

Catatonia: A Review

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Background. To write an up-to-date review paper on catatonia using published literature.

Methods. This review involved a search using the terms “catatonia,” “stupor,” “catatonic schizophrenia” and “catalepsy” in the Cochrane Database of Systematic Reviews, the Medline database and EMBASE and PsychINFO. Additional use was made of these databases in searching for randomized controlled trials, meta-analyses, cohort studies, case-control studies, case series, case reports and reviews.

Results. Available evidence indicates that catatonia is a common neuropsychiatric syndrome characterized by the presence of various motor signs and symptoms. The underlying pathophysiologic-mechanisms points to a heterogeneous group of etiologies. Current classifications are based on the type of presentation and the duration of symptoms; agitated versus retarded and acute versus chronic. Available data supports the efficacy of benzodiazepines and electroconvulsive therapy (ECT) in the treatment of this condition, but the treatment response is limited by the chronicity of symptoms.

Conclusions. Catatonia is a common disorder that occurs in a wide variety of psychiatric, neurological and medical conditions. At the current time, there is sufficient evidence to consider it as a specific nosologic syndrome with different subtypes and treatment responses.

Keywords Catatonia, Stupor, Catatonic schizophrenia, Malignant catatonia, Neuroleptic malignant syndrome

INTRODUCTION

The concept of catatonia was first introduced by Karl Kahlbaum in 1874. He described it as an “insanity of tension” and thought that it was a specific clinical disorder with characteristic signs, symptoms and had a predictable course. Some years later Kraepelin subsumed catatonia into his category of dementia praecox (1). Bleuler following Krapelin’s conceptual model, interpreted catatonic symptoms mainly as psychogenic reactions that represented secondary symptoms of what he called “schizophrenia (2).” Catatonia was then considered a subtype of schizophrenia and its incidence and prevalence seemed to decrease with the advent of antipsychotic medications and more treatment options. Around the 1960s it became clear that catatonia was still prevalent and frequently encountered in mood disorders, neurological and other medical conditions (2).

With the aim of defining a clear clinical syndrome, the Wernicke-Kleist-Leonhard school claimed to define valid nosological entities with specific etiology, prognosis and treat-

ment within the catatonic syndrome to their classification of psychoses (3). Their main focus was on delineating the psychomotor disturbance of catatonia, and they proposed that it is necessary to distinguish a quantitative increase in psychomotor activity from qualitative psychomotor disturbances. They created three separate forms of psychoses: motility psychosis, periodic catatonia and systematic catatonias. Motility psychosis presents with quantitative psychomotor disturbances and is distinguished from catatonic psychoses, which are characterized by qualitative psychomotor disturbances. Periodic catatonia has an acute onset and shows both akinetic and hyperkinetic phases. Finally, systematic catatonia tends to begin insidiously and have a chronic and progressive course without remission (2). Although this classification has received increasing interest in recent years, it is yet to be widely accepted in the psychiatric community.

There has been a long debate in the field of mental health in trying to establish the validity of separate psychiatric entities (4). DSM-IV has been criticized for creating arbitrary boundaries between diagnoses and for basing diagnostic criteria solely on symptom clusters and not in relation to a clear etiology (4,5). Although new research has given us more insight into the pathophysiology of psychiatric disorders, we are still unable to clearly define a disorder by a specific etiology and

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pathophysiology (4). On the other hand, basic science and clinical research suggest that there is sharing of signs, symptoms, natural history and outcomes by various neurobiological syndromes (4). Kendell and Jablensky in their seminal paper indicated that, based on the current concept, only a few diagnostic categories in psychiatry are almost universally accepted as valid (4). They suggested that a diagnostic category should be described as valid only if one of two conditions has been met. If the defining characteristic of the category is a syndrome, this syndrome must be demonstrated to be an entity, separated from neighboring syndromes and normality by a zone of rarity. Alternatively, if the category's defining characteristics are more fundamental—that is, if the category is defined by a physiological, anatomical, histological, chromosomal, or molecular abnormality—clear, qualitative differences must exist between these defining characteristics and those of other conditions with a similar syndrome (4). To further clarify the validity of psychiatric diagnosis, Fujii and Ahmed proposed specific criteria to define a neurobiological syndrome (5). Their definition describes a neurobiological syndrome as a constellation of symptoms that is reliably associated with neuropathology in a circumscribed structural location or neural circuit. They describe these syndromes as having similar neurobiological disturbances (location or neural circuit). When the neurobiological disturbances are smaller, they are associated with milder symptoms. Additional symptoms such as cognitive, psychiatric or neurological symptoms that are related to other networks should simultaneously be affected by the underlying neurochemical or neuropathologic processes. The treatment for these neurobiological disorders should also be similar.

