

# Catatonia: a critical review and therapeutic recommendations

## *Catatonia: una revisione critica del concetto e indicazioni terapeutiche*

N. Bartolommei, L. Lattanzi, A. Callari, L. Cosentino, F. Luchini, M. Mauri

Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, Università di Pisa

### Summary

#### Objectives

This review has the aim of improving early recognition and effective treatment of catatonia, critically going through its historical descriptions and revisiting its nosographical collocation in current classification systems.

#### Methods

A PubMed search was done using the keywords “catatonia”, “catatonic schizophrenia”, “stupor”, “catalepsy” and “catatonia treatment” (until 2011).

#### Results

In 1874, Kahlbaum first described catatonia as a disease of its own, characterized by specific disturbances in motor and behavioural functioning; in contrast, Emil Kraepelin classified catatonic features as a clinical expression of *dementia praecox*, with a chronic course and poor prognosis. Catatonia occurs in children, adolescents and adults, and develops in association with a wide variety of psychiatric, neurologic and general medical conditions. The neurobiological pathways of catatonia are still unclear. In particular the role of GABA and other neurotransmitters has been explored, but not completely defined. Nosological and diagnostic definition of disorder are still argued by clinicians and researchers. Although the main psychiatric classifications continue to sustain Kraepelin's view of catatonia as a clinical subtype of schizophrenia, in a clinical setting, catatonic symptoms are more commonly observed in

patients with mood disorders and general medical conditions. Symptomatology is characterized by a wide array of manifestations: negativism, mutism and stupor represent the most common symptoms. The lack of consensus about diagnostic criteria often complicates recognition of catatonic symptoms. The issue in diagnostic assessment is to differentiate catatonia from other overlapping psychomotor disorders and to identify the underlying psychiatric and general medical disorders. Early and correct diagnosis is crucial to start effective treatments and avoid potentially severe (sometimes lethal) somatic complications. Benzodiazepines and electroconvulsive therapy are the therapeutic mainstay for catatonia. Intravenous administration of BDZ is first-line treatment, where ECT is commonly used in non-responders to BDZ, malignant catatonia and malignant neuroleptic syndrome. Nonetheless, many authors suggest that ECT, preferably in combination with BDZ, should be considered in the early course of all types of catatonia to improve prognosis and avoid complications.

#### Conclusions

Further research should better define the neurobiological basis and improve clinical and nosographical collocation of catatonia; evidence-based therapeutic protocols are needed that would allow adequate and early treatment to prevent somatic complications of catatonia.

#### Key words

Catatonia • Neuroleptic malignant syndrome • Benzodiazepines • Electroconvulsive therapy

The first description of catatonia dates to 1874 when the German psychiatrist Karl Kahlbaum<sup>1</sup>, in his monograph entitled *Die Katatonie oder das Spannungsirresein*, coined the term to describe a disorder in which the core symptoms were behavioural and motor features (negativism, mutism, immobility, rigidity, mannerisms, stereotypies) accompanied by affective, cognitive and neurovegetative symptoms. According to Kahlbaum, the two fundamental characteristics of catatonia were: the centrality of behavioural and motor alterations and the nosological autonomy of the disorder, considered as an independent diagnostic entity. In his description, the clinical course of catatonia typically had a cyclical trend, with a gradual

onset followed by a static period and remission, while prognosis was generally considered good in most cases. By observing a high frequency of acute mood disorders in catatonic subjects, of both polarities, Kahlbaum highlighted its similarity with manic-depressive psychosis and proposed its classification as a single entity. In contrast, Emil Kraepelin<sup>2</sup> had different ideas about the diagnostic implications of catatonia. Kraepelin recognized that catatonia was one of the possible clinical expressions of a psychotic disorder, with a worsening clinical course, which he called *dementia praecox*. According to Kraepelin, catatonia was not an independent diagnostic entity, but one of the various clinical subtypes of *dementia praecox*.

#### Correspondence

Lorenzo Lattanzi, Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, Università di Pisa, via Roma 67, 56126 Pisa, Italy • Tel. +39 050 992479 • E-mail: llattanzi@blu.it

cox<sup>3</sup>, characterized by chronicity and poor prognosis. From a psychopathological standpoint, while Kahlbaum highlighted the psychomotor component, according to Kraepelin<sup>4</sup> catatonic symptoms were a manifestation of a deficit in will that the German author considered a central feature of *dementia praecox*.

Eugene Bleuler, in 1916<sup>5</sup>, classified catatonia among the subtypes of schizophrenia, a term coined to substitute *dementia praecox*. The symptoms and clinical signs that for the Swiss author defined catatonic schizophrenia were in large part the same as those already observed by Kahlbaum and Kraepelin, although Bleuler gave them less diagnostic relevance. The studies of Wernicke, Kleist and Leohnard on the clinical and psychopathological characterization of catatonia successively led to the elaboration of a nosologic system in which psychotic disorders with prevalent psychomotor symptoms were grouped into two categories: motor psychoses, characterized by hyperkinetic psychomotor alterations and psychotic symptoms, and catatonic schizophrenia which was further divided into a systematic form, with a chronic course, and a non-systematic form, whose variants included periodic catatonia distinguished by intermittent behaviour, with alternating hyperkinetic phases and akinetic states, and an important hereditary aetiological component with dominant autosomal transmission<sup>6-9</sup>.

