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Catatonia in Autism Spectrum Disorder in Youth: Systematic Review

Sepehr Aziz, Robert L Hendren*

University of California, San Francisco, USA

***Corresponding author:** Robert L Hendren, University of California, San Francisco, USA

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Abstract

Background and Objectives: Autism with catatonia is increasingly reported in the literature but is not well understood. This review of catatonia in ASD in youth summarizes the literature related to etiology, differential diagnosis, and treatments and then presents and discusses three brief illustrative cases. The Discussion focuses on the concepts, controversies, and treatments.

Materials and Methods: To identify prior studies associated with catatonia and ASD, we searched PubMed, Embase, Web of Science, and PsycINFO databases using the following search string: (autism OR autistic) AND (catatonia OR catatonic). Inclusion and exclusion criteria were pre-defined in a protocol and applied to studies identified by our search. All studies meeting inclusion criteria were grouped according to content and summarized.

Results: The screening process identified a total of 33 eligible articles describing cases of catatonia in autism. Reports of catatonic autism are consistently associated with symptoms of agitation, stereotypy, posturing, negativism, mutism, stupor, grimacing, and occasionally, repetitive Self-Injurious Behaviors (SIBs). There is variability in these symptoms which can occur in clusters with variability in a paucity of psychomotor activity or with excitatory activity. Initial success with lorazepam and with ECT suggests that there is an excitatory- inhibitory mechanism involved but the effects of GABA or glutamatergic interventions may be initially effective but do not endure.

Conclusions: While catatonic autism seems to be increasingly identified, studies of etiology, and effective longer term targeted treatments are needed.

Keywords: Autism; Catatonia; Differential Diagnosis; ECT; Systematic Review; Treatment

Introduction

Autism Spectrum Disorder (ASD) is characterized by marked impairments in verbal and non-verbal communication combined with restrictive, repetitive patterns of behavior [1]. The prevalence of ASD has risen significantly since the 1980s from 3.3 cases of pervasive developmental disorders per 10,000 children. In 1996, the prevalence was 3.4 cases of autism per 1000 children [2]. Using data from 2012, the Autism and Developmental Disabilities Monitoring (ADDM) Network, estimated 1 in 68 children were affected [3] and recently, the Centers for Disease Control and Prevention (CDC) estimated autism prevalence to be 1 in 59 among the US children, based on an analysis of 2014 medical records and, where available, educational records of 8-year-old children from 11 monitoring sites [4].

Catatonia is a complex neuropsychiatric syndrome marked by the presence of a constellation of various psychomotor disturbances ranging from stark unresponsiveness to severe agitation. While for many years catatonia was thought to be a symptom of schizophrenia and other psychotic disorders, it is now accepted as a syndrome seen in the context of many different disorders, including neurodevelopmental, psychotic, bipolar, and depressive disorders, as well as other medical conditions [1,5]. Variability of presentation as well as the wide spectrum of clinical features, often in opposition (e.g. stupor vs agitation), can lead to reduced diagnoses and missed treatment opportunities. More recently, there has been an increasing amount of literature examining the prevalence and manifestation of the syndrome of catatonia as a comorbidity in autism spectrum disorders [6-12]. Such research is of particular importance due to the similarity and

overlap of symptoms (e.g. mutism, echolalia, stereotypic speech, repetitive or stereotypic behaviors, posturing, mannerisms, grimacing, rigidity, and purposeless agitation) [8-10], which has led to some such as Hare and Malone in 2004 to question whether catatonia in autism should be considered as a particular intrinsic expression of the underlying autistic spectrum disorder, rather than as a comorbidity [13]. This review of catatonia in ASD reports the results of our systematic review for the etiology, differential diagnosis, and treatments and then presents three brief illustrative cases. Our Discussion will focus on the concepts, controversies, treatments and the current state of the art.