The DSM-IV-TR still considers catatonia to be a subtype of schizophrenia, although it also includes a diagnostic code for catatonia due to a medical condition, and allows the term to be used as a descriptive term for the characterization of manic and major depressive syndromes (6). However, many others still feel that catatonia should be recognized as a separate diagnostic entity because of its predictive value for treatment decisions and prognosis. Catatonia has recently been described as a syndrome that occurs in almost any kind of psychiatric disorder, including schizophrenic psychoses, (2,7) but it is not only limited to psychiatric illness. Many authors now agree that catatonia is a neuropsychiatric syndrome that can occur in schizophrenia, mood disorders, mental retardation, neurological diseases, metabolic conditions and drug intoxications (8). Taylor and Fink suggest that since catatonia can be easily identified, has a characteristic course and responds to specific treatments, it should be considered as an individual category in psychiatric diagnostic systems (1). Our aim is to write an up-to-date review on catatonia based on the available literature. Using this literature, we indicate that catatonia can be defined as a valid neurobiological syndrome as suggested by Taylor and Fink and in keeping with the criteria proposed by Fujii and Ahmed (1,5).

METHODS

The first step in data collection involved a search for evidence-based clinical practice guidelines in the Cochrane Database of Systematic Reviews (up to the 2nd quarter of 2007). Next, articles were located in the Medline database (between 1966 and July 2007), EMBASE (1980 to 2007 Week 24), and PsychINFO (1967 to July Week 4 2007) using the search terms “catatonia,” “stupor,” “catatonic schizophrenia” and “cataplexy.” Additional use was made of these databases in searching for single randomized controlled trials, meta-analyses, cohort studies, case-control studies, case series, case reports and reviews. Cross-referencing of articles from the bibliographic database constructed via the initial search was also done. All English language articles for which at least an abstract was available and described some aspect of catatonia including historical perspective, epidemiology, risk factors, pathophysiology, neurobiology, differential diagnosis and treatments was reviewed. Information available from these articles was supplemented and cross referenced with data available from an excellent textbook on catatonia (9).

Epidemiology

The incidence and prevalence of catatonic symptoms have varied widely among different studies, and across time. It appears that there has been a decline in the incidence of catatonia since Bleuler initially estimated that 50% of his patients with schizophrenia had at some time shown catatonic symptoms (8,10). Theories that have been proposed to explain this phenomenon include: a decline in interest in the motor aspects of psychiatric disorders, beneficial effects of modern pharmacotherapy with deinstitutionalization and improved active rehabilitative efforts (8,11,12). However, studies from developing countries indicate that this decline is more apparent than real, as many schizophrenia patients still present with catatonic features despite access to modern treatment (13,14).

Although for many years catatonia was solely linked to schizophrenia, there is extensive evidence suggesting that this disorder might present more frequently in other psychiatric disorders. Abrams and Taylor studied 55 patients with catatonic symptoms and found that only 4 met criteria for the diagnosis of schizophrenia, whereas over two thirds met criteria for the diagnosis of a mood disorder (7). Huang et al. studied 34 patients with the diagnosis of catatonia according to DSM-IV criteria and found that 23% had bipolar disorder, 26% had schizophrenia, 9% had a mood disorder, 24% presented with neuroleptic-induced intoxication and 41% had a general medical condition (15). Benegal et al. studied 65 patients with catatonic syndrome according to ICD-9 criteria admitted to an inpatient facility and found that 23% had bipolar disorder, 17% had paranoid schizophrenia, 6% had chronic schizophrenia, and 3% had catatonic schizophrenia. Acute schizophrenia, schizophrenia NOS and

reactive depressive psychosis represented 1.5% each, and in the remaining 46%, no specific underlying etiology could be found (16). In a recent study conducted in a psychiatric intensive care unit, the two most common diagnoses associated with catatonia were: schizophrenia (54%) and mania (17%) (17). Catatonia seems to be particularly linked with mania; and according to some authors, its severity correlates with the severity of the manic episode (1).

Many medical disorders can also present with catatonic symptoms. Endocrine abnormalities, viral and bacterial infections and electrolyte imbalances can all present with catatonia (9). Neurological conditions like epilepsy, strokes of the anterior brain region and traumatic brain injury may also present with catatonia (9). Withdrawal from drugs like benzodiazepines, L-dopa, gabapentin and overdose with street drugs like LSD, PCP, cocaine, Ecstasy, disulfiram (18) levetiracetam can result in catatonia (9,18–21). A retrospective study tried to identify clinical characteristics that could differentiate catatonia caused by psychiatric conditions from the one caused by medical conditions. The only significant finding was that patients with medical catatonia presented with negativism more frequently than patients with psychiatric catatonia (22).

Current data indicate that catatonia is less common in childhood than in adults (22). A review by Dhossche and Bouman found only 29 cases of catatonia in children and adolescents reported in the world literature between the years of 1966–1996 (23). In the psychiatric population, the estimated prevalence rates of catatonia in this age group vary between 0.6% and 17% (24). Among children and adolescents with autism and pervasive developmental disorders, the rates range from 11.6% to 17% (24). Adolescents, males and those of non-European origin were over-represented in cases presenting with catatonia in this age group (24). Tables 1 and 2 indicate the prevalence and common conditions associated with catatonia (1,7–9,13,17–21,25,29).