In 1934, Stauder also described a particular form of catatonia characterized by acute onset, rapid evolution generally poor prognosis which he termed *die todliche katatonie*, often translated as malignant or lethal catatonia<sup>10</sup>. In later years, other authors provided additional descriptions of the same syndrome, reporting high fever and severe alterations of the autonomous nervous system as key symptoms, together with its acute onset and often poor prognosis<sup>11-14</sup>. In the 1980s, the first publications on malignant neuroleptic syndrome emerged, with clinical aspects similar to malignant catatonia, which was distinguished mainly for its onset after the assumption of neuroleptics<sup>15 16</sup>.

The Kraepelin is conception that catatonia was a clinical expression of schizophrenia predominated for many years, in both the literature and clinical practice, also influencing international classification systems of mental disturbances. In the DSM, starting from the second edition in 1968<sup>17</sup>, catatonia was classified among the possible subtypes of schizophrenia; similarly, the ICD of the WHO in 1948<sup>18</sup> recognized a catatonic subtype of schizophrenia. Starting from the mid 1970s, a number of clinical studies prepared the basis to re-examine the diagnostic meaning of catatonic symptoms, reconsidering its association with schizophrenia and the original conception of Kahlbaum about its strict relation with mood disorders. A follow-up study in 1975 in 500 psychiatric patients revealed that about 10% presented catatonic characteristics, and that the majority had a diagnosis of mood

disorder<sup>19</sup>. At the same time, Taylor and Abrams<sup>20-23</sup> also demonstrated that there was higher prevalence of catatonia in patients with bipolar disorder compared to those with schizophrenia. Recent studies have confirmed the heterogeneity of clinical conditions associated with catatonia. In a cohort of psychiatric inpatients, catatonia was observed in 7% to 17% of cases, commonly in those with mood or substance abuse disorders<sup>24</sup>. Catatonic manifestations have also been described in subjects with Gilles de la Tourette syndrome and in somatic pathologies such as epilepsy, fever of unknown origin, paraneoplastic syndrome and in children with autistic disorder or mental retardation<sup>25-27</sup>.

At present, debate on the nosographic placement of catatonic symptoms lies around the possibility to definitively separate the link between catatonia and schizophrenia, and reclassify catatonic syndrome as an independent diagnostic entity. In the last edition of the DSM<sup>28</sup>, even if Kraepelin is vision of catatonia is predominant, catatonia is recognized not only as a diagnostic subtype of schizophrenia, but also as an organic mental disorder and as a specific characteristic of major depression or mania within mood disorder. In redefining catatonia as an independent diagnostic category, Taylor and Fink<sup>29 30</sup> highlighted that the disorder is amply diffuse among psychiatric patients, manifests with a typical symptomatic pattern and a relatively constant clinical course and responds to specific treatment. Thus, it has a clinical picture that can be subjected to diagnostic assessment and reliable prognosis.

The possibility to assign greater relevance to catatonia in the next edition of the DSM is still a matter of debate, although it would favour not only early diagnosis, and therefore rapid and efficacious treatment, but also stimulate research on the neurobiological basis of catatonia<sup>31</sup>. From a clinico-therapeutic standpoint, in fact, the modest recognition of catatonic forms, and thus the delay in treatment, facilitate the onset of severe, life-threatening medical complications (electrolyte disorders, pressure ulcers, rhabdomyolysis and acute renal insufficiency, thromboembolic disorders, acute urinary retention, systemic infection and aspiration pneumonia).

## Epidemiology

In the main epidemiological studies, the prevalence of catatonia in psychiatric patients varies from 7% to 31%<sup>29 32-34</sup>. It appears to be more frequent in hospitalized patients, and can be present both in adults and adolescents, as well as infants: in the USA, each year, 90,000 individuals are hospitalized for catatonia<sup>2</sup>, and according to the results of 10 international prospective studies, catatonia is diagnosed in about 10% of hospital admissions. These patients often present with an association of

catatonic symptoms and signs, usually more than 5; the most frequent symptoms are mutacism (68% of cases), and negativism or psychomotor arrest (62% of cases)<sup>35</sup>. Uncertainty about the nature and diagnostic relevance of catatonia certainly do not facilitate the recognition and correct interpretation of catatonic symptoms. Moreover, in industrialized countries classic catatonic manifestations such as immobility or negativism have become less frequent, and catatonia often presents in other forms that require specialists with good clinical insight for correct diagnosis<sup>36</sup>. Thus, it is believed that catatonia is not correctly recognized in a substantial number of cases. For example, in a study in Holland in psychiatric patients, the percentage of clinically diagnosed cases was 2%, while that revealed by researchers using specific scales was more than 18%<sup>37</sup>.

In contrast to the conception of Kraepelin, catatonic symptoms are frequently observed in association with mood disorders. In three studies carried out at different times, 28% to 31% of catatonic subjects presented with a manic or mixed episode<sup>29,38</sup>. Nonetheless, it is estimated that up to one-half of catatonic patients may have a mood disorder<sup>36</sup>. From the analysis of data from 5 studies, it emerged that catatonia was associated with a schizophrenic disorder in only 10-15% of cases<sup>29</sup>.

