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THERAPY IN PRACTICE

Catatonia in Patients with Autism: Prevalence and Management

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Abstract Although recent studies have shown that catatonia can occur in patients with autism spectrum disorders (ASDs), the overlap of the behavioral features between these disorders raises many diagnostic challenges. In fact, in clinical practice it is common to misinterpret catatonic symptoms, including mutism, stereotypic speech, repetitive behaviors, echolalia, posturing, mannerisms, purposeless agitation and rigidity, as features of ASDs. The current medical treatment algorithm for catatonia in ASDs recommends the use of benzodiazepines. Electroconvulsive therapy (ECT) is indicated when patients are unresponsive, or insufficiently responsive, to benzodiazepines. Other pharmacological options are also described for the treatment of catatonic patients resistant to benzodiazepines and ECT, and there is evidence for the effectiveness of a psychological treatment, co-occurring with medical treatments, in order to support the management of these patients. In this article we provide a summary of studies exploring catatonia in ASDs and our clinical experience in the management and treatment of this syndrome through the presentation of three brief case studies. Moreover, we review the mechanisms underlying symptoms of catatonia in ASDs, as well as the diagnostic challenges, providing an outline for the management and treatment of this syndrome in this clinical population.

1 Introduction

Catatonia is a cyclic course syndrome characterized by alterations in motor, vocal and behavioral signs, generally occurring in the context of various medical and neuropsychiatric conditions [1–3]. This syndrome, firstly described by Kahlbaum as a separate disorder [4], was subsequently incorporated by Kraepelin in the equation of 'catatonia = schizophrenia' leading to decades of misconception that all catatonic symptoms indicated schizophrenia [1]. Currently, prevalence estimates of catatonia in psychiatric populations range from 0.6 % for adolescents, to between 6.9 % and 10 % for adult psychiatric inpatients [5–7]. In clinical practice it is common to misinterpret catatonic symptoms, such as mutism, stereotypic speech, repetitive behaviors, echolalia, posturing, mannerisms, purposeless agitation and rigidity, as features of autism spectrum disorders (ASDs) [5, 8, 9]. Given the overlap of symptoms, a correct distinction between these two conditions is crucial: indeed, not every autistic patient showing these symptoms should be considered catatonic; however, on the other hand, any autistic patient showing changes in the symptomatology should be evaluated for catatonia (Table 1). Differences in age-of-onset between catatonia and ASDs can be essential to explain similar but slightly different symptom profiles, as well as differences in the course and outcome of these disorders [8]. Specifically, age-of-onset of catatonic regression is typically observed at a later age than autistic symptoms [9]. For instance, in the study of Wing and Shah [10], none of the patients meeting the criteria for catatonia had the full syndrome under 15 years of age. This study also observed that individuals with ASDs and catatonia showed particularly characteristic symptoms, such as slowness and difficulty in initiating movements, increased passivity and amotivation, as well as a worsening of ritualistic and repetitive behaviors or the reversal of day and night, that may be specific features of catatonia in autism. Therefore, only an exacerbation of certain autistic behavioral features, as well as changes in

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Table 1 Catatonic signs and symptoms overlapped with autism spectrum disorder (ASD)

	Definition
Catatonic signs	
Ambitendency	The patient appears ambivalent toward examiner's instructions, alternating between resistance and cooperative behaviors
Passive (mitgehen)	The patient can be positioned in any posture, even when he/she is requested to resist
Automatic obedience	Exaggerated cooperation and automatic obedience to every examiner's request
Aversion	The patient avoids the examiner when he/she is called
Grasp	Automatic grasping of the patient's hand
Immobility/stupor	Extreme immobility and hypoactivity
Negativism (Gegenhalten)	Resistance to the examiner attempting to move parts of the patient's body
Obstruction	A suddenly block of a movement
Psychological pillow	A reclined posture that is maintained for long periods
Waxy flexibility	The patient can be positioned by the examiner in uncomfortable postures
Autonomic abnormalities	Abnormality of temperature, blood pressure, respiratory and pulse rate
Catatonic-like signs seen in ASD	
Echolalia/echopraxia	Imitation of examiner's movements and speech
Excitement	Purposeless and excessive hyperactivity
Grimacing	A sharp contortion of facial expression
Mutism	Extreme verbally unresponsiveness
Logorrhea	Excessive, incessant, and monotonous speech
Posturing/catalepsy	Maintenance of the same posture for long periods
Mannerisms	Repetitive and purposeful movements
Stereotypies	Repetitive and not goal-directed motor activity
Perseveration	Persistence of a particular movement
Rigidity	Maintenance of a rigid posture
Verbigeration	Verbal perseveration of words or sentences
Staring	Fixed and not modulated gaze
Withdrawal	A broad retirement
Combativeness	Episodes of anger and disposition to fight that are not influenced by external stimuli

the type and pattern of pre-existing symptoms, or the onset of new symptoms, in a patient affected by ASD, can lead to a comorbid diagnosis of catatonia [11]. Given the increasing evidence that catatonia can occur in ASD patients, the epidemiology, aetiology, phenomenology and appropriate treatment of this syndrome in ASDs should be better clarified. In this article we provide a summary of studies exploring catatonia in ASDs and our clinical experience in the management and treatment of this syndrome through the presentation of three brief case studies. Moreover, we review the mechanisms underlying symptoms of catatonia in ASDs, as well as the diagnostic challenges, and we provide an outline for the management and treatment of this syndrome in this clinical population.

