Catatonia

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Abstract

Catatonia is a neuropsychiatric disorder characterized by motor, affective and cognitive-behavioral signs, which lasts between hours to days. Intensive research over the past two decades has led to catatonia being recognized as an independent diagnosis in the international classification of diseases 11th revision (ICD-11) since 2022. Catatonia is found in 5–18% of inpatients on psychiatric units and 3.3% of inpatients on medical units. However, an unknown number of patients with catatonia remain unrecognized and are at risk of life-threatening complications. Hence, recognizing the symptoms of catatonia early is crucial to initiate appropriate treatment to achieve a favorable outcome. Benzodiazepines such as lorazepam and diazepam, electroconvulsive therapy (ECT), and NMDA antagonists such as amantadine and memantine, are the cornerstones of catatonia therapy. In addition, dopamine-modulating second-generation antipsychotics (for example, clozapine or aripiprazole) are effective in some patient populations. Early and appropriate treatment combined with new screening assessments has the potential to reduce the high morbidity and mortality associated with catatonia in psychiatric and non-psychiatric settings.

[H1] Introduction

Catatonia is a complex neuropsychiatric disorder that has fascinated clinicians and scientists for over two centuries **(Table 1)**. Catatonia is characterized by a diverse array of motor signs (for example, rigor, dyskinesia, negativism, posturing, catalepsy, gegenhalten and/or stereotypies), affective signs (such as, anxiety, flat affect, affective lability, aggression, impulsivity and/or combativeness), and cognitive-behavioral signs (for example, mutism, echolalia, echopraxia and verbigeration). Studies have reported a global incidence of catatonia of ~10 per 100,000 person-years[1-3]. Catatonia often goes undiagnosed and continues to challenge our understanding of the human brain and mind. The major classification systems, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR)[4] and the International Classification of Diseases (ICD-11)[5], now recognize catatonia as occurring in a wide range of medical, neurological and psychiatric conditions, although it was thought to be a subtype of schizophrenia for much of the 20th century[6]. In addition, catatonia can co-exist with psychiatric disorders such as schizophrenia or other primary psychotic disorders, mood disorders or neurodevelopmental disorders, particularly, autism spectrum disorder[7]. Medical conditions associated with catatonia include neoplasms, head trauma, cerebrovascular illness, encephalitis, diabetic ketoacidosis, hypercalcaemia, hepatic encephalopathy and homocystinuria[1]. Catatonia can be regarded as a syndrome and as a putative, independent diagnostic entity. In clinical practice, the diagnosis of catatonia is an intricate process involving physical examination, laboratory investigations, interviewing and observation of the patient.

The prompt recognition and management of catatonia in its early stages, as well as the close monitoring of affected individuals, is crucial to prevent serious complications such as pneumonia, urinary tract infection, sepsis, deep venous thrombosis, pulmonary embolism, pressure sores, acute kidney injury and cardiac arrhythmia, which can be ultimately fatal[8]. Prompt treatment can be effective for managing the acute phase of catatonia, which is often characterized by severe symptoms and lasts between a few hours to a few days, but in rare cases also weeks[9]. The prognosis of catatonia is typically good, including complete remission in some patients; however, the prognosis can vary in association with other underlying psychiatric, neurological and medical diseases. Several studies have extensively investigated the use of benzodiazepines, specifically lorazepam and electroconvulsive

therapy (ECT), for acute catatonia[10], evidence for treating chronic catatonia that occur in association with chronic psychoses, particularly schizophrenia is limited[9,11-13]. Finally, in addition to an enhanced understanding of disease mechanisms, improved education of psychiatric and non-psychiatric clinicians in the field of catatonia is urgently needed[14].

In this Primer, we review the epidemiology, assessment, diagnosis, and treatment of catatonia. Furthermore, we provide a modern and comprehensive perspective on our current understanding of catatonia pathophysiology (brain-mind approach). In addition, we highlight the outstanding issues in current clinical practice and discuss potential strategies to manage people with catatonia, which will improve patient outcomes and quality of life.

[H1] Epidemiology

[H2] Limitations

From a clinical and nosological perspective, determining the exact prevalence of catatonia is challenging for a number of reasons[15]. Firstly, although the ICD-10, DSM-5-TR and ICD-11 mention catatonia, consensus regarding specific signs and symptoms that define a catatonic condition or catatonic syndrome is lacking. Notable discrepancies are present in the existing diagnostic methods and catatonia rating scales, particularly, duration of the evaluation and the number, nature and definition of signs that constitute a catatonic syndrome. Currently, the ICD-10, DSM-5-TR and ICD-11 list 5, 12 and 23 signs and symptoms, respectively, for catatonia[16]. Furthermore, the number of clinical features for defining catatonia range from 2 to 40 in current investigations including case reports, case–control studies, neuroimaging and clinical studies[17]. Even simple signs such as mannerism, Gegenhalten, verbigeration or rigidity have contradictory definitions in different classification systems and rating scales. Secondly, the symptom threshold for catatonia diagnosis depends on the classification system and the scale used and therefore, no clear definition of acute catatonia and chronic catatonia is presently available. Furthermore, as catatonia can occur as an independent disorder or as a syndrome in association with other disorders, a large number of patients can meet the criteria according to the Bush-Francis Catatonia Rating Scale (BFCRS; 23 items) or Northoff Catatonia Rating Scale (NCRS; 40 items)

if, say, they had psychotic depression, hypoactive delirium or mania, but many of these patients will not meet the stringent ICD-11 or DSM-5-TR criteria. Moreover, features of catatonia including hypokinetic and hyperkinetic signs might fluctuate over time, which makes the timepoint of assessment a crucial factor. Finally, misconceptions in a clinician's understanding of catatonic signs and symptoms can often lead to over diagnosis or under diagnosis of catatonia[14].

[H2] Incidence and prevalence

[H3] General population.

Only a few studies have investigated the incidence and prevalence of catatonia in the general population. For instance, based on medical records, one study estimated an incidence of catatonia of 10.6 (95% CI: 10.0–11.1) per 100,000 person-years in the general population[18]. A large study conducted in US non-federal general hospitals estimated an incidence of 0.05% based on discharge diagnosis with an ICD-10 catatonia code[19].

[H3] Specific patient population

Several studies have estimated the prevalence of catatonia in different patient populations receiving mental health services[3,15,20]. One study examined the prevalence of catatonic schizophrenia across a large cohort of patients who were admitted to psychiatric hospital (n=19,309) and the occurrence of catatonic symptoms in individuals with schizophrenia (n=701) and individuals with psychosis (n=139) [21]. The prevalence of catatonic schizophrenia among individuals with a psychiatric diagnosis decreased from 7.8% between 1980–1989 to 1.3% between 1990–2001 ($p < 0.001$). Possible reasons for this shift include the prescription of psychotropic drugs and the resulant lack of serious psychiatric disorders, the declining role of the medical physical examination or a lack of knowledge about catatonia[22]. An independent sample of individuals diagnosed with schizophrenia has also revealed a potential under-diagnosis of catatonic schizophrenia[23]. Another study that evaluated 241 patients with psychiatric disorders found that 44 individuals (18.3%; 79.6% men and 20.5% women met the screened positive on the Bush Francis Catatonia Screening Instrument (BCFSI) and 16 (6.6%) met the DSM-5-TR criteria for catatonia[24]. In addition, 34% of patients with catatonia had co-occuring medical conditions. By contrast, an earlier, 7-year county-wide register study of 798 cases of catatonia found significantly more

women than men in the catatonic cohort (p=.02)[25] compared with patients with schizophrenia patients (female:male ratio was 1.3:1). Another study[26] found that periodic catatonia affected both sexes equally in all age groups. A meta-analytic summary of studies of catatonia prevalence found that 9.0% (95% CI: 6.9–11.7%) of inpatients and outpatients with psychiatric disorders exhibit catatonic signs at some point of their illness[15]. According to this study, the prevalence of catatonia was found to range between 14% and 71% in mood disorders, 4% and 67% in schizophrenia spectrum disorders (SSD) and between 4% and 46% in general medical illnesses. In another study, 24.4% of patients with SSD fulfilled the criteria for catatonia according to the NCRS (at least 1 symptom from each domain)[27]. Furthermore, a study that examined the prevalence of catatonia in 120 patients with an earlier diagnosis of delirium found that 26% of the patients had catatonia and delirium, whereas 7% had only catatonia[23].

