APA Resource Document

Resource Document on Catatonia

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This resource document is intended to support psychiatrists, trainees, and other mental healthcare workers and to provide a framework for assessing the adequacy of existing violence prevention policies and a list of resources for the development of state-of-the- art policy approaches. This document is not intended to be comprehensive or completely systematic in nature, nor is it a practice guideline. It is highly recommended that mental healthcare employees pursuing improvements in local policies consult with their facility/practice administrator, risk manager, and legal counsel as well as local, state, and federal regulations and policies that pertain to healthcare and workplace violence.

Prepared by the Catatonia Work Group of the Council on Consultation-Liaison Psychiatry

Authors: Jo Ellen Wilson[1,2], Mark A. Oldham[3], Andrew Francis[4], Dina Perkey[5], Eric Kramer[5], Shixie Jiang[6], Jennifer Yoon[5], Scott Beach[7,8], Gregory Fricchione[7,8], Matthew Gunther[9], Jihoon Ha[10,11], James Luccarelli[7,8], Jordan Rosen[12], Dallas Hamlin[4], Joseph D. Dragonetti[13], Avi Gerstenblith[14], Anne Louise Stewart[12], Jon Sole[9], James A. Bourgeois[15]

[1]Department of Veterans Affairs, Geriatric Research, Education and Clinical Center (GRECC), Tennessee Valley Healthcare System, Nashville, TN
[2]Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN
[3]University of Rochester Medical Center, Rochester, NY
[4]Department of Psychiatry and Behavioral Health, Penn State Health Milton S. Hershey Medical Center, Hershey, PA
[5]Department of Psychiatry and Human Behavior, University of California, Irvine Health, Orange, CA
[6]Department of Psychiatry, University of Florida, Gainesville, FL
[7]Department of Psychiatry, Massachusetts General Hospital, Boston, MA
[8]Harvard Medical School, Boston, MA
[9]Stanford University, Division of Medical Psychiatry, Department of Psychiatry and Behavioral Sciences, Stanford, CA
[10]Weill Cornell Medical College, Cornell University, New York, NY
11New York-Presbyterian, New York, NY
[12] Department of Psychiatry and Neurobehavioral Sciences, University of Virginia School of Medicine, Charlottesville, VA
[13]Department of Psychiatry and Behavioral Medicine, Wake Forest University School of Medicine, Winston-Salem, NC
[14]Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD
[15]Department of Psychiatry and Behavioral Sciences, University of California, Davis Medical Center, Sacramento, CA

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Introduction

Catatonia is a neuropsychiatric syndrome characterized by marked and oftentimes contradictory abnormalities in behavior, motor tone, and volition (1). Historically, catatonia has been described in the setting of severe psychiatric illnesses, such as schizophrenia spectrum disorders, manic or major depressive episodes in bipolar disorder, major depressive disorder, or, less commonly, in other psychiatric illness (e.g., autism spectrum disorder). Recent studies (2-4) have shown that catatonia signs and symptoms can also occur due to major neurologic and general medical illness, including critical illness. This resource document summarizes the current literature on the phenotype, diagnosis, and management of catatonia. The authors provide a contemporary review of catatonia to assist psychiatrists and other clinicians who may encounter and care for patients experiencing catatonia.

Karl Kahlbaum first described the syndrome of catatonia in his monograph *Die Katatonie oeder das Spannugsirresein,* (5) published in 1874. Although he described catatonia across a variety of general medical, neurologic, and psychiatric illnesses, catatonia became regarded primarily, if not solely, as a subtype of schizophrenia over the ensuing years. Through the revised third edition of *The Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III-R*), catatonia was recognized exclusively as a subtype of schizophrenia. Beginning with *DSM-IV*, catatonia has been recognized in association with a growing range of primary psychiatric and general medical conditions, and descriptions of the catatonia phenotype have expanded in detail and range of diagnostic features (6).

The prevalence of catatonia in acute inpatient psychiatric settings ranges from 9 to 20% (7-10). Work by Abrams and Taylor revealed a high prevalence of catatonia in certain illnesses, including depressive and bipolar disorders, with up to 20% of patients with an acute manic episode exhibiting classic catatonic signs (11-15). Although epidemiological studies on catatonia in medically ill populations are often confounded by catatonia under-detection, it is well-established that catatonia can manifest as a harbinger of many acute onset general medical conditions (10, 16-18). Studies of patients seen by psychiatric consultation-liaison services at general hospitals report a 1.6–8.9% prevalence of catatonia across all medical services, varying across age groups and associated medical conditions (19, 20). Catatonia can have a variable presentation; in many patients, especially at onset, it can be *incomplete* regarding range of symptoms and/or *intermittent* in terms of timing. Nonetheless, even *partial or subthreshold* presentations of catatonia, in the appropriate context, warrant evaluation and management to mitigate progression and complications

Patients with catatonia have increased morbidity and mortality (21-27). It puts patients at risk for a variety of medical complications, including aspiration, dehydration, malnutrition, contractures, pulmonary embolism (PE), and rhabdomyolysis, which can lead to renal failure (21). In one study from France of 35 patients aged 12 to 18 years with catatonic schizophrenia, patients with catatonia had a 60-fold increased risk of premature death, including suicide, when compared to the general population (22). In a case series from a death registry of state

psychiatric hospitals in Kentucky, death secondary to PE, in the context of hypoactive catatonia, was considered the most common preventable cause of death over a 15-year period (23).

Without treatment, *malignant* catatonia can be lethal, although the data on the natural history of this condition is scant (24, 25). Fortunately, for most patients with catatonia, prompt treatment with benzodiazepines and/or electroconvulsive therapy (ECT) can be lifesaving, regardless of the underlying etiology (26-35). Catatonia is an increasingly commonly recognized syndrome in critical illness, although it remains underreported in all clinical settings and is not part of most routine screening programs (3, 36, 37). Whereas the exclusion of concomitant catatonia diagnosis in the context of delirium has been a consistent feature of the DSM criteria, the ICD-11 recognizes catatonia as a distinct condition and allows for the co-diagnosis of both delirium and catatonia if they occur simultaneously. The ICD-11 criteria represent a more realistic and inclusive conceptual stance that reflects common presentations across medical settings.

Evaluation

Catatonia can present as *hypokinetic* (reduced activity), *hyperkinetic* (elevated activity), or *parakinetic* (odd, purposeless motor behaviors unrelated to *amount* of motor activity), so catatonia should be considered when a patient demonstrates an altered level of motor activity and/or peculiar behavior(s). This is especially relevant when the motor behavior is inappropriate to context or when occurring in the setting of *other* characteristic features of catatonia (e.g., mutism, negativism). The diagnosis of catatonia is based on observation, interview, physical examination, and review of vital signs and oral intake (1). Patients with catatonia may be unable to provide an adequate history, so collateral sources of information should be obtained when available. The observations of clinical staff (e.g., nurses) should also be sought because catatonic features often fluctuate over time and may not be present during the clinical examination.

Rating Scales

The assessment of catatonia should be systematic and evidence-based, using a validated rating scale and standardized diagnostic criteria. A catatonia-specific rating instrument should be used to provide a reliable assessment for catatonia screening, diagnosis, and severity measurement. We recommend the use of the Bush-Francis Catatonia Rating Scale (BFCRS) (38, 39). The first 14 items constitute a screening instrument and include all 12 *DSM-5-TR* (40) diagnostic criteria for catatonia, making it an efficient tool for clinical practice (2, 41). A score of two or more on the 14 screening items is considered "positive," and prompts completion of the full 23-item scale. The full scale includes all *ICD-11* criteria for catatonia (**Table 1**). The BFCRS is scored using a

standardized clinical examination, consistent with its initial validation study. Additionally, the BFCRS is the only catatonia scale that has been validated in response to lorazepam challenge (38, 42). The BFCRS is used serially to monitor treatment response alongside other changes in clinical status (42, 43). While use of a rating scale may help formalize clinical assessment, a formal diagnosis of catatonia should be made using diagnostic criteria (e.g., *DSM-5-TR*) (40, 44).

Another widely used catatonia rating instrument is the Northoff Catatonia Rating Scale (NCRS) (45). This instrument provides the most comprehensive evaluation of catatonic signs and symptoms. The NCRS is comprised of three categories: *behavior* (15 items), *motor* (13 items) and *affective* (12 items). It includes all diagnostic criteria of catatonia in the *DSM-5-TR* (40) and *ICD-11 (46)*. The NCRS differs from other catatonia scales in its requirement of at least one feature in *each* of its three domains and its emphasis on affective symptoms. The NCRS is not ideal for clinical use because it has not been validated based on a standardized clinical examination, and its 40 items take considerably longer to complete and score than the BFCRS (39).

Other catatonia rating instruments include the Rogers Catatonia Scale and the Kanner Scale (47, 48). Additionally, the Bräunig Catatonia Rating Scale might be valuable for clinical research; however, it is impractical for clinical use due to its 45-minute semi-structured interview format (39, 49).

Diagnostic Criteria

The index criterion for a diagnosis of catatonia according to the *DSM-5-TR* (40) is that the presentation be dominated by three or more of twelve classic catatonia features (**Table 1**). The *DSM-5-TR* (40) allows for a diagnosis of catatonia associated with a primary psychiatric condition, another medical condition, or unspecified catatonia. The diagnosis of catatonia in *ICD-11* (46) differs from that in *DSM-5-TR (40)* in a few notable ways. The *ICD-11* requires three of 15 (rather than 12) clinical features, and has promoted catatonia to its own diagnostic category (46). *ICD-11* also includes a diagnosis for substance-induced catatonia and allows for a simultaneous diagnosis and delirium (46).

