

**Catatonia in Medically Ill Patients**  
**An Evidence-Based Medicine (EBM) Monograph for**  
**Psychosomatic Medicine Practice**

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# **CATATONIA IN THE MEDICALLY ILL -- EBM SUMMARY**

## **KEY POINTS**

- Catatonia in medically ill patients is rare but often unrecognized.
- Catatonia occurs with varying degrees of severity, with malignant catatonia on the severe side of the spectrum.
- In the pediatric population, catatonia is exceedingly unrecognized and undertreated.
- Pediatric catatonia is often associated with general medical illness, as well as autistic spectrum and developmental disorders.
- Catatonic Disorder due to another medical condition (CD-AMC) is the most common form of catatonia in the medically ill population.
- The clinical presentation of CD-AMC is similar to catatonia in patients with psychiatric illnesses.
- Intravenous lorazepam is the preferred initial treatment for catatonia.
- Amantadine or memantine may be helpful augmentation agents.
- Electroconvulsive therapy (ECT) often produces remission when pharmacologic treatment options have failed.
- Dopamine antagonists can be used if the patient with catatonia has shown a favorable response to certain agents in the past, with careful monitoring for progression to malignant catatonia.

## **INTRODUCTION:**

### Objective and methods:

This monograph summarizes current knowledge related to the diagnosis, epidemiology, etiology, and management of catatonia in the medically ill population. Specifically, this monograph primarily discusses catatonia due to another medical condition (CD-AMC), previously known as catatonia due to a general medical condition (CDGMC) under DSM-IV-TR terminology. This monograph also discusses catatonia occurring in the setting of another mental disorder when encountered by a consultation psychiatry service in a general hospital setting. Malignant catatonia, otherwise known as the Neuroleptic Malignant Syndrome (NMS) is also discussed.

A more thorough review of the pathophysiology of catatonia, and catatonia occurring in the setting of another mental disorder (such as bipolar disorder, major depression, neurodevelopmental disorder, or schizophrenia) is beyond the focus of this monograph. Readers are encouraged to consult the recommended readings for more detailed information on this topic (Appendix A).

### Definition and Diagnostic Criteria:

Catatonia is a neuropsychiatric syndrome with motor, vocal, affective, and behavioral peculiarities, including alterations in external (environmental) and internal (proprioceptive) awareness. Features may include mutism or impoverished/quiet speech, reduced interaction with the environment (stupor), negativism, increased motor tone/rigidity, posturing and grimacing, gegenhalten, mitgehen/mitmachen, automatic obedience, ambitendency, echolalia, stereotypy, verbigeration, echopraxia, extreme anxiety/fear, and impulsive/bizarre behavior. In malignant cases (see “Malignant Catatonia” below), autonomic instability, severe muscle rigidity, and hyperthermia occur which can lead to rhabdomyolysis, coma, and death.

Catatonia most often occurs in patients with major depression or bipolar disorder. However, it is also seen in schizophrenia, or as a result of a medical condition.<sup>1</sup> When one includes NMS, then CD-AMC is the most common form of catatonia in the medically ill.<sup>2</sup>

The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) recognizes that catatonia can occur in the context of another mental disorder or as a disorder due to another medical condition. Additionally, patients not meeting full criteria can be coded as Unspecified Catatonia. The fifth edition improves upon the fourth, in that it now provides brief definitions for 12 symptoms delineated by the criteria. However, symptom duration and severity remains undefined.

The lexicon of some catatonic phenomena, such as waxy flexibility and catalepsy, are problematic in that they have been poorly defined, and are often incorrectly used by trainees and experienced clinicians alike, and even differ between published rating scales.<sup>3</sup> More work is needed to standardize the definitions of certain catatonic phenomena. A glossary of definitions for selected “problematic” catatonic phenomena is included in Appendix B.

Catatonic signs and symptoms in patients with CD-AMC appear to be indistinguishable to those seen in psychiatric patients with catatonia. This was the conclusion of one retrospective chart review of 47 cases, which revealed a slightly higher prevalence of negativism in patients with CD-AMC.<sup>4</sup> The same study also identified a higher frequency of echophenomena in CD-AMC patients, but in general found a similar distribution of catatonic signs regardless of the etiology of the catatonic disorder.

### Differential Diagnosis:

The differential diagnosis of catatonia includes other hypokinetic and hyperkinetic states with rigidity, such as Parkinson’s disease, advanced dementia, malignant hyperthermia, serotonin syndrome, stiff-person syndrome, locked-in

syndrome, and non-convulsive status epilepticus. Catatonia can also be mistaken for conversion disorder, selective mutism, oppositional defiant disorder, dissociative disorder, volitional uncooperativeness, maladaptive coping with medical illness, or behavior that is the product of ego defense mechanisms including denial, regression, acting-out, and reaction-formation.

Catatonia is not synonymous with akinetic mutism.<sup>5</sup> This latter neurologic syndrome generally differs from catatonia in pathophysiology and treatment, but is often loosely applied by clinicians to refer to any condition in which a patient is not moving and not talking. A key difference, however, is that akinetic mutism lacks the behavioral and affective alterations observed in catatonia. Most cases of akinetic mutism have an identifiable neurologic lesion. However, since all cases of akinetic mutism involve stupor, immobility, and mutism, the disorder fulfills DSM-5 criteria for CD-AMC. This is complicated by the fact that some medical conditions (e.g. prion disease) and medications (e.g. tacrolimus) have been implicated in the development of both akinetic mutism and catatonia.<sup>6, 7, 8, 9, 10</sup> In general, akinetic mutism should not be diagnosed as catatonia unless additional catatonic features are present, and catatonia should be ruled out in cases of akinetic mutism.

#### Catatonia and Delirium:

The DSM-5 notes that catatonic disorder due to another medical condition cannot occur exclusively during the course of a delirium. This is diagnostically problematic, as many patients with catatonic features in the context of another medical condition may also meet criteria for delirium, and assessment of alterations in consciousness in a mute and catatonic patient is challenging. The possibility of delirium and catatonia co-occurring has been hypothesized by Francis et al., and previously described in a series of 3 clinical cases and a cohort of 13 cases identified by a review of the literature.<sup>11</sup>

More recently, Grover et al. assessed 205 patients referred to the consultation psychiatry service with delirium for the prevalence of catatonic findings.<sup>12</sup> The study found 30.2% patients with delirium met criteria for catatonia by scoring positive on 2 of the first 14 items of the Bush-Francis Catatonia Rating Scale (BFCRS). 12.7% met criteria for catatonia using the proposed DSM-5 criteria. Excitement, immobility/stupor, and mutism were the three most commonly ranked items on the BFCRS, with a frequency of 72.7, 21.4, and 15.6 percent, respectively.

There does not appear to be any evidence in the literature that validates the exclusion of catatonia as a diagnosis in patients with delirium. Furthermore, in NMS, delirium is recognized as a diagnostic feature. It may now be possible by DSM-5 criteria to code catatonia associated with another mental disorder, and indicate delirium as the name of the associated mental disorder. Alternatively, cases of catatonia coexisting with delirium may be coded as Unspecified Catatonia.

### Malignant Catatonia:

Malignant catatonia is characterized by severe catatonia with muscle rigidity, hyperthermia, autonomic nervous system instability, delirium, and agitation, which can then proceed to coma and death.<sup>13</sup> It has also been called lethal catatonia. Unfortunately, the DSM-5 does not provide criteria for malignant catatonia. This monograph supports the conceptualization of Philbrick and Rummans that catatonia exists on a continuum, with simple catatonia on one end of the spectrum, and malignant catatonia being the more severe form of the disorder on the other end of the spectrum.<sup>14</sup>

When malignant catatonia occurs in the setting of exposure to dopamine antagonists, it has been called Neuroleptic Malignant Syndrome (NMS). Both disorders share many signs and symptoms.<sup>15</sup> However, the term is misleading, because NMS also can occur after abrupt discontinuation of dopamine agonists, and after exposure to agents that are not considered dopamine antagonists.<sup>16</sup> Up to 20% of cases of NMS may be indistinguishable from malignant catatonia.<sup>17</sup> The DSM-5 recognizes that malignant catatonia may be indistinguishable from NMS. For the purposes of this monograph, malignant catatonia and NMS are viewed as the same condition.

Delirious mania is a term applied to a neuropsychiatric syndrome characterized by acute onset of delirium, mania, psychosis, and catatonia. It has also been known as Bell's mania, manic delirium, and excited catatonia, yet none of these terms are recognized by the DSM-5.<sup>18</sup> Patients may rapidly progress to malignant catatonia within hours or days. The authors of a recent review describe a proposed work-up and treatment for delirious mania that is essentially identical to that of catatonia.<sup>19</sup> They suggest a workup for organic causes, but add that delirious mania cannot be due to another medical condition. There does not appear to be any reason to characterize delirious mania as anything other than a form of malignant catatonia with manic features, nor does it appear prudent to limit delirious mania as a condition of purely psychiatric etiology.