Several points need to be considered regarding the meta-analytic study mentioned above. Firstly, the study mentions significant amount of variation between studies, which cannot be accounted for by sampling variation alone[15]. The large studies, for instance, reported a significantly low prevalence (that is, 2.3% (95% CI: 1.3–3.9%; n > 1000). A number of these studies also calculated the prevalence among a group of patients with schizophrenia, a common condition associated with catatonia. The prevalence of catatonia did not have any correlation with whether participants were in high-income or low-income and middle-income countries. Secondly, many studies relied on clinical diagnoses, in which cases underdiagnosis is likely[21]. The higher prevalence reported in smaller studies may be explained by publication bias.

Catatonia is rarely identified in paediatric patients (<18 years of age) in general hospitals, owing to it being overshadowed by other serious medical and psychiatric conditions[28]. A study reported 900 pediatric hospitalizations (95% CI: 850–949) with a discharge diagnosis of catatonia in the USA in 2019 (291 with catatonia as the primary diagnosis and 609 with catatonia as a secondary diagnosis). The mean age of patients was 15.6 +/- 2.6 years with 9.9% of the population <13 years of age. In addition, the most common primary psychiatric diagnoses were psychotic disorders (18.3%), major depressive disorder (7.7%), bipolar disorder (4.3%), and substance-related disorders (2.2%)[28], respectively. The common diagnoses with non-psychiatric catatonia, which

constituted 11.8% of paediatric patients were encephalitis, autistm spectrum disorder, other neurologic illnesses (13 out of 18 being encephalopathy) and systemic lupus erythematosus (SLE). The authors concluded that rigorous diagnosis, evaluation, and treatment of paediatric patients with catatonia requires further investigation in large-scale studies[28].

Interestingly, another study examined anonymized mental healthcare records from ~400,000 individuals and found 21 individuals, each of whom experienced one episode of catatonia in the postpartum period. All 21 were admitted to an inpatient psychiatric department[29]. However, the incidence and prevalence of perinatal catatonia is unclear as case series of perinatal catatonia in the medical literature is sparse.

Finally, catatonia can occur throughout the entire lifespan, including in the elderly[30,31]; however, studies examining the prevalence of catatonia in geriatric psychiatric patients are rare. A study involving 98 patients >65 years of age admitted to a psychiatric unit in Hungary found 11.2% and 6.2% of patients full-filled the BFCRS and DSM-5-TR criteria, respectively[32]. However, in the UK, the prevalence was 27% and 39.6% using the BFCRS and DSM-5 criteria, respectively[33]. In Spain, the prevalence was 24.3% and 20.8% using the same criteria[33].

[H1] Mechanisms/pathophysiology

Although the understanding of the neuronal correlates of catatonia has improved substantially over the past decade, the precise pathogenetic mechanisms remains poorly understood. Since its first clinical description in 1874, three distinct clinical and neurobiological views have been recognized — psychomotor or affective disorder (Kahlbaum's legacy)[34,35], purely motor disorder (Kraepelin's and Bleuler's legacies)[36-38] and the neuropsychiatric perspective of the Wernicke-Kleist-Leonhard (WKL)[39,40] school. This conceptual distinction is also reflected in the research on catatonia mechanisms[18,19]. Neuroimaging studies employing motor and/or behavioral rating scales (such as the BFCRS) have suggested alterations in dopamine-mediated cortical and subcortical motor regions as the neuronal and biochemical bases of catatonia[41]. By contrast, research using the NCRS (a rating scale that includes affective, motor and behavioral **[Au:OK?Yes]** signs predicated on a psychomotor approach) have found abnormal higher-order frontoparietal networks, which are

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insufficiently modulated by glutamate and GABA transmission[41]. Studies have shown that[42,43] periodic catatonia may be associated with left premotor cortex hyperperfusion. Here, we discuss the pathophysiology of catatonia on two specific levels — the biochemical (molecular) and the systemic (network-based) regardless of whether catatonia is associated with a psychiatric or medical disorder **(Fig 1)**. Notably, the vast majority of neuroimaging case–control studies on the pathophysiology of catatonia have been conducted in patients with catatonia diagnosis according to DSM-IV/-5-TR, ICD-10, BFCRS or NCRS criteria[17].

[H2] Risk factors and causes

Risk factors for catatonia include neuroinflammatory, psychopharmacological and genetic factors. Neuroinflammation can play a key role in the development of catatonia[44,45]. **[Au: Please check if edits to this statement are correct. I have rewritten the sentence]** Two studies[3,46] have shown that inflammatory brain disorders, including encephalitis (the most common) and SLE, accounted for 28.8% of patients with catatonia associated with medical disorders. Other autoimmune diseases including Sjogren's syndrome[47] and antibody-mediated encephalitis, particularly NMDAR encephalitis, have been associated with catatonia[48-50]. Although a rare autoimmune disorder, NMDAR encephalitis is the most frequent autoimmune cause of catatonia[44,51], with an estimated prevalence ranging from 30 to 70%[52-54] of immune-related cases[55]. The autoantibodies produced by the circulating immune cells can cross the blood–brain barrier and activate inflammatory cascades in the brain[56].

Catatonia has also been associated with infectious encephalitis caused by herpes simplex virus[57], HIV infection[58-61] and COVID-19[62-64] infection, as well as by *Treponema pallidum* (syphilis)[65-67] and *Borellia burgdorferi*[68-70] (Lyme disease) infections. In cases of infectious encephalitis, antibody-producing cells that cross the blood–brain barrier can have pathogenic effects on neuronal plasticity, which might lead to altered glutamatergic signalling and consequently, neuronal death[56]. Furthermore, as a result of injury or activation of the innate immune system against infected cells, a cortico-striato-thalamo-cortical (CSTC) loop dysfunction (for example, motivation and movement systems) might develop, leading to catatonia[45].

Interestingly, scientific evidence suggested that environmental stressors, such as urban upbringing, exposure to crime, illicit drugs, maltreatment, etc., which engage amygdala-related threat signalling can enhance an individual's vulnerability to

catatonia via pro-inflammatory processes[45,71]. Indeed, stressful life events (for example, childhood maltreatment) are associated with increased expression of pro-inflammatory cytokines and decreased expression of type I interferon genes, which are involved in innate antiviral responses and antibody synthesis[72]. Furthermore, chronic stress-related cytokine production is thought to disrupt the immune balance of T helper 1 (T_H1) and T helper 2 (T_H2) cells, predisposing individuals to autoimmune disorders[73]. Additionally, preliminary evidence shows that severe catatonic signs are associated with a loss-of-function allele of a myelin-specific gene (*rs2070106*), changes in the expression of myelin-specific gene and neurochemical abnormalities (for example, low-grade inflammation or neurodegeneration)[74-76].

Catatonia may also result from dopaminergic hypofunction in the mesostriatal pathway[77,78]. Several reports have suggested that the acute use of first-generation antipsychotics (FGA) elevates the risk of antipsychotic-induced catatonia compared with second-generation antipsychotics (SGA)[79], although one review contradicted this interpretation[80]. Notably, three patients with catatonia associated with schizophrenia showed reduced striatal dopaminergic function using ^{18}F-DOPA PET[81]. Furthermore, antipsychotics and other D_2 antagonists can increase $GABA_B$ activity and this mechanism has been suggested to trigger antipsychotic-induced catatonia[82]. However, dopamine receptor agonists, such as methylphenidate, can also help treating catatonia (especially in affective disorders) by improving dopaminergic transmission[83-87]. On the other hand, methamphetamine (an indirect norepinephrine and dopamine receptor agonist) use can trigger catatonia, supporting the contribution of an overactive dopaminergic system in this disorder[88,89].

The above mentioned evidence suggests an interplay and a delicate balance between dopamine agonism and antagonism, evident by the effectiveness of aripiprazole in some cases of catatonia associated with a chronic psychotic disorder, and when co-administered with a benzodiazepine for safety[90-92]. Aripiprazole,a partial D_2 agonist, also has effects on the receptors, D_3 and 5-HT_{2C}, possibly mediating antidepressant effects, especially the improvement of psychomotor slowing[92]. These properties may explain its effectiveness and favourable adverse effect profile compared with other antipsychotics used to treat catatonia.

Of note, antipsychotic drug-induced dopamine antagonism substantially influences glutamate pathways, with notable distinctions between FGA and SGA[93]. Haloperidol,

a FGA, enhances extracellular glutamate levels by antagonizing D_2 and $5HT1_A$ receptors, increasing glutamate release, whereas $5HT2_A$ antagonism curbs this release[93]. By contrast, SGA, such as clozapine and quetiapine, have minimal impact on extracellular glutamate levels in key brain regions such as the striatum and frontal cortex, potentially owing to their differing receptor binding profiles and transient receptor engagements[94]. This pharmacological distinction suggests that SGA may offer neuroprotective advantages by mitigating glutamate-mediated neurotoxicity compared with their typical counterparts, thereby reducing the risk associated with elevated extracellular glutamate levels. Furthermore, aripiprazole and cariprazine might also modulate NMDA and AMPA-type glutamate receptor subtypes, which are critical to glutamatergic neurotransmission[95-97]. In particular, one study found that both aripiprazole and cariprazine influence glutamate levels. For instance, the authors observed that cariprazine reduced NMDA receptor levels while increasing AMPA receptor levels in certain brain regions, a pattern that was also noted with aripiprazole but to a different extent[98].