Materials and Methods

In consultation with an experienced medical librarian, we searched PubMed, Embase, Web of Science, and PsycINFO databases using the following search string: (autism OR autistic) AND (catatonia OR catatonic), yielding a total of 812 articles (as of August of 2019). We limited the results to journal articles written in English and published after January 1, 1994, the year of release of DSM-IV, reducing the number of articles to 443. Duplicates were removed leaving a total of 210 articles. Inclusion and exclusion criteria were predefined in a protocol and applied to the deduplicated studies in the abstract screening process. Remaining articles were further assessed for relevance. Inclusion criteria included studies with primary data describing cases of autism with concurrent catatonia in humans under the age of twenty one (21). We excluded articles without clinical description of cases, articles without clear description of autism or catatonia, and articles describing cases of patients over the age of twenty (20).

We performed title and abstract screening in duplicate using Rayyan. Full-text screening was performed in duplicate yielding a final set of articles. The previously developed inclusion and exclusion criteria were used for both levels of screening. Differences of opinion were resolved by discussion for both levels of screening. A visual summary of our methods is presented in (Figure 1).

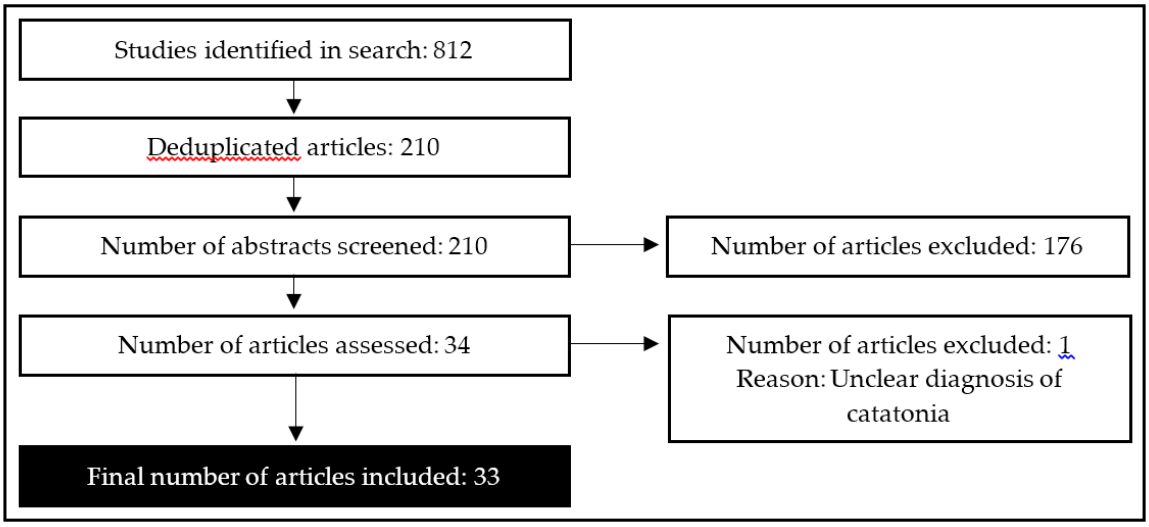

Figure 1: Visual representation of article inclusion and exclusion process.

Results

The screening process identified a total of thirty-three (33) eligible articles describing cases of catatonia in autism [6,7,10,11,13-41]. Five (5) of these publications describe more than three cases and twenty-eight (28) report on one to three cases (mostly one).

Twenty-one (21) of the reports were published before 2014 and twelve (12) were published 2014 or later. Review of the multiple and single case reports yielded common themes for assessment and diagnostic criteria, rating scales, medical work-up, differential diagnosis, etiology, prevalence and treatment. The common themes from this comprehensive review are summarized below. A systematic review published in 2014 by DeJong et al [42] regarding the efficacy of treatments reported for autistic catatonia identified 22 relevant papers with a total of 28 child and adult cases. Treatments reported included Electroconvulsive Therapy (ECT), medication, and behavioral

interventions. Treatment description and outcome measurement was judged to be generally poor.