According to some studies, the catatonic manifestations most commonly associated with the chronic forms are stereotypies, mannerisms, automatic movements and bizarre posture; in contrast, immobility, mutacism and neurovegetative alterations appear to more frequently characterize the acute forms<sup>39</sup>. Catatonic symptoms are often observed in association with a wide variety of medical illnesses. In three epidemiological studies in hospitalized catatonic patients, the percentages of catatonia reported to be due to a general medical condition ranged from 20% to 25%<sup>40-43</sup>.

Catatonic forms can also be observed in infants and adolescents. In a review of 30 case reports on catatonic manifes-

tations in children and adolescents, Dhossche and Bouhman<sup>44,45</sup> revealed that one-third of subjects were affected by a medical or neurological condition, six patients presented with a mood disorder, three with schizophrenia and 11 with a diagnosis of atypical psychosis. A recent investigation in 506 patients with autism or mental retardation reported the presence of catatonic characteristics in 6% of cases and in 17% with an age greater than 15 years<sup>46</sup>.

## Diagnosis

Definition and classification of catatonia within the framework of the DSM-IV<sup>28</sup> have been the subject of much criticism (Table I). In fact, the DSM-IV summarizes some of the catatonic symptoms that can be encountered in clinical practice: catatonia due to a medical condition is described (code 293.89) as well as catatonic type schizophrenia (code 295.20). In addition, the DSM-IV designates catatonic manifestations that specify an affective episode (manic, mixed or depressive), without however assigning a diagnostic code. Lastly, diagnosis of malignant neuroleptic syndrome, considered by some as a variant of malignant catatonia, is classified separately in the section on drug-induced movement disorders (code 333.92).

The DSM-IV continues to refer to the conception of Kraepelin according to which catatonia is inextricably linked to schizophrenia: one of the five criterion A symptoms for schizophrenia is grossly disorganized or catatonic behaviour. However, none of the mood disorders requires alterations in catatonic psychomotor behaviour as diagnostic criteria<sup>31</sup>. The main criticism regarding the nosographic placement of catatonia in the DSM is related to the failure to recognize the ubiquitous nature of the syndrome, which hinders correct diagnosis and adoption of an adequate treatment protocol.

The "Work group on schizophrenia and related disorders" in the DSM-5<sup>35</sup>, with the aim of stressing that catatonia is not invariably linked to schizophrenia, recently proposed

**TABLE I.**

Most common clinical types of catatonia (modified from Bhati et al., 2007)<sup>125</sup>. *Forme di catatonia di più frequente riscontro nella pratica clinica (da Bhati et al., 2007, mod.)*<sup>125</sup>.

DSM-IV Code	Diagnosis	Prognosis	Morbidity and mortality
296.xx	Mood disorder with catatonic manifestations	Good	Moderate
293.89	Catatonia due to a general medical condition	Good-poor	High
295.20	Schizophrenia, catatonic type	Good-fair	Moderate
333.92	Malignant neuroleptic syndrome	Fair-poor	High
None	Serotonergic syndrome	Fair-poor	High

The Table includes the DSM-IV codes (if available) in order of highest frequency seen in clinical practice. Prognosis indicates expected outcomes after appropriate treatment with a benzodiazepine and/or ECT.

two modifications: 1) to substitute the term 'catatonic behaviour' with 'alterations in psychomotor behaviour' among the diagnostic criteria for schizophrenia; and 2) to use a specifier to define three groups of patients: with schizophrenia, with mood disorder and with a general medical condition.

Recently, the number of symptoms/signs needed to diagnose catatonia has been debated<sup>41</sup>. In the DSM-IV<sup>28</sup>, there are 12 possible clinical manifestations (psychomotor arrest with catalepsy, waxy flexibility or stupor, tendency for fixed posture, echolalia, echopraxia, psychomotor agitation, negativism, mutacism, motor stereotypies, mannerisms, grimaces), which according to some authors<sup>47</sup> constitute an incomplete set of symptoms. For the DSM-IV, the number of signs/symptoms needed for diagnosis varies according to the pathological condition underlying the suspect catatonic syndrome. For the catatonic schizophrenia subtypes and for catatonic manifestations of mood disorders at least two signs are required, while a single motor symptom is needed for diagnosis of catatonia due to a general medical condition. Assessment of severity or duration of manifestations is not required<sup>28</sup>.

The use of rating scales, developed in recent years in order to offer an instrument for correct definition and monitoring of catatonic symptoms over time, can be particularly useful in clinical practice. For example, the Bush-Francis Catatonia Rating Scale (BFCRS)<sup>41</sup>, composed of 23 items, defines each catatonic sign, describes the severity (with a score from 1 to 3) and outlines a standardized scheme for objective examination. In addition to the signs described in the DSM-IV, the BFCRS proposes other catatonic signs/symptoms including: fixed gaze, verbigeration, inhibition, impulsivity, automatic obedience, *mitgehen*, *gegenhalten*, grasping, perseveration, neurovegetative alterations, aggressiveness and ambivalence.

In a case-report up 2004, Scarciglia et al.<sup>48</sup> described the use of the Catatonia Rating Scale for longitudinal evaluation in a catatonic patient, underlining its validity not only for description of symptoms, but also as a diagnostic tool in order to monitor clinical conditions over time.