Physical Examination, Laboratory, Neuroimaging, and Electroencephalogram (EEG)

Every patient presenting with a first-lifetime episode of catatonia deserves a detailed clinical evaluation, and the clinician should consider conducting a workup for a range of potential psychiatric and non-psychiatric causes. Whether a workup is repeated on subsequent episodes of catatonia should be based on history and clinical examination, considering the overall severity of illness, clinical course, and possible underlying general medical and psychiatric comorbidities. When evaluating a patient presenting with a recurrent episode of catatonia, the clinician should verify that an adequate workup was completed previously, rather than presuming that it has been completed. For every presentation of catatonia, a thorough clinical evaluation and workup is essential for addressing potential causes and complications of catatonia and for care planning. Physical examination is essential. Specific tests may be performed to rule out conditions that resemble catatonia and, in the case of validated catatonia, evaluate for potential underlying causes (**Table 2**). Consistent with the concept that

catatonia can overlap with and coincide with delirium (as in the ICD-11 construct), simultaneous management of manifest clinical signs and symptoms of catatonia and ascertainment of risk factors is essential.

The medical workup for potential attributable causes of catatonia should be informed by data on the relative distribution of catatonia causes (50). The first step is to consider substance-induced catatonia. The medication list, including recently discontinued medications, should be reviewed for potential causes (e.g., benzodiazepine or clozapine withdrawal, pembrolizumab-induced encephalitis). Substance use disorders (including intoxication and withdrawal states) should also be considered (e.g., cannabis-induced catatonia; sedative, hypnotic, or anxiolytic withdrawal catatonia). The possibility of multiple concurrent substance use disorders needs to be considered.

Evaluating for an underlying cause of catatonia generally includes the usual comprehensive delirium workup. Priority should be given to evaluating for neurologic causes (*e.g.*, encephalitis, structural central nervous system lesions, seizures), as two thirds of catatonia attributed to non-psychiatric medical illness is due to such primary neurologic conditions. In the clinical evaluation of catatonia, electroencephalography (EEG) may be helpful in evaluating for an attributable neurologic cause of catatonia (51). An EEG that reveals diffuse slowing makes concurrent delirium with catatonia more likely. EEG is also key to ruling out non-convulsive status epilepticus (NCSE) manifesting as catatonia (52). The finding of the extreme delta brush

pattern on EEG in adults is pathognomonic for anti-NMDA receptor encephalitis (NMDARE, which may present with catatonia) but is a rare finding (53).

Neuroimaging may be pursued to assess for structural neurological causes of catatonia where adequate clinical suspicion exists. Although over 75% of patients with catatonia exhibit non-focal neuroimaging abnormalities, such as generalized atrophy and white matter abnormalities (54), most of these structural changes are non-specific and unlikely to be the sole proximal cause of catatonia. Therefore, except in rare instances, brain CT is unlikely to significantly inform the care of a patient with catatonia. Instead, brain MRI, which may reveal evidence of inflammation, cytotoxic edema, or space-occupying lesions, is preferred to brain CT when investigating for a potential structural neurologic cause of catatonia.

The decision of whether to pursue lumbar puncture for CSF studies should be guided by the clinical picture and, generally, made in collaboration with neurology. Autoimmune encephalitis is a well-established cause of catatonia with anti-NMDA receptor antibodies being the most common pathogenic antibody identified (55). The co-occurrence of catatonia and delirium should raise suspicion for autoimmune encephalitis (56). Additionally, the Antibody Prevalence in Epilepsy and Encephalopathy (APE2) score can also help to estimate the likelihood of autoimmune encephalitis and inform the decision of when to pursue specialized antibody testing (57).

The potential risks and benefits of the degree of clinical evaluation should be considered, as extensive testing may contribute to patient anxiety, incur excess costs and potential harms, and possibly delay empiric catatonia treatments.

Differential Diagnosis

Catatonia diagnosis is based on characteristic clinical features in the *DSM-5-TR* (40) or *ICD-11* (46). Although these two sets of diagnostic criteria differ, they concur that catatonia diagnosis requires the presence of at least three or more of these features (**Table 1**). No one clinical finding in catatonia is specific, thus other neurological and psychiatric conditions should be considered on the differential diagnosis. There are specific conditions which need to be considered as part of the differential diagnosis for each type of catatonia (i.e., the motoric types hypokinetic, hyperkinetic, and parakinetic, as well as with any motoric type of catatonia when malignant). Although not included as a diagnostic feature in *DSM-5-TR* or *ICD-11*, a positive response to lorazepam challenge as documented through improvement in scores on a standardized rating scale (see below) may increase the certainty of a catatonia diagnosis.

The following conditions share clinical features with hypokinetic (stuporous) catatonia.

Abulia/Akinetic Mutism

This disorder, characterized by reduced or absent volition, is typically due to neurologic injury affecting the ventromedial prefrontal cortex or anterior cingulate cortex (e.g., stroke, traumatic brain injury). Patients exhibit severe reductions in spontaneous movement and speech, which can resemble catatonia. However, abulia does not typically present with other classic signs of catatonia (e.g., mutism, catalepsy, posturing, echophenomena), and the presence of such would warrant further consideration of catatonia.

Hypoactive Delirium

Delirium presents with cognitive disturbances, particularly in the domains of attention, orientation, and memory. Evaluating for catatonia in the context of delirium and *vice versa* can be challenging. Both conditions can present with decreased responsiveness to external stimuli and lack of movement. Classic findings more specific to catatonia are often helpful in identifying catatonia in patients with or at risk for delirium.

Major Neurocognitive Disorder/Dementia

In later stages of major neurocognitive disorder (MNCD)/dementia, patients can develop hypokinesis and mutism. However, they do not develop classic specific catatonia symptoms such as posturing, catalepsy and waxy flexibility unless comorbid catatonia is present. Moreover, significant chronic impairment in multiple cognitive domains is typical of neurocognitive disorders (58), but not of catatonia. Obtaining a chronological history of clinical progression can be clarifying, given that most MNCDs tend to develop and worsen over time.

Locked-in Syndrome

Patients with the devastating condition locked-in syndrome are immobile and mute. These patients are often motivated to try to communicate with eye movements (which may be their only residual voluntary movements), whereas patients with hypokinetic catatonia often do not attempt to communicate spontaneously. Locked-in syndrome is caused by brainstem lesions identified on brain MRI.

Late-Stage Parkinson's Disease

Late-stage Parkinson's disease (PD) may present with immobility, rigidity, and markedly decreased speech. These patients have a known diagnosis of PD and other distinguishing features of PD, including resting tremor, positive response to levodopa and postural instability, and/or a positive dopamine transporter scan (Dopamine Transporter [DaT] Scan; based on single-photon emission computed tomography) (59).

Stiff-Person Syndrome

Patients with stiff-person syndrome (SPS) have difficulty with movement due to muscle stiffness and spasm. The condition is exacerbated by emotional stress. Symptoms such as limited movement and positive response to benzodiazepines in SPS can somewhat resemble hypoactive catatonia. SPS differs from catatonia in that these patients are verbal and are typically fully cognitively intact. A diagnosis of SPS is supported by elevated levels of glutamic acid decarboxylase (GAD) antibodies (60-62).

The following conditions should be considered in a patient with hyperkinetic (excited) or parakinetic catatonia.

Akathisia

In hyperkinetic catatonia, there are often non-purposeful and abrupt states of psychomotor agitation that may resemble akathisia. However, patients with akathisia will often describe an inner state of restlessness and discomfort that leads to and perpetuates the motor symptoms.

Akathisia may be persistent and debilitating. For some patients, short-term use of a high potency antipsychotic, D2 antagonist antiemetic (e.g., metoclopramide) or other substance exposure could cause episodic akathisia that may respond to a beta blocker or benzodiazepine. Furthermore, patients with akathisia will not typically exhibit any other signs of catatonia.

Hyperactive Delirium

Both catatonia and hyperactive delirium can present with agitation. Distinguishing features of delirium include impaired or fluctuating level of arousal, attention, and other cognitive disturbances. EEG can be helpful to confirm the diagnosis of delirium. EEG in delirium will typically show diffuse background slowing in the delta range or a variety of other distinct abnormalities (63).

Manic Episode

Both a manic episode and hyperkinetic catatonia can present with disorganized and excessive speech, agitation and/or excitation. One distinguishing feature is that agitation in catatonia is not goal-directed, whereas a manic episode may include goal-directed agitation. It is important to keep in mind that a severe manic episode and catatonia may co-occur.

Malignant Catatonia

Malignant catatonia is a life-threatening subtype of catatonia with symptoms of altered level of arousal, rigidity, autonomic instability (e.g., hyperthermia, tachycardia), and elevated serum

creatinine phosphokinase. Importantly, malignant catatonia can occur in all motoric types of catatonia, from extreme hypokinesis to hyperkinesis.

Conditions that share clinical features with malignant catatonia:

Neuroleptic Malignant Syndrome (NMS)

This life-threatening idiosyncratic reaction to dopamine blocking (usually antipsychotic) medications very often presents with malignant catatonia. As such, many experts consider neuroleptic malignant syndrome (NMS) to be a type of malignant catatonia that is precipitated by dopamine receptor blocking agents. NMS classically presents with rigidity and hyperthermia, often accompanied by mutism, delirium, and additional features of autonomic instability, such as tachycardia and hypertension. When NMS is suspected, *immediate* cessation of antipsychotic and other dopamine blocking medications is imperative. NMS may be treated with supportive measures (e.g., monitoring of vital signs, fluids, cooling blankets), dantrolene, bromocriptine, and ECT (64).