Recent Multiple-Case Reviews

Wachtel (2019) describes his work with 22 patients with ASD and catatonia, six girls and 16 boys ranging from ages 8 to 26 years old, over a 12-year period. All but one patient was initially unsuccessfully treated with benzodiazepines in dosages ranging from 1 to 27 mg daily, and all patients underwent Electroconvulsive Therapy (ECT). Mean age of ECT start was 15.6 years old, and the total number of ECT received ranged from 16 to 688. ECT conferred prominent patient benefit in terms of catatonic symptom reduction, including alleviation of incapacitating, treatment- resistant self-injury [6]. The most common catatonic symptoms found included agitation, stereotypy, posturing, negativism, mutism, stupor, and grimacing, with the number of catatonic symptoms displayed by each patient ranging from two to eight. Comorbid, intractable, repetitive SIB was proposed as an additional sign of catatonia. Of the patients treated with a benzodiazepine, reasons for discontinuation included no benefit in terms of catatonic symptom reduction (N = 7, 31.8%), partial catatonic symptom reduction (N = 9, 40.9%), sedation (N = 3, 13.6%), and behavioral worsening (N = 2, 9.1%) [6]. Dhossche (2019) reviews ECT in his long practice of treating catatonic autism. He reports that in its malignant form, catatonia features autonomic dysfunction including fever, and becomes an acute, potentially life-threatening disorder. However, he also reports that it is a treatable condition that warrants prompt diagnosis and treatment with benzodiazepines as first-line treatment and electroconvulsive treatment as definitive treatment [11].

Assessment and Diagnosis

Diagnostic criteria

DSM III (1980) continued the accepted practice of defining catatonia as subtype of schizophrenia. DSM IV (1994) added catatonia as a disorder due to a general medical condition as well as a "features specifier" in mood disorders [5]. DSM 5 Criteria for catatonia are the same throughout the manual, independent from the initial diagnosis defined by the presence of at least 3 symptoms from a list of 12. DSM 5 added a schizophrenia specifier rather than subtype, added a specifier to 4 other psychotic disorders, and added Catatonia NOS [1,5].

The DSM 5, catatonia features 3 main categories:

1. catatonia associated with another mental disorder (293.89)
2. catatonic disorder due to another medical condition (293.89)
3. unspecified catatonia (781.99 and 293.89)

DSM 5 Catatonia Criteria
Catalepsy (i.e., passive induction of postures held against the gravity)
Waxy flexibility (i.e., slight and even resistance to repositioning by the examiner)
Stupor (no psychomotor activity, no reactivity to the environment)
Agitation, not influenced by external stimuli
Mutism (i.e., no or minimal verbal response- not applicable in case of established aphasia)
Negativism (i.e., opposing or not responding to external stimuli or instructions)
Posturing (i.e., spontaneous and active maintenance of posture against gravity)
Mannerism (i.e., odd caricatures of ordinary actions)
Stereotypies (i.e., repetitive, frequent, non-goal directed movements)
Grimacing
Echolalia (i.e., repeating the words spoken by the examiner)
Echopraxia (i.e., mimicking of movements made by the examiner)

Table 1: From The Diagnostic and Statistical Manual of Mental Disorders, 5th edition, (DSM-5).

While the DSM does not currently define different subtypes of catatonia, it is common in the literature and in current clinical practice to differentiate catatonia subtypes depending on presenting symptomatology into 1). Retarded – Mutism, inhibited movement, posturing, rigidity, negativism and staring, and 2) Excited – Excessive and purposeless motor activity, restlessness, stereotypy, impulsivity, frenzy agitation and combativeness [43-45]. Additionally, the presence of fever, autonomic instability, delirium, and rigidity in addition to other catatonic symptoms are often described as Malignant Catatonia, which, carries a higher rate of mortality compared to other presentations of catatonia [43,44].