## Differential diagnosis

A correct diagnostic approach in a catatonic patient requires identification of the pathological condition underlying the disturbance as a mental disorder, medical condition, neurological disturbance or assumption/suspension of drugs (Table II). Detailed anamnesis is therefore essential along with accurate objective neurological and general examination, assessment of vital signs, laboratory exams and microbiological cultures, in addition to toxicological and neuroradiological exams. It should also be kept in mind that some of the symptoms of catatonia are

common to a variety of psychomotor disorders (both hyperkinetic and hypokinetic).

Among the hyperkinetic states, drug-induced neuroleptic reactions should be excluded as well as acute dystonia (prolonged and involuntary muscle contraction that can provoke repeated movements and anomalous posture), tardive dyskinesia (involuntary hyperkinetic movements that frequently involve the mouth, lips and tongue), withdrawal dyskinesia and akathisia.

Even Gilles de la Tourette syndrome and obsessive-compulsive disorder (OCD) can manifest with hyperkinetic alterations in motricity similar to catatonia. Cases of catatonic patients have been described with tics and explosive crises that improve with electroconvulsive therapy (ECT)<sup>49</sup>. One case report described the association between beta-haemolytic streptococcal infection and the development of obsessive-compulsive behaviour that improved after treatment with lorazepam followed by plasmapheresis. The authors thus suggested that catatonia with OCD and tics may represent different aspects of paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS)<sup>50</sup>.

Even the hyperkinetic manifestations of hypocalcaemia can simulate catatonic syndrome, in addition to tetanus, rabies and intoxication from strychnine. In the differential diagnosis of catatonia, hypokinetic conditions such as drug-induced Parkinsonism, and in particular by typical antipsychotics. However, akinetic Parkinsonism does not generally respond to lorazepam, but rather to anticholinergics. It is often difficult to distinguish catatonia from other disturbances characterized by rigidity and hypokinesia in association with alterations in consciousness. Such is the case in stiff man syndrome and locked-in syndrome. The former is characterized by painful spasms from tactile and emotional stimuli or noise that benefits from therapy with baclofen, a gabaergic type B agonist, which can worsen some motor symptoms of catatonia<sup>51</sup>. Locked-in syndrome is associated with mutacism and immobility, except for vertical movement of the eyes and eyelashes through which the patient tries to communicate, in contrast to catatonic subjects who make no attempt to communicate. In differential diagnosis, it should also be considered that the aetiology of locked-in syndrome is related to lesions of the ventral pons and cerebral peduncles, and that patients do not respond to the lorazepam challenge test<sup>52</sup>.

Another condition to consider in differential diagnosis is malignant hyperthermia, which can be associated with malignant neuroleptic syndrome. Malignant hyperthermia is a rare, hereditary, autosomal dominant syndrome that manifests after surgical intervention as a severe reaction to some classes of drugs used for general anaesthesia, including halogenated gases and depolarizing neuromuscular blocking agents (in particular succinylcho-

**TABLE II.**

Differential diagnosis of catatonia (modified from Bhati et al., 2007)<sup>125</sup>. *Diagnosi differenziale della catatonia (da Bhati et al., 2007, mod.)*<sup>125</sup>.

Diagnosis	Characteristics similar to catatonia	Distinctive characteristics
Non-catatonic stupor	Immobility, mutism, absence of response to stimuli	Precipitating cause (e.g. cranial trauma, anoxia, drug intoxication)
Encephalopathy	Acute onset, bizarre behaviour, altered mental state	Generally associated with a somatic condition, reversible with treatment of the underlying medical condition
Stroke	Acute onset, can present with immobility, mutism and/or altered mental state	History of cerebrovascular disease, focal neurological signs, CT/MRI confirmation
Stiff man syndrome	Immobility, fixed posture	Rigidity and spasms caused by sudden stimuli
Parkinson's disease	Immobility, altered mental state, comorbid mood disorder	Symptoms improve with administration of dopamine agonists and anticholinergics, cogwheel rigidity
Locked-in syndrome	Immobility, mutism	Total paralysis with only vertical eye movement and only winking, associated with lesions of the pons and cerebral peduncles
Malignant hyperthermia	Immobility, mutism, altered mental state, instability of autonomic nervous system	Hyperthermia due to inhaled anaesthetics, autosomal dominant, diagnosed with muscle biopsy
Epileptic state	Immobility, mutism, altered mental state, bizarre behaviours	Epileptiform activity by EEG
Autism	Mutism, immobility, echolalia, echopraxia	Chronic with onset at infancy
Obsessive-compulsive disorder (Severe forms)	Echolalia/repeated echopraxia, comorbid mood disorder	Anxiety, knowledge of compulsive behaviour
Elective mutism	Mutism	Possible personality disorder or underlying paranoia

line). Diagnosis of malignant hyperthermia is confirmed by muscle biopsy.

The DSM-IV<sup>28</sup> recognizes the possibility that catatonia can manifest due to medical illnesses, such as aetiological infection and metabolic, endocrinologic or neurologic disorders that can cause delirium. Nonetheless, diagnosis of catatonia cannot be made if the disturbance presents only during the course of delirium. The correct distinction between the two syndromes has therapeutic implications as the administration of both typical and atypical antipsychotics, indicated in cases of delirium, can worsen catatonic symptoms.