Anti-NMDAR (Anti-N-methyl-D-aspartate Receptor) Encephalitis

This condition may present with full spectrum catatonia, or patients may have only some of the classic symptoms of catatonia, including autonomic instability, and/or elevated creatine phosphokinase (CPK) as seen in malignant catatonia. However, specific symptoms of catatonia such as staring, waxy flexibility and negativism are less frequently present in NMDARE, although may be present in severe cases of NMDARE induced catatonia. NMDARE may have an

incomplete response to a lorazepam challenge test, and some patients with catatonia may not experience a clinical response to lorazepam at all. Like some forms of catatonia, NMDARE may be sensitive to antipsychotic medication exposure and can exhibit worsening of catatonic signs in the setting of high dopamine blocking ("high potency") antipsychotic medication (65-67).

Serotonin Syndrome (SS)

Although seldom considered on the spectrum with catatonia, serotonin syndrome can present with many of the classic features of malignant catatonia, including autonomic instability, hyperthermia, and rigidity. Hyperreflexia, myoclonus, and gastrointestinal symptoms can help to identify SS. Quantification of use and doses of all serotoninergic agents taken prior to presentation is necessary.

Pathophysiology

Much is yet to be elucidated regarding the pathophysiology of catatonia, but the past two decades have brought new insights (**Supplement 1**). Catatonia appears to involve disruption of the cortico-striato-thalamo-cortical (CSTC) loop system (**Figure 1**). Catatonia may result from breakdown at key nodes in parallel and overlapping neural circuits involving this loop system, preventing integration of the salience and default mode network with executive function (1, 68). For example, disruptions in the lateral orbitofrontal circuit could produce repetitive and mimicking behaviors, whereas disruption in the motor circuit could produce rigidity (69). The anterior and midcingulate cortex (ACC/MCC) is of particular interest, given its paralimbic transmodal position between the prefrontal cortex and limbic regions (70).

Catatonia has been proposed to be an evolutionary-based fear response, a remnant of a defense strategy in prey animals when confronted by predators, conserved in humans and activated in times of extreme stress, akin to lower mammals "playing dead" (71). Catatonia has also been conceptualized as a form of limbic dysrhythmia with findings of diffuse slowing and dysrhythmic electroencephalogram (EEG) tracings resembling rhythms seen in nonconvulsive status epilepticus, and treatments (e.g., benzodiazepines, valproate) that overlap with seizure management (72). Finally, neuroendocrine abnormalities may also play a role in some cases of catatonia, perhaps via hypothalamic dysfunction (72). These diverse explanatory models of catatonia reflect the complex and challenging nature of this syndrome. Additional information regarding the pathophysiology of catatonia can be found in Figure 1 and Supplement 1.

Interventions

With very few exceptions, the following section discussing treatment options is based on case reports and series and other uncontrolled studies.

Benzodiazepines

Benzodiazepines are often the first-line treatment for catatonia. Benzodiazepines are positive allosteric modulators (PAMs) of the $GABA_A$ receptor and facilitate GABAergic transmission, which is thought to be disrupted in catatonia (73). Treatment with benzodiazepines typically falls into three phases: the *challenge* (also known as the lorazepam challenge test [LCT]), the *acute phase*, and the *maintenance phase*.

Lorazepam is best described in the literature for the management of catatonia, with reported response rates of 66–100% (74). Diazepam also appears to be effective, although no head-to-head comparison studies with lorazepam exist. Other benzodiazepines (e.g., clonazepam, oxazepam) have also been used, but there is a lack of data to support their routine use (75, 76).

After catatonia has been identified on clinical examination, the LCT is the typical next step to confirm diagnosis. Lorazepam is available in both oral and parental forms including intravenous (IV) and intramuscular (IM); the bioavailability of lorazepam is 90% for the oral formulation and close to 90% for the parenteral administration. IV administration is preferred due to its faster peak effect (1–3 minutes versus 2 hours for oral administration) and long effective length of action, outlasting some benzodiazepines with longer half-lives (77). Due to its half-life of 14 ± 5

hours, lorazepam should be administered at a minimum of three times per day, but frequency may be adjusted (e.g., every 4 to 8 hours) depending on clinical response. If lorazepam is unavailable IV, IM lorazepam is a second-line option for the LCT, followed by PO formulations. Diazepam IV may be considered as an alternative when parenteral lorazepam is unavailable.

In the LCT, the initial dose of lorazepam 2 mg IV is given (1 mg in children, older adults, or those at risk of respiratory compromise). A 50% or greater reduction on the BFCRS scale is considered a positive response. The response can occur within 5 minutes but may take 2 hours or longer, especially if oral lorazepam is used (74). If there is less than a 50% response in symptoms by 30 minutes with parenteral administration or 2 hours with oral administration, another dose of 2 mg can be given. Higher doses for the LCT have been studied (e.g., 4 mg starting dose) without any overall significant difference in response, although gegenhalten appeared to show a selective response to the higher dose (74, 78).

The use of a lower dose in children, older adults, or those at high risk for respiratory compromise increases the potential for an equivocal response. Re-challenge following suboptimal response may be considered in these populations depending on clinical condition. Sedation in response to an LCT does *not* rule out catatonia; whereas patients with catatonia typically have a higher sedation threshold, some patients will initially be sedated yet will later show a positive response to the LCT upon awakening. **Figure 2** provides an algorithm to guide next steps after an LCT.

Following a positive IV LCT, it is recommended that acute phase treatment consist of continued use of IV lorazepam for at least 24–48 hours following clinical improvement before switching to PO, if continued IV access is available. When converting from IV to PO, keep in mind that IV lorazepam may be more potent for catatonia than PO and that a dose increase may be needed when converting to PO. Patients with chronic catatonia, schizophrenia, autism spectrum disorders, and adolescents often need higher doses for maximal clinical response. While the IM form is acceptable for the LCT, it is not the preferred route for acute or maintenance phase treatment due to risk of elevating CPK via repeated injections and worsening the already-present fear response. Monitoring for respiratory suppression is also important. Sedation alone, unless leading to respiratory compromise, is not a reason to discontinue treatment if there has been observed clinical benefit. Maximal therapeutic response to scheduled lorazepam will typically occur in 3–7 days. If no response is seen in 7 days or if malignant features are present, ECT or pharmacologic augmentation strategies should be pursued (74-76).

There are no studies on benzodiazepine tapering and discontinuation after treatment response in catatonia. Ongoing maintenance therapy is recommended for patients with chronic or recurrent catatonia (74). Tapers should be done slowly to minimize the risk of precipitating catatonia recurrence. With hospitalized patients, we suggest a cautious taper of 10–25% per day, though tapering more slowly may be prudent, especially in older adults and those who have been on treatment for a longer period of time. In the outpatient setting, consider a trial reduction of up to 25% per week. A taper following acute catatonia can take 1–2 weeks, whereas tapering in more chronic catatonia can take months. An as-needed dose of

benzodiazepine should be prescribed for any recurrence in catatonia symptoms observed during the taper.

Electroconvulsive Therapy (ECT)

For patients with limited response to benzodiazepines or for patients with severe catatonia, including any case of malignant catatonia, the general recommendation is to start ECT as soon as possible (79). The U.S. Food and Drug Administration's (FDA) reclassification of ECT devices in 2018 noted that ECT is indicated in catatonia or severe major depressive episode associated with major depressive disorder or bipolar disorder in patients aged 13 years and older who are treatment resistant and/or who require a rapid response due to the severity of their psychiatric or general medical condition (79). ECT improves 80–100% of catatonia, including up to 60% of patients with catatonia whose symptoms do not improve with benzodiazepines. If there are concerns for malignant catatonia, ECT should be started urgently (76, 80, 81).

The two most common electrode placements for ECT for catatonia are bitemporal (BT) and right unilateral (RUL). There are no high-quality studies comparing the two placements, though bitemporal is generally preferred. RUL can be considered for patients who are treatment-naïve and/or have had prior response to RUL, whereas BT would be considered for patients with severe symptoms, hyperactive delirium, and/or prior BT response (82). A thrice weekly ECT schedule is most common, but daily ECT sessions, regardless of electrode placement may be useful in patients with severe symptoms (e.g., refusal of oral intake, severe inanition, malignant

features) (83). Although rapid responses are seen in some patients, to achieve meaningful response or remission, 12 ECT or more ECT sessions may be needed (39). For certain patients, maintenance ECT following response to the acute course of ECT can help prevent relapse of catatonia (84). Many patients who require ECT for treatment of catatonia will also benefit from concomitant maintenance treatment with a benzodiazepine (85-88).

Other Treatments

If benzodiazepines do not lead to catatonia resolution and ECT is delayed or unavailable, several alternative management strategies may be considered based on evidence from case reports, case series, and other uncontrolled studies. Despite a suboptimal clinical database, several other medications can be effective for catatonia. An algorithm for recommended psychopharmacologic management of catatonia is shown in **Figure 2**.