Benzodiazepine Challenge

Benzodiazepines can be helpful in supporting a diagnosis of catatonia through what has come to be known as the Lorazepam Challenge. The Lorazepam Challenge is implemented in patients exhibiting signs of catatonia by giving a 1 to 2 mg test dose by mouth, intramuscularly or IV, and then observing the patient for improvement for 5 -10 minutes following administration. If there has been no change, a second dose is given, and the patient is again reassessed. A positive response is a marked reduction of at least 50% of catatonic signs and symptoms [46].

Rating Scales

The Bush-Francis Catatonia Rating Scale (BFCRS), and the Pediatric Catatonia Rating Scale (PCRS) is an adaptation of the BFCRS designed to more accurately diagnose catatonia in children, including those with developmental and communicative delay [47,48]. The KANNER rating scale is a further measure proposed specifically for the diagnosis of catatonia in neurodevelopmental disabilities [49].

Medical Workup

While most children with catatonia are not found to have underlying organic illness, studies estimate that the proportion of organic conditions in catatonic syndromes in youth may represent a large minority of 15-20% [50] including concurrent medical conditions, including autoimmune disorders such as lupus and anti–N-methyl-D-aspartic acid receptor encephalitis, psychotic and affective disorders, toxic states, autism spectrum disorders, developmental disorders, tic disorders, posttraumatic conditions, and miscellaneous syndromes such as Kleine-Levin syndrome and pervasive refusal syndrome, among others [11,50,51]. As such, medical workup can be useful to rule out other concomitant conditions, particularly if there were no signs of psychiatric symptoms prior to the onset of catatonia. This workup may include blood work with basic hematologic and metabolic measures, comprehensive drug testing, brain imaging (EEG and MRI), autoimmune antibodies (lupus serology, PANDAS serology, anti-NMDA receptor antibodies), and other tests guided by clinical examinations [11,50,51]. A recent study by Ferrafiat et al in 2018, describes a causality assessment score as part of a systematic and stepwise approach to the assessment of pediatric patients presenting with catatonia suspected to secondary to an underlying medical condition, along with an algorithm to lead clinical workup decision making [51].

Differential Diagnosis

Some medical conditions may be present with symptoms similar to catatonia and should be considered during the initial assessment [45].

Neuroleptic malignant syndrome (NMS) shares clinical features with malignant catatonia including autonomic instability, fever, and rigidity, in patients with ASD being treated with neuroleptic medication. While NMS usually lacks classic signs of catatonia such as impulsivity, posturing, and repetitive stereotypic movements, some of these symptoms may already be present in patient with autism, confounding differentiation based on clinical observation alone. Lab abnormalities including elevated creatinine kinase and white blood count and low serum iron may be present in both NMS and malignant catatonia, but will be less consistently present in the latter. In either case, prompt withdrawal of neuroleptic medication is indicated.

Akinetic mutism may also present with immobility, mutism, and waxy flexibility, but lacks posturing, echolalia, or echopraxia. It will have detectable lesions on neuroimaging and is not responsive to benzodiazepine treatment.

Non-convulsive status epilepticus may also present with stupor and respond to benzodiazepine treatment. However, Non-convulsive status epilepticus will show epileptic activity on the Electroencephalogram (EEG).

Locked-in syndrome also presents with immobility and mutism, however, locked-in patients may try to communicate by other means such as blinking and with eye movement, which is not seen in catatonia. Neuroimaging will also typically reveal lesions in the brainstem.

Parkinson disease in its late states may also present with immobility, rigidity, and decreased speech output, but will lack other signs of catatonia such as waxy flexibility and posturing, and will include signs such as resting tremor not usually seen in catatonia. Additionally, Parkinson patients, typically, will not respond to benzodiazepine treatment, but will show positive response to levodopa.

NMDA receptor encephalitis as well as Delirium may also present with stupor and psychomotor symptoms but often lack other signs of catatonia, including waxy flexibility, staring, and negativism and, typically, are not responsive to benzodiazepine treatment.