Risk Factors and Predictors of Severity

The reported risk factors for catatonia include a history of perinatal infections, previous episodes of catatonia, a history of extrapyramidal side effects from medications, epilepsy, recent exposure to medications that lower the seizure threshold, long-term exposure to anticholinergic drugs and recent withdrawal or reduction in their dose, low iron or elevated CPK levels, frontal or basal ganglia diseases, and

Table 2 Conditions Associated with Catatonic

Psychotic disorders ^{1,7–9,13}	Paranoid schizophrenia, Catatonic schizophrenia, Psychosis NOS
Mood disorders ^{9,13,29}	Bipolar disorder- manic or mixed episodes Major depressive disorder
Medical conditions ^{8,9}	Endocrine abnormalities, infections, electrolyte imbalances
Neurological conditions ^{8,9}	Epilepsy, strokes, traumatic brain injury, multiple sclerosis, encephalitis
Drugs ^{8,9,18–21}	Withdrawal: Benzodiazepines, L-dopa, gabapentin Overdose: LSD, PCP, cocaine, Ecstasy, disulfiram, levetiracetam

behavioral syndromes associated with dehydration or hyponatremia (8,29). The risk of catatonia increases in relation with the severity or the time proximity to the risk factor (9). The risk factors for catatonia differ depending on the underlying disease. Catatonic symptoms in patients with depression have been associated with increased age, increased frequency of depressive episodes and more severe impairment of cognitive function and activities of daily living (30). Ungvari et al. studied 225 patients with chronic schizophrenia and found that catatonic patients significantly differed from the non-catatonic counterparts only with regard to age of onset, severity of negative symptoms and use of benzodiazepines. Although there was no significant association between the severity of catatonia and age or duration of illness, age of onset and more severe negative symptoms predicted severity of catatonia in their sample; earlier age of onset was the most consistent factor found in the catatonia group, and it also correlated with the severity of catatonia. They suggested that early age of onset might be a mediating factor contributing to poor prognosis in catatonic schizophrenia (8). Kruger and Brauning reported that catatonic patients with either pure or mixed mania had more severe depressive and manic symptoms and more severe general psychopathology when compared with non-catatonic patients with mania (27). Mimica et al. showed that patients with catatonic schizophrenia had a higher rate of family history of schizophrenia, were younger at their first admission, showed more aggressive behavior in the course of their illness, were more often hospitalized, and had longer hospitalizations (31). In a recent study, manic patients with catatonia had a higher frequency of prior suicide attempts, which could be related to the typical disturbance in impulse control observed in catatonia (26). Nevertheless, it is unclear if this finding is associated with the increased impulsivity often encountered in patients with catatonia, or if it is secondary to depressive symptoms or due to increased aggression. Although catatonia is less frequently described in childhood, it has been associated with autism and pervasive developmental disorders, childhood-onset schizophrenia and previous treatment with ECT (24).

Table 1 Setting and Illnesses

Setting/Illness	Prevalence
Psychiatric inpatient unit 1,25	7–38%
Schizophrenic patients 1,17	3–21%
Mood disorders 1,13,26,27	25–61.5%
Children and adolescents 1,28	0.6–17%

Classification and Clinical Features

There is no universally accepted psychopathological definition for catatonia, and no agreement about whether catatonia is a distinct, independent nosological entity, a syndrome, or just a number of motor symptoms occurring in a random fashion (8). Kahlbaum initially described 17 signs, but through the years, more than 60 different catatonic signs and symptoms have been described. The DSM IV-TR (6) includes the following signs and symptoms in their criteria for catatonic schizophrenia: motoric immobility as evidenced by catalepsy, excessive motor activity, extreme negativism or mutism, posturing, stereotyped movements, mannerisms, grimacing, echolalia and echopraxia. Taylor and Fink suggest in their excellent review that the most common signs are mutism, posturing, negativism, staring, rigidity, and echophenomena (1). In a recent study conducted by Ungvari et al., common catatonic signs and symptoms were stereotypes, posturing, mannerisms, perseveration, withdrawal, grimacing, staring, negativism, ambidexterity, echo-phenomena and immobility (32).

Catatonic symptoms often occur against a background of alternating periods of reduced movement, i.e., hypokinesia and excitatory phases of hyperkinesia (33). It has also been noted that the catatonic signs evolve in a predictable manner during these episodes and that some patients have a characteristic interval with few symptoms between the episodes (34). Francis et al. also reported that catatonic patients tend to have recurrent episodes and that the symptom profile of catatonic motor signs is highly consistent across these episodes (35). There is no agreed threshold for the number of symptoms or duration of symptoms that should be presented to justify a diagnosis of catatonia (36). The availability of several rating scales for catatonia might help to better define the syndrome and its epidemiology. Some of them have shown validity and good inter-rater reliability (25,37). DSM-IV-TR requires two prominent signs to be present in order to meet the criteria. Rosebush and colleague's criteria require 3 out of the possible 12 signs (38). Lohr and Wisenewski's criteria require 3 out of 11 symptoms, with emphasis on the relative importance of specific signs (39). Bush et al. developed a 23-item Bush-Francis Catatonia Rating Scale (BFCRS) and a truncated 14-item catatonia screening instrument. They suggest that catatonia should be defined by the presence of two cardinal features (immobility, mutism, withdrawal) or two cardinal signs plus two or more secondary features (staring, rigidity, posturing, grimacing, waxy flexibility) (25). In terms of symptom duration, most authors accept a range from several to 24 hours duration as being necessary for making a definitive diagnosis of catatonia (1).