The NMDA antagonists amantadine and memantine are second-line options for catatonia (80) and are typically used to augment benzodiazepines, though they are sometimes used as monotherapy. They may be useful in patients with comorbid catatonia and delirium, as they are unlikely to worsen the latter. They have also been used in catatonia associated with schizophrenia, which tends to be less responsive to benzodiazepines. Amantadine lowers the seizure threshold and should be used cautiously in patients at increased risk for seizures, including epilepsy and anti-NMDA receptor antibody encephalitis (89). Amantadine is not dialyzable and thus should also be used cautiously in patients with renal disease. In patients with catatonia, amantadine is typically started at 50 mg twice daily and increased gradually

every 3–4 days to a total daily dose of 400 mg. Memantine is typically well-tolerated without serious side effects. Dosing for catatonia starts at 5 mg twice daily with increases to 10 mg twice daily if needed. Additionally, the NMDA antagonist minocycline may be useful in rare cases, although the evidence base is limited (90, 91).

The antiseizure medications valproate and carbamazepine may also be effective for catatonia (39, 80). Like NMDA antagonists, they are often used adjunctively, though there are case reports of these as monotherapy for catatonia. Carbamazepine is less commonly used due to concerns of side effects and drug-drug interactions. Valproate may be a good option for catatonia patients with comorbid bipolar disorder; however, caution should be used in women of childbearing potential due to the risk for teratogenic effects and polycystic ovary syndrome. A serum valproate level in the usual therapeutic range for seizure disorder or bipolar disorder treatment may not be necessary for treating catatonia, as dose adjustments can be made depending on clinical response. Valproate has PO and IV formulations, but the latter must be administered as a slow infusion over 30 minutes, rather than as a bolus. Initial VPA dosing is typically 10 mg/kg/24h, with the upper limit of 20 mg/kg/24h. Carbamazepine dosing is typically 300–600 mg per day.

Antipsychotics have also been used in catatonia for decades, particularly in catatonia associated with a primary psychotic disorder, though with mixed results and the potential for precipitating NMS. Low serum iron is a risk factor for NMS, so obtaining a serum iron level is recommended before trial of an antipsychotic in catatonia (92). Aripiprazole may have an advantage over

other antipsychotics due to its partial dopamine antagonism/agonism (80). In catatonia caused by abrupt cessation of clozapine, re-initiation of clozapine is the treatment of choice (93). If clozapine therapy is interrupted for more than 48 hours, re-titration from a typical starting dose (e.g., 12.5 mg, 25 mg per day) is required. Other second generation antipsychotics, including olanzapine, ziprasidone, and risperidone, have also been reported as successful in catatonia treatment. This must be balanced with the risk of the potential to lead to clinical worsening or conversion to malignant catatonia (39, 80). High-potency first generation antipsychotics should generally be avoided in catatonia due to their increased risk for NMS and higher rates of extrapyramidal symptoms (including acute dystonia).

Antipsychotic medications may be used as an adjunctive treatment especially when catatonia is a complication of a primary psychotic illness, such as schizophrenia (94, 95). In such instances, low-potency second generation antipsychotics are thought to carry the least risk for precipitating malignant catatonia and should be given in combination with a benzodiazepine. Antipsychotics should *never* be given to patients already displaying malignant catatonia or NMS. It is important to recognize that quetiapine and most second generation antipsychotics have little literature supporting their use in treating catatonia. Suggested doses of aripiprazole, olanzapine, quetiapine, and clozapine are shown on Figure 2.

While catatonia is a high-risk condition with potentially poor prognosis, further research on the specific role of antipsychotics in its management is needed. This is especially important in cases of catatonia in the setting of schizophrenia and other psychotic disorders, where antipsychotic

maintenance is necessary for the associated psychosis. Due to the increased risk of high potency D2 blockers' precipitating catatonia and NMS when used to treat psychosis, lower potency D2 blocking antipsychotics are preferable in this clinical context.

Multiple other agents have been tried as adjuncts in the treatment of catatonia, although the evidence base for these treatments is limited to case reports and small case series. Some that have shown promise include the benzodiazepine agonist zolpidem (96), the anticholinergic agents benztropine and trihexyphenidyl, and the antiseizure medication topiramate (39, 80). Dopamine agonists, including stimulants and carbidopa-levodopa, have also been used with some success for catatonia, though nearly all patients have noted worsening of psychotic symptoms; as such, they are not recommended (97). Transcranial magnetic stimulation and transcranial direct current stimulation have also shown promise (98, 99).

Concurrent Management of Associated Psychiatric Condition

In addition to syndromal management as described above, the clinical approach to catatonia should address any associated conditions, including psychiatric condition (e.g., depressive, bipolar, psychotic disorders). With initial response to catatonia treatment, primary depressive, manic, or psychotic symptoms may become manifest and require separate management as described above. Antidepressants are well tolerated in catatonia, and some bipolar disorder treatments, such as antiseizure medications, may help augment the ongoing catatonia treatment as discussed previously.

Complications

Catatonia carries risk for acute and chronic complications, both of which lead to much of the morbidity and mortality associated with catatonia (**Figure 3**) (100). It is imperative to monitor closely for autonomic dysfunction to permit early identification of malignant catatonia. Correcting vital sign abnormalities is a crucial part of managing malignant catatonia.

Many other complications of catatonia mirror those for any patient who requires hospitalization. Prevention of deep vein thrombosis and falls is important for general medical and psychiatric inpatients with catatonia. Immobility/stupor and rigidity are specific catatonic signs that increase the risk of neuromuscular complications (e.g., neuropathies, muscle contractures, deconditioning, rhabdomyolysis) and pressure ulcers (100). Patients who are immobile are at risk for respiratory complications (e.g., pulmonary embolism, pulmonary atelectasis, pneumonia.

Nutritional deficiencies may occur due to the catatonic feature of withdrawal leading to poor oral intake. Dehydration predisposes patients to electrolyte disturbances and acute kidney injury. Malnutrition contributes to muscle atrophy, gastrointestinal hypomotility, and micronutrient deficiencies, which may lead to a need for enteral tube feeding (100). For patients who have catatonia that persists beyond several weeks, it is important to assess vitamin levels and replete if deficient. Urinary retention and urinary tract infections are also possible complications of catatonia.

The mortality rate of catatonia is difficult to quantify as the available evidence is inconsistent. Assessments of mortality risk due to catatonia are confounded by variations in catatonia severity, the common co-occurrence of delirium, and recent improvements in catatonia surveillance, recognition, and treatment (101).

Although the acute complications of catatonia pose the highest mortality risk, the long-term complications have significant implications for morbidity and subsequent quality of life. Patients with severe catatonia have post-hospital courses that resemble those of other patients after other critical illnesses. Post-intensive care syndrome (PICS) is a relevant framework that describes the numerous long-term complications and challenges that patients (and their families) may face and include physical problems, depressive disorders, neurocognitive disorders, and social challenges (102, 103). Accordingly, prevention and treatment of post-acute complications requires a collaborative multi-disciplinary approach involving physicians, nurses, physical therapists, occupational therapists, speech therapists, and dieticians (104).

Considerations in Specific Populations

Pediatrics

Catatonia is rarely diagnosed in pediatric patients, with an administrative claims study of hospitalizations in the United States in 2019 identifying 900 patients with catatonia among patients aged 18 and younger (105) compared to 13,630 in adults (106), meaning that 6.2% of catatonia was reported in youth. The overall severity of catatonia appears similar in pediatric and adult patients. A retrospective multisite cohort of 143 pediatric catatonia patients found a mean BFCRS of 15.0 ± 5.9 (107), comparable to the 14.7 ± 7.8 observed in a cohort of 232 adult catatonia patients (108). Despite this, there may be signs of catatonia that are relatively specific to pediatric patients, or at least more common in them (**Table 3**). These include incontinence, automatic compulsive movements, schizophasia ("scrambled" speech) (109) and acrocyanosis. A Pediatric Catatonia Rating Scale incorporating these items and elements of other catatonia rating scales has been developed and validated in an inpatient cohort, with the scale showing excellent discrimination between children with versus without catatonia (110).

Patients with genetic disorders or neurodevelopmental disorders are highly over-represented among pediatric patients with catatonia. In a prospective cohort of pediatric catatonia admissions, 21.3% had a genetic disorder (111) including a wide range of chromosomal abnormalities and inborn errors of metabolism. Among neurodevelopmental disorders, autism spectrum disorder (ASD) was diagnosed in 15.8% of pediatric catatonia patients (105). As multiple features of ASD, including impaired verbal ability, cognitive impairment, and/or impulsivity may overlap with features of catatonia, in patients with a baseline

neurodevelopmental disorder it is critical to only consider possible catatonic features that differ from the patient's ordinary clinical baseline (112). This deviation from baseline may be exemplified by Down syndrome regression disorder, a state of developmental regression in patients with Down syndrome that exhibits many catatonic features (113). While there are no prospective trials to guide catatonia treatment in pediatric patients, medications (especially benzodiazepines) and ECT are both utilized in pediatric patients as in in adults (113). Retrospective evidence suggest that the lorazepam challenge test is effective in pediatric patients, with a large effect size (Hedges's g = 1.20).

Medically Complex and Critically Ill

Critically ill patients present many diagnostic and management challenges with catatonia. The prevalence of delirium is 48–71% in the intensive care unit (ICU) (114-116). Many critically ill patients receive sedatives, analgesics, and antipsychotics, which can lead to decreased movement and interactions. Medications can precipitate syndromes, such as SS, NMS, and/or propofol infusion syndrome, with various features of catatonia. Benzodiazepines have a risk of increasing "next day" delirium in critically ill patients (117). These patients are at higher risk for respiratory compromise due to co-prescribed medications and/or co-morbid conditions, and the current standard of critical care is to minimize these medications' use in favor of less problematic agents (118).