2 Summary of Studies Exploring Catatonia in Autism Spectrum Disorders (ASDs)

Several recent studies suggest an increased recognition of catatonia as a comorbid syndrome of ASDs [3, 10, 12–35]. Nevertheless, most of these studies are case reports of ASD patients presenting catatonic signs, and they do not explore the association between these two disorders [16–35] (Table 2). For instance, Kakooza-Mwesige et al. [24] reviewed the evaluation, diagnosis, and treatment of catatonia in autism through the presentation of a case vignette of a boy with autism who showed catatonic symptoms at 16 years of age. The authors conclude that catatonia should be considered in any people with ASDs when there is a marked deterioration in movement and adaptive skills. Although, to our knowledge, this is the only case-report study spanning early childhood to adulthood, and the authors underline the importance of a specific assessment for catatonia in these patients, their conclusions leave an open question about the clinical overlap between these disorders. On the other hand, other studies suggested that catatonia should be considered as an expression of autism, rather than a comorbidity. Specifically, Realmuto and August [16], who described three autistic young adults who developed catatonic features (at the age of 16, 20, and 21 years, respectively), and Hare and Malone [19], who illustrated the case of an ASD 18-year-old boy with a series of motor and verbal catatonic signs, proposed the concept of 'autistic catatonia' and a treatment based on behavioral interventions. However, these authors conclude that more research is needed to investigate the aetiology and the more appropriate clinical intervention to treat patients with autistic catatonia. On the contrary, Fink et al. [21], in a series of six case reports (five boys and one girl) with a history of autism and a comorbid catatonia, provided a catatonia medical treatment algorithm suggesting that catatonia in ASD patients can be thought of as the sharing of a motor dysregulation process, or as the comorbidity of a mood disorder or epilepsy.

To our knowledge, so far only two systematic studies have investigated the prevalence of catatonia in ASDs [10, 12]. These studies adopted the same diagnostic criteria for catatonia and reported similar prevalence rates. Specifically, Wing and Shah [10] evaluated 506 children and

Table 2 Summary of case-report studies exploring catatonia in autism spectrum disorders (ASDs)

Study, year	Sex	Diagnosis	Treatment
Case reports in paediatric patients			
Realmuto and August, 1991 [16]	1 M	ASD and catatonic symptoms	Haloperidol
Dhossche, 1998 [17]	1 M	ASD and a comorbid catatonia	Clozapine and lorazepam
Zaw et al., 1999 [18]	1 M	ASD and catatonic stupor	Zolpidem and ECT
Hare and Malone, 2004 [19]	1 M	ASD and catatonic symptoms	Behavioral intervention
Ghaziuddin et al., 2005 [20]	1 M	ASD and a comorbid catatonia	ECT
Fink et al., 2006 [21]	5 M/1 F	ASD and catatonic symptoms	Lorazepam and bilateral ECT
Bailine and Petraviciute, 2007 [22]	1 M	Asperger syndrome and catatonia	Lorazepam and bilateral ECT
Wachtel et al., 2008 [23]	1 F	ASD and a comorbid catatonia	Lorazepam and ECT
Kakooza-Mwesige et al., 2008 [24]	1 M	Autistic and catatonic symptoms	Lorazepam and bilateral ECT
Quigley et al., 2009 [25]	1 F	Asperger disorder and catatonia	Lorazepam
Wachtel et al., 2010 [26]	1 M	ASD and malignant catatonia	Lorazepam and bilateral ECT
Wachtel et al., 2010 [27]	2 M	ASD and a comorbid catatonia	Lorazepam and bilateral ECT
Ghaziuddin et al., 2010 [28]	2 M	ASD and catatonic symptoms	ECT
Consoli et al., 2010 [29]	1 M	ASD and catatonic symptoms	Lorazepam, fluoxetine, packing therapy[a]
Bozkurt and Mukaddes, 2010 [30]	1 M	ASD and catatonic symptoms	Lorazepam
Dhossche et al., 2010 [31]	2 M	Tic, self-injurious behavior, catatonia. One patient met criteria for autism	ECT
Case reports in adult patients			
Realmuto and August, 1991 [16]	2 M	ASD and catatonic symptoms	Haloperidol and nortriptyline
Shah and Wing, 2006 [32]	1 M	ASD and catatonic symptoms	Intensive psychological intervention
Tan et al., 2006 [33]	1 M	ASD and catatonic stupor	Olanzapine and ECT
Takaoka and Takata, 2007 [3]	1 F	High-functioning autism and catatonia	Fluvoxamine
Shepherd et al., 2009 [34]	1 M	Autism, bipolar disorder, and catatonia	Lorazepam
Wachtel et al., 2010 [27]	1 M	ASD and a comorbid catatonia	Lorazepam and bilateral ECT
Wachtel et al., 2010 [35]	1 M	ASD and catatonic symptoms	Lorazepam and bilateral ECT

