

Electroconvulsive therapy in catatonic patients: Efficacy and predictors of response

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Abstract

Recent evidence favors the view of catatonia as an autonomous syndrome, frequently associated with mood disorders, but also observed in neurological, neurodevelop-

mental, physical and toxic conditions. From our systematic literature review, electroconvulsive therapy (ECT) results effective in all forms of catatonia, even after pharmacotherapy with benzodiazepines has failed. Response rate ranges from 80% to 100% and results superior to those of any other therapy in psychiatry. ECT should be considered first-line treatment in patients with malignant catatonia, neuroleptic malignant syndrome, delirious mania or severe catatonic excitement, and in general in all catatonic patients that are refractory or partially responsive to benzodiazepines. Early intervention with ECT is encouraged to avoid undue deterioration of the patient's medical condition. Little is known about the long-term treatment outcomes following administration of ECT for catatonia. The presence of a concomitant chronic neurologic disease or extrapyramidal deficit seems to be related to ECT non-response. On the contrary, the presence of acute, severe and psychotic mood disorder is associated with good response. Severe psychotic features in responders may be related with a prominent GABAergic mediated deficit in orbitofrontal cortex, whereas non-responders may be characterized by a prevalent dopaminergic mediated extrapyramidal deficit. These observations are consistent with the hypothesis that ECT is more effective in "top-down" variant of catatonia, in which the psychomotor syndrome may be sustained by a dysregulation of the orbitofrontal cortex, than in "bottom-up" variant, in which an extrapyramidal dysregulation may be prevalent. Future research should focus on ECT response in different subtype of catatonia and on efficacy of maintenance ECT in long-term prevention of recurrent catatonia. Further research on mechanism of action of ECT in catatonia may also contribute to the development of other brain stimulation techniques.

Key words: Electroconvulsive therapy; Catatonia; Mood disorders; Schizophrenia; Benzodiazepines; Antipsychotics

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Core tip: Catatonia is a treatable autonomous syndrome, frequently associated with mood disorders, but also observed in neurological, neurodevelopmental and toxic conditions. Electroconvulsive therapy (ECT) is effective in 80% to 100% of all forms of catatonia, even after pharmacotherapy with benzodiazepines has failed, and is considered first-line treatment in patients with neuroleptic malignant syndrome. Increasing the knowledge on the mechanism of action of ECT in catatonia may contribute to the development of other brain stimulation techniques, such as transcranial magnetic stimulation and deep brain stimulation. ECT response in different subtype of catatonia and efficacy of maintenance ECT in long-term prevention of recurrent catatonia deserve further research.

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INTRODUCTION

Originally described by Karl Kahlbaum^[1] in 1874, catatonia is a severe neuropsychiatric syndrome characterized by prominent motor features including immobility, mutism, negativism, rigidity, posturing, staring, stereotypy, automatic obedience, echo-phenomena and mannerism. Mutism and stupor are generally considered the most typical symptoms of catatonia^[2-4].

Although Kraepelin^[5] admits the presence of catatonic symptoms in manic-depressive insanity, he marks catatonia as a principal sign of dementia praecox. The association of catatonia with dementia praecox^[2] was suggested by its poor prognosis and its possible evolution toward a chronic deteriorative course. Kraepelin's position was essential for the development of subsequent psychiatric nosography until nowadays and the view of catatonia as a subtype of schizophrenia has hidden its recognition as an independent syndrome for more than a century^[6].

In DSM-5^[7], catatonia is still included in the chapter of schizophrenia spectrum and other psychotic disorders. The manual does not treat catatonia as an independent class but recognizes "catatonia associated with another mental disorder" (catatonia "specifier"), "catatonic disorder due to a general medical condition" and "unspecified catatonia". The catatonic subtype of schizophrenia has been deleted. According to the Manual, catatonia is considered only a specifier for schizophrenia, as for bipolar and major depressive disorders and for other additional disorders (schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, substance-induced psychotic disorder, neurodevelopmental disorders and others).

Currently, a large body of evidence seems to

support the view of catatonia as an independent neuropsychiatric syndrome associated with several psychiatric disorders, and in neurologic, metabolic and endocrine conditions such as infections, toxic states, epilepsy, and traumatic brain injury^[8]. Both catatonia associated with psychiatric disorders and with somatic conditions show similar clinical presentation, symptom severity, course and treatment indications^[9,10].