Paroxysmal Sympathetic Hyperactivity (PSH) is a syndrome known to neurology and intensive care medicine that occurs in the setting of severe brain injury. It has also been known as autonomic dysfunction syndrome, sympathetic storm, or paroxysmal autonomic instability with dystonia. Due to a confusion of eponyms, diagnostic criteria, nomenclature, and definitions, a recent international panel issued a consensus statement that the syndrome is a diagnosis of exclusion, and that the core features of PSH include: transient and paroxysmal increases in sympathetic activity (tachycardia, tachypnea, hypertension, hyperthermia, sweating) and rigidity with extensor posturing.<sup>20</sup> Patients usually display intermittent agitation, dystonia, catatonic posturing, opisthotonus, and may transition to malignant catatonia/NMS.<sup>21</sup> Indeed, PSH shares many clinical features and similar proposed pharmacologic treatment to malignant catatonia/NMS.<sup>22</sup> Cases of catatonia in setting of brain injury have been discussed in the literature since at least 1959.<sup>23</sup> It is unclear how PSH could be conceptually different from a brain injury induced form of malignant catatonia, and further research is needed.

Excited Delirium Syndrome (ExDS) is a syndrome known to law enforcement, prehospital care, emergency medicine and forensic medicine, wherein the pathophysiology is not understood. The majority of cases of ExDS occur in the setting of intoxication with a sympathomimetic agent, historically cocaine, but also methamphetamine, phencyclidine (PCP), lysergic acid diethylamide (LSD), and more recently synthetic cathinones (“bath salts”).<sup>24, 25</sup> ExDS cases have also been described in patients with psychiatric disease. According to the 2011 ExDS Task Force consensus, the features of ExDS include: acute onset, fulminating delirium and psychosis with extreme aggression (frenzy/rage), hyperkinetic agitation, attraction to bright lights/loud sounds/reflective surfaces, spontaneous disrobing, keening (unintelligible animal-like noises), extreme pain tolerance, excessive strength, hyperthermia, diaphoresis, and tachypnea.<sup>26</sup> Patients may progress to sudden respiratory and cardiac arrest. The DSM-5 does not recognize ExDS as a disorder. However, the 2011 ExDS Task Force likens ExDS with delirious mania. ExDS could be best viewed as a form of malignant catatonia usually due to intoxication with a sympathomimetic agent.

In conclusion, malignant catatonia has gone by many different names. A lack of open communication between medical disciplines has further compounded the problem, with different fields ascribing their own name or multiple names to the same syndrome. While further research is needed to better characterize malignant catatonia in its various forms, the medical community should also work on a unified model for better conceptualization of this syndrome.

## **PEDIATRIC CATATONIA:**

### Introduction:

Catatonia in the pediatric population has clinical features identical to catatonia in adults. Evidence suggests the disorder is not rare, but rather unrecognized and undertreated. While adult catatonia is seen more frequently in the context of a mood disorder, pediatric catatonia may be seen more frequently in boys and in the context of schizophrenia.<sup>27, 28</sup> However, the latter may be an artifact on the part of pediatric clinicians still regarding catatonia as a sign of schizophrenia.

Pediatric catatonia is also associated with a high prevalence of general medical conditions and developmental disorders. Pediatric catatonia is particularly associated with high morbidity. One prospective study found that catatonia in adolescence increases the risk of premature death (including suicide) by 60-fold.<sup>29</sup>

### Occurrence:

Catatonia occurring in children and adolescents has not been fully investigated in the general hospital setting, nor in the medically ill pediatric population. Thus, the occurrence of catatonia in the pediatric population is difficult to characterize.

Failure to identify and treat pediatric catatonia was highlighted by a recent retrospective study reviewed 101 patients receiving psychiatric care at a university hospital.<sup>30</sup> Identified subjects were patients who were either already diagnosed with catatonia or NMS, or with a disorder that has a perceived risk for catatonia, including autism (autism spectrum disorder), psychosis not otherwise specified, intermittent explosive disorder, mental retardation (intellectual disability). 17.8% met at least 3 of the following catatonic features: unexplained excitement/agitation, unusual movements, reduced movements, repetitive or stereotyped movements, and reduced/loss of speech. However, only 2 patients were diagnosed with catatonia by the treatment providers, and only 1 of which was treated with a benzodiazepine. While this study also found an increased incidence in boys as noted by other studies, only 1 of 101 patients was diagnosed with schizophrenia. The authors also found a higher frequency of an agitated form of catatonia rather than the more classic stuporous form of the disorder. Associated medical conditions were not documented as part of this study.

One prospective study of 58 patients presenting to a psychiatric hospital reported 22.4% cases were associated with a general medical condition, and 31% had a history of developmental disorder.<sup>31</sup> Among patients with a medical condition, lupus encephalitis was the most common illness, followed by singular presentations of anti-NMDA-receptor encephalitis, cyclosporine treatment, epilepsy, post-hypoglycemic coma, Huntington's chorea, Fatal Familial Insomnia, and various genetic/metabolic disorders.

The findings are similar to a literature review by Lahutte et al., which found 38 reported cases of pediatric catatonia associated with medical conditions.<sup>32</sup> The most common medical conditions included: lupus encephalitis (4), viral encephalitis (4), typhus (4), epilepsy (3), and 3,4-methylenedioxy-*N*-methamphetamine (MDMA) intoxication (3).

#### Co-occurrence with Autism Spectrum Disorder:

Catatonia and catatonic-like features are also often found in patients with autism spectrum disorders (ASDs), which has led to hypotheses that catatonic and autistic features may be related.<sup>33</sup> Catatonic phenomena in patients with ASDs are typically observed at a later age than when the autistic symptoms were first observed. Case reports of catatonia in ASD patients have often reported antecedent stressful life events as precipitants for the development of catatonia.

One six-year retrospective study by Wing and Shah, of 506 children and adults referred to an ASD specialty center found 30 patients (6%) with essential features of catatonia (which they defined as: increased slowness affecting motoric and verbal responses, difficulty initiating and completing actions, increased reliance on prompting by others, and increased passivity or apparent lack of motivation).<sup>34</sup> All 30 patients were 15 years old or older, representing 17% of all patients seen within this age range. The majority of patients first developed catatonic features between the ages of 10-19 years.

A prospective study of 120 ASD patients reported 13 patients (12%) were clinically diagnosed with comorbid catatonia, all diagnosed at or after adolescence, although the study was unclear regarding methods used to make this diagnosis.<sup>35</sup> Slowness initiating movements appeared to be the most common finding, similar to the Wing and Shah study.

Further studies to determine prevalence, mechanisms, and optimal management of catatonia in ASD patients are needed. Mazzone et al. recently proposed an algorithm for management and treatment of catatonia in ASD patients, not unlike to the proposed standard algorithm proposed in this monograph in Appendix D.<sup>36</sup>

#### Assessment and Rating Scales:

There is no evidence to suggest that catatonia in children should be assessed or rated differently than in adults. The Bush Francis Catatonia Rating Scale (BFCRS) is the gold standard for screening and rating catatonia in adults, although it has not been validated in the pediatric population. The Kanner scale was developed to better capture catatonic features in patients with ASD and pervasive developmental disorders, however, it has not been validated.

### Treatment of Pediatric Catatonia:

Catatonia in children and adolescents is treated identically to catatonia in adults. However, among cases of catatonia due to a general medical condition, while benzodiazepines are often recommended, in practice they are rarely prescribed, which may indicate a need for greater awareness of the condition.