Another frequent but as yet unexplained cause of catatonia is the rapid discontinuation of psychotropic agents. A systematic review of withdrawal catatonia identified 55 case reports, which reported eight distinct classes of medications that induced withdrawal catatonia, namely, (in order of descending frequency) benzodiazepines, clozapine, combined alcohol and benzodiazepines, alcohol alone, glutethimide, zolpidem, gabapentinand GABA[99]. Another review examining case reports or case–series and five original studies on clozapine withdrawal found that 30 out of 72 patients with non-psychosis symptoms of clozapine withdrawal **[Au:OK? No]** showed catatonia[100]. This is in line with other case reports that have described catatonia induced by clozapine[101-109], olanzapine[110] or benzodiazepine[110-116] withdrawal. Clozapine withdrawal psychosis and catatonia are more likely to be explained by mechanisms other than rapid dissociation from the D_2 receptor, possibly including serotonergic and cholinergic rebound, $GABA_B$ receptor interactions or a complex multi-receptor interaction[99,117,118]. Although no cases of catatonia following withdrawal of aripiprazole, paliperidone or amisulpride were identified, one case report has described catatonia following discontinuation of each of quetiapine[119] and risperidone[120].

[H2] Molecular and immunological pathways

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The biochemical and molecular mechanisms of catatonia is thought to involve dysfunction in the GABAergic, glutamatergic, dopaminergic and serotonergic neurotransmitter systems. Dysregulation of GABAergic signalling has been associated with stress vulnerability and negative affect in catatonia.[121] Furthermore, catatonia is associated with higher rates of negative affect amongst patients with SSD than the general population.[122] In addition, a few small uncontrolled studies have demonstrated that administering $GABA_A$-positive allosteric modulators, such as lorazepam and zolpidem, could be a useful and life-saving therapeutic option for catatonia[123]. Based on case reports of catatonia[104] and animal studies[124], some authors have hypothesized that aberrant fluctuation of $GABA_A$ and $GABA_B$ neurotransmission may also lead to catatonia [125,126]. This suggested mechanism supports the effectiveness of anxiolytic medications, specifically $GABA_A$-positive allosteric modulators, in the treatment of affective catatonic signs that are often observed in daily clinical practice. This approach is also in line with the hypothesis that severe affective emotional dysregulation leads to various affective symptoms and a hyperkinetic or an akinetic psycho-motor clinical phenotype[122]. Moreover, fMRI studies have demonstrated an association between the alterations in $GABA_A$ receptors and changes in activation patterns as well as functional connectivity in the medial and lateral orbitofrontal cortex (OFC), prefrontal cortex (PFC) (brain regions that are responsible for the processing of negative emotions) and the posterior parietal cortex[127-129]. Overall, an imbalance between excitatory and inhibitory GABAergic neurons may result in catatonia[44,130].

Second, autoimmune catatonia may result from glutamatergic hypofunction, which is frequently induced by NMDAR encephalitis[44]. Furthermore, an increasing number of case reports have shown complete remission of acute catatonia independently of its origin after the administration of NMDAR antagonists (amantadine and memantine)[131-133]. However, neuroimaging studies investigating the involvement of NMDA receptors in the pathophysiology of catatonia have not yet been conducted.

Third, catatonia may be linked to irregular dopaminergic activity within the mesostriatal pathway. Notably, antipsychotic medications can reduce dopaminergic activity, whereas stimulants might enhance it, potentially influencing the incidence and characteristics of catatonia.[77,78].

Fourth, case reports have found that atypical antipsychotics or antidepressants increasing serotonergic neurotransmission[134,135] may be useful as adjunctive treatment for catatonia with comorbid mood disorders (for example, psychotic depression)[136,137]

or for chronic catatonia[138]. However, no large-scale neuroimaging studies testing this hypothesis are available.

[H2] Systems perspective

From a systems perspective, patients with post-acute akinetic catatonia with SSD or mood disorders have shown altered functional connectivity of the OFC to the premotor cortex[139] and reduced $GABA_A$ receptor density in the left sensorimotor cortex[140]. Studies have shown that lorazepam reduced the OFC dysfunction and restored emotional regulation in these patients[129]. Furthermore, preliminary evidence shows that cortical features (such as, cortical thickness, surface area and gyrification) of different evolutionary and genetic origins across various motor and non-motor regions contribute differently to catatonia associated with SSD [141,142]. FMRI studies in catatonia associated with SSD have shown large-scale functional brain network dysconnectivity[143], which might result from abnormal white matter microstructure. To date, four diffusion MRI studies[144-147] have shown that microstructural alterations within white matter tracts connecting psychomotor-related regions such as OFC, PFC, primary motor cortex, the supplementary motor area and the basal ganglia, can contribute to the development of catatonia. Further studies have suggested a key role for alterations such as reduced volumes of subcortical and cortical limbic structures in affect dysregulation in catatonia[148].

Employing multimodal neuroimaging fusion analysis[149-151], one study[152] found reduced gray matter volume and intrinsic neural activity in frontothalamic and frontoparietal networks in patients with catatonia with SSD compared with patients with SSD alone. In particular, reduced gray matter volume in the frontothalamic network (for example, frontal cortex, primary motor cortex and basal ganglia) may reduce intrinsic neural activity in the frontoparietal circuit (superior, middle, medial and inferior frontal cortices including OFC), consequently resulting in impaired processing of negative emotional stimuli and the cessation of sensorimotor functioning, which can ultimately lead to affective and behavioural catatonic signs[152]. In particular, the OFC is responsible for impulse control, affect regulation, and decision-making[153-155]. Aberrant OFC–prefrontal/parietal cortical connectivity in catatonia can reflect disrupted 'horizontal modulation' of the cortico-cortical networks[139,156], which can further lead to aberrant function of subcortical structures such as the limbic system, the raphe nucleus (serotonergic system) and the substantia nigra (dopaminergic system)[157]. This

alteration may be the mechanism underlying impulsive behavior and/or aggression, as well as disturbed affective/mood regulation (for example, fear)[158,159], which are characteristic symptoms of catatonia[160].

Another line of imaging studies in catatonia has focused solely on the subcortical and cortical motor systems. These studies have reported both decreased and increased structural and functional changes in MRI measures of the motor cortex or supplementary motor cortex, as well as in subcortical regions such as the basal ganglia and cerebellum [142,161,162]. Notably, these findings are, in principle, also compatible with findings from studies focusing on psychomotor functioning. The abnormalities in these motor regions can still result from aberrant activity of primarily non-motor regions involved in other functions like OFC, PFC or raphe nucleus and default mode network regions, thus accounting for psychomotor abnormalities and not exclusively motor symptoms [157].

Finally, a systematic review[163] analyzed 33 neuroimaging studies and 171 case studies on catatonia. Structural and functional case–control MRI studies have reported alterations in the fronto-parietal and limbic regions, the thalamus, and the striatum; however, observational structural MRI studies have revealed multiple cortical and subcortical brain changes in catatonia, including diffuse atrophy and signal hyperintensities in the frontal lobe and cerebellum[164]. Abnormalities were found primarily in the OFC (hypoactivation), medial PFC (hyperactivation and hypoactivation), primary motor cortices (increased connectivity), supplementary motor area (hyperactivatio and hypoactivation), and cerebellum (increased connectivity) in task-based and resting-state fMRI studies (for systematic review see[165]). Finally, mixed changes in perfusion and metabolism were observed in the motor cortex, PFC and basal ganglia regions. Most case reports described broad white matter lesions and hypoperfusion of the frontal, temporal or basal ganglia[163]. However, heterogeneity in results, study populations and neuroimaging techniques requires cautious interpretation.

