ABSTRACT
Catatonia is a complex neuropsychiatric syndrome characterised by a broad range of motor, speech and behavioural abnormalities. ‘Waxy flexibility’, ‘posturing’ and ‘catalepsy’ are among the well-recognised motor abnormalities seen in catatonia. However, there are many other motor abnormalities associated with catatonia. Recognition of the full spectrum of the phenomenology is critical for an accurate diagnosis. Although controlled trials are lacking benzodiazepines are considered first-line therapy and N-Methyl-D-aspartate receptor antagonists also appears to be effective. Electroconvulsive therapy is used in those patients who are resistant to medical therapy. An underlying cause of the catatonia should be identified and treated to ensure early and complete resolution of symptoms.

INTRODUCTION
Catatonia is a complex neuropsychiatric syndrome characterised by a broad range of motor, speech and behavioural abnormalities. ‘Waxy flexibility’, ‘posturing’ and ‘catalepsy’ are among the well-recognised motor abnormalities associated with catatonia. However, there is a wide spectrum of speech and other neurological abnormalities seen in this condition. This article attempts to summaries the clinical features of catatonia; discuss some diagnostic challenges, possible mechanisms and available treatment options in this poorly understood condition.

Catatonia was first described by German psycho-pathologist Karl Kahlbaum in Die Katatonie oder das Spannungsirresein in 1874 as a motor syndrome in patients with behavioural disorders.1 2 He considered catatonia as a distinct clinical entity with progressive symptoms. Catatonia was subsequently classified by psychopathologists Kraepelin and Bleuler as ‘dementia praecox’ (premature dementia), a condition which was later classified as schizophrenia.3 The uncertainty about its definition was partly responsible for the long-standing neglect of catatonia in clinical and scientific literature and for its frequent underdiagnosis.4 It is clear that catatonia is no longer limited to schizophrenia, and that it can be seen in the setting of a variety of other conditions such as psychiatric disorders other than schizophrenia, medical, neurological and surgical conditions, as well as in the setting of certain drugs and toxins.5 6 7

The frequency of catatonia in acute psychiatric admissions is approximately 10%, but estimates range from 5% to 20% based on diagnostic criteria used in prospective studies conducted during 1–12 months of observation at psychiatric units.4 8 9 Other surveys have reported a prevalence ranging between 7.6% and 38% among all psychiatric patients.10 The percentage of catatonia due to a general medical condition is reported to range from 20% to 39%.11 Catatonia may be subtle and overlooked, which may account for reports suggesting a declining incidence. People with bipolar disorders probably constitute the largest subgroup of catatonic patients.5 10 12 In a minority of cases, no cause is found and the current prevalence of idiopathic catatonia is unknown.

Owing to the wide range of underlying diagnoses, patients with catatonia may present as a medical or psychiatric emergency,13 or develop symptoms during hospitalisation, such as in the intensive care unit (ICU), which can be challenging from a diagnostic standpoint.14 15 Catatonia usually presents acutely but may present insidiously, and can be transient or chronic, and last for weeks, months and even years.15 Catatonic patients are at risk for severe complications such as pneumonia, decubitis ulcers, malnutrition, dehydration, contractures and thrombosis and delays in diagnosis and management are associated with increased morbidity.11 Although it may become life-threatening,16 catatonia has an excellent prognosis if recognised and treated early.

DIAGNOSTIC CRITERIA AND RATING SCALES
The diagnosis of catatonia is based on clinical observations. The revised diagnostic criteria were published in the fifth Diagnostic and Statistical Manual of Mental Disorders (DSM-V) in 2013.17 While the DSM-IV used different sets of criteria for diagnosis of catatonia in schizophrenia and primary mood disorders versus neurological/medical conditions, the revised DSM-V criteria can be applied across all of the different clinical settings. According to DSM-V criteria, to make a diagnosis of catatonia one has to have a minimum of 3 of the following 12 clinical features, either observed or elicited during examination: (1) mutism, (2) stupor, (3) catalepsy, (4) waxy flexibility, (5) agitation, (6) negativism, (7) posturing, (8) mannerisms, (9) stereotypes, (10) grimacing, (11) echolalia, or (12) echopraxia.17 The criteria seem rather arbitrary, and the list of associated features highlights the clinical heterogeneity of this neuropsychiatric disorder.