Prevalence rates of catatonia range from 6% to 38% among psychiatric inpatients^[8]; it is mainly associated with mood disorders (about 30% of cases), in particular with mania or mixed states^[11]. Catatonic patients are at risk for severe complications including pneumonia, decubitus ulcers, malnutrition, dehydration, contractures, and thrombosis^[12,13].

If correctly diagnosed, catatonia is a treatable syndrome. Intravenous benzodiazepines (generally lorazepam) are the most commonly used treatment, with a reported remission rate of about 60%-70%, regardless of the cause or of clinical manifestations^[14]. Intravenous administration is preferred to assure adherence and rapid, complete absorption. As patients improve, they should be switched to oral medication. The dosing schedule varies with the severity of catatonia and the presence of fever and vegetative signs. For stuporous patients, dosing starts at 3 mg daily, increasing every one or two days to 6, 9, and 12 mg as tolerated, depending upon response and clinical urgency. A dose of 6 to 21 mg daily is effective for most patients, but a dose of 30 mg per day is occasionally necessary. A successful acute treatment course will take from 4-10 d^[2,15,16]. Prolonged trials are not advised for severe catatonia, as complications have been reported^[4]. Electroconvulsive therapy (ECT) is first-line treatment in malignant catatonia (MC) and in case of resistance to benzodiazepines^[17].

The intimate relation between convulsive therapy and catatonia began in 1934 at Royal Hungarian State Psychiatric Institute in Budapest, where Laszlo Meduna induced for first time epileptic fit with intramuscular injections of camphor in five patients with catatonic features. These patients, diagnosed with catatonic schizophrenia were in stuporous state, requiring tube-feeding for several months; they were in serious physical condition and almost certainly destined to fatal outcome. After several sessions of convulsive therapy, the severity of catatonic stupor improved and tube-feeding was no longer necessary in any of the patients. In the early 1930s, this observation was regarded as a therapeutic breakthrough, given the lack of effective interventions for such severe mental illness^[18]. Subsequently, ECT became the dominant method of convulsive treatment and the clinical experience of more than seventy years has shown that catatonia is a clinical condition with a rapid, dramatic and often life-saving response to ECT.

In the present article, we reported a systematic review of the literature about the use of ECT in catatonia, discussing available evidence on efficacy,

safety and predictors of response.

RESEARCH

A systematic review of the existing literature has been conducted through PubMed and Scopus using combinations of the following search terms: "catatonia", "electroconvulsive therapy", "treatment", "response", "von Meduna", "Cerletti", "schizophrenia", "mood disorder", "bipolar disorder", "depression", "neurodevelopmental disorders", along with terms related to each of the areas of focus listed above. Regarding ECT, Randomised Controlled Trial (RCT) only considering catatonia are not available. So we mash up information from available clinical studies, case-reports, case-series and expert descriptions. In particular we focus our attention on prospective and retrospective case series that included more than 10 patients. Reference lists from each article were assessed for additional citations of interest. Unless otherwise noted, the referred studies focus on adults. We excluded articles in languages other than English. Two reviewers evaluated the results of the searches on the basis of title and/or abstract, and assessed the citations for their suitability for inclusion based on the full publications.

CONCLUSION

The results of the 8 open observational studies including at least 10 patients with different form of catatonia are reported in Table 1. Few case series with 5 patients or less^[19-21]; and a large number of single case reports have also been published describing the efficacy and tolerability of ECT in catatonia in a variety of clinical situations.

Efficacy

Retrospective observational studies report a response rate to ECT in catatonic patients ranging from 80% to 100%^[22-26]. Hawkins *et al.*^[14] (1995) reviewed the treatments of catatonia in clinical records of 178 patients in 270 episodes. ECT alone was employed in 55 (about 30%) patients, obtaining the resolution of catatonic symptoms in 85% of the cases. When the presence of MC was suspected, the response to ECT was 89% (9 of 11). In another study^[27] 50 catatonic patients were addressed to four step of treatment: in each ECT or drug treatment were administered, according to the patient and his/her family's choice, except for the last step where only ECT was administered. Response rates, defined as the number of patients who respond completely to ECT divided by the total (cumulative) number of patients, were equal to 100%. The Authors concluded that ECT should be the first choice treatment for catatonic symptoms, especially when doses of benzodiazepines above the upper limits cannot be applied, as in this study. In a recent observational study by our clinic (Medda *et al.*^[28], submitted to press) we observed a favorable response to ECT (measured as a

CGI final score ≤ 2) in 21 (81%) out of 26 catatonic in-patients resistant to BZDs. This figure is in line with previous reports.

