the patient. Contrary behavior, does the opposite of the instruction |
| Posturing | Maintains posture(s), including mundane (e.g., sitting or standing for hours without reacting) |
| Mannerisms | Odd, purposeful movements (hopping or walking tiptoe, saluting passers-by and exaggerated caricatures of mundane movements) |
| Stereotypies | Repetitive, nongoal-directed motor activity (e.g., finger-play, repeatedly touching, patting or rubbing self) |
| Grimacing | Maintenance of odd facial expressions |
| Echolalia | Mimicking of examiner's speech |
| Echopraxia | Mimicking of examiner's movements |
| Symptom definitions have been taken from [10] |]. |

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| Table 2. Definitions of catatonic symptoms that are not included in DSM-5. | |
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| Symptom | Definition |
| Ambitendency | The patient appears stuck in indecisive, hesitant motor movements |
| Automatic or passive obedience (mitgehen) | Exaggerated cooperation with examiner's request, or repeated movements that are requested once Raising arm in response to light pressure of finger, despite instructions to the contrary |
| Autonomic abnormality | Abnormality of temperature (fever), blood pressure, pulse rate, respiratory rate and inappropriate sweating |
| Combativeness | Usually in an undirected manner, without explanation |
| Gegenhalten/counterpull | Resistance to passive movement that is proportional to strength of the stimulus; response seems automatic rather than willful |
| Grasp reflex | Strike open palm of patient with two extended fingers of examiner's hand. Automatic closure of patient's hand |
| Impulsivity | Patient suddenly engages in inappropriate behavior (e.g., runs down the hallway, starts screaming or takes clothes off) without provocation. Afterwards, behavior cannot be explained |
| Perseveration | Repeatedly returns to the same topic or persists with same movements |
| Rigidity | Maintenance of a rigid position despite efforts to be moved |
| Staring | Fixed gaze, little or no visual scanning of environment and decreased blinking |
| Symptom definitions have been taken from | m [10]. |

Possible laboratory tests, primarily to assess various underlying conditions, include a complete blood count and metabolic panel, erythrocyte sedimentation rate, MRI, electroencephalogram, cerebrospinal fluid analysis, antinuclear antibodies, and urine and organic metabolic testing [11,86]. A drug screen to detect common illicit and prescribed substances is necessary. The fact that there is no biologic marker diagnostic of catatonia complicates an adequate differential diagnosis. A benzodiazepine challenge of 1 or 2 mg of lorazepam administered per os (PO), intramuscularly or intravenously, can verify the diagnosis of catatonia [5,9,11]. If no change is observed, a second dose is administered after 5 min intravenously, 15 min intramuscularly or 30 min PO. When a single dose of lorazepam improves catatonia, lorazepam can be prescribed at regular intervals to maintain the improvement [11]. The use of the GABA receptor modulator zolpidem has also been developed as an alternative catatonia challenge test (5 or 10 mg PO) [87].

Treatment of catatonia

As discussed, the most important argument in favor of classifying catatonia as a distinct syndrome is its specific response to benzodiazepines and ECT.

Benzodiazepines

The efficacy of sedative drugs – that is, barbiturates – in catatonia was discovered more than 80 years ago [88]. In the 1980s, benzodiazepines replaced the use of barbiturates. In catatonia, prospective studies found 70–90% response rates, irrespective of the excited or stuporous character of the state [43]. Some studies reported rapid and dramatic improvement of the catatonic symptoms, even after a single benzodiazepine dose [83,89]. As a result, lorazepam 2-4 mg was recommended as the first treatment of choice in catatonia. In case of nonresponse, after 1-2 days, the dose should be increased to 8-16 mg/day. It is suggested that response to benzodiazepines is particularly high in mood disorders. Studies in schizophrenia, catatonic type, have yielded low – below 50% – response rates to low doses of lorazepam [90], and benzodiazepines were found ineffective in the long-term treatment of chronic catatonic schizophrenia [91]. In the absence of a sustained response, ECT is to be proposed without delay [9,92].

Antipsychotics

Given the fact that catatonia often results in a diagnosis of schziophrenia, antipsychotics are used frequently, in spite of the fact that these drugs can induce or worsen catatonic symptoms. This unfavorable effect is especially characteristic for first-generation antipsychotics [93]. The role of the second-generation antipsychotics in the treatment of catatonia is more heterogeneous, and several authors have reported a good response. Clozapine, olanzapine and risperidone were reported to be effective in the treatment of catatonia associated with schizophrenia [92]. Only one randomized controlled trial is available to date. In this study, 14 stuporous psychotic patients were randomized to either ECT or risperidone (4-6 mg/day). The ECT-treated patients showed significantly

greater improvements than those receiving risperidone [94].

Electroconvulsive therapy

While controlled studies are lacking, clinical evidence suggests that ECT is more effective than benzodiazepines in the treatment of catatonia, irrespective of the underlying condition. Several authors reported successful treatment with ECT after failure of benzodiazepine treatment [95,96], and in a case series, the ECT-benzodiazepine combination appeared to be superior to monotherapy [97]. Studies aimed at identifying response predictors suggest that catatonia associated with schizophrenia is less responsive to both drugs and ECT [98,99], while patients with mood disorders showed more favorable response [100]. Dodwell and Goldberg found perplexity - which can be seen as a proxy measure for catatonic semi-stupor - to be a predictor of good response to ECT in patients with schizophrenia [101].

Conclusion & future perspective

Catatonia should be considered in any patient when there is a marked deterioration in psychomotor function and overall responsiveness. Patients with severe mood disorders should

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be examined routinely for catatonic signs and symptoms because it is easily recognisable and treatable, and has a good prognosis. Changes in the current diagnostic systems, that is the dissociation of catatonia and schizophrenia, and the creation of an unspecified catatonia category, might increase diagnostic accuracy and can promote further research. An area of future research concerns the biology of catatonia, which is currently in its infancy, and its relation or overlap with the biology of isolated catatonic symptoms such as echophenomena, stereotypy or psychomotor retardation, which also occur in other syndromes and disorders, and sometimes define them (e.g., stereotypic movement disorder or Tourette's syndrome).

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