A systematic literature search was performed using PubMed to identify case report studies that assess catatonic symptoms in individuals with ASDs. Trial quality was assessed according to a standardized and validated set of criteria. We searched MEDLINE databases from December 1991 to January 2012, with the search terms 'autism', 'autistic disorder', 'autism spectrum disorder' and 'pervasive developmental disorder' in combination with 'catatonia', and 'catatonic symptoms'

ECT electroconvulsive therapy, *F* female, *M* male

[a] Packing therapy: envelopment in damp sheets for 1-h sessions in a patient expressing cenesthesic sensations and spontaneous fantasies [27]

adults referred to a specialist clinic for ASDs, 30 of whom, aged 15 years or above, met the criteria for catatonia, representing 17 % of all referrals in that age range. In a second study, Billstedt et al. [12] followed prospectively 120 patients with ASDs for a period of 13–22 years, and re-evaluated these patients at ages 17–40 years, estimating a catatonia rate of 12 %. It is worthy to note that all these patients were diagnosed with a comorbid catatonia at or after adolescence. Different results were obtained by a recent follow-up study on 135 ASD patients, aimed at investigating the presence of comorbid psychiatric disorders through a questionnaire completed by caregivers. In this cohort, 16 % of participants developed a new psychiatric disorder, and among them only five patients had a comorbid obsessive-compulsive disorder and/or catatonia [14]. However, the slightly lower rate of catatonia documented in this study may be related to the use of a different methodology and a tool investigating new-onset psychiatric disorders at large. Finally, Ghaziuddin et al. [15], in a retrospective chart review including 101 child and adolescent psychiatric inpatients, reported that 17.8 % met the study-defined criteria for catatonia. Although, the prevalence rate found by Ghaziuddin et al. [15] is similar to the Wing and Shah [10] rate, this study investigated psychiatric inpatients in general and not specifically individuals affected by ASDs. Table 3 shows a summary of studies exploring the presence of catatonia in ASDs.

3 Brief Report of Three Case Studies

In order to illustrate the management and treatment of catatonia in ASDs, we report our clinical experience with three pediatric autistic patients showing catatonic

Table 3 Summary of studies exploring the prevalence of catatonia in autism spectrum disorders (ASDs)

Study, year	Type of study	Findings
Wing and Shah, 2000 [10]	Systematic study	506 referrals to a specialist clinic for ASDs (from 15 to 50 years)
		Catatonia was detected in a total of 30 ASD patients (6 %) of all referrals
Billstedt et al., 2005 [12]	Systematic study	120 patients with ASDs. Catatonia rate estimation of 12 %
Ohta et al., 2006 [13]	A long-term prospective study	11 patients with ASDs; two reported a typical catatonia (age of onset 19 years)
Hutton et al., 2008 [14]	A follow-up study	135 patients with ASDs assessed for psychiatric comorbid disorders. 16 % reported a new psychiatric disorder, of which 5 patients reported a catatonia
Ghaziuddin et al., 2012 [15]	Retrospective chart review	101 child and adolescent psychiatric inpatients. 17.8 % met the study-defined criteria for catatonia

A systematic literature search was performed using PubMed to identify clinical studies that assess catatonic symptoms in individuals with ASDs. Trial quality was assessed according to a standardized and validated set of criteria. We searched MEDLINE databases from December 1991 to January 2012, with the search terms 'autism', 'autistic disorder', 'autism spectrum disorder' and 'pervasive developmental disorder' in combination with 'catatonia', and 'catatonic symptoms'

symptoms during adolescence. Implications for clinical practice will be discussed, as well as different possible etiology and the consequent indication to different treatment approaches.

Case 1 F is a 16-year-old boy with ASD and epileptic seizures treated with carbamazepine. He showed a non-verbal intelligence quotient (IQ), assessed by Leiter-R [36], indicating moderate intellectual disability (IQ = 48). At 15 years of age, *F* started to show combativeness and auto/hetero aggressive behaviors, and he started treatment with risperidone (2.5 mg/day). One month later, *F* began to present a progressive slowness of movements, mutism, increasing stereotypies, autonomic crises accompanied by abnormality of temperature and grimacing, all symptoms alternated with excessive hyperactivity. He was hospitalized, and after a comprehensive psychological, physical, and medication management evaluation he was diagnosed with catatonia. Therefore, risperidone was weaned and discontinued, and the patient's symptoms started to improve. In addition to the pharmacological modification, *F* started an intensive cognitive-behavioral psychological therapy to manage the behavioral dyscontrol. This case, in a patient who showed catatonia-like condition after 1 month of risperidone treatment, depicts a classic 'knee-jerk reaction' in autism caused by antipsychotic medications (see paragraph 7 in the section on Management and Treatment of Catatonia in ASDs).