In a recent review of the ECT experience in a large Dutch teaching hospital^[29], 27 cases of catatonia were identified among the 285 ECT treated patients over a 18-year period. Of the entire sample 48% presented mood disorders and 44% psychotic disorders. Although pharmacotherapy had failed in 85% of the patients, ECT was effective in improving 59% of the cases. The reduced treatment response in this study, compared with other reports (59% vs 85%-100%), may be related to the high prevalence of psychotic disorders, the delayed use of ECT (after two months of pharmacotherapy) and the previous use of antipsychotics in many of these patients. Finally, one third of the patients suffered from neurological comorbidity. The same study reported the benefit of daily ECT in catatonic patients with autonomic disturbances (that can be considered mild cases of MC). The need for daily ECT was already suggested in 1952, when a classic study by Arnold and Stepan reported that this procedure seems to avoid fatalities in MC^[30].

Some authors approach neuroleptic malignant syndrome (NMS) and MC as separated entities^[9]. However, once the overlap of the syndromes was recognized, ECT began to be applied to patients with NMS^[31]. In a review of the most recent literature of 46 published reports describing experiences with 55 patients, ECT was effective in 40 (73%) patients with NMS^[32]. Complete recovery of symptoms was reported in 25 (63%) of the cases, and partial recovery was noted in 11 (28%).

A literature review of ECT in children and adolescents^[33], reporting data from the Paris clinic of David Cohen, identified 59 cases with 47% having mood disorders, 27%, schizophrenia, and 23% brain and pervasive developmental disorders. Favorable outcomes were reported in 76% of the treated patients, with only 1 patient considered as non-responder.

In conclusion, available empirical evidence clearly indicates that ECT is effective in 80%-100% of all forms of catatonia, even after pharmacotherapy have failed. ECT should also be first-line treatment in patients with MC, NMS, delirious mania or severe catatonic excitement, and in general in all catatonic patients that are refractory/partially responsive to benzodiazepines and amobarbital^[17]. According to some Authors, ECT should be preferred to benzodiazepines as their effect on catatonic symptoms can be only transient and not every sign/symptom of an acute catatonic stupor responds well to benzodiazepines^[34,35].

Administration and technique

Since catatonic patients frequently present with compromised medical status, every effort should be made to optimize the patient's physical condition^[36]. In malignant forms with hyperthermia and autonomic instability, ECT should be started within the first five days of hospitalization, to increase response rates and

Table 1 Studies that investigate efficacy of electroconvulsive therapy in catatonia (number of patients receiving electroconvulsive therapy ≥ 10)