Etiology

A unifying pathogenesis of catatonia remains elusive although there are several models of catatonia. Current theories suggest motor circuitry, epilepsy, neurotransmitters, genetics, endocrinology, immunology, and traumatic fear [11]. The vagal theory of catatonia unifies some various aspects of catatonia and stimulates further studies on autonomic dysfunction and the use of anticholinergic agents and, at least theoretically, vagal nerve stimulation [52]. Given that GABA dysfunction is implicated in catatonia in typically developing as well as autistic populations, it is possible that the additional baseline GABA abnormalities in the autistic brain alter the response to benzodiazepine therapy for catatonia [6].

Association between Catatonia & Levels of Hair & Serum Trace Elements & Minerals in ASD.

In their recent study, Tinkov et al investigated the association between catatonia in Autism Spectrum Disorder (ASD) and the levels of hair and serum trace elements and minerals in children with ASD [15]. The levels of hair and serum trace elements and minerals of boys suffering from ASD with (n=30) and without (n=30) catatonia, as well as 30 age- and sex-matched neurotypical controls were assessed using ICP-MS. Hair Calcium (Ca) and Selenium (Se) levels were lower in ASD patients as compared to the controls. Hair Mercury (Hg) levels in ASD patients were more than 3-fold and 2-fold higher as compared to the controls and children with catatonia in ASD. Hair Iodine (I) and Manganese (Mn) were the lowest and the highest in ASD+Catatonia, respectively. Serum Aluminum (Al) and Cadmium (Cd) levels in healthy controls were significantly higher in comparison to the patients of both groups. Serum Chromium (Cr), Copper (Cu) levels were significantly increased in patients with ASD and catatonia, whereas Vanadium (V) levels were elevated in patients both with and without catatonia. Multiple regression analysis demonstrated that hair Hg and serum Al and Cd levels were negatively associated with catatonia in ASD.

Prevalence

Studies from the United States and Europe have revealed that catatonia occurs in 12%–20% of individuals with autism [6,53,54], and a growing body of literature has documented the full range of psychomotor agitated and retarded catatonic symptoms in autism, including intractable self-injury.

Treatment

Treatments for Catatonia in Autism

The most frequently used treatment for Catatonic Autism include benzodiazepines, most frequently Lorazepam, given 10 to 30 mg a day. The best response occurs when it is implemented quickly, and that immediate response is generally the best indicator of ultimate response. There is no consensus on how long benzodiazepines are to be continued, and generally they are discontinued once the underlying illness has remitted, however, in some cases catatonic symptoms may return once the benzodiazepine is tapered off necessitating an extended period of treatment [46]. While Lorazepam is the most commonly used benzodiazepine, there have been no head to head studies comparing efficacy of other benzodiazepine choices. ECT is described as the most effective treatment for catatonic autism and the most experienced experts in catatonic autism advocate for its use for every child with an ASD and catatonia, either with or without concomitant SIB [6,11,46].

The AACAP ECT guidelines recommend three criteria be met, (i) the patient should have an ECT-responsive condition, (ii) high illness severity, and (iii) at least two failed medication trials [55].

Less Commonly Reported Treatments for Catatonic Autism

Catatonia as a symptom of various disorders improved in several case studies when memantine was used in combination with other medications [56].). Lithium was used as a rescue therapy for regression and catatonia features in two SHANK3 patients with ASD as described in case reports [30]. Quetiapine was reported to improve symptoms of catatonia in a patient with autism and comorbid bipolar disorder and idiopathic basal ganglia calcification [57]. Lorazepam, fluoxetine and packing therapy is described as helpful in an adolescent with pervasive developmental disorder and catatonia [19].