Several rating scales have been developed for the assessment of catatonia.18 The Bush-Francis Catatonia Rating Scale (BFCRS) is the most widely used scale. This includes 23 items and up to 30 signs. Some of the signs (described below) are not listed in the DSM-V criteria, such as excitement, staring, rigidity, withdrawal, automatic obedience, impulsivity, ambivalence, grasp reflex, verbigeration, mitgiene, autonomic abnormality, combativeness and perseveration.
Movement disorders

There is also a screening version of BFCRS known as Bush-Francis Catatonia Rating Screening Instrument (BFCSI), which contains 14 most common catatonic signs (excitement, immobility/stupor, mutism, staring gaze, posturing/catalepsy, grimacing, echopraxia/echolalia, stereotypes, mannerisms, verbigeration, rigidity, negativism, waxy flexibility and withdrawal). If two or more of the BFCSI signs are present for 24 h or longer, catatonia should be considered as a possible diagnosis. To avoid overdiagnosis, signs such as ‘impulsiveness’ and ‘combativeness’ were excluded from the screening instrument.

Items from the BFCRS are scored on a 0–3 point scale, whereas items from the BFCSI are scored as ‘absent’ or ‘present’. Another catatonia rating scale, the Modified Rogers Scale (MRS), has also been validated.

The primary aim of this review is to draw attention to the broad spectrum of phenomenology associated with catatonia by highlighting the most characteristic clinical features and provide illustrative videos.

**CLINICAL FEATURES**

The catatonic syndrome is seen in two principal forms: hypokinetic (withdrawn type) or hyperkinetic (excited type). Some patients, however, may display features of both types during the course of the illness. Patients with hypokinetic or withdrawn type of catatonia, typically appear awake and watchful, but with minimal spontaneous speech and movement. It is commonly associated with mutism, stupor, negativism, obsessive slowness and posturing. Hyperkinetic or excited type catatonia is characterised by agitation, combativeness, disorganised overproductive speech (verbigeration), stereotypes, grimacing and echophenomena. There is no difference in the expression of catatonic symptoms based on the underlying cause, whether it is psychiatric or medical.

Mutism, manifested by minimal or no verbal communication, is probably the most frequently observed sign of catatonia in the acute hospital setting, but the diagnosis is not applicable if there is evidence of aphasia. Although typically associated with hypokinetic catatonia, mutism can also accompany a hyperkinetic movement disorder. Catatonic stupor is manifested by patient’s absence of movement or other reaction to any stimulus while awake. Patient is typically extremely hypoactive, immobile and minimally responsive to stimuli including pain. Stupor can occur independently or in combination with mutism. Differentiating sedation from catatonic stupor can be challenging, but the latter is usually associated with normal awake EEG.

Patients with catatonia can go through periods of agitation during which they can injure themselves or others. These periods of agitation may be associated with autonomic instability manifested by hyperthermia, tachycardia and hypertension. Individuals in this excited state may display extreme hyperactivity with constant motor unrest and purposeless motor activity, and may eventually collapse from exhaustion.

One of the most recognisable clinical features of catatonia is posturing which refers to spontaneous and active maintenance of a posture against gravity (see online supplementary videos 1–3). Waxy flexibility refers the characteristic motor sign of catatonia elicited by the examiner who manipulates the body or extremities to assume certain postures which the patient can maintain for a prolonged period of time (see online supplementary videos 1–3). There may be an initial resistance which is soon followed by slow release, as if bending a warm candle hence the term waxy flexibility. Catalepsy refers to the maintenance of fixed postures in the sitting or standing position for prolong periods of time with minimal movement regardless of external stimuli, including pain (see online supplementary videos 1–3). The positions assumed by the patient may be unusual and appear uncomfortable to the observer. The patients can adopt statuesque postures with minimal movement lasting for several hours without any apparent fatigue or discomfort. Other examples include twisting of the body, standing on one leg like a stork, holding one arm outstretched for a long time, and squatting with extension of arms. Another dramatic posturing is the ‘psychological pillow’ where the patient lies in bed with the head and shoulder raised as if there is an imaginary pillow. The head is raised a few inches above the bed surface which is maintained for prolonged period of time.

In negativity there is increasing resistance to passive manipulation of the limbs which is known as gegenhalten or paratonia. When eliciting the phenomenon of gegenhalten, it appears to the examiner as if the patient is deliberately opposing the passive movement. Social negativism may include turning away when addressed, refusing to open the eyes and closing the mouth when offered food or liquids.

Stereotypy is a common movement disorder seen in catatonia (see online supplementary videos 1 and 3) which is defined as involuntary, coordinated, patterned, rhythmic, seemingly purposeless movement or utterance performed repeatedly over time. Some of the motor stereotypies that are seen in catatonia include body rocking, shoulder shrugging, hand waving, opening eye wide and then squeezing them shut, nose wrinkling, and repetitive mouth and jaw movements. Stereotypies may be accompanied by self-injurious behaviour, such as head banging, self-hitting, punching, biting, kicking and scratching directed at any body surface. In addition to motor stereotypies patients with catatonia can have phonic stereotypies which include repetitive, apparently meaningless utterances, such as sniffing, clicking, snorting, moaning and other meaningless sounds, similar to phonic tics (see online supplementary video 3). These patients can also have facial grimacing and exaggerated facial expressions (see online supplementary videos 1–3).