One case series of 66 children ages 9-19 with catatonia found benzodiazepines to be effective in 65% of patients, but only 51 out of the 66 ever underwent a benzodiazepine challenge.<sup>37</sup> The previously mentioned review by Lahutte et al. revealed that benzodiazepines and electroconvulsive therapy were respectively used in only 39% and 32% of reported cases.<sup>32</sup>

## **ADULT CATATONIA:**

### Occurrence and Etiology:

The occurrence of adult catatonia in the general medical setting is difficult to characterize, in part due to the lack of a standardized approach to identification and diagnosis. Among all patients encountered by a consultation-liaison psychiatry service, the incidence of catatonia ranges from 1.6-5.5%, based on 2 retrospective and 3 prospective studies:

- Zarr and Nowak (1990) retrospectively found 11 cases of catatonia out of 349 consult requests throughout the general medical hospital, a frequency of 3% (although the criteria for catatonia diagnosis were not specified).<sup>38</sup> They also reported an occurrence of 9.1% among patients on a burn unit, but this was only 2 out of 22 consultations to the burn unit.
- Carroll et al. (1994) prospectively screened for catatonia in all patients referred to the consultation service of a large general medical hospital and cancer center over a 6 month period. They found 5 cases of catatonia out of 297 consult requests, a frequency of 1.6% (DSM-IV criteria).<sup>39</sup> One patient had AIDS, 3 had bipolar affective disorder, 1 had schizophrenia, and 1 had mental retardation. 4 patients had delirium as well as catatonia.
- Cottencin et al. (2007) retrospectively found 12 cases of catatonia out of 656 consult requests, a frequency of 1.82% (using Carroll 1992 criteria).<sup>40</sup> Of these cases, 5 had no other psychiatric diagnosis, 1 had schizophrenia, 5 had major depressive disorder, and 1 had bereavement.
- Jaimes-Albornoz and Serra-Mestres (2013) prospectively screened for catatonia in all patients referred to the consultation service of a large general medical hospital over a 4 month period.<sup>41</sup> They found 13 cases of catatonia out of 236 consult requests, a frequency of 5.5% (DSM-IV criteria).
- Denysenko et al. (2014) prospectively screened for catatonia in all patients referred to the consultation service of a small community hospital over a 12 month period.<sup>42</sup> They found 13 cases of catatonia out of 661 consult requests, a frequency of 1.97% (DSM-5 criteria).

In the Jaimes-Albornoz study, when cases were stratified based on age, the frequency of catatonia was higher in patients over the age of 65. Catatonia was found in 7 (6.3%) out of 112 patients older than 65 years using DSM-IV criteria (an additional 3 patients were included by using Fink/Taylor Criteria, for a total frequency of 8.9%). In comparison, catatonia was found in 3 (2.4%) out of 124 patients younger than 65 years (using DSM-IV and Fink/Taylor Criteria). Among the patients over the age of 65 years, 4 patients had catatonia due to a medical condition, including thalamic infarct (1),

hyponatremia (2), and Parkinson's disease dementia with agitated behavior and exposure to antipsychotics (1). 2 developed catatonia following extubation in the setting of resolving critical medical illness. They also had a pre-hospitalization history of depression in treatment with serotonergic antidepressants and antipsychotics. Among the 10 cases in patients older than 65 years, 4 had a history of depression, 2 had a history of alcohol dependence, 4 had dementia, 3 had delirium.

Smith et al. (2012) performed a 20-year retrospective cohort analysis of all adult patients at a tertiary care medical center, meeting DSM-IV-TR criteria for CD-AMC, catatonic schizophrenia, or mood disorder with catatonic features.<sup>43</sup> They found 236 patients, but only 95 met all study inclusion criteria. Of the 95 patients: 33.7% had major depressive disorder, 22.1% has bipolar affective disorder, 21% had CD-AMC, 11.6% had schizophrenia, and 11.6% had schizoaffective disorder. Excluded from the study were 18 patients with NMS, 13 with delirium, and 68 for whom catatonia was suspected but could not be clinically confirmed. Thus if patients with NMS were included as neuroleptic-induced catatonia, then CD-AMC would be the most prevalent disorder, representing more than a third of all catatonic medically ill patients.

In conclusion, catatonia in a general medical hospital is not exceedingly rare, and is likely to be underestimated and under recognized. The prevalence of CD-AMC compared to psychiatric catatonia is difficult to determine, as many patients who meet criteria for CD-AMC also have a concurrent psychiatric disorder. The prevalence of catatonia in the geriatric medical population may be higher than in the general medical population. Cases of catatonia that come to the attention of a consultation psychiatry service appear to occur with similar frequency in both large, tertiary care medical centers as well as small, community hospitals. Additional research is needed to better determine the prevalence of adult catatonia in the medically ill.

## **MEDICAL CONDITIONS ASSOCIATED WITH CATATONIA:**

The majority of the literature on CD-AMC is based on case reports, and the number of case reports on catatonia has increased dramatically. Some medical conditions or drugs may be more commonly associated with CD-AMC than others. Readers looking for a more in-depth discussion are encouraged to consult Appendix A.

### **Anti-NMDA-receptor Encephalitis (ANRE):**

ANRE is associated with IgG antibodies to the NR-1a subunit of the N-methyl D-aspartic acid (NMDA) receptor, and has only been recently characterized.<sup>44</sup> In a case series of 100 ANRE patients, 77 first presented to psychiatry with predominantly psychiatric symptoms. 76 had seizures. 86 had altered consciousness progressing to catatonia, often with autonomic instability, posturing, oral-facial dyskinesia, and choreoathetosis. Patients were almost always female, with a median age of 23 but cases ranged across the lifespan. While an ovarian teratoma is most often associated with the development of ANRE, a mass was only identified in 59% of cases.

Case reports of ANRE-associated catatonia may indicate that the disorder is common in children and young adult females.<sup>45, 46</sup> One case series of 8 patients hypothesized on there being 3 distinct “phenotypes” for ANRE in children: classic catatonic/stuporous, non-catatonic with prominent psychiatric/behavioral symptoms, and a persistent catatonic form lasting >60 days, the last of which had the poorest prognosis.<sup>47</sup> Despite the high incidence of catatonia with autonomic instability in patients with ANRE, treatment with high-dose benzodiazepines and ECT is rarely applied despite the reported effectiveness of these catatonia interventions.<sup>48</sup>

Immunotherapy treatment (corticosteroids, intravenous immunoglobulin, rituximab, cyclophosphamide, or plasma exchange) has been reportedly helpful. Definitive treatment via surgical excision of the tumor (if found) often improves neuropsychiatric symptoms, but patients may need weeks or months to improve, and only 65% might be expected to make a full recovery.<sup>49</sup>

Cases wherein immunotherapy or tumor removal was delayed, or wherein no tumor was identified, may be at risk of symptomatic relapse years later, which suggests a possible role for long-term follow-up.<sup>50</sup> Readers looking for more information on treatment and long-term prognosis of ANRE are directed to Appendix A.

### **Paraneoplastic Limbic Encephalitis:**

Catatonia due to paraneoplastic limbic encephalitis has been described in case reports since at least the 1980's.<sup>51</sup> Cases reported in the literature appear to display behavior that is difficult to manage, only partially responsive to benzodiazepines, and

often progressing to malignant catatonia requiring ECT. Surgical excision of the tumor usually resolves the psychiatric symptoms.

### Systemic Lupus Erythematosus (SLE):

SLE is the most common reported rheumatologic condition associated with catatonia, and may be the most common cause for CD-AMC in the pediatric population. A recent 2013 case report of lupus catatonia in a 22 year old female also found 22 other cases of catatonia in patients with lupus (all female, 5 were under 18 years old).<sup>52</sup>

Patients do not need to demonstrate lupus cerebritis to have catatonia, and many case reports have reported lupus catatonia with normal brain imaging on CT and MRI. Some patients may be responsive to benzodiazepines, steroids, cyclophosphamide, rituximab, while others may be recalcitrant to all such medications, and ultimately only responsive to ECT.<sup>53, 54</sup>

### Seizures:

Ictal catatonia has been reported in 3 case reports and in several review articles.<sup>55, 56, 57, 58</sup> Patients may present with non-convulsive status epilepticus or *de novo* absence seizures with catatonic features, including mutism and waxy flexibility. Benzodiazepine withdrawal may be a precipitating factor in some of these cases.

### Brain infections:

Encephalitis due to infectious causes has been associated with catatonia, including contemporary encephalitis lethargica,<sup>59, 60</sup> herpes-simplex virus,<sup>61</sup> subacute sclerosing panencephalitis,<sup>62</sup> neurosyphilis,<sup>63</sup> borrelia burgdorferi,<sup>64</sup> typhoid fever,<sup>65</sup> adenovirus,<sup>66</sup> and disseminated neurocysticercosis.<sup>67</sup>

Catatonia in patients with human immunodeficiency virus (HIV) has been reported as a consequence of the disease,<sup>68, 69</sup> or in the specific setting of progressive multifocal leucoencephalopathy,<sup>70</sup> or due to anti-retroviral medications.<sup>71</sup> It has been shown that the neurotoxic actions of HIV leads to over-activation of NMDA receptors, and increased levels of products of NMDA agonist potential in the cerebrospinal fluid have been found in HIV infected patients.<sup>72, 73</sup> The NMDA inhibitor memantine also inhibits HIV-induced glycoprotein 120 calcium changes, protects against glycoprotein 120-induced cell death, and may prevent dopamine depletion, suggesting a role for memantine in HIV-associated neurocognitive disorder as well as HIV-associated catatonia, although more research is needed.<sup>74</sup>

### Intracranial Mass Lesions:

Catatonia has been reported to occur in patients with brain tumors, particularly in the regions of the pituitary, corpus callosum, midbrain and brain stem, and surrounding the 3<sup>rd</sup> and 4<sup>th</sup> ventricles (the latter also associated with hydrocephalus).<sup>75, 76, 77, 78</sup> One case failed to resolve with pituitary tumor resection but did resolve with ECT.<sup>79</sup> Resolution of catatonia after brain tumor resection has also been reported.<sup>80</sup>

### Multiple Sclerosis:

Catatonia is a rare complication of multiple sclerosis, but often may be the presenting manifestation of the disease.<sup>81, 82, 83, 84, 85, 86</sup> Cases appear to be responsive to benzodiazepines and ECT.