[H1] Diagnosis, screening and prevention

[H2] Diagnosis

Catatonia is diagnosed primarily through clinical examination, with additional tests performed to exclude other differential diagnoses. The following diagnostic work-

up should be considered — patient history, clinical examination, urine and blood sample analyses (for detection of infection, other medical disorders and illicit substances), electrocardiography and brain MRI. Catatonia can currently be diagnosed using DSM-5-TR (mainly in English-speaking countries) and ICD-11 (in other parts of the world) classification systems. The criteria for each classification system are different. Furthermore, catatonic signs can be assessed with a variety of clinical scales[18,105], of which the NCRS and the BFCRS are the two commonly used. An additional indicator of catatonia is the lorazepam challenge test (LCT), which consists of the administration of per os (PO), intramuscular or intravenous lorazepam twice, separated by a 5-minute interval (for details see the Management section) [166] [167] **(Figure 2)**. The sensitivity and specificity of the LCT for the diagnosis of catatonia is still under scrutiny[168].

[H2] Diagnostic criteria

The DSM-5-TR describes three categories of catatonia — catatonia associated with another mental disorder [catatonia specifier for psychotic (brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, and substance-induced psychotic disorder) and major mood disorders]; catatonic disorder due to another medical condition; and catatonia not otherwise specified (NOS)[169]. Catatonia–NOS is particularly useful when the underlying medical condition contributing to catatonia is unclear or still being investigated, allowing for immediate treatment[169]. Catatonia–NOS also applies to catatonia cases involving psychiatric conditions such as autism and other neurodevelopmental disorders, where the presence of catatonia signs has important prognostic and treatment implications[169]. Catatonia is defined as the presence of three or more of the 12 psychomotor features in the DSM-5-TR. Catatonia is not considered as a separate diagnosis at the same hierarchical level as schizophrenia or major depressive disorder, but rather a set of psychomotor signs (that is, clinical features observed by physicians**)**, a loosely defined syndrome that can be associated (specifier) with several psychiatric and medical conditions.

Whereas the DSM-5-TR classification system tends to emphasize motor signs, ICD-11 defines catatonia more as a psychomotor disorder. To establish a diagnosis, the presence of three or more signs from one or any combination of the following three symptom clusters is needed — decreased psychomotor activity; increased

psychomotor activity; and abnormal psychomotor activity (**Box 1**). These criteria apply to all four diagnostic categories of catatonia as described in ICD-11, which include catatonia associated with another mental disorder; catatonia induced by substances or medications; secondary catatonia syndrome and catatonia, unspecified (for example, harmful effects of substances, not elsewhere classified; acute stress reaction; uncomplicated bereavement).

[H2] Clinical rating scales

At least nine catatonia rating scales have been published in English language in the international literature[105-108], which might be used in combination with ICD-11 and DSM-5-TR criteria in clinical practice and research. However, the rating scales differ substantially in the number and definition of signs, indicating that the boundaries of catatonia and the consensus among experts regarding what specifically constitutes a catatonic manifestation is not yet clear. The BFCRS is the most used in the scientific literature[170]. A 23-item BFCRS (inter-rater reliability: 0.93; mean agreement of items was 88.2% (SD 9.9)) and a reduced 14-item screening tool (inter-rater reliability: 0.95; mean agreement of items was 92.7% (SD 4.9)) was developed based on operationalized descriptions of catatonic manifestations found in published historical sources[14]. The BFCRS has excellent psychometric properties. In addition, extensive online instruction is available on how to rate each item on the BFCRS **(see related links)**. However, one study[171] highlighted the challenges in accurately diagnosing catatonia among psychiatrists (residents and fellows) and medical students, revealing major gaps in the understanding and recognition of its diverse signs. Using an online 50-item multiple-choice test and a 3-minute standardized patient video-based assessment based on the BFCRS, the study found that participants (n=482) correctly answered only 55% of the test questions and correctly identified 69% of the BFCRS items. Notably, psychiatrists achieved a seven-point higher score on the multiple-choice exam and correctly identified two additional items on the BFCRS than medical students. Several critical signs such as immobility or stupor, posturing or catalepsy, various forms of negativism (active, passive and contrary), and withdrawal behaviour (for example, refusal of food and fluids) were frequently misidentified by psychiatrists and medical students[171]. This study underlines the discrepancies between the BFCRS and DSM-5 definitions and emphasizes the need for enhanced educational efforts to

improve the accuracy of catatonia diagnosis, advocating for broader use of the BFCRS to strengthen diagnostic competency in clinical practice.

Another frequently used scale is the NCRS consisting of 40 items[172] based on contemporary and historical literature. The NCRS (intra-rater and inter-rater reliabilities (r = 0.80-0.96)) truly reflects the psychomotor concept of Kahlbaum[34,173], comprising 12 affective signs, in contrast to the BFCRS and all other catatonia scales, which include at most a few affective signs [174]. Catatonic signs on the NCRS are categorized into three clusters — behavioral, motor, and affective. A patient must experience at least one sign from each of the three domains to be classified as having catatonia. Factor analysis revealed four best categories to characterize catatonia, which comprise affective, hypoactive, hyperactive and behavioural signs. Three signs with the highest load (>0.5) were selected for each of these four categories[172] leading to 12 signs defining the Northoff Catatonia Screening Inventory (NCSI). Notably, depending on the scale used (motor versus psychomotor), different patients can be diagnosed as having catatonia and therefore, studies have identified several different neuronal correlates of catatonia.

The above-mentioned rating scales are designed for the evaluation of catatonia in general and are equally suited for all age groups. Furthermore, all scales were designed for the acute catatonia, and not for chronic cases. For instance, an earlier study found that the BFCRS requires considerable modifications when used in chronically ill patients with psychotic disorders[175]. Another limitation is the study period; all scales were developed for cross-sectional use and mainly focused on patients with acutecatatonia, assuming that all signs of catatonia may be present at a given examination.

[H2] Catatonia subtypes

In addition to the four ICD-11 categories of catatonia, three forms of catatonia exist that are clinically relevant, which include periodic catatonia, malignant catatonia and neuroleptic malignant syndrome. Periodic catatonia[42,176,177], a rare form of catatonia, comprises ~7% of endogenous psychoses cases[178] and is characterized by switches between stupor or akinesia and agitation or hyperkinesia across different body parts even within hours, along with parakinesias that make simple movements such as facial expressions appear stiff or jerky[40,177]. Studies have linked periodic catatonia to a deficit in intra-cortical inhibition, potentially owing to the degeneration of

GABA-ergic interneurons, highlighting its unique pathophysiology. This hypothesis has been supported by fMRI showing specific left premotor hyperactivity[42,43] and successful personalized repetitive transcranial magnetic stimulation (rTMS) treatments targeting the premotor area, suggesting a promising biomarker for diagnosis and targeted intervention[179]. Furthermore, patients with periodic catatonia responded well to FGA (60% response rate) and showed substantial improvement with clozapine and treatments such as benzodiazepines and ECT[180]. Malignant catatonia is a life-threatening form of catatonia accompanied by pronounced vegetative symptoms in addition to various psychomotor signs[8]. Malignant catatonia can result in life-threatening autonomic instability, including labile blood pressure, tachycardia, hyperthermia and diaphoresis (profuse sweating). Frequently, critically ill patients encounter several neurobiological and environmental factors including viral infections, neurological problems, the use of antipsychotic medication, or withdrawal from particular substances, which might predispose or precipitate catatonia. Malignant catatonia has a 50% mortality rate if not treated promptly[8]. However, no definition or diagnostic criteria are available currently in the DSM-5, ICD-10 or ICD-11 for malignant catatonia. Neuroleptic malignant syndrome (NMS; ICD-10: G21.0) is an extreme and life-threatening manifestation of catatonia associated with D_2 receptor antagonist induced antipsychotic-motor syndromes, which occurs after the initiation of antipsychotic treatment. Typical clinical features include hyperthermia (body temperature > 38 °C), diaphoresis, sialorrhea (hypersalivation), akinesia, dystonia, trismus (jaw muscle spasm), myoclonus, dysarthria, dysphagia, increased creatine kinase and transaminases resulting from rhabdomyolysis (which carries the potential for renal failure), impaired consciousness and signs of autonomic dysregulation (for example, tachypnea (due to respiratory acidosis), urinary incontinence, pallor and hypermetabolism). The signs and symptoms of NMS and malignant catatonia substantially overlap, making diagnosis and therapeutic management challenging[8,181]. Some authors have suggested NMS to merely be a drug-induced version of malignant catatonia with indistinguishable signs, symptoms and treatment response. A systematic review [80] explored the characteristics and links between antipsychotic-induced catatonia and NMS and found that SGA were implicated in most cases, often during monotherapy. The clinical overlap between antipsychotic-induced catatonia and NMS suggests a neurobiological and clinical continuum between these conditions.

[H2] Differential diagnoses

The diagnosis of catatonia requires careful consideration of various differential diagnoses as several psychiatric, neurological and other medical conditions can present with overlapping signs and symptoms **(Table 2)**.