Recent years have seen a surge in further identifying different subtypes and syndromes within the concept of catatonia. Taylor and Fink suggest that there are two distinct patterns to be distinguished in catatonia: one consisting of catalepsy, posturing, mutism and negativism, which has been linked to mania and schizophrenia; and a second one consisting of echophenomena, automatic obedience, verbigeration, and other stereo-

types which has been linked to mania (1). Huang et al. proposed that catatonia should be subdivided into "acute" and "chronic" conditions, and that the length of the disorder might give clinicians a clue to the underlying etiology. In their prospective study that included 34 patients admitted to a psychiatric inpatient unit, they found that most cases of catatonia linked with mood disorders and neuroleptic-induced disorders had a mean duration of less than 1.83 weeks, whereas half of the patients with catatonia due to underlying schizophrenia or general medical conditions had a mean duration which was longer than 3 weeks. Based on this evidence, they suggested that 2–3 weeks should be a cut-off for the acute and chronic conditions (15). Ungvari et al. noted that some signs and symptoms were more common in catatonic patients with chronic schizophrenia, including mannerisms, stereotypes, posturing and perseveration, and suggested that acute and chronic catatonic syndromes associated with schizophrenia may be different in clinical presentation and underlying brain dysfunction (8,32). The fact that patients with chronic forms of catatonia have a poorer response to benzodiazepines than patients who present with a more acute clinical picture might be further evidence to support the distinction between acute and chronic catatonia. On the other hand, Bush et al. reported a similar distribution of catatonic signs in chronic and acute catatonia, with mutism, immobility and posturing identified as the most common signs (25). However, Bush and colleagues reported that staring was found less often in chronic patients, whereas autonomic signs were frequently seen in acute catatonic episodes but were absent in chronic cases (40).

Morrison classified catatonia into two different categories: retarded and excited (41). The retarded form usually includes mutism, negativism, staring, rigidity and catalepsy. Excited catatonia presents with the typical features of catatonia, with the addition of excitement, impulsiveness and combativeness (42). It cannot be distinguished from delirious mania as it presents with an acute onset of symptoms consistent with mania, such as excitement, grandiosity, lability, delusions and insomnia, in addition to an altered, delirious mental state. Patients also present with characteristic signs and symptoms of catatonia, such as negativism, stereotypy, grimacing, echolalia and echopraxia (43). Chalasani et al. studied patients with catatonic symptoms admitted to inpatient facilities in India and Wales, and reported that the incidence of retarded catatonia was twice as common in India versus Wales, but they did not report any specific differences in terms of underlying etiology or demographic factors between the two clinical forms (42). Further research might help to provide more evidence to support the existence of different catatonic subtypes and to help clinicians diagnose and treat different varieties of catatonia.

There is recent evidence to suggest that there might be a phenomenological overlap between obsessive compulsive disorder (OCD) and catatonia, especially regarding complex repetitive compulsive acts and manneristic stereotypes of catatonia (8,44). Kruger et al. found that 83% of patients with schizophrenia and

OCD also met the narrow criteria for catatonia, while only 8% of non-OCD schizophrenia subjects qualified for the diagnosis of catatonia (44). However, this association has only been assessed in a few studies and more evidence is needed before a definitive conclusion about this association can be reached.

Conditions that May Be Mistaken for Catatonia

Many of the signs of catatonia can also be present in many psychiatric and neurological disorders. Table 3 (1,8,25,29,36,38,40,43,45–65) enumerates these disorders.

Pathophysiology

The pathophysiology of catatonia remains poorly understood; and it most likely represents a heterogeneous group of etiologies. There are different hypotheses that try to elucidate the specific etiology of catatonia, ranging from psychological and “hysterical” reactions, to abnormalities in several neurotransmitters and activation dysfunctions in various brain structures. Perkins suggested that catatonia could be the ultimate response to fear in individuals who are under severe emotional and physical stress, and in whom regression to a primitive form of expression has occurred (66). Moskowitz suggested that catatonia could be understood as a primitive fear response, similar to the animal defense strategy of tonic immobility when faced with imminent danger (66).