Mannerisms is another observed clinical feature which is characterised by repetitive, idiosyncratic movements or gestures that are unique to the individual such as using hands when talking. Echophenomena include echopraxia and echolalia. Echopraxia refers to mimicry of examiner’s movements or imitation of other person’s movements or gestures. Echolalia means nearly simultaneous repetition of words or phrases spoken by others.

Catatonic excitement refers to extreme hyperactivity with constant motor restlessness which is apparently non-purposeful. Although similar, catatonic excitement is different from akathisia in that it does not appear to be associated with a feeling of restlessness and an uncomfortable sensation or an urge to move. Patients with catatonia can have staring gaze where the eyes are focused at a distance with little eye contact (see online supplementary video 1). There is little or no visual scanning of environment and there is decreased blinking.

Rigidity consists of a stiff position which the patient attempts to maintain despite efforts to be moved. Catatonic rigidity is not typically accompanied by cogwheeling or tremor, which helps to differentiate from parkinsonian rigidity. The state of withdrawal, also interpreted as ‘social negativism’, is a condition manifested by the patient’s refusal to eat, drink or make eye contact.

Some patients with catatonia can also demonstrate exaggerated cooperation for example, automatically obeying every instruction of the examiner which is known as automatic obedience (see online supplementary video 2). Automatic obedience can also mean the performance of tasks at the command of the examiner even though the tasks are inappropriate or dangerous such as by...
reaching into pocket and state: ‘stick out your tongue, I want to
prick it with a pin’.19 Mitmachen and Mitgehen are two forms of
automatic obedience. In Mitmachen the body of the patient can
be put into any posture, even if the patient is given instructions
to resist. Mitgehen is an extreme form of automatic obedience in
which the examiner is able to move the patient’s body with the
slightest touch, but unlike waxy flexibility the body part immedi-
ately returns to the original position. This can be tested by asking
the patient to extend their arm and then place the examiners
finger beneath the hand and try to raise the arm slowly using
gentle push upwards after stating: ‘Do NOT let me raise your arm’.
When the examiner’s finger retracts the patient’s hand
moves downward in an attempt to keep in physical contact with
the examiner’s finger.20 Catatonic patients can exhibit a great
deal of impulsivity manifested by suddenly engaging in an
inappropriate behaviour such as running down hallway, scream-
ing or taking off clothes without any provocation. Ambitendency
refers to a state of indecisive or hesitant movement (see online
supplementary video 2). This could manifest as alternating
cooperation and then resistance in following examiner’s instruc-
tions. One can also elicit the grasp reflex, in which, the patient
forcibly and repeatedly grasps the examiner’s hand when offered.22
Verbigeration is the frequent repetition of meaningless
words and phrases (see online supplementary video 3). Motor
perseveration is manifested, for example, by persistence of a par-
ticular movement long after the original command or intent.
Speech perseveration is exemplified by repeatedly returning to the
same topic after it has lost its initial relevance. Catatonic combat-
iveness usually occurs in an undirected manner, with no, or only
a facile explanation afterwards. Autonomic abnormalities include
changes in temperature, blood pressure, heart and respiratory
rate, and diaphoresis.

SUBTYPES OF CATATONIA
Malignant catatonia and periodic catatonia are two major sub-
types of catatonia.23 Malignant catatonia is characterised by
sudden development of intense excitement, delirium, high fever,
hypertension, catalepsy, mutism, rigidity, stereotypies and pos-
turing.23 Because of accompanying marked autonomic instabil-
ity and hyperthermia this form of catatonia is potentially
deadly.24 The neuroleptic malignant syndrome (NMS) is consid-
ered by some as a medication-induced variant of (malignant)
catatonia.25 Numerous medical conditions leading to malignant
catatonia have been reported. Although randomised clinical
trials are lacking, electroconvulsive therapy (ECT) is effective in
the treatment of malignant catatonia.26
Periodic catatonia has a rapid onset and consists of brief,
recurrent hypokinetic or hyperkinetic abnormalities with epis-
odes lasting 4–10 days which recur over a period of weeks to
years.27 Patients are generally asymmetrical between episodes,
but may exhibit inter-ictal facial grimacing, stereotypies and
negativism, particularly late in the course of the illness.28
Periodic catatonia is rare and appears to segregate within families
in an autosomal dominant pattern. There is evidence for
linkage to long arm of chromosome 15q15 which was replicated in
two independent genome-wide linkage scans based on over
12 multigenerational pedigrees.28 Overall, periodic catatonia is
considered to have a better prognosis than the malignant form
of catatonia.