The prevalence of catatonia in the critically ill is not well described in the literature. It is likely underdiagnosed due to under-recognition as well as due to the presence of many comorbid

conditions that can be associated with signs of catatonia (100). Multiple catatonic features including excitement, immobility, mutism, staring, and withdrawal overlap with features of delirium. Whereas the *DSM-5-TR* (40) does not allow catatonia to be diagnosed in the presence of delirium, studies have indicated that the two conditions commonly co-occur. For instance, a prospective assessment of 378 critically ill patients who received daily catatonia and delirium assessments found that 22% displayed features of both disorders (4). In another study, among 205 medical inpatients diagnosed with delirium, 30% also had catatonia (3). Optimal diagnostic criteria for catatonia in the presence of co-occurring delirium remain unclear and in need of further study. Wilson, et al., studied 136 critically ill patients in one academic medical center and found that 43% had delirium, 3% had catatonia without signs of delirium, and 31% met diagnostic criteria for both (2). The authors proposed using a higher cut-off of diagnosable catatonia criteria in the critically ill. The authors noted that the use of at least four signs of catatonia led to a 91% sensitivity and specificity for a catatonia diagnosis according to the *DSM-5* criteria (2). Further studies examining response of catatonia to benzodiazepine challenge are warranted to both further clarify diagnostic accuracy and stratify the appropriate risk-benefit ratio for when to intervene with benzodiazepines in this population. While functional or legal barriers to ECT exist in some institutions, ECT can be performed in the ICU and could be considered in catatonia that is comorbid with delirium especially when the patient may be intolerant of or unresponsive to benzodiazepines.

Pregnancy and the Postpartum Period

During pregnancy, the risks and benefits of treatment for both the patient and fetus must be considered. Untreated catatonia can have serious adverse outcomes for the patient as reviewed elsewhere in this document, and harm may come to fetus through a variety of mechanisms such as malnutrition due to poor oral intake of mother. Like all other psychiatric treatments in pregnancy, it is important to determine if the benefits of treatment outweigh the risks of untreated disease. There is a limited literature regarding lorazepam and ECT during pregnancy. Recent reviews of benzodiazepines in pregnancy suggested a statistically significant (though unclear if *clinically* significant) risk of congenital malformations, preterm birth, spontaneous abortion, low APGAR score, and low birth weight, but the reviews recognized numerous limitations of these studies, including significant confounders, heterogeneity of available retrospective studies, and inconsistent findings between studies. (119). As the doses of benzodiazepines can be significantly higher in catatonia than in other indications, the British Association for Psychopharmacology recommended not to exceed 4 mg daily of lorazepam for catatonia in pregnancy and to strongly consider ECT for non-responsive cases (39). ECT is generally safe in pregnancy, with a recent review of reviews suggesting that the procedure is well-tolerated (120). This is consistent with the current APA position on use of ECT in setting of severe postpartum depressive disorders (*APA TASK FORCE ON ECT*).

Research on the incidence of peripartum catatonia is limited. In one study of postpartum psychosis due to any psychiatric cause (N = 200), 20% of the cohort was found to have catatonic features (121). Among patients diagnosed with catatonia, the mean BFCRS score was 14.97 ± 3.2. Catatonic features responded to lorazepam in half of these women and, of those who did not respond to lorazepam, most responded to ECT (121). The risks of catatonia in the postpartum period may include the usual medical risks associated with untreated catatonia, plus impaired parent-child bonding and risk of harm to newborn through neglect accompanying hypoactive catatonia symptoms or inadvertent harm due to hyperactive catatonia symptoms. Other studies of lactating mothers found negligible relative infant doses of benzodiazepines in mothers taking benzodiazepines for anxiety (122).

Older Adults (including Major Neurocognitive Disorder/Dementia)

In middle-aged and older adults, catatonia is more often discovered in the general medical setting, though this is confounded by the fact that older patients more often develop conditions that may cause catatonia. A recent systematic review found a very large variation in the prevalence of catatonia across clinical settings treating older adults, ranging from 5.5% in a US consultation-liaison psychiatry setting using the BFCRS for diagnosis versus 39.6% of older adults in a psychogeriatric unit in the United Kingdom using *DSM-5* criteria(123). Delayed diagnosis and treatment of catatonia can lead to medical complications, and middle aged to older adults are at greater risk (100). When using lorazepam to treat catatonia in older adults, especially when comorbid with delirium, it is advisable to start with lower than usual doses

such as 0.5 or 1 mg LCT due to risk of worsening delirium, falls, or other complications as outlined by the Beers criteria. There is insufficient evidence to suggest starting with alternative treatments such as NMDA antagonists for catatonia in populations especially vulnerable to delirium, but this has successfully been trialed in case reports (123).

Ethical and Legal Considerations

Catatonia that does not improve with optimized doses of lorazepam should be referred for ECT. Inasmuch as severe catatonia impairs cognitive function and communication, such severely ill patients will often lack decisional capacity (DC). Catatonia's clinical features may preclude the patient from meaningfully processing the risks and benefits of treatment options. Additionally, stupor, mutism, echolalia, verbigeration, or perseveration can prevent a patient from demonstrating DC by way of impaired communication. When delirium co-occurs with catatonia (2), there is an additional layer of complexity to the consent process, as delirium impairs attention, concentration, and other cognitive domains, all of which can fluctuate over time. Patients with catatonia where ECT is indicated but who cannot obtain it due to lack of local ECT resources or other structural barriers to access are at high risk of death or permanent physical sequelae. As such, it is important to give adequate weight to the ethical principle of beneficence in relation to the patient's autonomy.

Many of catatonia's clinical features make it difficult, if not impossible, to evaluate a patient's decisional capacity (DC). Nevertheless, patient autonomy deserves adequate protections, especially in cases without medical urgency, so concerted efforts should be made over time to provide information about catatonia and its treatment, as well as to evaluate DC, recognizing that the ability to provide informed consent may fluctuate along with fluctuations in specific features of catatonia. The consent process is an inherent and often iterative part of the physician-patient relationship. Adult patients are presumed "competent" unless found to be "incompetent" by a court of competent jurisdiction . In cases that are not considered medical

emergencies, ethical principles of informed consent include the disclosure of information, demonstration of DC and the voluntary nature of the decision (124, 125).

When the patient lacks DC for non-emergent catatonia treatment (124), surrogate or judicial consent will be needed, but this process will vary based on relevant statutes in the patient's jurisdiction and hospital policies. Depending on the jurisdiction, laws pertinent to surrogate consent for other medical/surgical interventions may not apply to ECT, and a judicial opinion specifically authorizing ECT by surrogate consent may be needed. It is important to keep in mind that with reduction or resolution of catatonic symptoms, a patient may regain DC and then be able to determine for themselves whether they wish to continue with ECT and other treatment. For patients with recurrent catatonia, advanced directives for mental health treatment (also called "self-binding directives" or "Ulysses agreements") can be completed while a patient has DC. Such agreements are not in widespread use but may be considered depending on the legal jurisdiction.(126, 127)

Clinicians should address any modifiable factor contributing to impaired DC . For example, a physician might replete B1 (thiamine) and B12 (cobalamin) in a patient with poor nutritional status especially if cognitive impairment is present. The clinician should prioritize understanding the patient's previously expressed wishes for treatment when they lack DC by working with the legally appropriate surrogate decision maker, consulting with the ethics committee, if available, and considering the patient's values and goals when proposing non-voluntary treatment, especially in the case of pursuing ECT. Advance directives, if available, could offer valuable

insights into the patient's treatment preferences regarding ECT (128). Surrogate decision-makers must carefully consider the patient's values where known and best interests, acknowledging the potential of ECT to restore DC and ultimately promote respect for autonomy (128, 129).

Educational Resources

Misconceptions about catatonia and its clinical features are common among psychiatrists, psychiatry trainees and other medical professionals. In a recent online study, participants correctly answered only half of multiple-choice questions and correctly scored roughly two thirds of BFCRS items (130). Catatonia is a psychomotor syndrome in which idiosyncratic behaviors and motoric abnormalities are prominent, and these findings can be difficult to understand based on narrative descriptions alone.

Videographic resources' have been developed for the assessment of catatonia using the BFCRS: https://bfcrs.urmc.edu. These resources are free for educational and clinical use and have been demonstrated to improve catatonia identification (131). These online resources include (1) a detailed BFCRS Training Manual and Coding Guide, which describes use of the BFCRS and explains each item in detail, (2) educational modules on using the BFCRS that include standardized patient videos and test questions with answers, (3) standardized patient videos depicting individual BFCRS items, and (4) an interactive BFCRS calculator with descriptions and videos that has been optimized for use on mobile devices. These materials may be used as a formal educational module, *a la carte*, or as point-of-care clinical resources.

Additional online resources are available on the Catatonia Information Center (https://sites.psu.edu/catatonia/), the Catatonia resources page at the University College London (https://www.ucl.ac.uk/mental-health/research/catatonia), the National Neuroscience Curriculum Initiative (https://nncionline.org/course/catatonia/), and the patient Catatonia Foundation, which was created by families affected by catatonia (https://www.thecatatoniafoundation.org/).