In intensive care units, the question often arises as to whether the patient is suffering from catatonia, delirium, or both. The differential diagnosis is not trivial and requires clinical experience, as both conditions can present with altered mental states and sensorimotor abnormalities, albeit having distinct underlying causes and treatment approaches[182-185]. There are typical signs of delirium that are not characteristic features of catatonia and vice versa[182-185] (**Table 3**). For instance, one study[185] found that 74% of critically ill patients experienced delirium at some point and 31% also showed signs of catatonia, consistent with earlier studies[186] that demonstrated that 12.7–30.2% of critically ill patients with delirium also showed signs of catatonia. Catatonic signs were more common in patients with delirium than in patients without delirium, potentially due to critical illness-related signs such as autonomic abnormalities and stupor. Importantly, the study suggested a revised cut-off value on the Bush-Francis Catatonia Screening Instrument (BFCSI) for diagnosing catatonia in critically ill patients to enhance specificity and aid effective treatment planning[185]. This investigation called for a reevaluation of the nosology of catatonia in the context of critical illness and delirium, proposing adjustments to the DSM-5 based on these insights.

[H2] Catatonia across the lifespan

Although most studies on catatonia have examined individuals between 18 and 64 years of age, catatonia can also occur in children and adolescents (paediatric catatonia[91,187]), and in older adults (geriatric catatonia[188-190]).

Paediatric catatonia is a rare but serious neuropsychiatric condition that can manifest with a range of unique clinical features. The diagnostic criteria for children and adolescents are the same as those for adults. Paediatric catatonia, especially those with neurodevelopmental disorders, presents and progresses in a different way with acrocyanosis (bluish or purple colouring of the hands and feet owing to poor circulation), automatic compulsive movements, schizophasia, loss of previously

acquired skills or communicative abilities and urinary incontinence [28,191-193]. The use of Pediatric Catatonia Rating Scale (PCRS; Cronbach's α for total score=0.67), a modified version of the BFCRS, is recommended for the assessment of paediatric catatonia[194].

Geriatric catatonia is highly prevalent[33], although it maybe diagnostically challenging owing to comorbid medical conditions, cognitive impairment and age-related changes[32]. The potential for polypharmacy (the regular use of five or more medications) in the elderly further complicates the clinical picture, as certain medications (for example, haloperidol, baclofen, opioids, amoxicillin, ciprofloxacin) can exacerbate catatonic signs. Hence, recognizing catatonia in this population is crucial, as symptoms can manifest as motor abnormalities, stupor, mutism or other atypical behaviors, which may be initially attributed to dementia or other geriatric conditions. Characteristic manifestations of catatonia in the elderly include urinary retention, excitement, impulsivity, aggression, immobility, staring, mutism, negativism, rigidity, posturing, verbigeration, perseveration and autonomic abnormalities[30]. The symptomatologic overlap is greatest when it comes to the behavioral variant of frontotemporal dementia (bvFTD) [195,196]; for example, one study demonstrated that an individual with both disorders share a fronto-striatal dysfunction. In particular, aphasia should not be confused with a decreased verbal output or stereotypic repetition induced by catatonia. The primary cognitive impairment described in the case reports was verbal fluency/generation, a function mediated by the dorsal medial frontal system. Overall, according to the authors[195,196], symptoms of catatonia often varied, aligning with psychopathological changes within the associated medical condition or psychiatric disorder. By contrast, frontotemporal dementia consistently worsened over time. Similarly, improvement of cognitive symptoms quickly following the administration of lorazepam is typically indicativee of catatonia. Furthermore, an important co-morbidity of catatonia in elderly individuals is delirium, which is problematic because delirium is essentially an exclusion criterion according to the DSM-5-TR. Studies in acute medical settings showed that delirium coexisted in 30–50% of patients with catatonia who were>65 years of age; in these cases, the clinical presentation was typically retarded-stuporous[197,198]. Interestingly, in acute psychogeriatric wards, the prevalence of delirium as a co-morbidity decreases, because delirium was reported in 4.8%[33] and 10%[199] of catatonic cases.

[H1] Management

[H2] General principles of treatment

The management of catatonia encompasses three critical facets — the direct management of the catatonic syndrome itself, incorporating interventions such as benzodiazepines, ECT and alternative therapies such as selected (or certain) antipsychotics; the treatment of any underlying conditions including medical or psychiatric diseases, or a composite of both; and the prevention of any medical complications that may arise as a consequence of the catatonic state.

[H2] International guidelines

To date, six international guidelines for the treatment of catatonia have been published[1,200-202]. The European Association of Psychosomatic Medicine[203] and the US Academy of Consultation-Liaison Psychiatry[200] have developed guidelines for managing catatonia in patients with a pre-existing medical condition. The general treatment strategy for catatonia is prompt administration of lorazepam irrespective of the aetiology[1,168]. Partial responses to lorazepam can be supplemented with adjunctive use of amantadine or memantine[90]. Patients who do not show improvement with benzodiazepines within few days or exhibit malignant catatonia should be provided with ECT. When treating catatonia associated with another medical condition, removal of the causative agents and the treatment of the underlying medical condition should be a priority. Current evidence does not sufficiently support the use of antipsychotics or stimulants for the treatment of Catatonia associated with another medical condition[200]. The guidelines on schizophrenia provided by the World Federation of Societies of Biological Psychiatry[201], the American Psychiatric Association, and the German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN) acknowledge catatonia and recommend treatment options such as benzodiazepines, ECT or glutamate antagonists (amantadine and memantine)[90]. The British Association of Psychopharmacology (BAP)[1] formulated evidence-based consensus guidelines regarding the treatment of all types of catatonia (for special considerations in the treatment of catatonia see Table 4) and recommends benzodiazepines, ECT other pharmacological (for example, antipsychotics, anticonvulsive drugs and glutamate antagonists) and neuromodulatory therapies (such as rTMS) for the treatment of catatonia.

[H2] GABAergic medications

The treatment of catatonia with benzodiazepines is considered a cornerstone of therapy, particularly in cases of acute and severe catatonia. Benzodiazepines, such as lorazepam or diazepam, are preferred agents owing to their rapid onset of action and effectiveness in targeting the underlying GABAergic dysregulation often associated with catatonia. Any treatment of catatonia should begin with the diagnosis according to ICD-11 or DSM-5, a clinical assessment of the urgency of intervention and, if not diagnostically entirely clear, a LCT **(Figure 3).** Earlier studies[166,167] have demonstrated a notable and rapid reduction in the BFCRS score within 10–15 minutes after lorazepam administration. No correlation was observed between the severity of catatonia and the effectiveness of lorazepam[167,204 205], nor between lorazepam dose and response[206].

A systematic review of catatonia treatment[207] showed lorazepam was the most extensively studied medication for catatonia. The average proportion of response and remission rates documented in Western studies ranges from 66% to 100%[207]. In Asian studies, the response rates ranged from 0% to 100%[207]. However, a 12-week-long, random assignment, double-blind, placebo-controlled cross-over trial with lorazepam conducted in Hong Kong[13] in clinically stable patients with chronic schizophrenia, who also displayed enduring catatonic features, showed that lorazepam had no effect. Further, a Cochrane review[208] identified only one double-blind cross-over study that compared lorazepam with oxazepam in the treatment of catatonia associated with SSD and mood disorders in 17 patients. The study found no significant difference between the two benzodiazepines. Properly designed and powered studies investigating the efficacy of lorazepam in different types of catatonia are warranted.

Although lorazepam was used in the majority of studies on catatonia, diazepam can also be administered to treat catatonia. A few small uncontrolled studies have shown improvement of catatonia with diazepam if there was no response following lorazepam delivery[209,210]. However, double-blind randomized controlled clinical trials comparing the efficacy of lorazepam and diazepam in catatonia are lacking. Zolpidem, a selective positive modulator of the $GABA_AR$, has also demonstrated efficacy in catatonia[211-213]. For diagnostic and therapeutic purposes, zolpidem is typically administered orally, and the lack of parenteral formulation restricts its application.

Finally, successful treatment of catatonia with lorazepam or other benzodiazepines will require careful and gradual tapering of the medication owing to the risk of GABAergic withdrawal rebound catatonia. Occasionally, patients can be recommended to stay on the benzodiazepine for an extended period of time[214]. In particular, when patients respond to intravenous lorazepam, transition to oral medication can sometimes result in the return of catatonic signs owing to longer elimination half-life (~14–20h) of intravenous lorazepam than the oral form (~8–11h)[215]. This can require an adjustment of the oral dose of lorazepam to prevent rebound catatonia. Therapy with benzodiazepines must always be monitored clinically because long-term usage, which may be necessary in particular cases, can result in the development of tolerance, dependency and the occurrence of withdrawal symptoms upon cessation, making prescribing difficult[216].