Ref.	Sample (n)	Patients receiving ECT n (%)	Diagnosis	Design	ECT technique	Outcome measures	Results	Variables associated with response
Unal <i>et al.</i> ^[23] , 2013	57	57 (100)	63% Mood disorders 29% psychotic disorders (including schizophrenia) 3.5% pts mental retardation 3.5% pts without psychiatric disorders	Retrospective All pts. received ECT in combination with oral BZDs	BL (bifrontal)	CGI, HDRS, YMRS, PANSS	Response = 100%	Not assessed
Tuerlings <i>et al.</i> ^[64] , 2010	34	34 (100)	59% mood disorders 77% schizophrenia and other psychotic disorders 37% somatic, toxic, post-traumatic stress disorder, mental retardation	Retrospective	Non specified	No standard diagnostic instruments or catatonia scales	58% pts treated with BZDs and/or ECT had clinically complete remission. 50% pts treated with ECT after unsuccessful medication trials recovered completely Response = 59%	Responders: Autonomic dysregulation Non-responders: Initial treatment with amantadine, bromocriptina and dantrolene More comorbid disorders
Van Waarde <i>et al.</i> ^[29] , 2010	27	27 (100)	48% mood disorders 44% psychotic disorder (including schizophrenia) 19% others (alcohol/substance abuse, mental retardation)	Retrospective	BL (bifronto-temporal) or UL (according to d'Elia)	Response defined as CGI ≤ 2	Response = 59%	Responders: Younger age Autonomic dysregulation at baseline (especially higher body temperature) Daily ECT during the first treatment week
Ravvedranathan <i>et al.</i> ^[25] , 2012	63	63 (100)	41% mood disorders, 49% psychotic disorders (including schizophrenia) 6% idiopathic catatonia	Retrospective	BL (bitemporal)	Response = complete resolutions of symptoms and/or BFCRS = 0	Response = 89%	Longer duration of motor and EEG seizure activity at the final ECT session Less morbidity in the year after ECT The Authors divide the responders in faster (≤ 4 sessions) and slower (≥ 5 sessions) Faster responders: Lower duration of catatonia Greater severity of BFCRS Lesser electrical charge used overall Shorter duration of inpatient stay Waxy flexibility and gegenhalten. Lower responders: echophenomena
England <i>et al.</i> ^[26] , 2011	25	12 (48)	Total sample: 36% bipolar disorder 32% pts with psychosis NOS 4% depressive episode and anxiety disorder 16% schizophrenia 8% without previous psychiatric history	Retrospective	BL	BFCRS, clinical evaluation	83% pts treated with ECT definite beneficial effects > BZDs, APs, MS, ADs	Not assessed
Hatta <i>et al.</i> ^[27] , 2007	50	17 (34)	Total sample: 34% mood disorders 46% schizophrenia and other psychotic disorders 20% medical condition	Observational study I step: BZDs or ECT II step: APs (RIS or HAL) or ECT III step: CPZ or ECT IV step: ECT	BL (bitemporal)	"Partial response": disappearance of one or more catatonic symptoms; "complete response": disappearance of all catatonic symptoms	(Cumulative) ECT 100% > CPZ 68% > RIS more catatonic symptoms; 26% > HAL 16%	Not assessed

Author	Year	n	Disorders	Design	Assessment	Response	Notes
Dutt <i>et al.</i> ^[24]	2011	51	75% psychotic disorders (including schizophrenia) 14% mood disorders 8% organic brain syndromes	Retrospective	Unspecified	Response = 100%	Not assessed
Rohland <i>et al.</i> ^[25]	1993	22	59% mood disorders 32% schizophrenia and schizoaffective disorder 9% organic mental disorder	Retrospective	BL (bitemporal)	Response = 93%	Trend toward a better response in affective than psychotic pts (non statistically significant)
Medda <i>et al.</i> (manuscript in preparation)		26	100% bipolar disorder	Observational	BL (bitemporal)	Response = 81%	Non-responders: Older age at onset of mood disorders Lower number of mood episodes Higher BFCRS total score at baseline Less psychotic symptoms Higher rate of past treatment with anticholinergics and dopamine agonists and lower rate of past treatment with typical antipsychotics

APs: Antipsychotics; CPZ: Chlorpromazine; RIS: Risperidone; HAL: Haloperidol; ADs: Antidepressants; MS: Mood stabilizer; BZDs: Benzodiazepines; BFCRS: Bush-Francis Catatonia Rating Scale; CGI: Clinical Global Impressions scale; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; PANSS: Positive and Negative Symptoms Scale; ECT: Electroconvulsive therapy.

reduce mortality rate.

Systematic studies focused on electrode placement, stimulus dosing, frequency of session and other aspects of ECT technique for treating catatonia are lacking and these parameters have not been standardized. As regard electrode placement, there is a general consensus that bitemporal placement is the most effective^[8]. The use of unilateral electrode placement is not recommended, although recently two case series illustrate successful use of right unilateral ECT in patients with catatonia^[19,37].

To limit the possibility of sub-convulsive stimulation in patients with serious concomitant medical conditions, most of the authors suggest to use the half-age method to determine the stimulus intensity^[8,38] and to measure the electroencephalographic (EEG) length of the seizures which should be at least 25 s. If the motor seizure duration decreased below 25 s, the stimulus setting was increased 1.5 times at the following session. The relief of catatonia often seems to require more frequent ECT session than in major depression and is generally given three times per week on alternating days. However, clinical urgency (MC, high risk of complications, delirious mania/excited catatonia with severe excitement and combativeness) may necessitate daily treatments until the patient is physiologically stable, which often occurs within 2 to 5 treatments. Then ECT is continued at more conventional frequencies^[39].