Conclusions

This review summarizes historical and current scientific and clinical literature on catatonia with a focus on clinical application. It aims to provide historical context and practical guidance on decision making for patients with catatonia who are often very ill and functionally impaired. As the phenotypic description of catatonia has evolved, its place as a prototype of a neuropsychiatric illness has become increasingly clear. One anticipates that diagnostic systems will continue to reflect this emerging consensus perspective, reinforcing the advances in catatonia's conceptualization in *ICD-11*.

The acute presentation of catatonia is a serious illness with potential morbidity that requires urgent management. As catatonia is frequently, though not necessarily, associated with one or more antecedent psychiatric illnesses, successful management of an episode of catatonia will often segue into subsequent management of its associated psychiatric conditions. The diagnostic, psychopharmacological, and neuromodulation management of catatonia should be seen on a continuum, as evaluations and interventions may evolve as the patient's status changes.

The authors appreciate that many general and child psychiatrists may encounter catatonia infrequently. The guidance provided by this review, supplemented by physician experience and appeal to the current literature, is meant to facilitate comprehensive, multispecialty, and multidisciplinary care. Catatonia is more commonly managed by inpatient psychiatrists and

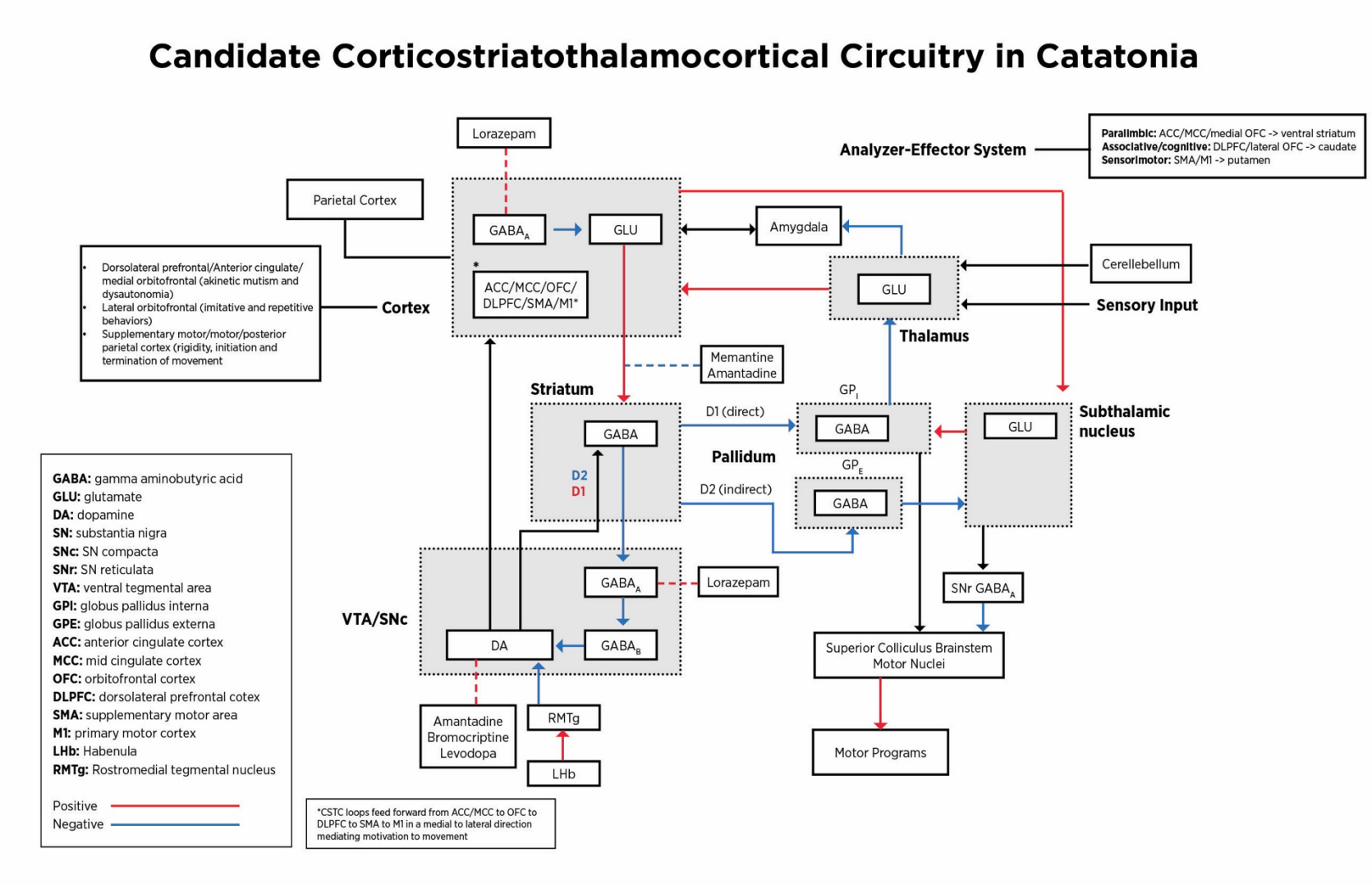
those in consultation-liaison psychiatry, who regularly see acutely ill patients. Outpatient psychiatrists may benefit from a regular relationship with a psychiatrist familiar with catatonia's presentation, medical workup and treatment to provide consultation and advice on those occasions when they are called to evaluate a catatonia patient in the hospital. The authors intend this Resource Document to be useful to the general or child psychiatrist who may not have ready access to a consultation-liaison psychiatrist on-site. Given that many patients with catatonia will receive ECT, connection with an interventional psychiatrist for access to this treatment is also valuable. The complexity of care associated with catatonia can present significant challenges in areas without local ECT resources, as patients may need transfer to an ECT-capable facility. It is likely that ECT may continue to have limited availability, so exploration of where ECT is available is important.

As with all complex illnesses with an evolving literature, catatonia deserves further research. Studies should explore the co-morbidity of catatonia with other illness, refine the catatonia phenotype and diagnostic criteria, and test clinical interventions in randomized controlled trials. Trials are difficult to accomplish in catatonia due to its high degree of diversity in terms of patient characteristics, and it is poses ethical challenges to conduct true placebo-controlled trials with acutely ill, medically unstable patients who have limited capacity to provide informed consent.

Ultimately, catatonia illustrates clearly the principle that "psychiatric illness is medical illness" and that "psychiatric practice is medical practice." Optimized management of catatonia

impacts overall medical prognosis and, in some cases, survival. As such, frontline catatonia management skills are essential for all psychiatrists, who are encouraged to reach out to subspecialty colleagues for active collaboration and care of patients with catatonia.

Figure 1. Candidate Cortico-striato-thalamo-cortical Circuitry in Catatonia (69).



Catatonic psychomotor disruption in motivation to movement is illuminated in ACC/MCC/OFC CSTC loop interactions with the dlPFC and SMA/motor CSTC loops in a spiraling striato-nigro-striatal medial-to-lateral fashion (1, 132-134). The thalamus communicates sensory information not only to the primary and unimodal sensory and motor cortices but also directly to the amygdala for fear conditioning and to the ACC for processing and emotion regulation. The thalamus also connects the cerebellar dentate region with the PFC, PMA, AMA and motor cortex and with the putamen resulting in significant modulation through the so-called basal ganglia–cerebellar–cerebral cortical network (135, 136). The ACC/MCC serves as a conflict monitor using active inference to analyze incoming sensory data, forming a cingulo-fronto-parietal network that detects conflicts in information processing to signal situations requiring cognitive control (137). To do this, the ACC/MCC/OFC selects the option policy and in collaboration with the executive dlPFC and in coordination with the self-regarding PPC, it operationalizes the response selection through the associative dorsal motor system. It also energizes switches between tasks to achieve a higher-level attachment goal. The ACC/MCC also relates the policy to the critic OFC in communication with the VS, which assesses the chosen option as predictive of future reward supporting maintenance or future punishment encouraging behavioral response flexibility (138).

The VTA/SN DA system functions as a modulator/manager for the CSTC circuits and it is assisted by the lateral habenula in the dorsal diencephalic network (139). The DA system optimizes ACC/MCC/OFC processes (138). The ACC/MCC/OFC makes use of memory, pain, expectation, and conation to direct the connectome to operationalize response selections in the face of conflicted and stress-inducing avoidance-approach options. Features of catatonia may emerge from dissolution of the salience network (implicit) and central executive network (explicit) emotion regulation pathways, which emanate from ACC and OFC/vmPFC in the former and from MCC and dlPFC in the latter case, thereby disrupting circuit-based control of the amygdalar fear conditioning stress pathway (140). This may result in gamma desynchrony at the electrophysiological level from a disruption in the excitatory: inhibitory balance of glutamate and GABA flows inciting a tension in the nodal CSTC system that may culminate in the psychomotor changes of catatonia. This nodal system provides many sites of etiological vulnerability to a wide variety of structural and modulatory insults (68, 69).

Figure 2. Treatment Algorithm for Catatonia.

Step 1	
Lorazepam/other BZP	Give initial "challenge" dose of 2 mg lorazepam; Maintenance dose of 6-30 mg lorazepam daily given in divided doses at least every 6-8 hours for at least 2-3 days; transition to PO not recommended in first 24-48 hours begin workup for ECT*; if IV lorazepam is unavailable, alternatives include IV diazepam, SL lorazepam or PO lorazepam

*Electroconvulsive therapy

Step 2	
ECT	At least 6 treatments (2-3 usually sufficient to lyse, though 10-20 sometimes needed); if not immediately available, skip to **Step 3**

Step 3	
Glutamate Antagonist	Amantadine 100 mg daily or memantine 10 mg daily; titrate as tolerated over 3–4 days to 600 mg daily or 20 mg daily, respectively

Step 4	
Anti-epileptic	Valproic acid 10-20 mg/kg, target dose usually 500-1500 mg PO or IV daily (Carbamazepine 300-600 mg PO daily could be an alternative for some patients but requires monitoring for drug-drug interactions)

Step 5	
Antipsychotic agent, with each dose given in combination with lorazepam	Target doses: Aripiprazole 10-30 mg, olanzapine 2.5-10 mg, or clozapine 200-300 mg daily* *If catatonia is secondary to clozapine withdrawal, clozapine is the treatment of choice

Modified from prior publications (102, 151).