DIAGNOSTIC CHALLENGES
The definition of catatonia both historically as well as in the
DSM-V criteria is very broad. Although only 12 clinical features
are included in the DSM-V diagnostic criteria, Kahlbaum in his
original description listed 17 signs, and other authors have
extended this list, some identifying 40 or more phenomena.17 29
The various phenomenological features are defined differently by
different authors creating ambiguity and lack of clear definition.
The DSM-V list of the various motor and speech abnormalities is
too vague and it does not capture the true clinical picture of cata-
tonia. Very opposing (eg, immobility vs excessive motor activity,
mutism vs echolalia) or closely similar (eg, posturing vs catalepsy)
motor and speech abnormalities are listed in parallel and are
given equal diagnostic weight. The published diagnostic criteria
and rating scales do not provide sufficient guidance as to how to
reconcile between different combinations of clinical findings. For
example, facial grimacing, phonic stereotypies, echopraxia and
echolalia can be seen not only in patients with catatonia but also
in Tourette syndrome, neuroacanthocytosis, autism and other
neurological disorders. This overlap with various disorders indi-
cates that catatonia is a symptom or a syndrome with different
aetiologies rather than a single clinical entity.

Several studies have examined the discriminative value of
various catatonia symptoms. One study found that 9 of the 12
items that are included in DSM-V possess very high discrimina-
tive value for catatonia, but noted that three items (agitation,
stereotypies and mannerisms) had a weak correlation with cata-
tonia. A subsequent study27 found that stereotypies and manner-
isms also to have high discriminating value for catatonia.

The lack of single unifying phenotype or a set of highly sensi-
tive and specific diagnostic criteria makes the diagnosis of cata-
tonia challenging for the clinician, even experienced movement
disorder specialist.30 The diagnosis may be especially diffi-
th in the acute inpatient setting or in the ICU.14 Differentiating cata-
tonia from delirium is especially important, as catatonia is
treated with benzodiazepines whereas delirium may be exacer-
bated by benzodiazepine. The lack of motor and speech abnor-
malities in delirium helps to differentiate it from catatonia.
On the other hand serotonin syndrome, central nervous system
infection, autoimmune encephalopathy or some other medical
and neurological conditions encountered in the acute hospital
setting may overlap with signs of catatonia, and in some cases
necessitate concomitant treatment for both catatonia and the
underlying condition. In the absence of any clinical, physio-
logical, imaging or other diagnostic markers that are reasonably
sensitive and specific in defining catatonia, the diagnosis rests on
the clinical history and observation of characteristic signs.

PATHOPHYSIOLOGY
The specific pathophysiological mechanisms underlying catato-
nia are not well understood. Neurochemical studies have
focused on the inhibitory neurotransmitter γ-aminobutyric acid
(GABA) A. The role of GABA in catatonia is supported by the
observation of a dramatic response to treatment with benzodia-
zepines and zolpidem, both GABA A agonists, in patients with
catatonia.12 11 13 The GABAergic hypothesis is also supported by
the observation that ECT, which is used in drug resistant
catatonia or as a first-line therapy in malignant catatonia, also
enhances GABA function. Furthermore, the single photon emis-
tion tomography (SPECT) with iodine-123-iodomazenil showed
significantly lower iomazenil binding, an index of benzodiazep-
ine GABA-A receptor density, in the left sensorimotor cortex of
patients with akinetic catatonia compared to psychiatric and
healthy controls.34

There are case series and case reports showing the effectiveness
of N-Methyl-D-aspartate (NMDA)-antagonists35 in catatonia,
suggesting that glutamate hyperactivity might be related to
catatonic symptoms.36 It has been postulated that NMDA

---

Movement disorders

hyperactivity causes dysregulation of GABA-A function and that NMDA antagonists can indirectly restore GABA-A function in the frontal lobes, though more slowly than GABA-A agonists.

In addition, there is an increased familial transmission in first degree relatives, particularly for periodic catatonia (27%) versus general catatonia (5%) suggesting a genetic link. Several other pathophysiological models of catatonia have been proposed notably motor circuitry dysfunction and a link with epilepsy, endocrine and immune dysfunction but there are insufficient data to substantiate these hypotheses and further studies are needed.

AETIOLOGY

Catatonia can occur in the setting of number of aetiologies (table 1). The disorder is increasingly recognised as a comorbid syndrome of autism, autism spectrum disorders and patients with intellectual disability. In adolescents with autism the prevalence of catatonia is between 12% and 17%. It is important for clinicians to be aware of the possibility of catatonia when investigating reasons for the deterioration in skills and behaviour occurring in adolescents and adults with autistic spectrum disorders.