Case 2 A is a 13-year-old girl with prior diagnoses of ASD and mild intellectual disability (Leiter-R: IQ = 58). At 11 years of age, after exposure to some stressful life events, *A* showed a 6-month history of overall progressive slowing movements, episodes of stupor, loss of most of her speech, echopraxia, and inability to start movements without external prompts. She started treatment with aripiprazole (15 mg/day) without any effect. At 12 years of age, *A* was hospitalized and completed all physical and medical examinations, including electroencephalogram (EEG) and magnetic resonance imaging (MRI), which did not show any abnormality. As a result, *A* was diagnosed with catatonia and was treated with lorazepam, with increased doses up to 10 mg/day. She also started intensive cognitive-behavioral therapy, aimed at reducing stress sources and creating routine and repetitive physical activities. *A* reported a mild improvement in motor signs with an increment of spontaneous activity, although an endurance of mutism. After 1 month of lorazepam (10 mg/day), she showed a relapse with an exacerbation of catatonic signs, especially of echopraxia, obstruction and aversion. Therefore, lorazepam was increased to 20 mg with an improvement and resolution of catatonic symptoms. Although many clinicians usually hesitate to increase lorazepam to 20 mg daily because this dosage exceeds conventional psychopharmacology, this case suggests that in some patients with catatonia higher doses of this medication may be necessary, well tolerated without sedation, and life saving.

Case 3 G is a 14-year-old boy with ASD, a comorbid obsessive-compulsive disorder and a borderline IQ, as reported by the Wechsler Intelligence Scale for Children-Revised (WISC-R) [Performance IQ = 75 and Verbal IQ = 77] [37]. At 11 years of age, after his parents' divorce, causing a sudden change and restructuring of his life, *G* was hospitalized for the manifestation of severe catatonic signs. In particular, *G* showed episodes of stupor, hypoactivity, broad withdrawal, posturing, catalepsy, psychological pillow, rigidity, mutism and severe difficulties with eating. Thus, *G* was diagnosed with catatonia and submitted to the challenge test for lorazepam. He was treated with increasing doses of lorazepam, as high as 20 mg/day. However, after a 2-week trial, no improvement of catatonic symptoms was observed. Therefore, he was treated with risperidone (2 mg/day), and a starting dose of

50 mg/day of sertraline, subsequently increased to 100 mg/day. This medication therapy, along with structured psychological therapy, resulted in a crucial remission of catatonic symptomatology. *G*, who developed catatonic symptoms after the disruption of his regular routine and did not improve with a high lorazepam dosage, is, to our knowledge, the first case reported in the literature of an ASD patient with catatonia resistant to benzodiazepine treatment in which other pharmacological options were successfully considered (see paragraph 7 in the section on the Management and Treatment of Catatonia in ASDs).

4 Catatonia and Autism: Mechanisms Underlying Symptoms

To date, the mechanisms underlying catatonia are still unclear, yet many hypotheses have been proposed and the similarities between catatonic symptoms and some features of ASDs can contribute to shed light on this issue. Some authors suggested that catatonia may be induced by a massive blockade of dopamine. Therefore, medications such as dopamine-blocking antipsychotics, exacerbating dopamine deficiency, specifically at the D_2 receptor, can worsen catatonic symptoms [11, 38]. A decrease in the activity at the D_2 receptor can lead, in turn, to a release of excitatory neurotransmitters, such as glutamate, in order to regulate dopamine activity. However, glutamate hyperactivity can cause neuronal damages and may induce symptoms similar to catatonia. In order to explain the etiology of catatonia, some studies have also hypothesized an alteration of basal ganglia modulation [39]. According to this suggestion, the motor symptoms of catatonia might be caused by a deficiency of cortical gamma-aminobutyric acid (GABA), which acts as the prime inhibitor neurotransmitter. Consequently, this hypothesis can explain the therapeutic effects of benzodiazepines and electroconvulsive therapy (ECT), which cause an increase in GABA activity [9, 39, 40]. Moreover, it has also been proposed that catatonia and autism may share a common genetic linkage, and, specifically, a common susceptibility region, 15q15–q21, supposed to encode for the γ-GABA receptors B3, A5, and G3, in line with the therapeutic effects documented for benzodiazepines in catatonia as well as the role of GABA in ECT [41]. Furthermore, it has been suggested that catatonia may be due to an intense evolutionary-based fear response, closely related to the animal defense strategy tonic immobility [42]. The GABA system appears to play a prominent role in tonic immobility and this peculiar response to fear seems to be similar to the catatonia observed in patients after exposure to traumatic events [43–45]. Previous literature studies reported that the development of catatonic symptoms in autistic patients was, in the majority of cases, immediately preceded by stressful life events, such as bereavement, pressure at school, or lack of occupation [10, 19]. Interestingly, one peculiar feature of ASDs is the need to perform ritualistic behaviors, repetitive actions, and routine and structured activities, and changes in these routine actions, or the discrepancy between social context expectations and autistic functioning, can cause stress in these individuals, especially in high-functioning subjects, which may be involved in the development of catatonia. Therefore, it is possible that catatonia is a consequence of stressful life events in autistic patients showing a predisposition to develop these symptoms. This model led some authors to assume that catatonia in autistic patients may reflect an extreme adaption to environmental factors, so that it should be considered as a peculiar intrinsic expression of ASDs, called 'autistic catatonia', rather than a comorbid disorder [19, 46].