As benzodiazepines remain one of the most effective treatments for this condition, and a reversal of therapeutic effects of lorazepam on akinesia by GABA-A (Gamma Amino Butyric Acid-A) antagonists has been reported, the GABAergic system has been implicated in its pathophysiology (67). Lorazepam leads to the potentiation of inhibition mediated by GABA-A receptors, and an alteration in density of GABA-A receptors in cortical motor areas may thus be assumed to be present in akinetic catatonia (68). Northoff et al. investigated 10 akinetic catatonic patients with SPECT (Single Photon Emission Computerized Tomography), 2 hours after injection of iomazenil (a benzodiazepine) and compared them with healthy and psychiatric controls. The study found reduced iomazenil binding and altered right-left relations in akinetic catatonia, which suggests a decrease in the density of GABA-A receptors in the primary motor cortex. Patients also showed significant right-left alterations in the right lower prefrontal and parietal cortex, but the significance of this finding is still unclear (68). The efficacy of Zolpidem, a selective GABA-A agonist with a hypno-selective profile, in the diagnosis and treatment of catatonia gives further credence to the involvement of GABAergic system in the pathophysiology of catatonia (69–71).

The dopaminergic system has also been implicated in the pathophysiology of catatonia. Hietala et al (72). studied presynaptic dopamine function in caudate and putamen of patients with schizophrenia by PET (Positron Emission Tomography)

and reported that patients with catatonia had lower presynaptic dopaminergic function in comparison to patients with other types of schizophrenia. Philbrick and Rummans (45) suggest that in malignant catatonia, autonomic instability could be secondary to increased sympathetic discharge and recruitment of peripheral dopamine receptors triggered by central dopaminergic blockade secondary to neuroleptics. Northoff et al (59). suggest that prefrontal and limbic glutamatergic pathways to the supplementary motor area and motor cortex could be hypo-functional in catatonic patients, and that the secondary diminished release of GABA in frontal interneurons, which in turn would lead to less inhibition of glutamate, would result in frontostriatal glutamatergic hyperfunction. It has been suggested that serotonin could play a role in the pathophysiology of catatonia by increased activity at the 5-HT1A receptor, but this finding has not yet been widely replicated (22).

Areas of the brain involved in the pathophysiology of catatonia remain unclear. SPECT scans have shown hypoperfusion in frontal, temporal and parietal lobe regions of patients with catatonia (9). Another study using computed tomography (CT) found diffuse enlargement in almost all cortical areas in patients with catatonic schizophrenia (73). Northoff et al. studied akinetic catatonic patients and found alterations in the orbitofrontal cortical activation pattern and in functional connectivity to the premotor cortex in negative and positive emotions compared to psychiatric and healthy controls (74). Catatonic behavioral and affective symptoms correlated significantly with activity in the orbitofrontal cortex, which is an area of the prefrontal cortex closely associated with social adjustment and emotional regulation, whereas catatonic motor symptoms were rather related to activity in the medial prefrontal cortex, which is involved in monitoring action (75,76). Fisher speculated that catatonia could involve the mesencephalobasal forebrain-medial frontal system that has been postulated for akinetic mutism (18). Diminished glucose utilization in dorsal frontal and parietal lobes of both cerebral hemispheres has been reported in catatonia using PET and single photon emission computed tomography (SPECT) (77).

Northoff hypothesized that the different symptoms in catatonia may be accounted for by dysfunction in orbitofrontal-prefrontal/parietal cortical connectivity reflecting “horizontal modulation” of cortico-cortical relation (58). Alteration in “top-down modulation” reflecting “vertical modulation” of caudate and other basal ganglia by GABA-ergic mediated orbitofrontal cortical deficits may account for motor symptoms in catatonia. He further hypothesized that the clinical similarities between Parkinson’s disease and catatonia with respect to akinesia may be related to the involvement of the basal ganglia in both disorders. Clinical differences with respect to emotional and behavioral symptoms may be related with involvement of different cortical areas, that is, orbitofrontal/parietal and premotor/motor cortex implying distinct kinds of modulation—“vertical” and “horizontal” modulation, respectively (58).