Catatonia is also recognised in the setting of various autoimmune disorders including anti-NMDAR encephalitis, that is typically found in young women with ovarian teratomas, but can be also encountered in men and in adults aged 45 years and above. The encephalitis is less severe in patients aged ≥45 years than in young adults, but the outcome is poorer in older patients, partly because of delays in diagnosis and treatment. Anti-NMDAR encephalitis typically begins with a prodrome of a febrile, flu-like illness, which is followed by a spectrum of neuropsychiatric sequelae such as behavioural and cognition symptoms, memory deficit, psychosis, speech disorder, seizures, dysautonemia and hypoventilation. Movement disorders associated with anti-NMDAR encephalitis include chorea, athetosis, stereotypies (particularly involving the orofacial region), dystonia, ataxia, facial and limb myorhythmia, and opisthotonus. The exact prevalence of catatonia in anti-NMDAR encephalitis is unknown but many patients exhibit physical manifestations consistent with catatonia which may include mutism, facial and limb stereotypies, facial grimacing, staring episodes, waxy flexibility and posturing among others. Treatment of this condition is mainly focused on tumour resection and immunotherapy. However, when associated with catatonia it can be underdiagnosed and inadequately treated. A treatment algorithm which includes management of catatonia was recently published. Other autoimmune encephalopathies such as systemic lupus erythematosus and antiphospholipid syndrome as well as infectious encephalitis can also present with catatonia (table 1).

TREATMENT

Before discussing various treatment strategies in catatonia it is important to note that many recommended treatments have not been subjected to rigorous, controlled trials. Furthermore, the currently available rating scales, such used to monitor response to treatment, as the BFBCRS, lack the sensitivity necessary to measure minimal clinically meaningful improvements. One of the challenges in using rating scales is that catatonic symptoms fluctuate over time and may require longer periods of observation to obtain the full clinical picture. While the patient is being treated for catatonia it is also very important that an underlying aetiological cause is searched and treated without delay.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Underlying causes of catatonia (other than schizophrenia and mood disorder)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Typhoid fever</td>
</tr>
<tr>
<td></td>
<td>Neurocysticercosis</td>
</tr>
<tr>
<td></td>
<td>Prion disease</td>
</tr>
<tr>
<td></td>
<td>Viral encephalitis</td>
</tr>
<tr>
<td></td>
<td>Subacute sclerosing pan encephalitis</td>
</tr>
<tr>
<td></td>
<td>Neurophilis</td>
</tr>
<tr>
<td></td>
<td>Autoimmune and inflammatory</td>
</tr>
<tr>
<td></td>
<td>Systemic lupus erythematosus or antiphospholipid syndrome*</td>
</tr>
<tr>
<td></td>
<td>Anti-NMDAR encephalitis*</td>
</tr>
<tr>
<td></td>
<td>Paraneoplastic encephalitis</td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular</td>
</tr>
<tr>
<td></td>
<td>Takotsubo cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td>Renal failure in dementia with Lewy body disease</td>
</tr>
<tr>
<td></td>
<td>Metabolic</td>
</tr>
<tr>
<td></td>
<td>Wilson’s disease</td>
</tr>
<tr>
<td></td>
<td>Hyponatraemia or hypernatraemia</td>
</tr>
<tr>
<td></td>
<td>Glucose-ephsophate deficiency</td>
</tr>
<tr>
<td></td>
<td>Neurodegenerative disorders</td>
</tr>
<tr>
<td></td>
<td>Westphal variant of Huntington’s disease</td>
</tr>
<tr>
<td></td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td></td>
<td>Familial frontotemporal dementia</td>
</tr>
<tr>
<td></td>
<td>CNS</td>
</tr>
<tr>
<td></td>
<td>Posterior reversible encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Subdural hematoma</td>
</tr>
<tr>
<td></td>
<td>Pontine and extrapontine myelolysis</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td></td>
<td>Hematology</td>
</tr>
<tr>
<td></td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td></td>
<td>Thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td></td>
<td>Psychiatric</td>
</tr>
<tr>
<td></td>
<td>Autism*</td>
</tr>
<tr>
<td></td>
<td>Alcohol withdrawal</td>
</tr>
<tr>
<td></td>
<td>Medications</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine-associated hyponatraemia</td>
</tr>
<tr>
<td></td>
<td>Pegylated interferon-2b and ribavirin for hepatitis C</td>
</tr>
<tr>
<td></td>
<td>Lorazepam withdrawal</td>
</tr>
<tr>
<td></td>
<td>Paliperidone palmitate</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Zolpidem withdrawal</td>
</tr>
<tr>
<td></td>
<td>Temazepam withdrawal</td>
</tr>
<tr>
<td></td>
<td>Quinolones</td>
</tr>
<tr>
<td></td>
<td>Clozapine withdrawal*</td>
</tr>
<tr>
<td></td>
<td>Manganese neurotoxicity</td>
</tr>
<tr>
<td></td>
<td>Clozapine benzodiazepines withdrawal</td>
</tr>
<tr>
<td></td>
<td>Ziprasidone</td>
</tr>
<tr>
<td></td>
<td>Lithium toxicity</td>
</tr>
<tr>
<td></td>
<td>Tramadol and meperidine</td>
</tr>
<tr>
<td></td>
<td>Azithromycin</td>
</tr>
<tr>
<td></td>
<td>Levetiracetam</td>
</tr>
<tr>
<td></td>
<td>Efavirenz</td>
</tr>
<tr>
<td>Surgical causes</td>
<td>Liver or kidney transplantation*</td>
</tr>
<tr>
<td></td>
<td>Renal transplant</td>
</tr>
<tr>
<td></td>
<td>Temporal lobectomy</td>
</tr>
</tbody>
</table>