Albeit catatonia has historically been associated with schizophrenia, recent studies have demonstrated that this syndrome is most frequently linked to mood disorders [11, 47, 48]. Even though understanding the manifestation of mood symptoms in ASDs remains difficult, because autistic symptoms can mask disorders in comorbidity, previous reports have shown the presence of various types of internalizing disorders in persons with ASDs, including depression and bipolar disorder [49–58]. Therefore, catatonia could be due to an exacerbation of mood symptoms already present in these patients, and catatonic manifestations are sometimes the only and easier clinical signs to detect mood alterations in patients with ASDs.

5 From DSM-IV-TR to DSM-5: Diagnostic Peculiarity in ASDs

Different criteria for diagnosis of catatonia are used in clinical practice and research. According to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV-TR) [59], catatonia was a specifier of schizophrenia, primary mood disorder, and mental disorder due to a general medical condition not otherwise specified. To satisfy the DSM-IV-TR criteria for catatonia, the patient had to report at least two of the motor symptoms if the context was a psychotic or mood disorder, whereas only one symptom cluster was needed if the context was a general medical condition. Changes made to the *DSM, 5th Edition* (DSM-5) [60] diagnostic criteria for catatonia report that all contexts require three catatonic symptoms (from a total of 12 characteristic symptoms). Moreover, catatonia may be diagnosed as a specifier for depressive, bipolar, and psychotic disorders, as a separate diagnosis in the context of another medical condition, or as another specified diagnosis (Table 4).

Table 4 Catatonia diagnostic criteria: from DSM-IV-TR to DSM-5

DSM-IV-TR	DSM-5
The clinical picture is dominated by at least two of the following to be a specifier of a psychotic or mood disorder, and one of the following as a specifier of a general medical condition	The clinical picture is dominated by at least three of the following to be a specifier for depressive, bipolar, and psychotic disorder, as a separate diagnosis in the context of another medical condition, or as another specified diagnosis
1. Motoric immobility as evidenced by catalepsy (including waxy flexibility) or stupor	
2. Excessive motor activity (that is apparently purposeless and not influenced by external stimuli)	
3. Extreme negativism (an apparently motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism	
4. Peculiarities of voluntary movement as evidenced by posturing (voluntary assumption of inappropriate or bizarre postures), stereotyped movements, prominent mannerisms, or prominent grimacing	
5. Echolalia or echopraxia	

DSM-IV-TR Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision, *DSM-5* DSM, 5th Edition

Generally, the presence of catatonia in autistic patients should be assessed only when there is a conspicuous and obvious change in symptoms such as a marked increase or decrease of motor and speech behaviors, compared with the previous level [61, 62]. The criteria proposed by Fink and Taylor [11] are widely used for the diagnosis of catatonia because of their clinical relevance and conformity to DSM-IV [11]. However, these criteria are less applicable to the majority of autistic patients, considering, at baseline, the overlap of symptoms between these disorders. Therefore, Dhossche et al. [61] suggested two specific diagnostic criteria, proposing longer time criteria to recognize a change from baseline in the behavioral patterns of patients with ASD [61]. Specifically, the first criterion (A), proposes that a marked change in motor behaviors, expressed by immobility, decreased speech or stupor, or, on the other hand, excitement, or a mixed presentation that may include periods of markedly reduced motor activity alternating with excitement, should be assessed for a duration of at least '1 day', rather than '1 h'. The second criterion (B), suggests '1 week', alternatively to 'on two or more occasions', of marked increase from baseline, in the absence of a change in motor behaviors, drastically decreased speech, or stupor, of at least two of the following: slowness of movement or speech, difficulty in initiating movements or speech unless prompted, freezing during actions, difficulty crossing lines, inability to cease actions, stereotypy, echophenomena, catalepsy, automatic obedience, posturing, negativism, or ambitendency.

6 Differential Diagnosis of Catatonia

An important issue for the diagnosis of catatonia, including in autistic patients, is to make an adequate differential diagnosis with other conditions, syndromes, or disorders featuring abnormal psychomotor activities, that may overlap with this syndrome. When a marked decrease in motor activity is observed, differential diagnosis be made from neurological conditions, such as acute dystonia, tardive dyskinesia, akathisia, withdrawal-emergent dyskinesia, parkinsonism, and Parkinson's disease.