Table 3 Disorders and Salient Features

Disorder	Salient Features
Malignant Catatonia	First described by Stauder in 1934. It is characterized by acute onset of fever, mutism, stereotypes, posturing and autonomic instability. Has a fulminant course. Prompt treatment is needed to avoid death (45). Neuroleptics may exacerbate simple catatonia and transform it into the malignant form (46).
Malignant Hyperthermia	It has an autosomal dominant inheritance. Symptoms are similar to malignant catatonia and it may be associated with neuroleptic malignant syndrome (1,47). It is precipitated by muscle sensitivity to inhalation anesthetics and depolarizing muscle relaxants during surgical procedures and is confirmed by muscle biopsy.
Neuroleptic Malignant Syndrome (NMS)	Salient features are autonomic instability, rigidity, and changes in mood and alertness. Some believe it is an example of malignant catatonia triggered by exposure to antipsychotics (38,101). Low serum iron levels occur in NMS and non-NMS malignant catatonia. Non-NMS converts to NMS following exposure to neuroleptics. NMS is a form of malignant catatonia and the two conditions share similar pathophysiology (48). About 0.5 % to 1% of patients treated with neuroleptics develop NMS (43). Patients with NMS receive much higher neuroleptic doses than controls, with greater dose increases and more parenteral injections. It can also occur in patients taking carbamazepine, valproate, and after the acute withdrawal of levodopa or amantadine (38,49–51) Risk factors for the development of NMS include psychomotor agitation, confusion, disorganization and catatonia (52). Another important and common risk factor for NMS is dehydration (29). The mortality rate for NMS varies between 4% and 20% (36).
Serotonin Syndrome (SS)	Patients present with a similar clinical picture to malignant catatonia. They also have gastrointestinal symptoms, including sialorrhea, nausea, abdominal pain and diarrhea. Patients present with myoclonus, hyperreflexia and midriasis (53). 65% of the patients, who met symptom criteria for NMS, also met criteria for SS (54). It usually resolves with the withdrawal of the serotonergic medication and supportive measures. It is unclear if benzodiazepines are helpful for the treatment of this syndrome.
Extrapyramidal Symptoms (EPS)	Some consider EPS and catatonia to share the same pathophysiology (55). Often, it is not possible to differentiate between catatonic motor signs and extrapyramidal movement disorders (56). Presenting symptoms of akinetic parkinsonism often resembles akinetic mutism (8). McKenna et al (57). found associations between tardive dyskinesia and positive catatonic phenomena and between parkinsonism and negative catatonic phenomena in patients with schizophrenia. However, some researchers indicate that extrapyramidal symptoms can be differentiated from motor symptoms of catatonia. Northoff et al (58). suggest that Parkinson's disease (PD) should be considered a motor disorder and catatonia a psychomotor disorder. In Parkinson's disease there is no posturing or catalepsy but cogwheel rigidity characteristic of the disease, but in catatonia patients have a smooth rigidity known as "flexibilitas cerea (59)." With the exception of neuroleptic-induced parkinsonism, both PD and parkinsonism rarely occur before the age of 50. These patients have a gradual onset of symptoms. Catatonia tends to be more commonly seen in young patients and has a more abrupt onset (24,38). Benzodiazepines that are helpful in the treatment of catatonia usually show little benefit in treating patients with Parkinsonism or Parkinson's disease (1). Bush et al. (40) found that catatonia coexisted with parkinsonism in 12%, tardive dyskinesia in 10%, akathisia in 7% and both tardive dyskinesia and parkinsonism in 24% of their sample. Bush et al. reported that catatonia was distinguishable from other motor disorders using the Bush-Francis Catatonia Rating Scale. Ungvari et al. reported that only akinesia seemed to overlap with motor retardation and severity of catatonia in patients with catatonic schizophrenia (7).
Locked in Syndrome	Patients usually have lesions in the ventral pons and both cerebellar peduncles (60). These patients are immobile except for eye and blink movements. They do not present with any other catatonic signs or symptoms. They try to communicate using eye movements and blink responses. They do-not respond to treatment with benzodiazepines (1,9).
Elective Mutism	Occurs in patients with preexisting personality disorder during times of stress (1,9). They usually don't have any other signs of catatonia. They don't often respond to treatment with benzodiazepines (61).
Delirious Mania	This disorder is characterized by altered sensorium, perceptual abnormalities, restlessness and agitation (9,43). Motor abnormalities like negativism, automatic obedience, echolalia and echopraxia are often present. Sleep is poor and patients present with flight of ideas, rambling speech alternating with mutism. Autonomic arousal characterized by tachycardia, tachypnea and elevated blood pressures. Symptoms usually develop within hours to days (9,43). The presence of symptoms of mania and delirium with or without catatonia should indicate a diagnosis of delirious mania. Medical work up including brain imaging is often negative (9,43). Often, delirious mania is indistinguishable from excited catatonia, and malignant catatonia (43). These patients may develop NMS from antipsychotics and lithium (43). ECT can be helpful in the treatment of patients with this disorder.
Delirium	Delirium may be characterized by acute psychomotor hypoactivity or hyperactivity and a "disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to sustain focus or shift attention" (DSM-IV-TR). Delusions and hallucinations are common, and symptoms classically wax and wane. It is very difficult to distinguish delirium from catatonia, especially malignant catatonia as both present with acute onset of excitement, fever, autonomic instability, and catalepsy. However some authors indicate that in catatonia, consciousness and alertness are not typically impaired (62–64). Some authors also indicate that catatonia responds well to monotherapy with lorazepam, whereas delirium does not (9,62,65).

Treatments

Benzodiazepines and Electroconvulsive Therapy (ECT) are currently considered the treatments of choice for catatonic symptoms. Benzodiazepines may relieve the syndrome in more than 80% of the treated patients (43). Lee et al. reported a remission rate of 72% within 6 days in patients with catatonia who were treated with benzodiazepines. Rosebush et al. reported that 93% of episodes of catatonia showed significant response to lorazepam and 80% responded completely and dramatically (38). In another study 89% of patients had significant improvement following a 48-hr trial of benzodiazepines (78).