The total number of ECT treatments that will be needed cannot be predicted. It was established on the basis of the clinical response after 5 or 6 treatments, and then again after 10 or 12 sessions. After that, termination of ECT should be considered when a full clinical response is achieved or when are not obtained further clinical improvement after two consecutive sessions. This number is usually between 12 and 20 treatments^[21], however some patients manifest a complete remission after only a few treatments.

Usually all psychotropic medications were discontinued during the ECT course, however, as regard BDZs, literature is not consistent on this point. Some physicians describe discontinuing benzodiazepine treatment just prior to ECT, whereas others recommend continuing benzodiazepines during and beyond the ECT treatments and postulated a synergistic effect^[40] (see Combined treatment: ECT plus benzodiazepines).

Succinylcholine has been traditionally the muscle relaxant of choice for ECT owing to its rapid onset of action and ultra-short duration of action. However, in catatonic patients the use of succinylcholine should be avoided for the increased risk of severe hyperkalemia^[41] and the susceptibility to NMS and malignant hyperthermia (MH)^[42]. Although rocuronium neuromuscular blockade can also be reversed with neostigmine, the use of rocuronium and sugammadex for the maintenance and reversal of neuromuscular blockade respectively, has the advantage of producing muscle relaxation similar to that of succinylcholine with regard to onset of action and duration of effect^[43,44].

Combined treatment: ECT plus benzodiazepines

Because benzodiazepines are the first choice in the treatment of catatonia, patients treated with ECT are often receiving them. For patients with a partial but incomplete response to lorazepam, the drug should be continued during ECT to maintain the therapeutic effect^[23]. Others authors recommended reducing or suspending the dose of BDZ when it interferes with ECT, increasing seizure threshold and shortening seizure duration, despite adjustments in ECT technique^[15]. A case series of four hospitalized patients without catatonia prior to ECT who developed catatonic signs during ECT treatment, suggest that catatonia can emerge paradoxically when benzodiazepines were tapered or discontinued in preparation for ECT. This suggests that benzodiazepine withdrawal may be a risk factor for appearance of catatonia during ECT, in non catatonic patients^[45].

In a recent study with a retrospective collection of 57 catatonic patients' records, the use of benzodiazepine-ECT combination achieved full recovery in the whole sample, composed by 63.2% of cases with mood disorders and 29.8% with psychotic disorders^[23]. Some case-series describe a response to benzodiazepine-ECT combination, which seemed to be superior to monotherapy^[40]. The Authors state that initially the patients showed a non-response to lorazepam, but lorazepam became effective at the same or lesser dosage after ECT was initiated. So, a synergistic effect of the combination ECT plus benzodiazepine has been hypothesized, suggesting that ECT may facilitate the therapeutic response to lorazepam. The converse is also supported, since the benefit of ECT is enhanced later in the treatment course after the addition of lorazepam^[40]. Notably, the dosage of lorazepam varies among patients but was lower than that usually prescribed for catatonic states and the last dose was administered at least 12 h prior to ECT^[46]. The short half-life of lorazepam and the absence of active metabolites may minimize possible antagonism with ECT. A synergism between the treatments could be explained by the common anticonvulsant properties of benzodiazepines and ECT (increase seizure threshold, decrease cortical excitability)^[47,48].

ECT in maintenance treatment protocol

To prevent relapse, continuation treatment is necessary for most psychiatric conditions. In most cases ECT is stopped when catatonic symptoms are resolved, but sometimes a continuation phase is useful. No systematic data are available on the preventive efficacy of maintenance ECT (mECT) for periodic catatonia. Many patients have been sustained in the community with mECT at bi-weekly, monthly, and bi-monthly intervals, with or without daily benzodiazepine dosing^[8]. There are no studies that suggest the optimal schedule for such treatment. For some patients with rapid cycling or in mixed affective states, mECT may be a better option than complex polypharmacy^[8]. The successful use of continuation ECT without medication has been described in patients with catatonic schizophrenia^[49] and with recurrent catatonia^[50].