Continued
Benzodiazepines are widely considered the first-line treatment for catatonia, which can provide a rapid and dramatic improvement in symptoms (table 2).

There are no double-blind randomised controlled trials documenting the efficacy of benzodiazepine in catatonia. The evidence comes from a number of case series and case reports which document a response rate of 60–80%. Among the benzodiazepines, lorazepam is often selected as the drug of choice, which can be administered orally or parenterally. An open trial involving 13 acute catatonic patients, 2 mg of intravenous lorazepam reduced catatonia scores on the BFCS by 60% within 10 min. The typical starting daily dose is 3 mg/day which can be titrated up as necessary. Dosages of 20–30 mg/day in divided doses are occasionally necessary and the response can be quite dramatic. Within 3 h of receiving lorazepam 1–3 mg sublingually or intramuscularly, the vast majority of catatonic patients, who have been immobile, mute, withdrawn and refusing to eat or drink, enjoy complete release from their symptoms. Once the troublesome symptoms are controlled the effective dose of lorazepam that achieved a complete resolution of the catatonic signs should be maintained for several days until the underlying cause of catatonia is found and appropriately treated.

Intravenous test dose of lorazepam (1–2 mg) can also be used as a diagnostic test for catatonia. The reduction or the full relief of catatonia symptoms within a few minutes is diagnostic. Absence of the response, however, does not rule out the diagnosis of catatonia as approximately 20% of participants do not respond to such a challenge. While benzodiazepines are safe medications when used in the short term, several issues should be kept in mind during treatment such as sedation and the risk of hypoventilation in patients with obesity, or those with obstructive sleep apnoea, falls in elderly patients or those with balance problems.

Zolpidem (10 mg/day), a non-benzodiazepine GABA agonist of the imidazopyridine class that potentiates GABA by binding to GABA-A receptors at the same location as benzodiazepines, was reported to improve catatonic symptoms. Zolpidem is increasingly recognised as another pharmacological treatment option for catatonia and is even suggested as an effective and prompt pharmacological test for catatonia.

NMDA receptor antagonists have been shown to be effective in catatonia based on case series and multiple care reports. Amantadine and memantine which exert NMDA receptor antagonist effect are reported to be effective in catatonia. Amantadine doses from 100 up to 400 mg/day have been used and memantine 10 mg/day up to 20 mg/day have been shown to be effective. Memantine, unlike amantadine, has no significant effects on dopamine neurotransmission. Other medications, including topiramate, amobarbital, tetrabenazine, corticosteroids and rituximab have all been used as either primary or adjunctive treatments for catatonia with variable and poorly documented success (table 2).

Neuroleptics, particularly typical antipsychotics, are generally not recommended as treatment for acute catatonia, even for catatonic episodes due to schizophrenia. Indeed, there is some evidence that classic antipsychotics may precipitate malignant catatonia and NMS, underscoring again the importance of correctly diagnosing the disorder. This is an important issue in treating patients presenting with psychosis and catatonia. The literature on the use of atypical antipsychotics in catatonia consists of case reports and retrospective studies. One retrospective study found that clozapine stood out uniquely as an antipsychotic agent that was uniformly beneficial. There are several case reports showing benefit with olanzapine. Quetiapine has also been used in patients with acute catatonic schizophrenia with good outcome as well as risperidone.