The relationship between coma and catatonia has also been debated. In particular, it has been considered that catatonia can be included in the differential diagnosis of comatose patients and in the same way, stupor and loss of consciousness alone can represent the sole manifestations of catatonia<sup>53</sup>. In a recent case report, it was described that patients with alterations in consciousness similar to coma and without other catatonic features, with the exception of resistance to opening the eyes, respond to intravenous BDZ and ECT<sup>54</sup>.

Other conditions that can be confused with catatonia are non-psychiatric stupor, meningoencephalitis, stroke, non-convulsive epilepsy and autism. In these cases, treatment of the underlying condition normally resolves catatonic symptoms with generally good outcomes.

## Neurobiology

A renewed interest in catatonia has led to better understanding of neurobiological mechanisms of catatonia, even if current knowledge is still insufficient to formulate an exhaustive pathophysiological description of the disturbance.

## Neuroanatomical studies

Lesions in various regions of the brain have been associated with the onset of catatonic manifestations (including the frontal and parietal lobes, basal ganglia, pons, cerebellum and corpus callosum)<sup>55</sup>. However, subjects with focally-localized brain lesions in these areas rarely develop catatonic syndrome, and catatonic symptoms

are more frequently observed in association with neurological pathologies that diffusely involve the CNS. This would seem to substantiate the hypothesis<sup>43</sup> that catatonia is due to dysfunction of neural circuits with involvement of multiple structures rather than focal alterations.

### Neurochemical studies

Dysfunction of various neurotransmitter systems has been implicated in the pathogenesis of catatonic symptoms. Clinical experience on the efficacy of BDZ in treatment of catatonic patients would appear to provide evidence that the GABAergic system plays a role in catatonia. Important empirical evidence on the role of GABA dysfunction in catatonia was first shown by a neuroimaging study in 1999, in which Northoff et al.<sup>56</sup> analyzed the density of the GABA-A receptor in 10 catatonic patients, comparing the results to those in healthy subjects and non-catatonic psychiatric patients. It was revealed that the bond of the radioligand, iomazenil, with the GABA-A receptor was significantly lower in catatonic patients compared to either healthy control subjects or non-catatonic psychiatric patients. Moreover, the low density of the GABA-A receptor in the right lateral orbitofrontal cortex and in the right posterior parietal area correlated with the presence of both motor and affective symptoms. Neuroimaging studies have also shown that the administration of lorazepam was able to correct the anomalous activity of the right orbitofrontal cortex seen in catatonic patients when subjected to negative emotive stimuli<sup>57,58</sup>.

Information about the involvement of the GABAergic system in the pathogenesis of catatonia has also been obtained by studies on the normal functioning of the neurotransmitter. In fact, a central role has been attributed to GABA in tonic inhibition of neural circuits at the basis of innate and learned behaviours<sup>59</sup>. Among the variety of psychomotor catatonic manifestations, two apparently opposite symptoms such as immobility and aimless agitation, which can however also be described as primary modes of reflexive response to oppressive conditions of stress or danger, can be activated when innate, genetically-programmed neural circuits are freed of tonic inhibition<sup>36</sup>.

The hypothesis that the glutamatergic system is involved in catatonia<sup>60,61</sup> is based on clinical evidence of the efficacy of treatment with NMDA antagonists in cases resistant to lorazepam. In particular, it has been hypothesized that hyperactivity of the NMDA receptor can give rise to dysfunction of GABA-A, and thus the clinical efficacy of glutamatergic antagonists such as memantine, mediated by the indirect effect on the function of the gabaergic system; this would also explain the slower therapeutic action compared to BZD<sup>61</sup>. Northoff further suggested that hyperactivity of NMDA or excess glutamate could be the basis of dysfunction of the right parietal lobe, associated

with bizarre posture and other catatonic symptoms observed in patients with lesions of the right parietal lobe<sup>62</sup>. The role of dopamine in the pathogenesis of catatonia appears to be complex and difficult to define. According to Northoff, the increased levels of plasma and urinary levels of dopamine metabolites, such as homovanillic acid, seen in several studies in catatonic patients, suggests hyperactivity of the dopaminergic system<sup>63-65</sup>. However, evidence from other investigations seems to support the hypothesis that there is a deficit in the dopaminergic system<sup>66</sup>. Further controversy exists due to observations regarding the risk of development of symptoms similar to catatonia such as malignant neuroleptic syndrome in patients administered neuroleptic agents.

### Neuroimaging studies

A study on regional perfusion using SPECT showed that catatonic subjects had lower levels of blood flow in the right prefrontal lateral cortex and right posterior parietal region compared to healthy controls and non-catatonic psychiatric patients<sup>67</sup>. The reduced perfusion of the right posterior parietal cortex seems to correlate with the motor manifestations of catatonia. In particular, it was hypothesized that dysfunction in this cortical area is involved in posture defects of the catatonic patient. Functional neuroimaging studies, in fact, have demonstrated that subjects with catatonia present defects in termination of movements that, as for motor anosognosia, are related to the right parietal cortex due to its functional role in spatial coordination<sup>68,69</sup>.