Safety

Questions are often raised as to the safety of ECT and general anesthesia in patients with general medical illnesses that are co-morbid with or the cause of catatonia. Safety concerns necessitate pre-procedure medical consultation to optimize the patient's general status and reduce risks. As an example, the motor immobility and muscle damage have been recognized as risk factors for hyperkalemic states and may increase the likelihood of ventricular tachycardia (as torsade de pointes)^[51], associated with the muscle relaxant succinylcholine. This risk can be reduced using a non-depolarizing muscle relaxant (e.g., rocuronium). Furthermore, in catatonic patients deemed to be at high risk for the development of deep venous thrombus/pulmonary embolism (DVT/PE), a prophylaxis against DVT is recommended, by means of attempts to improve mobility, mechanical tools such as graduated compression stockings and intermittent pneumatic compression. Pharmacologic prophylaxis may be carried out with low-molecular weight heparin (e.g., enoxaparin) or warfarin^[52]. Warfarin should be continued in patients receiving ECT^[53].

ECT results in significant cardiovascular effects, although they are generally transient and resolve without adverse sequelae. The initial electrical stimulus produces a vagally transmitted parasympathetic bradycardia or even asystole lasting several seconds^[54]. As the seizure develops, this state is followed by sympathetic stimulation originating in the hypothalamus and descending *via* the brainstem, spinal cord, paravertebral stellate ganglia, and cardiac accelerator nerves. Adrenal stimulation leads to an abrupt increase in catecholamine release, which lasts several minutes postictally. A variety of cardiac dysrhythmias may occur, usually after the seizure, with reported incidences ranging from as low as 8% to as high as 80% or more in patients with known cardiovascular disease. Sympathetically mediated dysrhythmias include sinus tachycardia, bigeminy, trigeminy, and ventricular tachycardia and fibrillation. In healthy young people, the tachy-dysrhythmias seen are generally brief,

require no intervention, and do not preclude further ECT^[55].

With modern anesthesiological procedures, ECT is remarkably safe even in the medically compromised, the elderly, and in pregnancy. In pregnant patients, in fact, during the first and second trimesters, ECT is a procedure with a ratio risk/benefits particularly favorable and may be used when a rapid benefit is needed or when medications are not tolerated or fail^[54]. During the later stage of pregnancy, modification in ECT procedure should be considered in order to lower the risk for both the mother and the fetus (for instances, hydration, monitoring of fetal heart and tocography, placing a wedge for displacing utero, *etc.*).

Although medical illnesses may limit the use of several drugs, there are no absolute contraindications to the use of ECT in the widest range of patients with catatonia, with virtually any physical comorbidity and regardless the etiology. There are case reports of the effectiveness of ECT for treating catatonia in patients with comorbid medical illnesses such as lupus cerebritis, breast cancer, Graves' disorder and others^[56-58]. ECT can be effective in treating children with catatonia, and it is estimated that half of children who receive ECT do so because of a diagnosis of catatonia^[59].

Emergence of catatonia during ECT

The appearance of catatonia during ECT has been described in four patients^[45]. Catatonia resolved with benzodiazepines and continuation of ECT. The emergence of catatonia after two sessions of ECT was also described in a patient with bipolar disorder^[60]. When the patient was given a single unmodified ECT, three weeks later, after complete resolution of symptoms, catatonia reemerged.

Considering the universal efficacy of ECT in relieving catatonia, reports of the emergence of catatonia during ECT are puzzling. A possible explanation is that the patients experienced recurrence of their catatonic symptoms because of the rapid withdrawal of benzodiazepines prior to ECT. Rapid withdrawal from benzodiazepines may evoke catatonia^[61].

Predictors of response

In a recent report, favorable response to ECT has been correlated with young age, presence of autonomic dysregulation at baseline (especially higher body temperature), daily ECT during the first treatment week, longer duration of motor and EEG seizure activity at the final ECT session and less morbidity in the year after ECT^[29]. Acutely catatonic patients with an underlying mood disorder may respond more favorably to ECT than schizophrenic patients^[25] and ECT does not appear to benefit chronic catatonia in some schizophrenic patients^[62,63].