Figure 3. Complications of catatonia according to organ system.

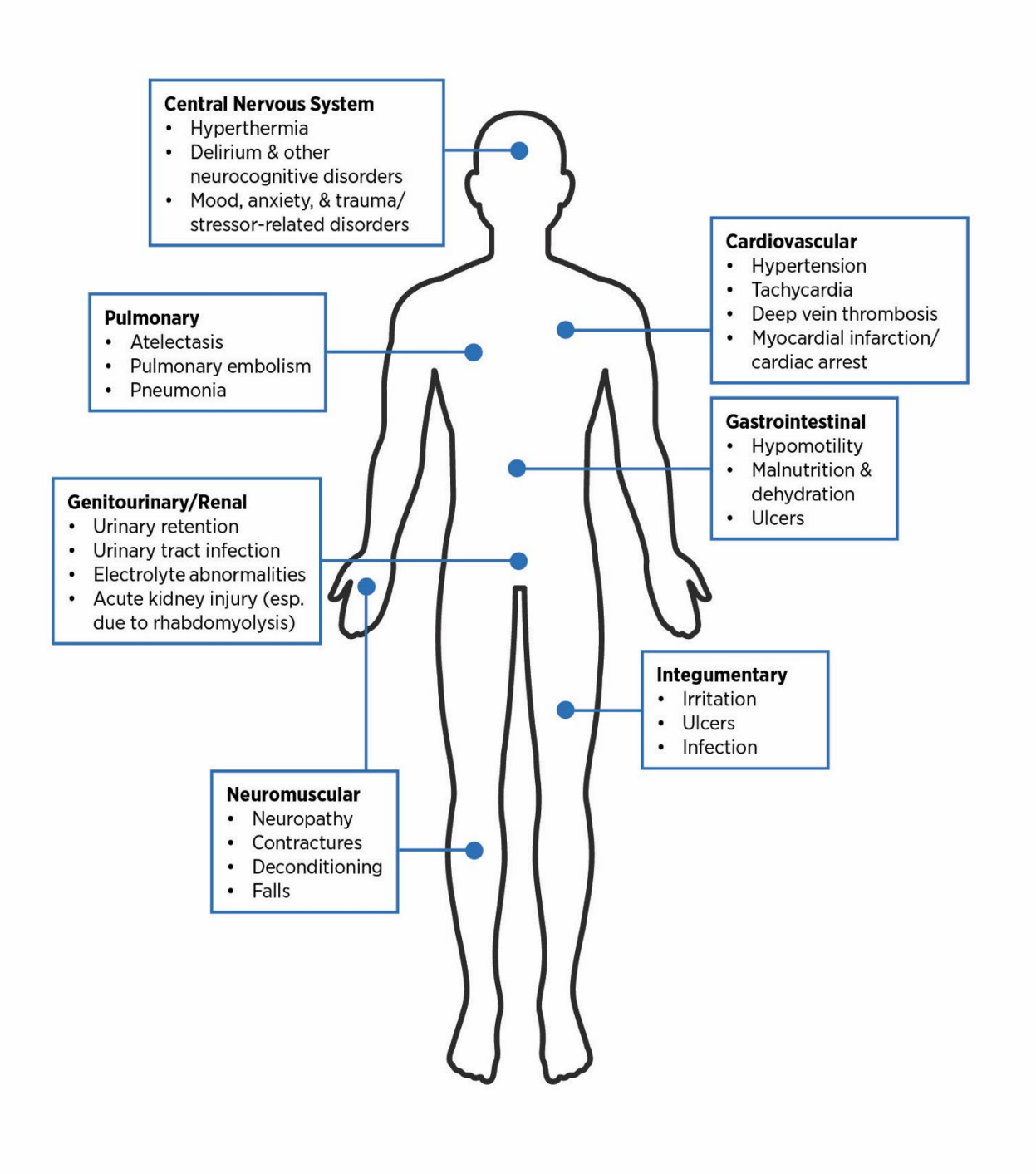


Table 1. Shared psychomotor features of catatonia between the Bush Francis Catatonia Screening Instrument / Rating Scale, ICD-11 and DSM-5-TR criteria for catatonia.

Psychomotor activity	Assessment	BFCSI (2 of 14)	BFCRS (44, 47) (severity measure)	IDC-11 (43) (3 of 15)	DSM-5-TR (42) (3 of 12)
Increased	Observe	Excitement	Impulsivity	Increased Psychomotor Activity	Agitation
			Combativeness		
Abnormal	Observe	Grimacing			
		Mannerism			
		Stereotypy			
		Verbigeration			
		Posturing/Catalepsy	Posturing		
			Catalepsy		
	Elicit	Echolalia/Echopraxia	Echolalia	Echolalia/Echopraxia	Echolalia
			Echopraxia		Echopraxia
			Automatic obedience		
			Mitgehen		
			Gegenhalten		
	Observe/Elicit		Perseveration		
	Exam		Grasp reflex		
		Waxy flexibility			
Decreased	Observe/Elicit	Stupor			
		Mutism			
		Withdrawal			
			Ambitendency		
	Elicit	Negativism			
	Observe	Staring			
	Exam	Rigidity			
Other	Exam/Collateral		Autonomic abnormality		

Table 2. Differential diagnosis for catatonia.

Diagnosis	Features Similar to Catatonia	Distinguishing Features
Abulia/Akinetic Mutism Spectrum	Mutism, immobility, rigidity, negativism, withdrawal	Echophenomena, catalepsy, excitement, stereotypy, impulsivity, automatic obedience
Delirium (Hypoactive)	Mutism, excitement, immobility, rigidity, negativism, withdrawal, combativeness	Catalepsy, posturing, echophenomena, automatic obedience, severity of cognitive impairment
Dementia	Mutism, hypokinesis, withdrawal	Echophenomena, catalepsy, posturing, longitudinal decline, severity of cognitive impairment
Locked-in Syndrome	Mutism, immobility, withdrawal, rigidity, negativism	Structural imaging results, engagement and motivation with communication, echophenomena, catalepsy, posturing
Parkinson's Disease	Immobility, withdrawal, rigidity, negativism	Positive DaT Scan, response to levodopa, tremor, gait, overall psychomotor and cognitive responsiveness and engagement
Serotonin Syndrome	Rigidity, immobility, muscle resistance	Presence of serotonergic agent, myoclonus, hyperreflexia, gastrointestinal symptoms
Stiff-Person Syndrome	Rigidity, immobility, muscle resistance	Lack of mutism or any cognitive impairment, muscle spasms, GAD65 antibodies, progressive course
Akathisia	Psychomotor excitement	Lack of mutism, immobility, automatic obedience, echophenomena, and virtually all other signs
Delirium (Hyperactive)	Psychomotor excitement, combativeness, impulsivity, withdrawal, negativism, rigidity	Multiple domains of cognitive impairment with deficits in arousal are commonly found in delirium
Manic episode	Psychomotor excitement, impulsivity, disorganized thoughts	Mania typically presents with mood elevation, abnormal sustained energy, and lack of any cognitive impairments

DaT, dopamine transporter

Table 3. Considerations in specific populations.

POPULATION	Special Considerations
PEDIATRICS	• May display different signs than adults • High rate of genetic disorders • Patients with neurodevelopmental disorders (NDDs) may display regression from baseline function
ELDERLY	• May have higher rates of catatonia than younger patients • Vulnerable to complications based on existing chronic comorbidities • Catatonia may present frequently with delirium
PREGNANCY	• Rates of catatonia in pregnancy are unclear • ECT and benzodiazepines remain effective, but effects on the patient and fetus must be considered • ECT may be preferred treatment in later pregnancy/postpartum
CRITICAL ILLNESS	• May have both catatonia and delirium • Exam confounded by sedatives, analgesics, anticholinergics, and antipsychotics
COMORBIDITY	
DELIRIUM	• Clinical features of catatonia and delirium may overlap • Optimal diagnostic criteria for each condition are not clear when both are present due to some phenotypic overlap
NMS	• May conceptually overlap with malignant catatonia • Treated similarly to malignant catatonia
AUTOIMMUNE ENCEPHALITIS/NMDARE	• Encephalitis may precipitate catatonia • Treatment of underlying inflammation is critical to resolution of catatonia

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APA Resource Document

Resource Document on Catatonia: Supplement 1

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This resource document is intended to support psychiatrists, trainees, and other mental healthcare workers and to provide a framework for assessing the adequacy of existing violence prevention policies and a list of resources for the development of state-of-the- art policy approaches. This document is not intended to be comprehensive or completely systematic in nature, nor is it a practice guideline. It is highly recommended that mental healthcare employees pursuing improvements in local policies consult with their facility/practice administrator, risk manager, and legal counsel as well as local, state, and federal regulations and policies that pertain to healthcare and workplace violence.