### Delirium (Encephalopathy):

Cases of catatonia occurring in the setting of uremic encephalopathy,<sup>87</sup> thermal injury,<sup>88</sup> and posterior reversible encephalopathy syndrome (PRES)<sup>89, 90</sup> have been reported. Francis and Lopez-Canino identified 16 patients who met criteria for delirium and catatonia occurring simultaneously, with mutism, withdrawal, posturing, and immobility as the most frequent features.<sup>91</sup>

### Glucose-6-phosphate dehydrogenase (G6PD) Deficiency:

An association between G6PD deficiency and catatonia has long been suggested in the literature.<sup>92, 93</sup> Some patients with G6PD deficiency may be more at risk for bipolar disorder with catatonic features, or schizoaffective disorder with psychotic mania.<sup>94</sup> It is unknown if the catatonia and G6PD deficiency are genetically linked, or if the G6PD deficiency confers a risk of developing catatonia, perhaps through an oxidative stress mechanism causing oxidative brain damage.<sup>95</sup>

### Vitamin B12 Deficiency:

Catatonia has been reported in several case reports in patients with vitamin B12 deficiency, even with only moderately low levels.<sup>96, 97, 98, 99</sup>

### Hyponatremia:

Several case reports have described catatonia in the setting of hyponatremia.<sup>100, 101, 102, 103, 104</sup> The catatonia improved with correction of the electrolyte disturbance and/or treatment with benzodiazepines in all but 1 case that was recalcitrant

to electrolyte correction or lorazepam and required ECT.<sup>105</sup> Catatonia has also been described in cases of extrapontine myelinolysis caused by the rapid correction of hyponatremia.<sup>106, 107</sup>

### Stroke, Dementia, and Other Brain Degeneration Disorders:

Other brain diseases associated with catatonia have been reported, and which responded to a variety of treatments. Catatonia has also been reported in the setting of left middle cerebral artery occlusion, successfully treated with olanzapine 2.5mg IM q12hrs for 4 days.<sup>108</sup> The authors chose olanzapine for its high affinity for 5HT2a antagonism and low D2 blocking activity.

Three patients with catatonia and frontotemporal atrophy were reported with successful treatment with lorazepam with or without ECT and augmentation with memantine.<sup>109</sup>

There have been several cases of catatonia in the setting of Lewy body dementia.<sup>110, 111, 112, 113</sup> Dopamine antagonists exacerbated the catatonia in 1 case, and patients responded to treatment with high dose lorazepam or ECT. Donepezil may have induced catatonia in 1 case,<sup>114</sup> even though acetylcholinesterase inhibitors have usually been reported to improve psychotic symptoms in patients with Lewy body disease,<sup>115</sup> and psychosis induced by abrupt withdrawal of donepezil has been demonstrated.<sup>116</sup>

### Takotsubo Cardiomyopathy:

Catatonia in the setting of takotsubo cardiomyopathy and major depression has been described in only 1 published and 1 unpublished case.<sup>117, 118</sup> Both catatonia and takotsubo cardiomyopathy have been independently associated with excessive catecholamine levels, which may suggest a common pathophysiology.<sup>119, 120</sup>

### Wilson's Disease:

Catatonia in the setting of Wilson's disease is rare but has been reported in several cases.<sup>121, 122, 123</sup> In 20% of cases of Wilson's disease, psychiatric manifestations may precede other symptoms of the disease.<sup>124</sup> Patients respond to the usual treatments for catatonia. Dopamine antagonists should be used cautiously (quetiapine or clozapine are preferred) in patients with Wilson's disease, due to an increased risk for extrapyramidal side effects and malignant catatonia/NMS.<sup>125</sup>

### **Special Note on Ferropenia:**

Low serum iron has been associated with catatonia, particularly in malignant catatonia/NMS.<sup>126</sup> Rosebush and Mazurek prospectively measured serum iron concentration in 26 episodes of NMS in 23 patients and found serum iron concentration was 10 micromol/L or lower in 25 (96%) of episodes.<sup>127</sup> Another study measured serum iron concentration in 39 episodes of catatonia and found low serum iron levels in 17 (44%) of episodes.<sup>128</sup> Cases with low serum iron levels were associated with malignant catatonia, poor response to lorazepam, and conversion to NMS.

Peralta et al. examined serum iron levels in 40 patients with catatonia compared to 40 non-catatonic psychotic inpatients and found the incidence of ferropenia (serum iron <50 microgram/dL) in 35% of the catatonic group compared to 7.5% of the noncatatonic group.<sup>129</sup> They did not find any cases that progressed to NMS.

The pathophysiology of ferropenia in catatonia/NMS remains unknown. Rosebush and Mazurek hypothesized that ferropenia may be the result of an acute phase reaction that leads to a reduction of dopamine D2 receptors in the brain, leading to NMS.

Recent research has shown that iron is required to generate calcium signals after NMDA receptor stimulation.<sup>130</sup> Thus an alternative hypothesis suggested by the author of this monograph (L.D.) may be that ferropenia caused by an acute phase reaction leads to catatonia through disruption of NMDA-mediated neurotransmission, or that ferropenia reflects acute serum iron depletion secondary to NMDA hyperactivity in the brain during an acute catatonic episode. Further research is needed to determine the cause of ferropenia in catatonia, and the risk that ferropenia poses in the development of malignant catatonia/NMS.

## **DRUG TOXIDROMES AND WITHDRAWAL SYNDROMES ASSOCIATED WITH CATATONIA:**

### Tacrolimus and Cyclosporine:

Numerous reports have described cases of catatonia in patients treated with the tacrolimus, a macrolide molecule used for immunosuppression.<sup>131, 132, 133, 134, 135</sup> Cases are often associated with mutism, akinesia, and neurologic symptoms including myoclonus, tremor, ataxia, and dysarthria. Mutism without other signs of catatonia are possibly much more common.<sup>136</sup> Many of these cases have occurred without the development of PRES, even at normal therapeutic serum tacrolimus levels not otherwise considered toxic. Cases of tacrolimus-induced catatonia are very likely to be misinterpreted as delirium, akinetic mutism, or go unrecognized. Cases usually respond to benzodiazepines and discontinuation of tacrolimus, although in some cases, residual dysarthria or ataxia may persist for months or years.

The mechanism behind tacrolimus-induced catatonia is unknown. Calcineurin modulates NMDA and gamma-aminobutyric acid (GABA) activity. As a calcineurin inhibitor, tacrolimus potentiates NMDA receptor activity<sup>137</sup> which may lead to catatonia. An alternative hypothesis, which may explain tacrolimus-induced neurotoxicity and PRES but not exactly catatonia, reasons that tacrolimus may disrupt the blood-brain barrier and cause vasogenic edema via increased nitrous oxide production.<sup>138, 139</sup>

Only one case of cyclosporine-associated catatonia has been reported,<sup>140</sup> although cyclosporine-induced mutism has been reported in at least 9 patients.<sup>141, 142</sup> Similarly to tacrolimus, cyclosporine inhibits GABA activity which may explain the pathogenic mechanism.<sup>143</sup> Sirlomus, which is not a calcineurin inhibitor, has not been associated with catatonia.

### 3,4-methylenedioxy-N-methylamphetamine (MDMA):

Three case reports have described catatonia after acute intoxication with MDMA, otherwise known as “Ecstasy,” “Mandy,” or “Molly.”<sup>144, 145, 146</sup> Serotonin hyperactivity or hyponatremia have been suggested as a potential mechanisms.

### Steroids:

Corticosteroid-induced neuropsychiatric disturbances are varied in severity and symptomatology, with most cases occurring at prednisone-equivalent levels greater than 40mg/day.<sup>147</sup> However, only 3 cases of steroid-induced catatonia have been reported.<sup>148, 149, 150</sup>

### Antibiotics:

Fluoroquinolones such as ciprofloxacin and levofloxacin have been reported to induce catatonia in case reports.<sup>151, 152, 153</sup> Diminished renal clearance of the drug is a risk factor for quinolone neurotoxicity, and patients may also present with psychosis, convulsive seizures, electric-like shocks in extremities, and myoclonic jerks.<sup>154</sup>

Beta-lactam antibiotics, particularly the cephalosporins, have been less commonly implicated in catatonia.<sup>155</sup> The underlying mechanism for inducing catatonia may be the GABA receptor antagonism common to both quinolones and beta-lactam antibiotics.