Furthermore, tic disorder, Gilles de la Tourette syndrome, and compulsions in obsessive-compulsive disorder may also overlap and precede catatonic symptoms. Decreased speech or mutism may be confused with a conversion disorder or a selective mutism, especially after exposure to stressful events or a trauma. Finally, epilepsy is often difficult to distinguish from catatonia due to the overlap between psychomotor seizures and catatonia and the increased presence of seizures in catatonic patients. Electroencephalographic patterns are usually normal in catatonic patients [11]. Nevertheless, non-specific findings of diffuse slowing have been reported, and other reports showed a dysrhythmic EEG consistent with non-convulsive status epilepticus that resolved when catatonia remits [11, 63]. This is in line with the theory that there is localized brain excitation in catatonic patients in specific deep brain structures that are not detected by EEG, which improves with anticonvulsant medications, but particularly with benzodiazepines and ECT [64, 65].

6.1 Rating Scales for Catatonia

Rating scales are important tools that can help clinicians and researchers through the diagnostic process. Various rating scales for the evaluation of catatonic symptoms have been published. The most widely used is the Bush-Francis Catatonia Rating Scale (BFCRS) [5], a standardized instrument available in a short version of 14 items for the screening of catatonia and in a longer version of 23 items. Other rating scales are: (i) the Catatonia Rating Scale (CRS) [66], a 21-item clinician-administered rating scale for the severity of catatonic symptoms; (ii) the Modified

Rogers Scale (MRS) [67], which rates abnormalities in movement, volition, speech, and overall behaviors, and permits the distinction between extrapyramidal side effects and catatonic signs; (iii) the Northoff Catatonia Rating Scale (NCRS) [68], a 40-item scale for three different categories of catatonic symptoms (i.e. motor, behavioral, and affective); (iv) the Braunig Catatonia Rating Scale (BCRS) [66], a 21-item scale with a possible score from 0 to 4; (v) the Kanner Scale [68], which assesses catatonic signs in neuropsychiatric disorders. Although all these rating scales are useful tools for clinicians, the variety of neuropsychiatric and general medical conditions associated with catatonic signs lead these tools to be insufficient in detecting catatonia in specific patient populations [69]. Moreover, to date, there are no scales specifically designed to assess catatonic symptoms in patients with autism, and in view of the overlap between the two disorders, the available tools are probably not appropriate for this clinical population and modifications would be needed.

7 Management and Treatment of Catatonia in ASDs

7.1 Comprehensive Catatonia Diagnostic Evaluation

A complete diagnostic evaluation of catatonia in children and adolescents with ASDs should include psychological, physical, and medication management investigations (Fig. 1). First, an initial assessment, in order to collect information on case history, current clinical picture, skills, disabilities, and motor competencies, is important for the diagnostic process of children and adolescents with ASDs who develop catatonia-like deterioration [32, 61]. A broad psychological evaluation on the possible exposure to traumatic or stressful life events, and on the presence of diagnostic criteria for catatonia in autism, should also be undertaken. Moreover, possible catatonia-like deterioration in patients with ASDs should prompt a thorough clinical assessment. Full physical examination, and laboratory and imaging investigations should be based on clinical findings. Infectious, metabolic, endocrinological, neurological, and autoimmune diseases have been associated with catatonia and should therefore be ruled out [11, 70]. All patients should be evaluated through basic investigations, including complete blood count, metabolic tests, renal, liver and thyroid function tests, and blood glucose measurements [2, 11, 70]. Additional analyses based on the findings of the former examinations, such as MRI, computed tomography, EEG, electrocardiogram, urine culture, blood culture, test for HIV, test for syphilis, heavy-metal screen, auto-antibody screen, and lumbar puncture could be required [2, 11, 70]. In case reports, illicit drugs (such as PCP, mescaline, ecstasy, cocaine, opiates and opioids) have been associated with the emergence of catatonia [11]. Furthermore, literature data report that catatonia precipitated in some patients following the withdrawal of benzodiazepines, gabapentin, and dopaminergic drugs, particularly if done rapidly [11]. Therefore, a drug screen to detect illicit and prescribed substances should be performed, and all prescribed medications should be evaluated since many of them can cause catatonia-like conditions as possible side effects [11, 71]. Literature studies showed that antipsychotic agents are contraindicated in patients with ASDs who exhibit catatonia signs, and should therefore be discontinued because of the reported increased incidence of malignant catatonia or neuroleptic malignant syndrome in patients with incipient signs of catatonia, as described in Case 1 (*F*), which illustrates a classic 'knee-jerk reaction' in autism caused by antipsychotic usage in this population [11]. Once there is remission of catatonia, antipsychotics could be useful to choose additional psychiatric diagnoses; however, any re-emergence of catatonic symptoms should prompt discontinuation.

Finally, when the diagnosis of catatonia is established and persists over time, the severity (mild, moderate, and severe) of the condition should be determined in order to help clinicians to choose the adequate level of medical service a patient needs and the appropriate treatment [61].