[H2] Electroconvulsive therapy

Since the 1930s, ECT has been a highly effective intervention in the treatment of catatonia. While often associated with controversy and misunderstanding, the role of ECT in catatonia therapy is grounded in its ability to rapidly and consistently alleviate catatonic signs, providing individuals with a swift path to recovery when other interventions have proven ineffective or when the condition poses substantial risks to patients' health and well-being (for example, elderly and/or patients with delirium)[31]. The mechanism of action of ECT in catatonia remains a subject of ongoing research, but its capacity to induce therapeutic seizures, restore neurotransmitter balance and modulate neuroplasticity are thought to contribute to its therapeutic efficacy[217,218].

A systematic review concluded that ECT, rTMS, and transcranial direct current stimulation (tDCS) reduced symptom severity, sometimes up to full symptom remission when treating catatonia associated with SSD and malignant catatonia[219]. **[Au: Please check if my edits are correct; I have edited them for brevity. OK]** In addition, one review specifically examined ECT for treating catatonia in children and adolescents and demonstrated a response rate of 75%[220]. The response rate was higher in patients with acute and less severe catatonia than in patients with severe catatonia[220]. Furthermore, another review has shown that ECT is a safe and effective treatment option for catatonia in older adults[30].

Based on an ECT registry in Singapore, one study[221] showed a significant improvement in overall psychiatric symptoms across five indications including catatonia after six sessions of ECT. A retrospective study examining data from 20 patients with catatonia showed that ECT effectiveness was more noticeable in motor-related symptoms, such as stupor and mutism than signs like echophenomena, dyskinesia, stereotypy, and perseveration.

[H2] Dopaminergic medications

The efficacy of dopamine receptor antagonists and partial agonists in the management of catatonia is a controversial topic. A systematic review [222] showed that catatonic signs might be indicative of a negative reaction to FGA in patients with chronic schizophrenia, and warned of the potential for inducing NMS. On the other hand, SGA, specifically clozapine, may be effective in treating schizophrenia with catatonic signs[222]. In patients who had been were taking FGA before developing acute catatonia, the risks and benefits of reducing or stopping FGA should be considered. A pharmacovigilance study using the VigiBase system found that the use of FGA was associated with a higher risk of catatonia than SGA, highlighting the pharmacodynamic hypothesis of antipsychotic-induced catatonia[223]. Another systematic review[224] identified that at least 80% of patients with catatonia experienced some improvement after treatment with clozapine. Furthermore, studies have shown beneficial effects of SGA other than clozapine in catatonia associated with schizophrenia or other primary psychotic disorders including case reports with aripiprazole, olanzapine, risperidone, ziprasidone and quetiapine[1].

Overall, the potential benefits and risks of antipsychotics should be thoroughly evaluated for each case. After the reversal of catatonia with lorazepam, depending on the aetiology, psychosis may continue and patients might need an SGA. Most often the use of an SGA, such as clozapine[1], aripiprazole or olanzapine[1], while continuing lorazepam to prevent the reemergence of catatonia and the development of NMS, may be indicated. According to the clinical experience of the authors, in some patients with psychotic catatonia with positive symptoms (for example, delusions, hallucinations or ego-disturbances) who were on antipsychotic medication before the onset of catatonia,

antipsychotics could be tapered off over weeks or months after an acute catatonic episode. However, this reduction should be done in the presence of catatonia-buffering benzodiazepines or maintenance ECT unless maintenance antipsychotics may be required according to national and international guidelines. However, no evidence nor guidelines exist for safely reducing or stopping antipsychotics in patients with catatonia.

[H2] Other therapies

If benzodiazepines have not helped and ECT is not viable or accessible, amantadine and memantine may be beneficial for alleviating catatonia[90]. Amantadine and memantine act as noncompetitive antagonists of the NMDA receptor. Both drugs can be given in addition to benzodiazepines or alone, but evidence regarding efficacy of monotherapy or combination therapy is lacking[1].

[H2] Perinatal catatonia

Catatonia can occur even in women without previous psychiatric history during pregnancy, childbirth and in the postpartum period. The question of which treatment option is best for catatonia patients during perinatal period arises. Studies examining the effects of benzodiazepines and ECT during the perinatal catatonia are restricted to single case reports[225-227], a case series[228] and a cohort study using electronic health records[29] showing no adverse effects or complications for the patient and the foetus or newborn[225,226,229,230]. One study [29] identified 21 women, who presented with catatonia after giving birth and were admitted to a psychiatric facility for an acute psychotic episode. All patients were treated with antipsychotics, 19 (90 %) received benzodiazepines and 2 (10%) received ECT and no adverse effects were reported. The presentation of catatonia during the peripartum period was similar to that of other types of catatonia. Furthermore, benzodiazepines might lead to adverse effects in both breastfeeding mother and her child. For example, a nationwide case-time-control study [231] (=design to effectively mitigates the influence of unmeasured confounding factors when exposure fluctuates over time[232]), analyzing 3 067 122 pregnancies found a higher risk (odds ratio [OR], 1.69; 95% CI, 1.52–1.87) of miscarriage linked to the use of benzodiazepines. Hence, benzodiazepines should only be given as briefly as possible during, if at all, until ECT can be commenced. In line with this recommendation, ECT should be regarded as a viable and secure alternative in therapeutic decision-making for managing perinatal catatonia. Overall, ECT and

793 medication choices should be made in consultation with a perinatal psychiatrist,
794 obstetrician or other healthcare provider with expertise in managing mental health in
795 pregnant women.
796
797 ***[H2] Paediatric catatonia***
798 A comprehensive assessment to identify the root causes, which may involve
799 medical and psychiatric factors, is crucial for the effective management of paediatric
800 catatonia. Prioritizing the safety of the child or adolescent is of utmost importance, as
801 catatonia can result in self-harming actions and aberrant cognitive development. A
802 multidisciplinary team is involved in the treatment process, and care must include
803 continuous monitoring, psychosocial support (including for the family members) and
804 long-term planning. Additionally, legal and ethical aspects should be taken into
805 account, particularly when contemplating interventions such as ECT. Finally, adopting
806 a thorough and personalized approach is crucial to achieve the most favourable results
807 in paediatric catatonia as missing this diagnosis could compromise the child's long-
808 term psychological and neurobiological development.
809
810 ***[H2] Geriatric catatonia***
811 Catatonia in elderly individuals can be challenging to manage, and the choice
812 of treatment should take into consideration the individual's overall health, medical
813 history and potential risks associated with certain medications, including
814 benzodiazepines[31]. Older adults can often exhibit increased sensitivity to medications
815 including benzodiazepines, owing to changes in metabolism and organ function, which
816 occur with aging. This heightened sensitivity can increase the risk of adverse effects,
817 including oversedation, cognitive impairment, delirium, falls due to poor balance and
818 subsequent injuries, or respiratory depression. Furthermore, elderly individuals often
819 take multiple medications, and benzodiazepines, even in low doses, can interact with
820 other drugs, potentially leading to adverse effects or reduced efficacy of other
821 medications. Nevertheless, the benefit-risk ratio may favor the use of a lorazepam trial
822 on an individual basis as catatonia may be misdiagnosed as dementia in elderly
823 patients with depression[233,234].
824
825 **[H1] Quality of life**

Although a few studies have mentioned proxies for quality of life such as global and social functioning[235,236], studies that specifically focused on the quality of life patients with catatonia are still missing. One main limitation is the lack of specific instruments for measuring quality of life in catatonia. Hence, an important first step towards this goal might be the examination of the subjective experience of these patients.

A systematic study examined the subjective experiences in 24 patients with acute, akinetic catatonia, three weeks after their initial diagnosis and admission[237].Patients with catatonia experienced a reduced subjective awareness of their abnormal movements. Instead, these patients perceived cognitive symptoms such as ambivalence or affective symptoms such as uncontrollable emotions very intensely. Further, the study differentiated between an emotional (intense anxiety) and a non-emotional, specifically cognitive (predominantly ambivalence) subtype of catatonia in terms of subjective experience[237].

[Au: Please check if my edits to this statement is correct I have now modified the sentence] In another study[238], catatonia patients' 'self' (according to personal construct systems developed by Landfield[239,240]) did not substantially differ from patients with schizoaffective or mood disorders. However, their 'ideal self' (based on Landfield[239,240]) exhibited notable differences compared with the control and the non-catatonic psychiatric group, particularly in terms of high self-esteem and high empathy. The concept of 'disease-self' in the acute catatonic state was characterized by a state of isolation and complete lack of social contact. We might speculate that these findings emphasize the importance of an engaged therapeutic interaction with the patient during the acute catatonic state.