Macrolide antibiotics such as clarithromycin and erythromycin have been associated with acute psychosis, mania, and depression. However, only azithromycin has been reportedly associated with catatonia in only one case report.<sup>156</sup> The mechanism is not currently understood.

### Disulfiram:

Disulfiram-induced catatonia has been described in multiple case reports since 1967.<sup>157, 158, 159, 160, 161, 162, 163, 164, 165, 166</sup> The theory is that disulfiram blocks dopamine beta-hydroxylase enzymes, which may cause elevated dopamine levels in the mesolimbic system, which in turn downregulates GABA activity in the thalamus and basal ganglia, thereby causing catatonic symptoms. Cases typically presented with mutism, stupor, withdrawal, and posturing, and were often also associated with delirium or encephalopathy.

### GABA agonist withdrawal:

Patients withdrawing from GABA-ergic drugs can develop catatonia, and the number of cases are probably underreported or considered part of a withdrawal delirium. Cases of catatonia have been reported in the setting of withdrawal from alcohol,<sup>167, 168, 169, 170</sup> benzodiazepine,<sup>171, 172, 173, 174, 175, 176, 177, 178, 179</sup> benzodiazepine mixed with meprobamate,<sup>180</sup> and glutethimide.<sup>181</sup>

Non-benzodiazepine GABA agonist withdrawal catatonia has also been described. A case has also been described of a patient with bipolar disorder rapidly tapered off gabapentin 500mg daily who developed catatonia within 48 hours of the last dose.<sup>182</sup> There was also a case of zolpidem withdrawal catatonia in a 27 year old female who abused 100-200mg zolpidem daily for 2 years.<sup>183</sup> Curiously, there have been no reported cases of catatonia induced by withdrawal from barbiturates.

### Baclofen:

Catatonias have been reported in patients exposed to baclofen, either on its own,<sup>184</sup> or together with withdrawal from benzodiazepines.<sup>185</sup> It is possible that baclofen, as a GABA-B receptor agonist, may worsen catatonic features.

### Dopamine antagonists:

Exposure to dopamine antagonists has been associated with the development of catatonic features, including malignant catatonia/NMS, in many case reports.<sup>186, 187</sup> Neuroleptic-induced catatonia responds favorably to lorazepam and cessation of neuroleptic medication.<sup>188</sup>

### Cocaine withdrawal:

A case of catatonia following withdrawal from a crack cocaine binge responsive to lorazepam was reported.<sup>189</sup> Also reported is a case of cocaine-induced catatonia with leukoencephalopathy resistant to lorazepam and made malignant with antipsychotics and which ultimately improved with coenzyme Q10, dantrolene, bromocriptine, and intensive care unit support.<sup>190</sup>

### Phencyclidine (PCP):

One series of 1000 cases of PCP intoxication found at least 87 cases of catatonia, with most cases resolving within hours or less than one day.<sup>191</sup> Symptoms included mutism, staring, posturing, catalepsy, rigidity, negativism, and stupor.

### Methoxetamine:

Three cases were reported of intentional methoxetamine intoxication that resembled a dissociative-catatonic state with hypertension and tachycardia that improved with benzodiazepines.<sup>192</sup> Methoxetamine is an NMDA antagonist and dopamine reuptake inhibitor chemically derived from and with intoxication symptoms clinically similar to ketamine and which can be easily purchased over the internet.

## **TREATMENT OF CATATONIA:**

There is no data to suggest that treatment of catatonia in the medically ill is any different than treatment of catatonia in any other clinical setting. There is broad agreement that in cases of CD-AMC, treatment should be directed not only towards lysing the catatonic phenomena, but also should include treatment of the suspected underlying medical condition and/or removal of any agents suspected of causing catatonia.

### **GABA agonists:**

In the 1980s, several case reports and case series began to report successful treatment of catatonia with benzodiazepines.<sup>193, 194, 195, 196, 197, 198</sup> In the 1990s, several open prospectively trials and one retrospective literature review demonstrated a 60-100% response rate of acute catatonia to benzodiazepines:

- Yassa et al. (1990) reported an open trial of 10 patients with catatonia who responded to low-dose lorazepam, 9 of which had continued to receive antipsychotic medication during treatment.<sup>199</sup>
- Rosebush et al. (1990) prospectively identified 15 patients with catatonia wherein treatment with lorazepam 1-2mg fully resolved catatonia in 12 (80%) of cases.<sup>200</sup>
- Ungvari et al. (1994) reported 15 of 18 (83%) patients with catatonia who responded lorazepam with significant or complete resolution of catatonic phenomena.<sup>201</sup>
- In an open trial of 13 patients, Bush et al. (1996) reported lorazepam 2mg IV reduced catatonic phenomena by 60% as measured with the BFCRS within 10 minutes of administration.<sup>202</sup>
- Payee et al. (1999), in a prospective open trial of lorazepam (dose range 3mg/day on day 1 up to 8mg/day on day 5) demonstrated a 70% response rate in 30 psychiatric patients with catatonia.<sup>203</sup> Non-responders were defined as patients who continued to have at least 2 symptoms of catatonia present after 5 days of treatment. Patients who responded to lorazepam had a mean drop in their baseline BFCRS of 17.63% by the end of day one compared to 10.85% in non-responders, which was statistically significant. 8 of the 9 lorazepam non-responders would later respond to ECT.
- A retrospective literature review by Hawkins et al. (1995) collected 70 publications comprising a total of 178 patients.<sup>204</sup> Benzodiazepines were effective in 70% of cases treated, ECT was effective in 85% of cases treated, and antipsychotics demonstrated poor efficacy.

There is only one published randomized, placebo-controlled, double-blind trial for the initial treatment of catatonia.<sup>205</sup> In this study, 20 inpatients with catatonic mutism were randomly assigned to intravenous saline or a 5% amobarbital solution. Patients were crossed over to the other infusion if the initial infusion had no response. 6 of 10 patients responded to the initial amobarbital infusion and 0 of 10 patients responded to saline. 4 saline non-responders subsequently responded to amobarbital. To date, there are no randomized controlled trials demonstrating effectiveness of benzodiazepines for the treatment for catatonia.

It is possible that patients with catatonia in the context of an affective disorder respond more favorably to a benzodiazepine than do patients with catatonia in the context of schizophrenia. Rosebush and Mazurek (2010) described their 20-year experience prospectively treating 180 episodes of catatonia in 148 patients.<sup>206</sup> The rate of effectiveness of benzodiazepines in patients with affective disorders and schizoaffective disorder were 80% and 70% respectively, while in patients with schizophrenia, benzodiazepines were the least effective (Rosebush et al. did not state their rate of effectiveness in schizophrenia in their paper).

On the other hand, Lee (2010) described his 8-year experience prospectively treating 127 cases of catatonia.<sup>207</sup> Benzodiazepines were effective in 78% (14/18) cases of neuroleptic-induced catatonia, 75% (12/16) of manic catatonia, and 67% (34/51) of schizophrenia catatonia, suggesting the differences in benzodiazepine response were not significant.

The poorer response rate of catatonia to benzodiazepines in patients with schizophrenia has been reported in only a randomized, double-blinded, placebo-controlled, crossover study by Ungvari et al. (1999).<sup>208</sup> In 17 patients with schizophrenia and chronic catatonia, neither placebo nor lorazepam 6mg/day had any clinically noticeable or statistically significant impact on catatonia or BFCRS scores. The authors noted that the chronic catatonia experienced by these patients with schizophrenia was clinically different from the acute catatonic syndrome.

### NMDA Receptor Antagonists:

NMDA receptor antagonists may be helpful as augmentation agents in lorazepam-resistant catatonia, although the exact mechanism is unknown, and may actually not be related to their effects on the NMDA receptor. NMDA antagonists may increase dopamine levels in the frontal cortex and striatum,<sup>209</sup> which may explain the anti-catatonic ability of certain NMDA receptor antagonists (memantine and amantadine), but does not explain the pro-catatonic effects of others (such as PCP and ketamine). Perhaps another physiologic mechanism might explain the clinical differences of ketamine and memantine on catatonia, such as their divergent effects on the expression of brain-derived neurotrophic factor (BDNF), or their divergent effects on the expression of certain glutamatergic postsynaptic density proteins.<sup>210 211</sup>

Memantine is a low to moderate noncompetitive NMDA receptor antagonist, with similar potencies at 5HT-3 receptors (as an antagonist) and at dopamine D-2 receptors (as an agonist).<sup>212, 213</sup> Memantine achieves peak serum concentrations within 6 hours. Evidence is limited to case reports but response has been demonstrated within hours-days of administration at starting at 5mg titrated by 5mg/day with sustained improvement at doses of 5-20mg/day in divided doses.<sup>214, 215, 216, 217, 218</sup> QT interval prolongation is a potential adverse effect.