Prepared by the Catatonia Work Group of the Council on Consultation-Liaison Psychiatry

Authors: Jo Ellen Wilson[1,2], Mark A. Oldham[3], Andrew Francis[4], Dina Perkey[5], Eric Kramer[5], Shixie Jiang[6], Jennifer Yoon[5], Scott Beach[7,8], Gregory Fricchione[7,8], Matthew Gunther[9], Jihoon Ha[10,11], James Luccarelli[7,8], Jordan Rosen[12], Dallas Hamlin[4], Joseph D. Dragonetti[13], Avi Gerstenblith[14], Anne Louise Stewart[12], Jon Sole[9], James A. Bourgeois[15]

Supplement 1: Pathophysiology

The ACC/MCC is involved in decision-making, especially under conditions of stressful conflict. The ACC/MCC also processes critical executive and value-based information from the dorsolateral prefrontal cortex (PFC), orbitofrontal PFC, frontopolar cortex, and anterior insular cortex (Figure 1) (1, 2). Integration of frontal and paralimbic cortices with parietal cortex in the cingulo-frontal-parietal executive network is key for motivated self-conscious movement initiation and termination, which may be aberrant in catatonia (3),76, 77).

One potential etiology for this aberrance involves disruption of corollary discharges to the basal ganglia (BG) that are meant to predict sensations arising from self-generated actions (4-7). The cerebellum is also an important modulator of the motivation-to-movement mechanism, and disorders of the cerebellum can precipitate catatonia. Patients with schizophrenia and catatonia have lower cortical inhibition than healthy controls. Patients with schizophrenia *without* catatonia have resting state functional connectivity among the anterior cingulate cortex, the primary motor cortex, and the cerebellum that increases with stronger cortical inhibition (8). In addition to these "bottom-up" theories, others have proposed a "top-down" hypothesis for catatonia, suggesting that medial prefrontal regions (e.g., orbitofrontal cortex) may experience dysfunction due to reduction in inhibition of glutamatergic neurons to provide psychomotor control (9).

This disabling of the motivation-to-movement system appears to represent alterations in the balance between excitatory and inhibitory flow intracortically and through the CSTC loops. Psychogenic disturbances, focal CNS lesions, neuroinflammation, and overall dysmodulation can impact tone in glutamate, $GABA_A$, and dopamine tracks. (10, 11). The excitatory-inhibitory balance can be disturbed at many levels in the system. Interestingly, the *hypokinetic* presentation of catatonia underlies a counterintuitive *overstimulation* of some CSTC circuits, mediated mostly through dopaminergic and GABAergic systems.

Dopamine blockade appears to be key in this process, partially through increasing activity of the indirect BG pathway that reduces volitional movement. Thus, antipsychotics manifest the ability to induce catatonia through inhibition of the inhibitory dopamine 2 autoreceptor of this pathway (12). GABAa agonists (e.g., lorazepam) can oppose this response by disinhibiting dopaminergic tone in the direct pathway, restoring inhibition in the cortex, thereby reducing corticostriatal hyperactivity. The use of NMDA receptor blocking agents (e.g., amantadine, memantine) may also be helpful in reducing corticostriatal hyperactivity.

Catatonic psychomotor disruption in motivation to movement is illuminated by ACC/MCC/OFC CSTC loop interactions with the dlPFC and SMA/motor CSTC loops in a spiraling striato-nigro-striatal medial-to-lateral fashion (9, 13-15). The thalamus communicates sensory information, not only to the primary and unimodal sensory and motor cortices, but also directly to the

amygdala for fear conditioning, and to the ACC for processing and emotion regulation. The thalamus also connects the cerebellar dentate region with the PFC, PMA, AMA, motor cortex and putamen, resulting in significant modulation through the basal ganglia–cerebellar–cerebral cortical network (11, 16).

The ACC/MCC serves as a conflict monitor using active inference to analyze incoming sensory data, forming a cingulo-fronto-parietal network that detects conflicts in information processing to signal situations requiring cognitive control (17). To do this, the ACC/MCC/OFC selects the option policy (a mapping of states to actions that determines behavior), and in collaboration with the executive dlPFC and, in coordination with the self-regarding PPC, operationalizes response selection through the associative dorsal motor system. It also energizes switches between tasks to achieve a higher-level attachment goal. The ACC/MCC also relates the policy to the critic (the module that evaluates the value of current state and computes reward prediction errors) OFC in communication with the VS, which assesses the chosen option as predictive of future reward supporting maintenance or future punishment encouraging behavioral response flexibility (18).

The VTA/SN DA system functions as a modulator/manager for the CSTC circuits, and it is assisted by the lateral habenula in the dorsal diencephalic network (19). The DA system optimizes ACC/MCC/OFC processes (18). The ACC/MCC/OFC makes use of memory, pain, expectation, and conation (volition) to direct the connectome to operationalize response selections in the face of conflicted and stress-inducing avoidance-approach options.

Features of catatonia may emerge from dissolution of the salience network (implicit) and central executive network (explicit) emotion regulation pathways, which emanate from ACC and OFC/vmPFC in the former and from MCC and dlPFC in the latter, disrupting circuit-based control of the amygdalar fear conditioning stress pathway (20). This may result in gamma desynchrony at the electrophysiological level from a disruption in the excitatory: inhibitory balance of glutamate and GABA flows, inciting a tension in the nodal CSTC system that may culminate in the psychomotor changes of catatonia. This nodal system provides many sites of etiological vulnerability to a wide variety of structural and modulatory insults (12, 21).

There is increasing interest in the idea of catatonia as an inflammatory and/or immune-modulated illness (22, 23)**. Support comes from evidence of inflammatory processes** *causing* **catatonia and catatonia-related syndromes, and** *treatments* **with immunomodulatory and anti-inflammatory properties improving symptoms of catatonia.** Inflammatory immune responses may compound the dysregulated neurotransmitter signaling seen in catatonia. Toxic psychological stress can be postulated to initiate immune pathways in innate immune cells (e.g., macrophages), such as the cyclic-GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway (cGAS-STING), where both non-pathogen damage-associated and pathogen-associated molecular patterns (DAMPs, PAMPs) activate and release cytokine cascades that cross the blood brain barrier. These deteriorate the structural integrity and function of neuronal support cells, impairing processes like synaptic transmission and dendritic

modeling (22). The subsequent neuronal dysfunction could alter the balance of excitatory and inhibitory neural circuits in the CSTC loop system, leading to the psychomotor dysfunction of catatonia (22, 23). The cGAS-STING pathway may also be activated in microglial cells under the burden of oxidative stress that precipitates the seepage of bacterial descendant mitochondrial DNA into the cytosol triggering a non-self neuroinflammatory response syndrome (24).

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APA Resource Document

Resource Document on Catatonia: Supplement 2

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This resource document is intended to support psychiatrists, trainees, and other mental healthcare workers and to provide a framework for assessing the adequacy of existing violence prevention policies and a list of resources for the development of state-of-the- art policy approaches. This document is not intended to be comprehensive or completely systematic in nature, nor is it a practice guideline. It is highly recommended that mental healthcare employees pursuing improvements in local policies consult with their facility/practice administrator, risk manager, and legal counsel as well as local, state, and federal regulations and policies that pertain to healthcare and workplace violence.

Prepared by the Catatonia Work Group of the Council on Consultation-Liaison Psychiatry

Authors: Jo Ellen Wilson[1,2], Mark A. Oldham[3], Andrew Francis[4], Dina Perkey[5], Eric Kramer[5], Shixie Jiang[6], Jennifer Yoon[5], Scott Beach[7,8], Gregory Fricchione[7,8], Matthew Gunther[9], Jihoon Ha[10,11], James Luccarelli[7,8], Jordan Rosen[12], Dallas Hamlin[4], Joseph D. Dragonetti[13], Avi Gerstenblith[14], Anne Louise Stewart[12], Jon Sole[9], James A. Bourgeois[15]

Supplement 2: Electroconvulsive Therapy

Precise rates of the mortality attributable to ECT are difficult to determine, but best estimates suggest a rate of fewer than 4 deaths per 100,000 treatments, with apparent decreases in mortality rates in recent years despite the frequent use of ECT in geriatric patients and patients with significant general medical conditions (APA ECT Task Force Report). With modern anesthesia, ECT can be safety administered in patients with cardiac complications (1) although there may be increased risk in those patients with certain high risk conditions.

Medical Conditions that May Elevate Risk for ECT

Certain conditions may elevate risk for ECT including uncontrolled hypertension, recent myocardial infarction (< 60 days), unstable angina, decompensated congestive heart failure, severe aortic stenosis, uncontrolled atrial fibrillation, unrepaired abdominal aortic aneurysms >5.0 cm, and tachyarrhythmias or bradyarrhythmias associated with hypotension or requiring urgent medical attention (2, 3). Patients at higher risk of cerebrovascular complications from ECT include those with signs or symptoms of an intracranial lesion (e.g., papilledema, focal neurological deficits, mass effect and/or brain edema on MRI) and those with an acute hemorrhagic stroke in the preceding 30 days, particularly if blood pressure remains poorly controlled. The presence of a pheochromocytoma is associated with a significant risk for hypertension with ECT (4-6), however, use of α- or β-blocking agents (4-6) can help to minimize this risk. For non-psychiatric physicians and other clinicians who are managing catatonia in a

general hospital, collaboration with a psychiatrist can help weigh risks and benefits of starting ECT for catatonia. There may be logistical and informed consent challenges in arranging for ECT.

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