A fast response (within the first four sessions) is correlated with greater severity of catatonia symptoms

as measured with specific rating scales, shorter duration of in-patient stay, psychopathological features like waxy flexibility and gegenhalten^[22]. Slow responders showed greater number days of catatonia at presentation and echophenomena. Consistently with this observation, in a case series^[21] three patients with prolonged catatonia (10-14 wk) have been treated with ECT with discrete success (two patients markedly improved, one partially), but they needed a great number of sessions.

Moreover, in the same study, the presence of cerebral pathology predicted a less good outcome. Catatonic patients previously treated with dantrolene, amantadine, and bromocriptine showed poor or no response with successive ECT^[64]. In these cases it is possible to hypothesize the presence of underlying neurological disorders. In fact, in a case series and review of literature, Swartz *et al.*^[20] reported the persistence of catatonia after an adequate (9 to 17 sessions) course of ECT in patients with a concomitant neurological condition, and a lack of stable remission. This suggests that chronic neurologic disease can provoke or exacerbate chronic or relapsing forms of catatonia. The Authors propose two explanations: the condition may be intrinsically less responsive to ECT or require exceptionally intense treatment. The latter may involve more ECT sessions, higher stimulus doses, and aggressive prophylaxis of catatonia after the ECT course. Moreover, it may involve adjunctive medication to mitigate the underlying neurologic condition. Finally, when a patient who shows signs of catatonia fails to achieve a good or stable remission with ECT, additional testing for an underlying neurologic condition may be considered. Consistently with these findings, in our study (Medda *et al.*^[28], submitted to press), we found that non-responders to ECT were characterized by older age at onset of mood disorders, lower number of mood episodes, higher Bush-Francis Catatonia Rating Scale (BFCRS) total score at baseline, less psychotic symptoms, higher rate of past treatment with anticholinergics and dopamine agonists and lower rate of past treatment with typical antipsychotics. We hypothesized that the use of dopamine agonists and the reduced use of neuroleptics in non-responders may be related to the presence of an extrapyramidal abnormality in these patients.

DISCUSSION

Catatonia has been erroneously considered as a subtype of schizophrenia during much of the twentieth century and is still included in the chapter of schizophrenia and other psychotic disorder in DSM-5. This diagnostic approach discourages the use of ECT as an early treatment option. On the contrary, the classification of catatonia within the frame of psychotic disorders encourages clinicians to treat catatonic patients with antipsychotic medications. Since the early 70's, however, catatonia was increasingly recognized as an

independent syndrome frequently associated with mood disorders and several neurologic conditions^[11,65-68]. The most commonly used treatment is intravenous lorazepam, with a reported remission rate of about 70%, regardless of the clinical manifestations^[69]. ECT is utilized when benzodiazepines fail to give adequate response^[14] or rapid response is required. Since neither benzodiazepines nor ECT are effective for schizophrenia and since antipsychotics are usually ineffective or even dangerous, catatonia appears to be pathophysiologically different from schizophrenia and clinicians should avoid antipsychotics and other dopamine-blocking drugs in catatonic patients.

From our systematic review of the available literature, ECT resulted effective in all forms of catatonia, even after pharmacotherapy have failed. Response rates range from 80% to 100% and resulted superior to those of any other therapy in psychiatry. A reduced treatment response in 2 reports^[29,64] might be explained by the delayed use of ECT, the previous use of antipsychotics in many of the selected patients, and the high rate of neurological comorbidity.

ECT should be considered first-line treatment in patients with MC, NMS, delirious mania or severe catatonic excitement, and in general in all catatonic patients that are refractory/partially responsive to benzodiazepines^[17,70,71]. Early intervention with ECT is encouraged to avoid undue deterioration of the patient's medical condition. Some clinicians approach NMS and MC as different entities, reserving benzodiazepines and ECT for patients with MC and dopamine agonists and muscle relaxants for patients with NMS. However, ECT was also successfully applied to patients with NMS^[72]. Likely the biggest obstacle for the appropriate use of ECT in catatonia, as well as in other clinical situations, is the social stigma against ECT. Society's wary stance regarding ECT stems from a combination of claims of overuse and misuse in its history. Furthermore, local laws on ECT often complicate the process of obtaining ethical consent in the severe and acute catatonic patient.