Typically patients respond within minutes to parenteral benzodiazepines and within 1–2 hours to an oral dose. Often high doses are required, up to an equivalent 16 mg of lorazepam a day (36). Akinetic-hypokinetic catatonic syndromes have been noted especially to respond to benzodiazepines irrespective of the etiology of the underlying disorder (32). Although Schmider et al. reported that both lorazepam and oxazepam significantly improved symptoms of psychomotor functioning, they also suggested that it is possible that tolerance develops to benzodiazepine receptor-mediated relief of catatonic symptoms, and that counteracting mechanisms are triggered after the initial benzodiazepine application (79).

Even though there is a lot of information available regarding the treatment of acute catatonia (38,80), there is minimal data on the treatment of chronic catatonia (8,81). There is some recent evidence suggesting that chronic catatonic symptoms do not show a favorable response to benzodiazepines. Ungvari et al. reported that schizophrenic patients in whom the classical catatonic symptoms developed gradually were either unresponsive to benzodiazepines or responded minimally, in contrast to the dramatic response of stuporous conditions of other etiologies. In this randomized, double-blind, placebo controlled cross-over study performed in 18 patients with chronic catatonia, neither placebo nor lorazepam had any statistically significant or clinically noticeable impact on the subjects psychopathology, including EPS or catatonia, all of which remained remarkably stable throughout the study (32). According to Rosebush and Mazurek, patients with underlying schizophrenia are least likely to respond to benzodiazepines, with a response rate ranging from 40 to 50% (82), which could also be associated with the typical chronicity of catatonic symptoms in patients with this subtype of schizophrenia. These findings suggest that acute and chronic catatonic syndromes might require different treatment approaches. It has also been noted that excited and malignant catatonia tends to respond less favorably to benzodiazepines (48). Recent studies suggest that there is a strong correlation between low serum iron levels in catatonia and poor responses to benzodiazepines (29% no response, 59% partial response and 12% dramatic response compared to 0% no response, 5% partial response and 95% dramatic response among those with normal serum iron) (84).

ECT is usually considered after patients fail a trial of benzodiazepines. Although there are not many well-designed,

controlled studies evaluating the efficacy of ECT in catatonia, most of the available studies report a favorable response. Wells reported that 27 (81.8%) of 33 patients with catatonic schizophrenia in his retrospective study showed “good” or “moderate” improvement with ECT, and only 6 (18%) had “minimal” to “no response (83).” Rohland et al. reported a resolution of 83.5% with of all catatonic symptoms according to Kahlbaum and Rosebush’s criteria in 28 catatonic patients who received ECT (84). Some studies recommend that ECT should be considered if catatonic symptoms are not relieved with benzodiazepines within a range of 48 to 72 hours (85). Often other clinical features, such as nutritional status or capacity to harm, play into such decisions. ECT might have the additional benefit of treating the underlying illness when catatonia is associated with an affective or psychotic disorder (86). Petrides et al. suggest that the concomitant use of ECT and lorazepam may have a synergistic effect in the treatment of catatonia. They reported 5 prospectively identified cases of catatonia treated either sequentially or concurrently with lorazepam and ECT. In each case, the combination of lorazepam with ECT was superior to monotherapy. In all five cases, there was no initial response to lorazepam, but lorazepam became effective at the same or a lesser dosages after ECT was initiated. In two of the five cases, the benefits of ECT were enhanced later in the treatment course after the addition of Lorazepam. They suggest that this could be due to post-ECT increase in the GABA receptor sites and concentrations in basal ganglia, complementary actions between dopamine and GABA in the basal ganglia and the common anticonvulsant properties of benzodiazepine and ECT (87).

Since catatonia was considered a subtype of schizophrenia, several antipsychotics have been used to treat this condition. Some authors now consider this treatment approach to be unsafe in this population, due to the risk of exacerbating the condition and possibly inducing malignant catatonia, or neuroleptic malignant syndrome. However, other authors argue against this assumption stating that the scientific evidence supporting the data that atypical antipsychotics might worsen catatonia is poor (86). There is also very limited evidence from retrospective studies and case reports suggesting that novel antipsychotics might be useful in the treatment of catatonia (86). Given the lack of data and consensus over the use of antipsychotics in the treatment of catatonia, it could be stated that at the present time the efficacy and safety of antipsychotic medications in the treatment of catatonia remains largely unknown.

Some experimental treatments have shown some favorable outcomes in the treatment of catatonia. Two recent case reports have found memantine to have a positive and sometimes dramatic response in patients with catatonic schizophrenia (88,89). It is conceptualized that there is a decrease in release of GABA to the supplementary motor areas and therefore less glutamatergic inhibition in catatonia, which would result in a net effect of increased glutamatergic function in the striatum. NMDA antagonists, such as amantadine or memantine could decrease the amount of glutamate in the striatum and relieve the catatonic phenomena through this pathway (89).