Functional alterations in the medial orbitofrontal cortex have been correlated with the affective component of catatonic symptoms. Patients often refer that during the catatonic state they feel intense anxiety. In a neuroimaging study, exposure to negative emotive stimuli led to altered activity of the medial section of the orbitofrontal cortex; additional investigations showed that lorazepam was able to normalize these defects<sup>57,58</sup>. Lastly, the results of some studies have suggested that the characteristic behavioural manifestations of catatonia seem to correlate with dysfunction of the lateral section of the orbitofrontal cortex<sup>69</sup>.

### Genetic studies

The first indications on a possible role of a genetic component in the development of catatonia came from studies on families with periodic catatonia, a clinical syndrome defined as a diagnostic entity according to the Wernicke-Kleist-Leohnard school, although it is not recognized in the DSM. The aetiology of periodic catatonia is characterized by a significant hereditary component with autosomal dominant transmission. Studies on families<sup>70</sup> have reported that the risk of developing the

disease in first-degree relatives with periodic catatonia is around 27%, while for systematic catatonia (another form of catatonic schizophrenia according to the classification of Leohnard) the risk of developing the pathology in first-degree relatives of affected patients is about 5%. Later investigations by the same group suggested an association between the long arm of chromosome 15q15 and periodic catatonia<sup>71 72</sup>.

Additional evidence for a possible genetic component in catatonia emerge from the association of catatonia with Prader-Willi syndrome (PWS)<sup>73-77</sup>, caused by genetic defects on the proximal area of the long arm of chromosome 15q11-13, of paternal origin, and characterized by a wide variety of clinical manifestations that also includes catatonic-like psychomotor alterations<sup>78-80</sup>. In the chromosomal region associated with PWS, among the various loci that seem to influence the clinical phenotype, including the possibility to develop catatonic symptoms, genes coding for subunits of GABA-A have been localized (GABRB3, GABRA5 and GABRG3), which provides additional confirmation of the role of the gabaergic system in catatonia<sup>36</sup>. Other genetic loci, localized in or near the PWS region, have been associated with catatonic schizophrenia<sup>71</sup> and autistic disturbances<sup>81 82</sup> in independent studies.

## Treatment of catatonia

Correct management of catatonia requires, first of all, identification and treatment of any underlying medical conditions (internal, neurologic, toxicological) that are responsible for clinical symptoms. It is also necessary to take adequate measures to reduce morbidity and mortality associated with immobility and malnutrition, which are common in catatonia independent of the aetiology. Numerous case reports have described the complications frequently experienced by catatonic patients: pressure ulcers, deep vein thrombosis with pulmonary embolism, fever, infections, urine retention and aspiration pneumonia<sup>83-87</sup>. It is therefore fundamental at the earliest stages of the diagnostic-therapeutic course to assist the patient using an integrated multi-disciplinary specialist approach (psychiatric, internist, nutritionist, infectologist, in addition to paramedical support). The first measures to prevent medical complications are anticoagulant therapy with subcutaneous heparin, placement of a urinary catheter and adequate nursing care. Catatonic patients generally refuse oral feeding and can experience severe malnutrition and dehydration. It is therefore necessary to provide adequate parenteral and/or enteral hydration and alimentation through a nasogastric tube or PEG (percutaneous endoscopic gastrostomy).

Elective treatment of catatonic symptoms consists in intravenous BDZ and/or a cycle of ECT<sup>24 47 88 89</sup>. The most

commonly used treatment is intravenous lorazepam, with a reported remission rate of catatonic manifestations of about 70%; ECT is effective in around 85% of patients<sup>90</sup>. The therapeutic response to ECT is particularly favourable compared to lorazepam in cases of malignant catatonia (89% vs. 40%, respectively)<sup>90</sup>. The lorazepam challenge test can be especially useful. In this case, intravenous lorazepam (1 mg) is administered: if there are no changes in symptoms after 5 minutes, another intravenous dose of 1 mg is given<sup>24</sup>. A negative result, even if it does not exclude a future response to lorazepam (at doses higher than those normally used), suggests that ECT should be preferred<sup>91</sup>.

In literature, cases of catatonia that have been effectively treated with other therapies have been described. These include transcranial magnetic stimulation (TMS)<sup>92-94</sup>, NMDA receptor antagonists<sup>61 95 96</sup>, zolpidem<sup>97 98</sup>, anti-epileptics<sup>99 100</sup> and atypical antipsychotics<sup>101-104</sup>. The role of these latter agents remains controversial as some case reports have suggested that atypical antipsychotics can induce catatonic manifestations<sup>105 106</sup>. On the other hand, there are reports that malignant neuroleptic syndrome can be induced by each of the second-generation antipsychotics<sup>107-111</sup>.

## Benzodiazepine (BDZ) and zolpidem

It has been hypothesized that BDZ, due to their agonist action towards GABA-A, can correct deficit in GABAergic neurotransmission in the orbitofrontal cortex that have been associated with motor and affective catatonic symptoms<sup>88</sup>. Response to BDZ appears to be better in acute catatonic states, associated with stupor, especially if associated with mood disorders, while a significantly lower probability of success, about 20-30%, is seen in cases of schizophrenia with long-term symptoms, possibly due to neurobiologic heterogeneity underlying the acute and chronic forms of catatonia<sup>88 112</sup>.