Commented [DH5]: I wanted to say that "Self" of catatonic patients did not differ significantly from the other groups.

In addition, another study analyzed electronic healthcare records from 68 patients with catatonia focusing on their psychopathology (using BFCSI) and internal subjective experience (using the text within the health records); 35% of the patients reported experiencing fear during catatonic episodes, whereas others reported more negative emotions[241]. Interestingly, most of the participants (72%) provided a meaningful narrative explanation for catatonia. The range of symptoms included hallucinations, such as auditory verbal commands to refrain from eating or speaking, as well as delusions, such as paranoia or a sense of being controlled by external forces. An additional category was explanations for certain peculiarities that included actions such as moving to maintain body warmth or choosing not to respond due to a desire for privacy. Most participants (88%) demonstrated some recollection of catatonia, but only

39% of the cases clearly demonstrated its awareness. Another study[242] found that the primary themes of catatonic episodes focused on longing for loved ones, increased fear, intense anxiety, negative emotions, aggression, obedience and withdrawal. Using a modified version of the self-report questionnaire called the Northoff Scale for Subjective Experience in Catatonia (NSSC), one study showed significant correlation between the total NSSC score and total scores of the NCRS, Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), and the rating scale for Trait Anxiety, thus confirming its validity[243,244]. The NSSC not only reflects the subjective experience of patients with catatonia but can also provide an indication of the severity of catatonic signs and other symptoms.

In summary, understanding the subjective dimensions of catatonia may have the potential to inform targeted neurobiological and psychotherapeutic interventions and support psychological and process-based mechanisms aimed at improving the well-being and quality of life of patients with catatonia. Hence, we strongly recommend post-acute psychotherapy for patients regarding their discrete complaints and personal problems. Using the framework of process-based therapy[245] might be a conclusive starting point for psychiatrists and psychotherapists to reorganize and combine established and evidence-based cognitive-behavioral strategies to meet the needs of affected individuals.

[H1] Outlook

Catatonia research continues to advance psychiatry, not only in relation to this intricate syndrome itself, but also in the wider domain of mental health disorders[246]. Catatonia features a peculiar combination of objective motor, affective, and behavioral signs combined with a distinctive subjective experience of these signs in a highly meaningful way[243,244], which distinguishes catatonia from primary motor disorders. Extrapolating findings from animal models of tonic immobility may advance our understanding of the underlying human neurobehaviour and fear neurocircuity[247].

As in various other mental disorders, catatonia paradigmatically illustrates the need to converge and integrate objective symptoms and subjective experience in their shared features. The starkness of catatonia's experience makes it easy to look into the extensional identity present in the science (brain) and psychological (mind) aspects of its psychomotor symptoms, which may even hold clues to the difficult problem of consciousness[250]. These characteristics include the changing patterns of time and

space in both mental and brain activity, as well as how they show up together in the signs of catatonia. Manifestations of catatonia are thus conceived as primarily spatial and temporal alterations as manifest in both the brain and the experience amounting to a phenomena, known asspatiotemporal psychopathology"[248,249,251-253]. A study involving patients with catatonia and Parkinson disease showed significant differences in all items including even in their first-person subjective experience of akinesia. This finding is clinically relevant as the consideration of the subjective experience of the spatial and temporal features may in the future help in differentiating catatonia from other more primarily motor disorders like Parkinson disease[237,254],thereby, improving its early recognition and treatment. This integration of subjective and objective parameters can lead us to better understand the origins of catatonia.

One key here is, for instance, the close relationship of GABAergic changes, aberrant interpretation of negative stimuli (based on OFC dysfunction and its complex interaction with anterior cingulate cortex, dorsolateral PFC, and frontopolar regions involved in emotion regulation[255] and psychomotor decision-making), and catatonic signs as illustrated by the often dramatic and immediate effects of lorazepam[256]. The rapid effect of lorazepam may help unravel the role of GABAergic neural inhibition for the processing of especially the affective functions including strong subjective experiences[121,122], for which future studies combining magnetic Rrsonance spectroscopy, neuromelanin MRI and fMRI are needed. In particular, studies examining the relationship between the network dysfunction (for example, default mode, sensorimotor and fronto-limbic network) and abnormalities in the GABAergic, glutamatergic and dopamine systems are warranted. Specifically, fluctuations of GABA, glutamate and dopamine selected regions of different networks such as the default mode (for example, anterior and posterior cingulate cortex), fronto-limbic (amygdala and hippocampus), salient network (insular cortex), and sensorimotor (for example, supplementary motor area) in different catatonic states should be investigated.

Advancing the development of more efficient therapies for catatonia, such as precise pharmaceutical interventions, refined ECT protocols, and individualized psychotherapy, will not only enhance the well-being of patients with catatonia but also set a paradigm for innovation in psychiatric care. Moreover, understanding why lorazepam works so quickly and accurately for psychomotor symptoms in catatonia can help us understand why lorazepam works so well for other psychiatric disorders

such as anxiety disorder, psychotic depression, mania or substance-induced psychotic disorders. The conceptual development in the last 150 years and the improved diagnostic accuracy in catatonia can act as a model for enhance diagnostic precision in other mental health disorders, minimizing misdiagnoses, and enabling early treatments. In addition, highlighting the often-good prognosis of catatonia might contribute to debunking the societal prejudice associated with mental illness by unraveling its intricate characteristics and emphasizing the importance of subject-oriented and scientifically-supported treatment. Overall, progress in catatonia research has the capacity to have a widespread impact on the field of psychiatry, promoting a more profound understanding of the human brain and its mind, by which we can facilitate the development of more efficient, personalized, and stigma-reducing strategies for mental healthcare.

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Author contributions

Introduction (DH, GF, GN, GU, AML); Epidemiology (DH, GN, JPR); Pathophysiology (DH, GN, FS, RCW, GU); Diagnosis, screening and prevention (DH, GN, JEW, SF, FS, GU); Management (DH, GN, JPR, GU, GF, FS); Quality of Life (DH, GN, KMK, SF); Outlook (DH, GN, AML, GU); Overview of the Primer (all authors)

Competing interests

The authors declare no competing interests.

Related links

Northoff Catatonia Rating Scale Assessment Resources: http://www.georgnorthoff.com/scales

Bush-Francis Catatonia Rating Scale Assessment Resources: https://www.urmc.rochester.edu/psychiatry/divisions/collaborative-care-and-wellness/bush-francis-catatonia-rating-scale.aspx

BAP guideline: https://www.bap.org.uk/pdfs/BAP_Guidelines-Catatonia.pdf

968
969 **Table 1: Overview of clinical picture of catatonia**

Prevalence	2.3–9% of patients with psychiatric disorders show signs of catatonia. Incidence in the general population: 10.6 (95% CI: 10.0-11.1) per 100,000 person-years
Gender ratio	1:1
Frequently used classification systems and rating scales	the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) and international classification of diseases (ICD)-11; Bush-Francis Catatonia Rating Scale (BFCRS) and Northoff Catatonia Rating Scale (NCRS)
Characteristic signs	Co-occurring motor, affective and cognitive-behavioral signs
Characteristic age of onset	Catatonia occurs throughout the entire lifespan. Catatonia is an important psychiatric disorder in children and adolescents, as well as in older (>65 years of age) patients.
Important comorbidities	Catatonia due to another psychiatric disorder — autism spectrum disorder, affective disorders, and schizophrenic disorders; Catatonia due to a medical condition — autoimmune encephalitis (especially NMDAR encephalitis), systemic lupus erythematosus, thyroid disease, epilepsy, and drug intoxications or withdrawals
Existing guidelines	Evidence-based consensus guidelines for the management of different catatonia subtypes: British Association for Psychopharmacology (BAP) (all catatonia categories); German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN) S3 Guideline for Schizophrenia (catatonic schizophrenia); Schizophrenia Guidelines of the American Psychiatric Association (APA) (catatonic schizophrenia); National Institute for Health and Care Excellence (NICE) (catatonic schizophrenia); World Federation of Societies of Biological Psychiatry (WFSBP) (catatonic schizophrenia); Guideline of the Academy of Consultation Liaison Psychiatry (catatonia associated with medical illness).