ECT has long been known to be particularly effective for catatonia, regardless of the aetiology. Although there is lack of data from randomised clinical trials supporting its efficacy and safety, ECT has been shown to be effective in cases of medication refractory catatonia. A retrospective study involving 27 patients (85% were resistant to medical therapy), 59% improved with ECT, especially younger patients with autonomic dysregulation. Authors concluded that daily administration of ECT may be more effective, whereas longer duration of seizure activity at the final ECT session was related to better response to ECT. In order to provide more lasting improvement, daily treatments for 2–5 days may be required. There are other studies showing effectiveness of ECT to range from 85% to 93% in catatonia patients. In a retrospective study involving 63 patients with catatonia, the fast responders were the ones with a shorter duration of illness illustrating the fact that early detection of illness plays a crucial role in treatment response. In the same study, participants with waxy flexibility and gegenhalten showed a faster response rate, while participants with echophenomena showed a slower response. Although there are no absolute contraindications to ECT, this treatment intervention should not be considered first-line therapy except for life-threatening malignant catatonia. Mortality in malignant catatonia may increase if ECT is not begun within 5 days of symptom onset. Some cases of catatonia may require maintenance ECT to prevent recurrent episodes. Although controlled trials are lacking the effectiveness of benzodiazepines and ECT in anti-NMDAR encephalitis and other paraneoplastic encephalitis has been well documented.

Fast repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex was also reported to be effective in two case reports (10 Hz). Although the long-term outcome of catatonia has not been rigorously studied, catatonia appears to have a generally favourable prognosis.

**SUMMARY**

Catatonia is a neuropsychiatric disorder that encompasses a wide range of movement disorders. As there is no catatonia-specific biomarker, recognition of the characteristic clinical features is critical to the diagnosis. Catatonia is no longer considered a subtype of schizophrenia and can be seen in the setting of other psychiatric disorders, general medical, neurological and surgical conditions, as well as drugs and toxic substances. The underlying pathophysiological mechanisms are still not clear and a ‘GABA hypothesis’ has been proposed. Most patients respond well to benzodiazepines or ECT and prompt treatment in the early phases of catatonia is important for the best outcome. The exact prevalence of idiopathic catatonia is unknown. However it is important that an underlying cause of the catatonia is identified.
and treated to ensure early and complete resolution of symptoms. Further studies are clearly needed to help better characterise the clinical features and to improve our understanding of the pathophysiology of this unique condition with the aim to develop pathogenesis-targeted preventive therapies and better symptom-atric treatments.

Acknowledgements The authors would like to thank Dr Amber Stocco for providing online supplementary videos 2 and 3 that accompany this manuscript.

Contributors SW involved in the manuscript preparation, writing of the first draft. JJ involved in the manuscript review and critique.

Competing interests JJ has no competing interests but during the past 2 years received: Current Research and Center of Excellence Grants: Adamas Pharmaceuticals, Inc (amantadine); Allergan, Inc (botulinum toxin); Auspex Pharmaceuticals, Inc (SD809); CHDI Foundation; GE Healthcare; Great Lakes NeuroTechnologies; Huntington’s Disease Society of America; Huntington Study Group; Ipsen Limited; Kyowa Haako Kirin Pharma, Inc (istradefylline); Lundbeck Inc (tetrabenazine); Medtronic; Merz Pharmaceuticals; Michael J Fox Foundation for Parkinson Research; National Institutes of Health; National Parkinson Foundation; Omeros Corporation (OMSB24); Parkinson Study Group; Pharma Two B; Prothena Biosciences Inc (PRX002); Psyadon Pharmaceuticals (ecopipam), Inc; St. Jude Medical; Teva Pharmaceutical Industries Ltd. Royalties: Cambridge; Elsevier; Future Science Group; Hodder Arnold; Lippincott Williams and Wilkins; Wiley-Blackwell. During the past 2 years JJ has served on the following editorial boards and foundation advisory boards: Editorial boards: Medlink: Neurology; Expert Review of Neurotherapeutics; Neurology in Clinical Practice; The Botulinum Journal; PeerJ; Therapeutic Advances in Neurological Disorders; Neurotherapeutics; Tremor and Other Hyperkinetic Movements; Journal of Parkinson’s Disease; UpToDate. Speakers Bureau: none; Stock Ownership: none. SW has no competing interests.

Provenance and peer review Not commissioned; externally peer reviewed.