Lorazepam is the most commonly used BDZ in treatment

**TABLE III.**

Lorazepam Challenge Test (modified from Dhossche and Watchel 2008)<sup>36</sup>. *Lorazepam Challenge Test (da Dhossche e Watchel 2008, mod.)*<sup>36</sup>.

### Lorazepam test

- 1 mg intravenous lorazepam
- If no response after 5 min, administer another 1 mg

### If positive

Treat with lorazepam increasing the dose up to 24 mg/day

### If negative

Bilateral electroconvulsive therapy

of catatonia<sup>24</sup>, although others such as diazepam<sup>113</sup>, oxazepam<sup>114</sup> and clonazepam<sup>115-117</sup> have been used with success. Even if there is no consensus on the posology of lorazepam treatment, many authors<sup>24 47 88 89</sup> have recommended an initial dose of 1-2 mg (parenteral) every 4-10 hours, with a subsequent increase in the following days until resolution of catatonic signs and symptoms, avoiding however excessive sedation and reducing the risk of aspiration pneumonia. The dosage of lorazepam can be increased up to 24 mg/day<sup>36</sup>; in addition, even in the case of initial response to treatment, it is necessary to continue therapy until complete clinical remission<sup>118 119</sup> to avoid the risk of recurrence. It has been shown<sup>120</sup> that patients with catatonic syndrome due to a general medical condition or affective disorder respond better to lorazepam compared to those with a diagnosis of schizophrenia. In some cases, in order to obtain complete remission of catatonic manifestations, it may be necessary to associate a cycle of ECT, as a synergistic effects between the two therapies has been reported<sup>121</sup>.

Zolpidem, a non-benzodiazepine agonist of the GABA-A receptor, has been utilized as an alternative to lorazepam<sup>97 98</sup>. Administration of zolpidem, characterized by a rapid onset of action (15-30 minutes), has also been proposed as a diagnostic test (Zolpidem Challenge Test) similar to lorazepam; however, its use in the treatment of catatonia is limited to a short duration, from 3-4 hours, and thus requires frequent administration.

### *Electroconvulsive therapy (ECT)*

The guidelines of the APA<sup>122</sup> indicate that ECT is the most effective treatment for catatonic syndrome, independently of its aetiology. Numerous studies and case reports have shown, in fact, that ECT has a high probability of success in treatment of all forms of catatonia, including malignant catatonia and malignant neuroleptic syndrome<sup>123</sup>. In particular, rapid treatment with ECT is unequivocally indicated in cases refractory to lorazepam<sup>124</sup>, the excited-confused subtype and the malignant forms of catatonia<sup>125</sup>.

In a recent retrospective assessment of 27 catatonic patients treated with ECT<sup>126</sup>, better response was associated with younger age, longer duration of seizure activity, more severe vegetative impairment (in particular higher fever) and early initiation of therapy. A delay in ECT, a diagnosis different other than mood disorder and previous long-term treatment with antipsychotics appeared to be associated with a negative response to therapy<sup>90 126</sup>.

Concerning the positioning of electrodes, evaluation of the seizure threshold, frequency and number of applications, there is still no standardized treatment protocol.

Bitemporal placement of electrodes with a brief impulse of initial current is generally recommended<sup>24</sup>. Even if rapid response to the first session of ECT is achieved, clinical evidence has shown that a cycle of 6 sessions should still be completed to prevent the risk of recurrence. In cases of malignant neuroleptic syndrome and malignant catatonia, the possibility of daily ECT should be considered during the first week of treatment<sup>126</sup> or until symptoms are resolved<sup>24</sup>. While this type of schedule can increase the probability of developing cognitive side effects (transitory temporal disorientation, short terms memory disorders), clinical assessment should be made considering the risk of morbidity and mortality associated with these forms of catatonia<sup>127-129</sup>. It has also been observed that cognitive collateral effects appear to be subjectively more pronounced than those revealed with standardized, objective neuropsychological evaluation<sup>130 131</sup>.

Rapid interruption of BZD before the first session of ECT can lead to exacerbation of catatonic manifestations<sup>132</sup>, and thus some authors have suggested that their administration should be continued before and during ECT<sup>133</sup>, taking advantage of a possible synergistic effect between the two therapies<sup>121</sup>. ECT poses an additional risk in patients who have been immobilized for a lengthy period of time: the transitory increase in kaliaemia, normally induced by ECT, can increase the possibility of a potentially lethal cardiac arrhythmia<sup>134</sup>. In this group of patients, it is also important to accurately exclude the presence of deep vein thromboses to avoid pulmonary embolism, a complication that has been reported in rare cases of patients undergoing ECT<sup>135-137</sup>. Adequate pharmacological prophylaxis, such as anticoagulants (low molecular weight heparin or warfarin), would nonetheless consent sufficiently safe treatment with ECT<sup>138 139</sup>. In any case, it is worthwhile to accurately evaluate the risk/benefit profile in patients at greater risk.

### *Repeated transcranial magnetic stimulation (rTMS)*

There have been some case reports that suggest rTMS may be effective in the treatment of catatonia<sup>92-94</sup>, and it has also been proposed in patients resistant to lorazepam<sup>93</sup>.