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973 Adapted from[260].
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975 **Table 2: The most important differential diagnoses of catatonia[a]**

Differential diagnoses	Distinguishing features from catatonia
Stiff-Person Syndrome	Head retraction reflex
Progressive encephalomyelitis with rigidity and myoclonus	GAD-65, glycine or DPPX antibodies usually present
Medication-induced parkinsonism or Parkinson's disease	Patients are usually interactive and cooperative Tremor usually present Insidious onset in case of Parkinson's disease **[Au: does this refer to medicine-induced Parkinson? Sorry, it should be Parkinson's disease]**
Dystonia	Stupor and affective catatonic signs absent Generally good response to anticholinergics
Akathisia	Lack of other behavioural signs of catatonia (for example, echophenomena, posturing, verbigeration, mutism, staring)
Serotonergic syndrome	Triggered by serotonergic drugs; often presents with myoclonus, hyperreflexia and diarrhoea
Aphasia	Motor function intact
Anarthria (complete loss of motor speech production)	Language preserved in written form
Selective mutism	Communication completely intact in certain settings
Non-convulsive status epilepticus	Often history of epilepsy; EEG usually helpful; CAVE: Distinguishing between both syndromes on the basis of physical examination may be difficult.
Locked-in syndrome	Individuals usually have preserved vertical gaze and blinking – generally keen to attempt to communicate using these MRI shows pontine lesions No response to benzodiazepines (for example, lorazepam challenge test) or other treatments
Delirium	Tends to resolve with reversal of underlying medical condition (though may be delayed)
Coma	No resistance to eye-opening
Vegetative state	No volitional responses and no visual tracking No resistance to eye-opening
Abulia	Intact motor functions; lack of internally generated actions, but response to external stimuli.
Autoactivation deficit syndrome	
Akinetic mutism	Lack of affective and positive or active motor (for example, catalepsy, echopraxia, mannerisms, stereotypies, gegenhalten, mitgehen) features
Functional neurological disorder	Usually progression from milder states of functional paralysis; not all symptoms of the three ICD-11 categories present
Intellectual disability	Chronic without sudden decompensation
Malingering or factitious disorder	Past benzodiazepine misuse Simulating clinical features (for example, pouring water to simulate incontinence) History of interpersonal problems

976 EEG, Electroencephalography, CAVE, Latin for "to be careful". **[Au: Please**
977 **complete the abbreviations]**

978 Adapted from Ref[1].

Commented [DM6]: Please can you expand what CAVE stands for?

Commented [DH7R6]: It is Latin for "to be careful". It is sometimes used in medical books. If you want to use a different term, I'm fine with that.

979 **Table 3: Differentiating signs of catatonia from delirium[a]**

Features [Au:OK? OK]	**Catatonia**	**Delirium**
Clinical status	Often medically stable; however, can exhibit malignant features or have catatonia secondary to primary medical condition, may affect all ages	Due to medical illness, advanced age is a risk factor but affects all ages
Arousal	Patients are usually awake and conscious. Typically alert but may exhibit reduced or increased arousal, mixed forms of hyperkinetic and hypokinetic states in relation to motor functions and behavior. When catatonia co-occurs with delirium reduced arousal or fluctuating consciousness may occur.	Most common feature is reduced level of arousal but hyperarousal and agitation may occur; fluctuating levels of consciousness a hallmark feature.
Psychopathological symptoms	Usually psychomotor signs with parakinetic movements, mostly without delusions and hallucinations but may be evident depending on the underlying psychiatric aetiology; decreased eyeblinking, speech latency and negativistic response to eye and mouth opening as signals of catatonia nested in delirium.	All positive symptoms possible, with hallucinations and delusions the most frequently present.
Thought process	Repetitive and stereotyped thoughts, and perseveration common but the absence of thought process abnormality is not unusual.	Disorganized or tangential thought process is common.
Language abnormality	Mute, whispered, verbigeration, or echolalia. Increased volume and rate may be present in catatonic excitement.	Low mumbling speech common in hypokinetic states and loud rapid speech may be present in hyperkinetic states.
Orientation	Often clear but may be difficult to assess. May be disoriented in co-morbid delirious states.	Clouded; typically disoriented.
Emotional state	Usually anxious or depressed in the akinetic state, occasionally aggressive and impulsive in the hyperkinetic state which may occur more frequently in mania.	Consistent with motor subtype and the pre-dominant psycho-pathological symptoms.
Interpersonal	Disengaged, negativistic; occasionally automatically obedient (for example, Mitgehen).	Inattentive often sedated with limited meaningful communication possible.
Response to benzodiazepines	Patients tend to become more alert and active (e.g., mutism improves). May initially become drowsy then show improvement in signs over time.	Exposure to benzodiazepines may cause delirium. Exposure typically leads to worsening of arousal and orientation.

980 **Adapted from Ref[257].**

Table 4: Special considerations in Catatonia management[a]

Special case	Treatment recommendation
Antipsychotic-induced catatonia	Stop antipsychotics and treat with benzodiazepines
Benzodiazepine withdrawal catatonia	Restart benzodiazepines
Chronic, mild catatonia in schizophrenia spectrum disorders	Treat with aripiprazole or clozapine with lorazepam if needed
Clozapine (and other SGA) withdrawal catatonia	Restart clozapine (sometimes rapid titration is needed) or start ECT
Malignant catatonia	Stop dopamine antagonists and treat with lorazepam and ECT
Neuroleptic malignant syndrome	Stop dopamine antagonists and anticholinergics and initiate supportive medical care in the ICU (benzodiazepines and dantrolene); treat with lorazepam and ECT
Perinatal period	ECT is the first-line therapy; long-term administration of benzodiazepines should be avoided in pregnant patients

SGA, second-generation anti-psychotic drugs; ECT, Electroconvulsive therapy; ICU, intensive care unit

Adapted from Ref[1]

[a]Importantly, —these tables are intended to help clinicians with the differential diagnosis, but do not necessarily rule out the diagnosis of catatonia. In addition to the medical and/or psychiatric diagnosis, these patients may also fulfil the criteria for catatonia according to ICD-11 or DSM-5-TR. In such a case, catatonia is not a differential diagnosis, but a comorbid diagnosis.

Figure legends

Figure 1. Overview of the neurotransmitter systems (biochemical level) and brain networks (system level) that are involved in the pathogenesis of catatonia. Biochemical level: positive symbol (+) represents that these agents improve catatonia; negative sign (-) indicates that these agents might induce or worsen catatonia. System level: mPFC: medial prefrontal cortex, OFC: orbitofrontal cortex, LiS: limbic system, RN: raphe nucleus, SN: substantia nigra, SMA: supplementary motor area, M1: primary motor cortex, BG: basal ganglia, MB: midbrain, CER: cerebellum. **(adapted from[259])**

Figure 2. Lorazepam challenge test (LCT) algorithm in urgent and low suspicion of catatonia. LCT is a diagnostic procedure that can be used to confirm or rule out catatonia. Lorazepam is administered to the patient orally, intravenously or intramuscularly. Before and 15-30 minutes after the administration of lorazepam, the patient should be examined for signs of catatonia using NCRS or BFCRS. A positive response, characterized by a marked reduction (50% or more) in catatonia signs, is strongly suggestive of catatonia. If catatonia symptoms improve, treatment with lorazepam can be continued. If catatonia symptoms do not improve, LCT should be performed at a higher lorazepam dose. If even a higher lorazepam dose does not improve the catatonia signs and there is still a strong suspicion of catatonia, ECT should be considered. **[Au: Please can you include couple of statements to describe the figure]**

Figure 3. A step-by-step algorithm for the management of catatonia. [Au: title ok? Yes]

The algorithm begins with the diagnosis of catatonia according to the international classification of diseases (ICD) -11 or the DSM-5-TR. Subsequent steps include the administration of first-line treatments such as lorazepam (benzodiazepines) and/or ECT, with pathways branching based on comorbid delirium or schizophrenia spectrum disorders (SSD). Abbreviations: NCRS: Northoff Catatonia Rating Scale; BFCRS: Bush-Francis Catatonia Rating Scale; ECT: Electroconvulsive therapy; CLZ: Clozapine; BZD: Benzodiazepines.

Box 1. Catatonic signs according to ICD-11

Decreased psychomotor activity

- Staring
- Ambitendency
- Negativism
- Stupor
- Mutism

Increased psychomotor activity

- Extreme hyperactivity or agitation for no reason with non-purposeful movements
- Uncontrollable, extreme emotional reactions
- Impulsivity (sudden engagement in inappropriate behavior without provocation)
- Combativeness (striking out against others, usually in an undirected manner, with or without the potential for injury).

Abnormal psychomotor activity

- Grimacing
- Mannerisms
- Posturing
- Stereotypy
- Rigidity
- Echolalia/Echopraxia
- Verbigeration
- Waxy flexibility
- Catalepsy

ICD, International classification of diseases. Adapted from Ref[5].

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