7.2 Treatment Approaches

The successful use of medical treatments for catatonia in ASD patients is based only on the limited literature data reported in case reports and case series [17, 18, 20–31, 33–35]. In fact, to our knowledge, there is a lack of controlled studies exploring the medical treatment of catatonia in ASD patients. Currently, benzodiazepines are the most frequently used medications [11, 62]. The medical treatment algorithm for catatonia in ASDs [11, 62] suggests a benzodiazepine challenge test of 1 or 2 mg of lorazepam (administrated orally, intravenously, or intramuscularly) [Fig. 1]. If the challenge test improves catatonic symptoms, treatment with increasing doses of lorazepam, as high as 24 mg/day, for adolescents is recommended [24]. In fact, as reported in Case 2 (*A*), higher doses of lorazepam may be necessary in order to improve catatonic symptoms, even if this dosage is considered 'high' in conventional psychopharmacology. Improvement should be observed at least after 1 week in severe catatonia, and after 2 weeks in mild and moderate cases. After the efficacy of lorazepam has been demonstrated, a continuation phase of 6–12 months can start. ECT is indicated when patients are unresponsive, or insufficiently responsive, to benzodiazepines and, in some patients, it could be life-saving. Generally, some technical issues, that can be extended to paediatric ECT and autistic youth, should be considered before starting ECT in order to

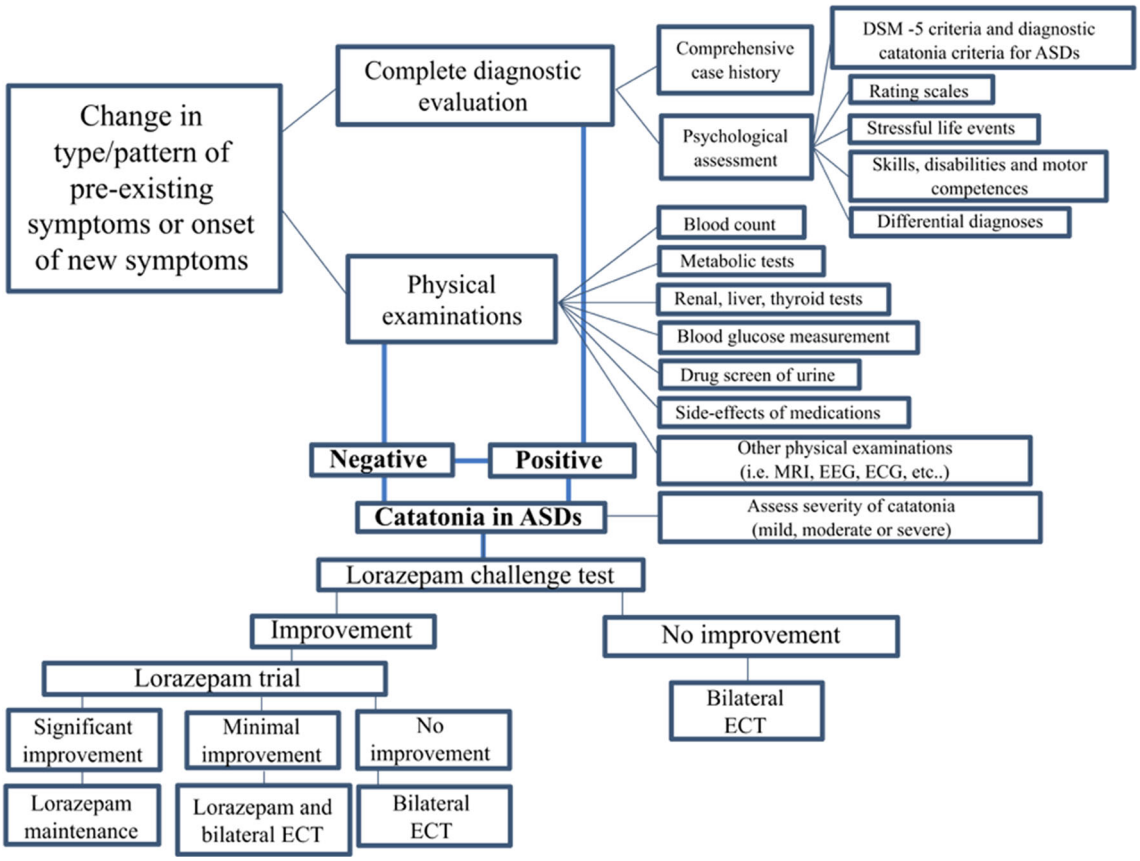

Fig. 1 Management and treatment of catatonia in ASDs. *ASDs* autism spectrum disorders, *DSM-5* Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, *ECG* electrocardiogram, *ECT* electroconvulsive therapy, *EEG* electroencephalogram, *MRI* magnetic resonance imaging