### *NMDA antagonists*

Antagonists of the glutamate N-methyl-D-aspartate receptor are a therapeutic alternative in the treatment of resistant catatonia or in the presence of contraindications to BZD and ECT<sup>140</sup>. Several case reports have suggested that amantadine and memantine are efficacious in the treatment of catatonia<sup>61 95 96</sup>. However, it should be considered that amantadine can have anticholinergic side effects, and can also increase dopaminergic tone<sup>60</sup>. In a recent review<sup>61</sup>, the effective use of amantadine (200-500



mg oral or parenteral) and memantine (5-20 mg oral) was described as adjunct therapy to standard BDZ/ECT treatment. The effect of NMDA antagonists is generally slower than BZD: the first signs of response are usually observed within 24 hours, although a more complete response occurs in about 3 weeks<sup>95</sup>.

### *Antiepileptics*

There is some evidence that antiepileptics such as topiramate<sup>100</sup> and valproic acid<sup>99</sup> can be used in cases that are resistant to BZD. Their efficacy can be ascribed to the GABA-ergic properties of anticonvulsants.

### *Atypical antipsychotics*

The role of atypical antipsychotics in the treatment of catatonia remains controversial. These drugs, in addition to blocking D2 dopamine receptors, have weak GABAergic action and 5-HT<sub>2</sub> serotonergic antagonism that can stimulate the release of dopamine in the prefrontal cortex, thereby improving catatonic manifestations<sup>141</sup>. Even if many case reports have described the efficacy of atypical antipsychotics in catatonic schizophrenia and in forms with prevalent psychotic symptoms, other studies indicate that the same drugs can induce catatonic syndrome<sup>106</sup>. Considering that all antipsychotics, including atypicals, can cause malignant neuroleptic syndrome<sup>107-111</sup> and that catatonic patients have an elevated risk of developing malignant neuroleptic syndrome<sup>142</sup>, some authors have sustained that the use of atypical antipsychotics is contraindicated in treatment of catatonia<sup>24</sup>.

In the literature, however, there is recent evidence on the efficacy of olanzapine, risperidone, aripiprazole and clozapine<sup>101-104,141</sup> in improving catatonic symptoms associated with psychotic disturbances. In a recent review<sup>103</sup>, it was hypothesized that the efficacy of atypical antipsychotics in this group of patients was due to a direct effect on the psychotic disturbance at the basis of the catatonic manifestation, which regressed after correct treatment of the underlying pathology. Accordingly, atypical antipsychotics may be indicated only in the forms of catatonia due to psychotic disorders, and not in the forms due to a general medical condition.

### **Conclusions**

The increased knowledge in recent years on the psychopathology and neurobiology of catatonia has led to a renewed interest of clinicians and researchers for the disturbance, despite persistent problems in diagnosis and nosology. The persistence of these uncertainties has clinical implications: in many studies carried out in a hospital setting, it has been reported that the fre-

quency of catatonia has been underestimated, and is higher when diagnosed by experts using standardized assessment tools. The most common diagnostic error, in fact, is "omission": the predominant clinical opinion that all catatonic patients are immobile, stuporous or mute does not prompt further evaluation of other signs/symptoms suggestive of catatonia, even if less typical. Moreover, the current diagnostic classification systems (DSM, ICD) have been widely criticized. Clinical evidence and epidemiology regarding the most frequent catatonic manifestations in bipolar patients provides support to disrupt the link between schizophrenia and catatonia, and to recognize the need for greater diagnostic autonomy. It has been suggested that symptomatic criteria should be re-examined with greater attention to the type, number and severity of the signs/symptoms needed for diagnosis.

A correct clinical approach to the catatonic patient requires recognition of the psychopathological manifestations underlying the condition, whether psychiatric or medical. An appropriate diagnostic approach thus entails precise anamnesis followed by accurate, objective psychiatric, general and neurologic examination and a battery of laboratory and instrumental tests. Early diagnosis is key for rapid and efficacious therapeutic intervention, thereby reducing morbidity and mortality given the high frequency of medical complications (hydroelectrolytic disorders, pressure ulcers, rhabdomyolysis and acute renal insufficiency, thromboembolic disorders, acute urinary retention, systemic infection and aspiration pneumonia). An integrated multidisciplinary approach is important for both diagnosis and treatment of the catatonic patient, and should involve psychiatrists, internists, nutritionists and infectologists, in addition to adequate nursing care.

For specific treatment of catatonic symptoms, therapy with intravenous BDZ and/or ECT should be considered elective. In the first instance, intravenous lorazepam should be initiated, with a reported percentage of remission of catatonic manifestations in about 70% of cases, while ECT is effective in around 85% of patients. In the case of no or partial response to BDZ and in the malignant catatonic forms, ECT is pivotal for the survival of these patients who are at a high risk of death. Despite clear evidence on the prompt treatment with ECT, not all therapeutic algorithms include the technique. Thus, many patients are deprived of the opportunity of effective treatment and are exposed not only to an increased risk of potentially fatal somatic complications, but also to inadequate treatment, for example with neuroleptics, which can aggravate the symptoms of catatonia and facilitate its evolution into malignant forms.

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