Table 2 Studies on treatment of catatonia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Type of study</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>A randomised, double-blind, placebo-controlled cross-over study of 18 patients</td>
<td>Not effective in chronic schizophrenia with catatonia</td>
</tr>
<tr>
<td>Ungvari et al</td>
<td>Prospective study of 28 patients</td>
<td>Sixteen of the 21 who completed treatment showed benefit. Four patients that failed lorazepam responded to ECT</td>
</tr>
<tr>
<td>Bush et al</td>
<td>Retrospective study of 107</td>
<td>Thirty two of 99 (32.3%) showed response (with complete resolution of catatonic symptoms). Improvement in catatonic symptoms was seen in 68 of 99 (68.7%) patients</td>
</tr>
<tr>
<td>Lorazepam/ECT</td>
<td>Retrospective study of 21 patients</td>
<td>Among 21 patients 13 (61.9%) patients responded within 2 h, 18 (85.7%) responded within 1 day, and all became catatonia-free within a week</td>
</tr>
<tr>
<td>Lin and Huang</td>
<td>Retrospective study of 12 patients</td>
<td>Eight patients complete remission (one dose of 2 mg lorazepam intramuscularly (IM)). Two patients needed two doses of 2 mg lorazepam IM. Two patients failed lorazepam but responded to one dose of 10 mg diazepam intravenous. All catatonic features remitted in 24 h with 100% response rate</td>
</tr>
<tr>
<td>Huang et al</td>
<td>Case report</td>
<td>Zolpidem was used as a diagnostic test in 6 out of the 12 patients. Response was seen in 4 and no response in 2 patients, Effective in case report</td>
</tr>
<tr>
<td>Lorazepam and risperidone</td>
<td>Case series 12 patients</td>
<td>Effective in case reports</td>
</tr>
<tr>
<td>Grenier et al</td>
<td>Case reports</td>
<td>Zolpidem was used as a diagnostic test in 6 out of the 12 patients. Response was seen in 4 and no response in 2 patients</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Case report</td>
<td>Effective in case report</td>
</tr>
<tr>
<td>Cottencin et al</td>
<td>Retrospective study of 21 patients</td>
<td>Among 21 patients 13 (61.9%) patients responded within 2 h, 18 (85.7%) responded within 1 day, and all became catatonia-free within a week</td>
</tr>
<tr>
<td>Peglow et al</td>
<td>Case series 25 patients</td>
<td>Effective in case reports</td>
</tr>
<tr>
<td>Amantadine de Lucena</td>
<td>Case reports</td>
<td>Effective in case reports</td>
</tr>
<tr>
<td>Hervey et al</td>
<td>Case reports</td>
<td>Effective in case reports</td>
</tr>
<tr>
<td>Amantadine/et al</td>
<td>Case series 5 patients</td>
<td>Effective in case series</td>
</tr>
<tr>
<td>Memantine</td>
<td>Case report</td>
<td>Effective in case report</td>
</tr>
<tr>
<td>Obregon et al</td>
<td>Case series 4 patients</td>
<td>Effective in case series</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Case reports and case series</td>
<td>Effective in case reports</td>
</tr>
<tr>
<td>McDaniel et al</td>
<td>Case report</td>
<td>Effective in case report</td>
</tr>
<tr>
<td>Olanzapine or clozapine</td>
<td>Case reports and case series</td>
<td>Effective in case reports</td>
</tr>
<tr>
<td>Nicolato et al</td>
<td>Case report</td>
<td>Effective in case report</td>
</tr>
<tr>
<td>Chang et al</td>
<td>Case report</td>
<td>Effective in case report</td>
</tr>
<tr>
<td>Spiegler et al</td>
<td>Case report</td>
<td>Effective in case report</td>
</tr>
<tr>
<td>Chattopadhyay et al</td>
<td>Case series 39 patients</td>
<td>Effective in case report</td>
</tr>
<tr>
<td>Olanzapine and amantadine</td>
<td>Case report</td>
<td>Effective in case report</td>
</tr>
<tr>
<td>Babington et al</td>
<td>Case report</td>
<td>Effective in case report</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Case reports</td>
<td>Effective in case reports</td>
</tr>
<tr>
<td>Yoshimura et al</td>
<td>Case report</td>
<td>Effective in case report</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Retrospective study 63 patients</td>
<td>Response to ECT was noticed in 56 out of 63 patients (88.89%).</td>
</tr>
<tr>
<td>Kopala et al</td>
<td>Retrospective study 27</td>
<td>Improvement was seen in 16 (59%) patients</td>
</tr>
<tr>
<td>Hesslinger et al</td>
<td>Retrospective study with 22 patients</td>
<td>Improvement was seen in 26 out of 28 cases (93%)</td>
</tr>
<tr>
<td>ECT</td>
<td>Retrospective study of 12 patients</td>
<td>Effective in case series</td>
</tr>
<tr>
<td>Raveendranathan et al</td>
<td>Case report</td>
<td>Effective in case report</td>
</tr>
<tr>
<td>van Waarde et al</td>
<td>Case report</td>
<td>Effective in case report</td>
</tr>
<tr>
<td>ECT and olanzapine</td>
<td>Case report</td>
<td>Effective in case report</td>
</tr>
<tr>
<td>Tan et al</td>
<td>Case report</td>
<td>Effective in case report</td>
</tr>
</tbody>
</table>

ECT, electroconvulsive therapy.
REFERENCES

Movement disorders