Amantadine is a moderate, reversible NMDA receptor antagonist that also facilitates dopamine release and dopamine reuptake. Successful improvement in catatonic features has been reported in case reports, mostly in patients with schizophrenia but also in patients with depression, bipolar disorder, dementia, adjustment reactions, and in catatonia in the medically ill setting.<sup>219, 220, 221, 222, 223, 224</sup> Amantadine was usually administered 100-400mg PO in divided doses, adjusted lower in patients with diminished renal function. A report of 2 cases described the successful treatment of malignant catatonia following 2-3 intravenous infusions of amantadine 200mg.<sup>225</sup>

Carroll et al. (2007) retrospectively reviewed 25 cases of catatonia effectively treated with either amantadine or memantine.<sup>226</sup> Most patients had schizophrenia, 1 had schizoaffective disorder, 4 had dementia, 1 had bipolar depression, 2 had major depression, 1 had autistic disorder, and 1 had borderline personality disorder. Improvement generally occurred 1-7 days after administration of either drug.

Amantadine may also be helpful in cases of akinetic mutism. One case report describes a man with akinetic mutism following a traumatic brain injury, wherein his symptoms would dissipate while speaking on the telephone, who improved in the realm of mutism, impulsivity, and disorientation after 2 weeks on amantadine 300mg/day.<sup>227</sup>

Dextromethorphan/quinidine (DMQ), the novel combination drug with potent sigma-1 receptor agonism and noncompetitive NMDA receptor antagonism, may be another agent with effectiveness in catatonia. One unpublished study reported three cases of lorazepam-responsive catatonia that further improved within 2 hours to 2 days of treatment augmentation with DMQ 20-10mg orally every 12 hours.<sup>228</sup>

### Minocycline:

Minocycline has been reported in several cases to effectively improve catatonic features in patients with schizophrenia, at doses of 150-300mg/day.<sup>229, 230</sup> A small 6-month double-blind randomized controlled trial of minocycline 200mg daily versus placebo in patients with schizophrenia showed improvement in negative symptoms and executive functioning.<sup>231</sup> The effect of minocycline in CD-AMC has not been reported, and the mechanism of action is unknown. Minocycline is not a direct NMDA receptor antagonist. Rather, it is a potent antagonist of nitric oxide-induced neurotoxicity, and nitric oxide production is largely signaled by NMDA receptor activation. The availability

of minocycline in intravenous form may be an advantage in patients unable to take medication orally.

### Antipsychotics:

There is concern that patients with catatonia can progress to malignant catatonia/NMS when treated with antipsychotics. The phenomenon of neuroleptic-induced catatonia and malignant catatonia/NMS has been described, even with atypical (second generation) antipsychotics, including clozapine.<sup>232</sup> However, neuroleptics have been successfully used for treating cases of catatonia. Olanzapine in particular, as a primary agent or in conjunction with more standard treatment (benzodiazepines, ECT, or amantadine), has been successful in treating catatonia in many case reports, including CD-AMC, chronic/refractory catatonia, and pediatric catatonia.<sup>233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243</sup> There have been no randomized controlled trials or comparison trials of benzodiazepine versus antipsychotics for the treatment of catatonia.

Only one randomized controlled trial with antipsychotics for the treatment of catatonia has been reported, in which risperidone plus sham ECT was compared to ECT plus placebo in non-affective catatonia not responsive to lorazepam.<sup>244</sup> 14 patients completed the trial, which showed that ECT (average 8.87 treatments) was superior to risperidone (4-6mg/day) in decreasing catatonia symptoms after 3 weeks. BFCRS scores declined approximately 90% in the ECT group compared to 50% in the risperidone group.

### ECT:

As mentioned above, one small randomized controlled trial by showed ECT to be superior to risperidone in treatment refractory non-affective catatonia (schizophrenia or psychosis not otherwise specified).<sup>244</sup> There have been no other randomized controlled trials of ECT for the treatment of catatonia.

Standard practice for catatonia, particularly in emergent/malignant cases, is to use bilateral electrode placement, daily, for up to five days, followed by conventional ECT three times weekly thereafter until sustained improvement occurs.<sup>245</sup> Bilateral ECT appears to be effective in lysing catatonia regardless of its etiology. Benzodiazepines should not be rapidly withdrawn prior to ECT, so as to avoid the possibility of ECT-emergent catatonia. Indeed, one report of 5 cases suggests a synergistic role of benzodiazepines with ECT for catatonia.<sup>246</sup> In all 5 cases, lorazepam alone failed to lyse catatonia, but after beginning ECT, the patients began to respond to lorazepam.

However, right unilateral ECT may also be an effective option with possibly fewer adverse effects. One case series of 5 patients with catatonia due to a variety of causes (1 Lupus, 1 Major depression, 1 Bipolar disorder, 2 Schizophrenia) demonstrated

success with using ultrabrief right unilateral ECT titrated to a charge equal to five times the determined seizure threshold.<sup>247</sup>

A more recent case series described 13 patients with catatonia (1 Lupus, 1 Paraneoplastic syndrome, 1 Schizoaffective disorder, 2 Schizophrenia, 6 Bipolar disorder, 2 Major Depression) treated with ultrabrief right unilateral ECT titrated to a charge equal to six times the determined seizure threshold.<sup>248</sup> Two patients (both with bipolar disorder) did not respond to unilateral ECT, nor did they respond to subsequent bilateral ECT. Of the 10 patients that did respond, the authors state that most demonstrated significant symptomatic improvement after only 1 treatment. Further studies are needed to determine the relative safety and efficacy of ultrabrief unilateral versus bilateral ECT.

#### Other Treatments:

Dantrolene and dopamine agonists such as bromocriptine have been reported as effective in malignant catatonia in case reports.<sup>249, 250, 251, 252, 253, 254</sup> In most cases, these agents have been used in combination with each other and with other treatments, including benzodiazepines and ECT.

According to Mann et al, in a review of 107 cases in the literature from 1986-2010 identified as having malignant catatonia but not NMS, none were successfully treated with dantrolene alone.<sup>13</sup> Curiously, dantrolene and bromocriptine only appear to be clinically considered in cases of malignant catatonia/NMS, thus it is virtually unknown if dantrolene and bromocriptine display any effectiveness in non-malignant catatonia.

## **CONCLUSIONS:**

Catatonia is an under-recognized disorder that occurs in about 2% of adult patients brought to the attention of consultation-liaison psychiatrists at both large and small hospitals. It is even less recognized in the pediatric and ASD populations.

CD-AMC (when including NMS) is the most common form of the disorder, followed by catatonia due to a mood disorder, and lastly by catatonia due to a psychotic disorder. Some patients may have both psychiatric and medical risks factors for developing catatonia, and delirium with catatonic features has been reported.

Differences between etiologies in relation to benzodiazepine treatment response do not appear to alter the general treatment approach. Rapid initiation with lorazepam or another benzodiazepine, sometimes at high doses (8mg/day of lorazepam or greater), leads to lysis of the disorder in most cases. Augmentation with memantine or amantadine may also be helpful. ECT should be offered in patients who have not responded to benzodiazepines within 3 days, or should be initiated emergently if the patient displays malignant features such as autonomic instability and hyperthermia. Dantrolene and bromocriptine have not proven to be effective in catatonia, should not be used in isolation without concurrent benzodiazepines, and their use should not delay definitive treatment with ECT.

Removing suspected offending agents and/or treating the underlying medical condition and/or drug withdrawal is required when treating suspected CD-AMC. Antipsychotics, particularly olanzapine, may be helpful in some cases of catatonia, although serum iron should be checked prior to initiating treatment with dopamine antagonists, benzodiazepines should be continued concurrently with the antipsychotic, and patients should be continuously monitored for symptoms of malignant catatonia/NMS.

Appendix A is a list of recommended readings, some of which have not been previously referenced in this monograph, but are included for further education. Appendix B is a glossary of signs and symptoms of catatonia that are often confusing. Appendix C is a brief annotated list of some of the more important papers on catatonia treatment. Appendix D is a proposed catatonia treatment guideline specific for the consultation-liaison psychiatrist.