The rapid improvement of catatonic signs before the alleviation of the underlying illness indicates that the improvement of catatonia does not necessarily depend on the treatment of the psychotic or the mood symptoms. The dramatic picture of catatonia and its rapid relief by ECT and benzodiazepines suggest that catatonia may be the final common outcome pathway for abnormal brain seizure activity. It is conceivable that ECT relieves catatonia by raising the seizure threshold and inhibiting the propagation of abnormal electrical signals through cerebral synapses. Catatonia is prominent in patients with epilepsy, and non-convulsive status epilepticus is included in the differential diagnosis of catatonia. Against such association, however, is the absence of electroencephalographic seizure activity in catatonic patients. However, electroencephalograms of catatonic patients are frequently difficult to interpret because of

muscle rigidity producing artifacts.

Little is known about the long-term treatment outcomes following administration of ECT for catatonia. However, it is clear that fatality rates from catatonia significantly decreased after the introduction and adoption of ECT as standard treatment in psychiatry^[73]. One small retrospective study suggested that patients with catatonic depression who were treated with ECT in addition to a tricyclic antidepressant, lithium, bupropion, or high-dose venlafaxine had better long-term outcomes over the course of four years compared to patients who received ECT and selective serotonin reuptake inhibitors^[74]. Cerebral pathology may predict a less favorable treatment outcome with ECT^[20,45,75].

Catatonic patients with a poor outcome are often diagnosed at first as suffering from a neurologic illness of unknown etiology, and are intensively treated with anticonvulsants. This makes it almost impossible to achieve effective seizures, and may represent a possible explanation for the failure of ECT^[8]. In some instances, catatonia may be late recognized with a delayed referral to ECT, after many weeks of unsuccessful or pejorative treatments (antipsychotics). In such circumstances, the number of ECT courses needed to effectively reduce catatonia is many times higher than the number usually employed to relieve acute catatonic syndromes. Moreover, the persistence of catatonia after ECT has been frequently reported to occur in patients with a neurological condition^[20]. This subtype of catatonia may be intrinsically less responsive to ECT or require more intense treatment. In line with this observation, previous treatment with amantadine and dopamine agonists is associated with poor response to ECT^[12,64]. The use of these drugs in non-responders, indeed, may be related to the presence of extrapyramidal abnormalities. It is likely that when catatonia is related to hypodopaminergic states, due to neurological conditions or antipsychotic treatments, ECT response may be less favourable.

On the other side, literature indicates that some clinical features such as young age, presence of autonomic dysregulation, severe psychotic underlying mood disorder, daily ECT during the first treatment week, longer duration of motor and EEG seizure activity at the final ECT session are associated with a favorable/faster response to ECT^[25,29]. A faster response has been also correlated with greater severity of catatonia symptoms, shorter duration of in-patient stay, psychopathological features like waxy flexibility and gegenhalten^[22].

In a recent review of the literature^[76], different subtypes of catatonia have been hypothesized being based on the existence of deranged "top-down" or "bottom-up" modulation of cortical-subcortical connections devolved to the control of psychomotor activity. "Top-down modulation" may be described as a regulation of subcortical structures by cortical areas as reflected, for example, in the modulation of caudate and other basal ganglia by lateral orbitofrontal cortex.

Such a top-down modulation has to be distinguished from "bottom-up modulation" as reflected in the modulation of premotor/motor cortical areas by basal ganglia. In catatonia, GABAergic-mediated deficit in orbitofrontal cortex may lead to alterations in "top-down modulation" of caudate and other basal ganglia *via* the "orbitofrontal loop", whereas, in hypodopaminergic states, a mediated deficit in striatum may lead to alterations in "bottom-up" modulation of premotor/motor cortex. Both catatonia and NMS have been reported in response to both standard and novel antipsychotic medications. As a consequence motor symptoms, in some catatonic cases, may be directly related to a striatal D2 receptor blockade that modulates the motor loop to the supplementary motor area and to the orbitofrontal cortex^[77]. Postulating the existence of different forms of catatonia, ECT would be more effective in "top-down" than in "bottom-up" variants of the syndrome.

Future research should focus on ECT response in different subtype of catatonia and on efficacy of mECT in long-term prevention of recurrent catatonia. Ultimately, a better understanding of the mechanism of action of ECT in catatonia may contribute to the development of other brain stimulation techniques.

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