Case Examples

Case #1

Joe, a 10 year old boy who was diagnosed with PDD-NOS, also has a history of extreme anxiety, depression and aggression with violent outbursts, severe OCD and increased non-specific movements followed by decompensation in overall function, mutism, decreased movements, and agitation. The initial assessment raised the question of psychotic catatonic and possible PANS. At age 12 he became increasingly violent, had positive ASL antibodies and was treated with IV IG which worsened his obsessions. Treatment with an SSRI also worsened his OCD; probiotics, curcumin and multivitamins were tried without benefit as was quetiapine and lithium.

At age 13, he would freeze in place and trembled all over. At age 14, he was diagnosed with psychosis NOS, PDDNOS, Anxiety Disorder NOS, and OCD. Had a history of initial improvement with lorazepam. Pregnancy, Labor and Delivery were without complications and his milestones were on target. In preschool, he had increasing, variable obsessions and a minor head injury. Cognitive testing showed progressive minor lowering in scores. In 2014, Joe was referred to Dr. Dirk Dhossche at the University of Mississippi Medical Center, was diagnosed with “excited catatonia” and received ECT, and lorazepam with aripiprazole. This was reported to “almost completely eliminate catatonia”. The mental health center in our region that referred him to Dr. Dhossche reported that since his return, he has been leading an almost “normal life” with aripiprazole and lorazepam. However, our was sent a discharge report from the University of Utah in

2016 saying he had been hospitalized for over a month with a diagnosis of Schizophrenia, Tourette's Disorder, OCD, and ASD.

Case #2

Rachael is currently a 26 year old female with a lifetime history of diagnoses of ASD and OCD. She was the product of an unremarkable pregnancy, labor and delivery, and had timely developmental milestones. In elementary school she was thought of as very shy and during middle school became progressively less verbal. In High school her counselor expressed concern to her parents that she was not socializing. However, her grades were "fine", reportedly straight A's but she continued to lose language and functional skills. When we first saw her at age 24 years, she had no eye contact with others, was reportedly withdrawn to her room at home, and had little movement except aggressive and SIBs. She had facial grimacing, her hair was hanging over her face, and she responded to questions with grunting, growling. She had reportedly become non-verbal after the death of her dog a few months earlier.

Rachael had a full evaluation in our autism clinic and was diagnosed with autism with a question of catatonia. An MRI and EEG were read as normal. We treated her with multiple high dose SSRI, antipsychotics, and mood stabilizers all without significant benefit. A genetics consult reported a normal karyotype and FISH for 15q11-13 and 22q11.2 deletions negative. CGH was unrevealing. CBC, Prolactin, thyroid testing, ammonia, amino acids and lactate were all normal. Our ultimate diagnosis was childhood disintegrative disorder and possibly schizophrenia. Based on the possibility that this was catatonic autism, lorazepam was titrated up to 18mg and Rachael showed steady and significant improvement with conversational speech, interactions with others, going out of the house, and full self-care. The downward titration after 6 months was unremarkable at first but at 4mg a day she began to do less well. Rachael is currently maintained on lorazepam 4mg a day, fluoxetine 60mg a day and clomipramine 25mg a day with improvement but not to the initial level. Memantine up to 30mg was negative. Rachael is still very OCD, works part time but her hours are being reduced and she has little communication with anyone including her mother and father. We have been considering lithium, TMS, and/or ECT with the family.