## APPENDIX A: List of Recommended Readings

### **Books:**

Caroff SN, Mann SC, Francis A & Fricchione GL (Eds.). (2004) *Catatonia: from psychopathology to neurobiology*. Washington, D.C.: American Psychiatric Publishing

Fink M, Taylor MA (2003). *Catatonia: a clinician's guide to diagnosis and treatment*. Cambridge, UK:Cambridge University Press

### **Papers:**

#### **General Adult Catatonia (Reviews):**

Fink M: Rediscovering catatonia: the biography of a treatable syndrome. *Acta Psychiatr Scand* 2013;127(Suppl. 441):1–47

Northoff G: What catatonia can tell us about “top down modulation”: a neuropsychiatric hypothesis. *Behavior and Brain Sciences* 2002;25:555-604

Carroll BT, Goforth HW, Thomas C, Ahuja N, McDaniel WW, Kraus MF, Spiegel DR, Franco KN, Pozuelo L, Muñoz C: Review of adjunctive glutamate antagonist therapy in the treatment of catatonic syndromes. *J Neuropsychiatry Clin Neurosci* 2007;19(4):406-412

Fricchione G, Bush G, Fozdar M, Francis A, Fink M: Recognition and treatment of the catatonic syndrome. *J Intensive Care Med* 1887;12:135-147

#### **CD-AMC:**

Carroll BT, Mendenhall B, Appiani F, Spiegel D, McDaniel W: Catatonia due to a general medical condition (organic catatonia). *Current Psychiatry Reviews* 2013;000-000

Duggal HS, Singh I: Drug-induced catatonia. *Drugs Today (Barc)* 2005;41(9):599-607

#### **Rating Scales:**

Sienaert P, Rooseleer J, De Fruyt J: Measuring catatonia: a systematic review of rating scales. *J Affect Disord* 201;135:1-9

Bush G, Fink M, Petrides G et al: Catatonia I: rating scale and standardized examination. *Acta Psychiatr Scand* 1996;93:129-136

### **Pediatric Catatonia:**

Consoli A, Raffin M, Laurent C, Bodeau N, Champion D, Amoura Z, Sedel F, An-Gourfinkel I, Bonnot O, Cohen D: Medical and developmental risk factors of catatonia in children and adolescents: a prospective case-control study. *Schizophr Res* 2012;137:151-158

Ghaziuddin N, Dhossche D, Marcotte K: Retrospective chart review of catatonia in child and adolescent psychiatric patients. *Acta Psychiatr Scand* 2012;125(1):33-38

Raffin M, Zugaj-Bensaou L, Bodeau N, Milhiet V, Laurent C, Cohen D, Consoli A: Treatment use in a prospective naturalistic cohort of children and adolescents with catatonia. *Eur Child Adolesc Psychiatry* 2014 Aug 27. [Epub ahead of print]

### **Catatonia in Autism**

Ohta M, Kano Y, Nagai Y: Catatonia in individuals with autism spectrum disorders in adolescence and early adulthood: a long-term prospective study. *Int Rev Neurobiol*. 2006;72:41-54

Mazzone L, Postorino V, Valeri G, Vicari S: Catatonia in patients with autism: prevalence and management. *CNS Drugs* 2014;28(3):205-15

### **Malignant Catatonia/NMS:**

Strawn JR, Keck PE Jr, Caroff SN: Neuroleptic malignant syndrome. *Am J Psychiatry* 2007;164(6):870-876

Neuhut R, Lindenmayer JP, Silva R: Neuroleptic malignant syndrome in children and adolescents on atypical antipsychotic medication: a review. *J Child Adolesc Psychopharmacol* 2009;19(4):415-422

Mann SC, Caroff SN, Ungvari GS, Campbell EC: Catatonia, Malignant Catatonia, and Neuroleptic Malignant Syndrome. *Curr Psychiatry Rev* 2013;9:111-119

### **Anti-NMDA-receptor Encephalitis:**

Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R: Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011;10:63-74

DeSena AD, Greenberg BM, Graves D: Three phenotypes of anti-n-methyl-d-aspartate receptor antibody encephalitis in children: prevalence of symptoms and prognosis. *Pediatr Neurol* 2014;51(4):542-549

## APPENDIX B: **Glossary of Terms:**

Many catatonic features lack standardized definitions and are often incorrectly used by clinicians. The following is an attempt to standardize the vocabulary in concordance with DSM-5 terminology.

Waxy Flexibility: (flexibilitas cerea) a physical examination finding in catatonia, in which despite instructions to maintain a flaccid muscle tone, there is present a light and even resistance (as opposed to cogwheeling) to the examiner's movement of the patient's extremity, with a quality similar to bending a piece of wax or plastic. Some clinicians differ from this explanation, and define waxy flexibility as the ability to reposition a patient, as if they were made of wax (catalepsy).

Mitmachen: (German for "working together" as in "participate") a physical examination finding in catatonia, in which despite instructions to the patient to resist any movement, the examiner is able to place the patient's body in any position. If the patient maintains this forced position as a posture, it is called catalepsy. Mitmachen is not frequently used as a descriptive term in North America.

Catalepsy: a physical examination finding in catatonia, in which despite instructions to the patient to maintain a flaccid muscle tone, the examiner is able to position the patient into postures that are subsequently maintained by the patient for an abnormally long period of time.

Mitgehen: (German for "going along") a physical examination finding in catatonia, in which despite instructions to the patient to resist any movement, the examiner is able to move the patient in any direction using very slight pressure. Mitgehen may be viewed as an extreme form of mitmachen and is also called the "anglepoise lamp" sign.

Negativism: an observable sign as well as a physical examination finding, usually in catatonia but also in other conditions, including autism spectrum disorder, intellectual disability, and traumatic brain injury. It is a phenomenon in which the patient refuses or does the opposite of what is asked or physically attempted by the examiner, in a manner that appears detached from a clearly identifiable motive. Motoric negativism can progress to rigidity. Refusal to eat or drink may also be viewed as a form of negativism. Negativism is often misinterpreted as volitional uncooperativeness.

Gegenhalten: (German for "holding against") (paratonia in neurology) a physical examination finding, in which the patient opposes movements with the same degree of force as applied by the examiner. The patient with gegenhalten needs not to display negativism.

Posturing: an observable sign in catatonia, in which the patient spontaneously develops and maintains a rigid, immobile posture, and maintains the posture for an abnormally long period of time. The posture may appear exaggerated, grotesque, bizarre, and contorting, or it may appear superficially ordinary and underwhelming, such as sitting in a chair or bed abnormally still and with a tense appearance. Psychological pillow is a form of posturing in which a supine patient spontaneously develops and maintains a head posture above the plane of the bed without apparent effort or strain.

Grimacing: (German Schnauzkrampf or “snout cramp”) an observable sign in catatonia, in which the patient spontaneously contorts the facial muscles and maintains a grimacing facial posture for an abnormally long period of time. Grimacing may also be viewed as a form of facial posturing.

Catatonic stupor: an observable sign in catatonia, in which a patient retains alert consciousness but has minimal interaction with the external environment. Patients with catatonic stupor may display increased response latency in speech or action, hypoactivity or immobility, minimal or no visual scanning of the environment, or dead pan staring.

## APPENDIX C: Annotated List of Important Pharmacologic Trials:

McCall WV, Shelp FE, McDonald WM: Controlled investigation of the amobarbital interview for catatonic mutism. *Am J Psychiatry* 1992;149:202-206. (Published erratum appears in *Am J Psychiatry* 1992;149:720.)

*20 inpatients with catatonic mutism were randomly assigned to intravenous saline or a 5% amobarbital solution. Patients were crossed over to the other infusion if the initial infusion had no response. 6 of 10 patients responded to the initial amobarbital infusion and 0 of 10 patients responded to saline. 4 saline non-responders subsequently responded to amobarbital.*

Bush G, Fink M, Petrides G, Dowling F, Francis A: Catatonia. II. Treatment with lorazepam and electroconvulsive therapy. *Acta Psychiatr Scand* 1996;93:137-143

*Prospective, open trial of 21 patients with catatonia of various etiologies (psychotic, affective, or another medical condition) systematically treated with lorazepam 4-8mg/day up to 5 days. 16/21(76%) responded to lorazepam. 4/5 non-responders went on to receive ECT, of which 4/4 improved with ECT.*

Payee H, Chandrasekaran R, Raju GV: Catatonic syndrome : treatment response to lorazepam. *Indian J Psychiatry* 1999;41:49-53

*Prospective, open label trial of 30 patients with catatonia symptoms were systematically treated with oral lorazepam. 21/30 (70%) catatonia resolved with lorazepam (dose range 3-8 mg/day). Most non-responders did well with ECT.*

Ungvari GS, Chiu HFK, Chow LY, Lau BST, Tang WK: Lorazepam for chronic catatonia: a randomized, double-blind, placebo-controlled cross-over study. *Psychopharmacol (Berl)* 1999;142:393-398