Carbamazepine has been used in the treatment of catatonia. Kritzinger and Jordan conducted an open prospective study in catatonic patients who did not respond, or only had a partial response to or experienced a recurrence when treated with lorazepam. Out of the 9 studied patients 4 had a complete resolution to carbamazepine, 1 had a partial response, and 4 did not show significant improvement (90). In a recent report, four cases of catatonia refractory to benzodiazepines and divalproex responded well to treatment with topiramate. In all four cases, subjects experienced complete remission of catatonic symptoms and they tolerated the treatment well (91).

Zolpidem, a selective γ -aminobutyric acid A agonist with a hypnoselective profile, has been found to be useful in the diagnosis of catatonia (69,70,92). The Zolpidem challenge test is counted as being positive if 10 mg of oral Zolpidem, produces at least 50% reduction in the symptoms of catatonia (70,93) Zolpidem has also been reported to be helpful in the treatment of catatonia in a few case-reports (69–71).

Painless and noninvasive stimulation of the brain has become possible by using transcranial magnetic stimulation (TMS). Studies indicate that fast repetitive TMS of the dorsolateral prefrontal cortex and slow repetitive TMS of the opposite area have been shown to improve depressive symptoms (94,95) One study has shown an improvement in hallucinations in schizophrenic patients using TMS (96). Two case reports also indicate the efficacy of TMS in the treatment of catatonia (97–98).

Although benzodiazepines and ECT remain the most studied and effective treatments at the current time, research into different experimental therapeutic options will help develop alternative treatments for patients with catatonia who are resistant to benzodiazepines and ECT. Table 4 provides an algorithm for the treatment of catatonia (9,90,99,100).

CONCLUSION

Contrary to Kraepelin's view of catatonia as an exclusive subtype of dementia praecox or schizophrenia, but in keeping

with Kahlbaum's original description of catatonia as a separate brain disorder with a cyclic, alternating, and ultimately progressive course, there is enough evidence at present to classify catatonia as a specific neurobiological syndrome (23).

Taylor and Fink concluded that catatonia can be distinguished from other behavioral syndromes by a recognizable cluster of clinical features with many pathophysiologic processes, a typical course and with specific treatments (1). In support of the criterion for a neurobiological syndrome set forth by Fujii and Ahmed, putative neural circuitries for catatonia have been described. They involve multiple focal sites such as the anterior cingulate gyrus, the thalamus (mediodorsal), the basal ganglia, the medial frontal cortex, the inferior orbital frontal cortex, and the parietal cortex. Neurochemical studies indicate glutaminergic antagonism, gamma-aminobutyric acid (GABA) antagonism, serotonergic actions, and dopamine antagonism. Diffuse disease processes associated with catatonia support the notion that pathway dysfunction rather than focal (site-specific) dysfunction causes catatonia. Severity of catatonia varies with the associated diagnoses and the presence or absence of different risk factors. The treatment for catatonia, regardless of the underlying or associated conditions, is consistently similar among the different presentations.

Research is needed to create a valid and standardized classification of the different subtypes of catatonia. This differentiation will help in further delineating specific diagnostic criteria, pathophysiology, treatment strategies and prognosis for catatonia. Another important area of research should involve the clarification of phenomenological similarity between catatonia, EPS, and neurological conditions like Parkinson's disease. Such a clarification may also provide clues into the pathophysiology of these signs and symptoms in schizophrenia (8,101). A clearer diagnosis will also help us distinguish catatonia from other conditions that may respond better to different treatments. Early diagnosis and effective treatments will reduce undue suffering to the patient and their families, avoid unnecessary diagnostic studies and treatments, thereby reducing the length of hospital stay and saving precious healthcare resources (7,47).

Table 4 Treatment Algorithm for Catatonia

Admit to hospital (9).
Investigate to exclude other medical and neurological conditions by standard blood laboratory tests, urinary drug screening, electroencephalography (EEG) and brain computerized tomography (CT) (9).
Withhold illicit drugs that may precipitate or worsen the catatonic episode (9).
Withhold or avoid medications that may precipitate or worsen the catatonic episode (9).
Maintain nutrition, hydration, mobilization, skin care and safety (9).
A trial of lorazepam as an initial step is warranted as it is a safe therapeutic option with a success rate of about 80%.
1. Start with an initial oral or parenteral dose of 1–2 mg challenge with a rating of catatonic signs after the first hour.
2. If necessary, the patient could receive up-to 24 mg a day with 6-day full days of treatment followed by the taper of this medication to the optimum dose.
If the patient failed to respond adequately to the lorazepam challenge test or there is inadequate response to lorazepam at 20 mg a day or more even after several days (maximum a week of treatment), the use of bilateral ECT treatments is warranted. Earlier use of ECT is recommended if there is autonomic instability, hyperthermia or malignant catatonia. If patient responds to ECT within the first few treatments, at least 6 sessions should be administered (9).
If the patient fails to respond to trials of lorazepam and or ECT, a trial of memantine, carbamazepine, or topiramate as monotherapy or in combination with lorazepam or ECT should be attempted (91, 99, 100).
If the patient responds to medications or ECT, they should be continued on those medications for 9–12 months or on ECT for 6 months (9).

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