maximize the effects. The first issue concerns electrode placement. A recent review on electrode placement for the treatment of major depression reported that bifrontal ECT is not more effective than bitemporal or right unilateral ECT, a result that is in sharp contrast with those of the UK ECT Review Group [73], which found unilateral ECT to be less effective than bilateral ECT [72, 73]. Nevertheless, there is a growing body of literature documenting that bilateral (bitemporal or bifrontal) electrode placement is more efficacious in individuals with ASDs experiencing catatonic deterioration, and therefore it is recommended. It is worthy to note that data regarding this treatment rely only on case studies [11, 17, 18, 20–31, 33–35, 61, 62] and therefore more studies are needed to shed light on this issue. Second, clinic guidelines overall suggest that before initiation of ECT all psychiatric medications should be stopped, as well as any other non-psychiatric medications, if possible. However, there is some evidence that the maintenance of lorazepam during ECT is indicated when the use of this medication has somewhat improved symptoms, without leading to a total remission. Before the seizure induction, an intravenous administration of flumazenil, a benzodiazepine antagonist, can be used in order to temporarily suspend the anti-seizure effects of lorazepam. The synergy of lorazepam and ECT treatment using flumazenil was observed in a case series, and the use of flumazenil has been proposed in benzodiazepine-free patients as a novel method for managing the decline of ECT seizure quality [24, 74, 75]. The remission of catatonia in paediatric patients in general and specifically in autistic youth, requires more frequent seizures than those necessary for the relief of major depression [11, 61, 62]. The UK standard practice of two seizures a week, although effective for major depression, may not be so for catatonia. A daily ECT treatment of 3–5 days might be necessary in severe or malignant catatonia. The number of sessions that will be needed before substantial improvement or remission occur cannot be predicted. Therefore, the patient's overall response should be evaluated after the first five or six treatments and then again after 10 or 12 treatments [11, 61, 62, 76]. Treatment course should be intensive and generally it should be followed by a maintenance treatment (weekly or bi-weekly ECT sessions for 6 months or longer) to prevent relapses [11, 61, 62].

Although benzodiazepines are the first-choice medications and, in patients with catatonia who are unresponsive or insufficiently responsive to benzodiazepines, ECT is the

second choice, in cases of catatonia resistant to benzodiazepines and ECT other pharmacological options can be explored. For instance, antipsychotics, which are generally not recommended for the treatment of catatonic symptoms because they can increase the risk to precipitate catatonic signs into malignant catatonia or neuroleptic malignant syndrome, could instead be useful in the treatment of non-malignant catatonia, as reported in Case 3 (*G*) and other case-report studies [2, 11, 77, 78]. Furthermore, studies on the treatment of catatonia suggested that mood stabilizers, particularly carbamazepine, could be an effective medication option for both the acute and maintenance phases of this syndrome [79]. Finally, case-report studies reported the effectiveness of *N*-methyl-D-aspartate (NMDA) receptor antagonists, specifically amantadine and memantine, for the treatment of catatonia [80, 81]. Nevertheless, when considering these other pharmacological options for treatment-resistant catatonia patients, caution is warranted because the literature on these treatments consists only of case reports and retrospective studies (randomized controlled trials are lacking). Moreover, none of these studies was conducted in ASD patients with catatonic symptoms. There is some evidence that when catatonic symptoms in ASD patients become chronic a psychological treatment, co-occurring with medical treatments, is useful in order to support the management of the patient, particularly for parents and caregivers, as exemplified in the three cases illustrated above [32]. An intensive and complete behavioral approach should be individually created based on the pre-morbid ASD symptomatology. First, the psychological intervention should help to identify the stressful life event(s) and to restructure the environment with the aim of reducing stress sources. Second, the psychological approach should help parents and caregivers to understand and conceptualize the catatonic syndrome. Moreover, the use of prompts as external stimuli and physical activities, especially routine, repetitive, and structured, seem to be beneficial.

8 Future Directions

Although recent studies have highlighted that catatonia syndrome can occur in ASD persons, further studies are needed on the prevalence rate of catatonia in ASDs. Shedding light on the epidemiology of this syndrome in this particular population is a crucial issue in order to help clinicians to develop an adequate management plan. The diagnostic challenges of catatonia in ASDs have underlined the need of specific diagnostic criteria and proper screening tools, specifically designed for this population, with the purpose of helping clinicians to recognize the catatonic signs in patients with ASD, and promoting research to unify the methodology. Furthermore, given the similarity between catatonic symptoms and some characteristics of ASDs, the study of the mechanisms underlying catatonia in autism can contribute to delineate the distinct features of these conditions. The lack of controlled studies on the medical and psychological treatment of catatonia in ASDs raises concerns on the appropriate treatment strategies for these patients, and longitudinal controlled studies are essential to address this issue. Indeed, new therapeutic trials tested the repetitive transcranial magnetic stimulation (rTMS), a non-invasive technique for indirect brain stimulation, as an emerging treatment modality for several neuropsychiatric conditions [82, 83]. Three case reports used the rTMS for the treatment of catatonia, corroborating the efficacy of this technique for the treatment of this syndrome [84–86]. Although further randomized controlled trials are needed in order to determine the role of rTMS in the treatment of catatonia, this technique could be an innovative future direction for the treatment of catatonia in ASD patients.

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