*In 17 patients with schizophrenia and chronic catatonia, neither placebo nor lorazepam 6mg/day had any clinically noticeable or statistically significant impact on catatonia or BFCRS scores. The authors noted that the chronic catatonia experienced by these patients with schizophrenia was clinically different from the more conventional acute catatonic syndrome.*

Girish K, Gill NS: Electroconvulsive therapy in lorazepam non-responsive catatonia. *Indian J Psychiatry* 2003;45(1):21-25

*Double-blind trial of 14 patients (3 female) with “non-affective” catatonia (schizophrenia or unspecified psychosis) non-responsive to lorazepam (6-8mg/day) taken from a pool of 68 patients with catatonia. Of note, 50/68 patients responded favorably to lorazepam (73.5%). Non-responders were randomized to three weeks of either bilateral ECT and placebo versus sham ECT versus*

*risperidone 4-6mg/day. Reduction in scores on BFCRS as well as the Positive and Negative Syndrome scale were greater in the ECT group.*

Kugler JL, Hauptman AJ, Collier SJ, Walton AE, Murthy S, Funderburg LG, Garcia KS: Treatment of Catatonia With Ultrabrief Right Unilateral Electroconvulsive Therapy: A Case Series. J ECT 2014 Sep 19 [Epub ahead of print]

*Retrospective case series of 11/13 cases of catatonia of various etiologies (psychotic disorder, affective disorder, or due to a medical condition) responded well to ultrabrief right unilateral ECT. The 2 non-responders also failed to improve with bilateral ECT.*

## APPENDIX D: Standardized Assessment and Work-up:

### Introduction:

The diagnosis and assessment of catatonia in the medically ill population can be difficult. This is complicated by the problem that many of the definitions for certain catatonic phenomena have not been standardized, even between different rating scales. Medically ill patients with catatonia may also meet DSM-5 criteria for delirium (see “Definition, Phenomena, and Diagnostic Criteria”)

The BFCRS is the gold standard catatonia rating scale. It consists of 23 items on a 3-point scale. The first 14 items can be used as a screening tool; catatonia should be considered if more than 2 of the first 14 items are present. Severity of catatonia is determined by rating all 23 items. The reliability of the BFCRS is dependent on appropriate use of a standardized examination protocol.<sup>255</sup> Other catatonia scales have also been developed and are generally well correlated. However, no catatonia rating scale has been validated specifically in the medically ill population.

A standardized approach should be used to assess for catatonia in medically ill patients. Given the frequency that catatonic findings are overlooked, we recommend screening every patient for catatonia as part of the routine psychiatric consultation. However, many medically ill patients present with hypoactivity/immobility, and certain behaviors such as automatic obedience, negativism (including refusal to eat or drink), agitation/excitement, or stereotypies may be nonspecific or impossible to determine in the severely ill, patients on diet restriction (nil by mouth), or patients with agitated delirium, major neurocognitive impairment, or in patients with difficulty coping with illness.

### Proposed Screen for Catatonia in the Medically Ill:

There is no validated screen for detecting catatonia in the medically ill. However, we propose considering the following screening examination when assessing the medically ill patient in the consultation-liaison setting:

#### *Proposed Screen for Catatonia in the Medically Ill*

Mnemonic: “A SLIME-Posture”

Acute or subacute onset within days, with at least 2 of the following findings on a general psychiatric medical examination (mental status examination):

Speech: Disordered Speech Quality (poverty of speech, decreased volume (whisper), or mutism). Disordered speech represents an acute change and may be intermittent or waxing/waning in severity.

**Latency:** Increased response latency (>5 seconds) in speech or affect or movement in response to a question or impulse or command.

**Interaction (stupor):** Decreased interaction with environment out of proportion to relatively preserved alertness, maintained for >1 minute

**Muscle:** Increased muscle tension (waxy flexibility, rigidity, clonus) on direct physical examination

**Eyes:** Staring (decreased blinking, deadpan, does not track targets), maintained for >1 minute

**Posturing:** (including grimacing), maintained for >1 minute

Two or more findings should prompt a more focused examination for catatonic phenomena.

#### Assessment and Examination:

A focused physical examination for catatonia should include testing for catalepsy, echolalia, echopraxia, negativism, automatic obedience, mitgehen, gegenhalten, ambitendency, and grasp reflex. The BFCRS provides a companion standardized examination procedure for these catatonic phenomena. Upon completion of the focused examination, the BFCRS should be used to score severity of the catatonic phenomena.

Once a presumptive diagnosis catatonia has been made, a pharmacologic challenge with a GABA-agonist should be performed and clinical response should be assessed using a standardized instrument. The BFCRS is both highly reliable and sensitive to clinical changes, allowing assessment of clinical response to treatment.

#### Pharmacologic Challenge:

Lorazepam is the preferred pharmacologic agent for determining GABA-agonist responsiveness in catatonia. We recommend an initial dose of 2mg intravenous push. In the patient who may be young, elderly, frail or for whom respiratory compromise is a consideration, an initial intravenous dose of 1mg can be used. Alternatively, zolpidem 10mg via enteral route can be considered in the patient with higher potential for respiratory compromise. A clinical response is defined as a 50% reduction in BFCRS score. Most patients will respond within 10-30 minutes, although some may take hours to respond, and some patients may initially fall asleep before later responding favorably.

If no or minimal response is observed within 20-30 minutes of the initial dose, a second dose should be administered. If the second dose produces no or minimal response within 20-30 minutes, a third dose can be administered. Failure of response to lorazepam does not negate the diagnosis of catatonia. 8mg daily or higher doses of lorazepam may be required.

### Initial Recommendations to the Primary Service:

As soon a presumptive diagnosis of catatonia is made, recommendations should include gathering history and work-up for causes that could be attributable to another medical condition, including:

- Electroencephalogram to rule out seizure activity
- Lumbar puncture with cerebrospinal fluid examination, viral serologies, and anti-NMDA-R antibodies.
- Serum ANA test and other tests for systemic lupus.
- Paraneoplastic antibody panel
- CT abdomen/pelvis to rule out ovarian mass which could be causing ANRE
- MRI brain with contrast to rule out mass, infection, CVA/hemorrhage, autoimmune process, or PRES.
- Substance use history and urine drug screen
- Serum B12 level

Recommendations should also include prompt identification and/or discontinuation of suspected pro-catatonic agents, including:

- Tacrolimus, cyclosporine
- Flouroquinolones, cephalosporins
- Dopamine antagonists (antiemetics, antipsychotics)
- Corticosteroids
- Disulfiram
- Baclofen

Recommendations may include treatment for withdrawal with the clinically appropriate medication, if the history identifies an agent whose discontinuation may have precipitated a withdrawal-emergent catatonia, including:

- Alcohol
- Barbiturates
- Benzodiazepines
- Gabapentin or pregabalin
- Amantadine or memantine
- Bromocriptine
- Levodopa/carbidopa

Recommendations should also include laboratory work to rule out associated rhabdomyolysis and the risk of developing NMS, including:

- Total Creatine Phosphokinase (CPK) (rhabdomyolysis)
- Serum Iron (risk of NMS, check prior to initiation of dopamine antagonist)

### Definitive Treatment:

Most patients respond to 3-8mg/day of lorazepam. Some patients, however, may require titration of up to 24mg/day of lorazepam to achieve a sustained response. Rarely, patients may require transfer to the intensive care setting for continuous intravenous infusions of a benzodiazepine.

Once sustained catatonia lysis occurs, the benzodiazepine should be tapered very slowly, slower than a typical taper when treating alcohol withdrawal, approximately 5-10 percent per day, while monitoring for any reemergence of catatonic phenomena.

ECT should be considered if benzodiazepines have failed to dramatically improve catatonia within the first 3 days. If the patient exhibit signs of malignant catatonia/NMS, treatment with ECT should not be delayed.

Memantine can be considered as a secondary or augmentation agent in patients who have failed or plateaued in their clinical response to lorazepam. Memantine can be started at a dosage of 5mg Q12 hours, titrated by 5mg/day up to 10mg Q12 hours. As memantine can prolong the QT interval, an electrocardiogram is recommended before initiation.

Amantadine can be considered as an augmentation agent alternative to memantine. It can be initiated at a dose of 100mg daily and titrated to up to 100mg four times per day. Amantadine does not appear to prolong the QT interval but may be harder to tolerate, possibly necessitating a slower titration.

In cases of catatonia wherein there are no symptoms of malignant catatonia/NMS, (with normal serum iron levels, no fever, no leukocytosis, normal CPK) augmentation with antipsychotics may be warranted. Olanzapine is a preferred option.

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