Case #3

Ben is a 21 year old male first seen at 15 years of age. He had an unremarkable pregnancy, labor and delivery and reached normal developmental milestones at a young age with some acquisition of words and then regression around 1 ½ years of age. He became more introverted then stopped in progression and had a regression of language and socialization. Ben was diagnosed with autism at 3 years of age. Ben functioned in a "high-functioning" autism range with progression in functioning and no problems until around 9 years-of-age when he began to have significant difficulties with impulse control and further withdrew socially. He began urinating throughout his home, carving with something sharp into wood and metal and screaming when his brother coughed, yawned, grimaced, sneezed, sniffed, cleared his throat or entered the room. He had difficulty crossing thresholds, and had many rituals. At age 12, he began to have severe anxiety and depression. Medications tried at adequate doses for adequate times included risperidone, aripiprazole without benefit and when they were stopped he began to rage, scream and break things. Asenapine helped for short while but then he returned to baseline. Ben said he heard voices and also seems to "get frozen" numerous times throughout the day, which was called "catatonia" by several evaluating psychiatrists and neurologists. Also, he had eye twitching, grimacing and mouth smacking when nervous. These were identified as mannerisms or stims by evaluating psychiatrists and neurologists. Ben has seen 3 neurologists who identified language delay with late regression and worsening catatonia. He had a normal MRI and chromosome array. CSF studies report only the methyltetrahydrofolate level low at 40 (40-120 normal range). Ativan up to 14 mg was of benefit at first then he became sedated and had enuresis. He was sent for ECT near his home town but the psychiatrist who was to administer it gave TMS and noted improvement in depression but not in other symptoms. He is currently taking sertraline 200mg, and clonazepam 0.1mg twice a day and remains as described above.

Discussion

In all the studies reviewed in this systematic review, catatonic autism is consistently associated with symptoms of agitation, stereotypy, posturing, negativism, mutism, stupor, grimacing, and occasionally, repetitive Self-Injurious Behaviors (SIBs). There is variability in these symptoms which can occur in clusters of a paucity of psychomotor activity or with excitatory activity. These symptoms do not represent a unifying cluster of behaviors that suggest clearly reproducible symptoms, a mechanism of action or underlying etiology. Studies are needed searching for revealing imaging, genetic, or biomedical biomarkers such as excitatory or inhibitory transmitters, gene environment byproducts such as oxidative stress, mitochondrial or microbial metabolic byproducts as none were found in this systematic review. The first step would be to identify more homogeneous symptom clusters that might allow subgroup analysis.

While many think catatonic autism is rare, several studies

report a prevalence of 12 to 20% in individuals with ASD. This number would suggest the diagnosis is being missed (or over diagnosed). Much more work is needed to refine the diagnostic criteria and if numbers are as high as suggested, begin larger scale studies of the validity of the diagnosis and biomedical underpinnings that can lead to better treatment targets. Longer term outcomes are not reported other than two case series supporting the continued benefits of long term ECT [7,11] Diagnostic outcome includes schizophrenia but also a non-descript psychiatric disorder. As Case #1 illustrates, reports of outcome vary based on who is providing the assessment and the nature of their contact. More rigorous prospective and continuous follow up is needed to know diagnostic outcome, function and treatment efficacy. Case #2 and #3 who are still being followed, maintain features of catatonic autism but have not clarified into a clear DSM 5 diagnosis. Some have suggested sending them to the Undiagnosed Disease Program.

Initial success with lorazepam and with ECT suggests that there is an excitatory- inhibitory mechanism involved but the effects of GABA or glutamatergic interventions may be initially effective but do not endure as seen in the literature and all three cases reported. Further study of these mechanisms may reveal more about the etiology and longer term effective treatments [52]. It Is not clear how long to maintain a high dose of lorazepam and what is a reasonable maintenance dose. Maintenance ECT is thought to be of benefit based on a limited number of cases but there are no guidelines for number, spacing and duration. Other potential treatments identified in the treatment review are limited to case reports and small case series.

Conclusions

In this systematic review of 33 publications meeting inclusion criteria, most are single case reports and many of the studies report on the same patient more than once, People who have been diagnosed with catatonic autism have symptoms in common but the descriptions of the disorder is quite heterogeneous in presentation andcourse.

While features of catatonia may persist long term, symptoms of psychosis, OCD, and unusual mannerisms are also frequently present and the diagnosis does not seem to clarify as a DSM 5 disorder. While catatonic autism seems to be increasingly identified, studies of etiology, and effective longer term targeted treatments are needed.

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45. Catatonia: Treatment and prognosis - UpToDate

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