Clinical features and predictors of non-response in severe catatonic patients treated with Electroconvulsive Therapy

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Abstract

OBJECTIVE

To explore the demographic and clinical features of severe catatonic patients, comparing responders and non-responders to ECT in order to detect possible predictors of non-response.

METHODS

This naturalistic study included 59 catatonic inpatients with a diagnosis of mood disorder according to DSM-IV-TR criteria. All patients were treated with bilateral ECT and evaluated before and after ECT course. The response to ECT was defined as a Clinical Global Impression (Improvement subscale) rating 1 “very much improved” or 2 “much improved”. Clinical variables were compared between responders and non-responders; logistic regression was used to predict the probability of non-response, with regard to the symptoms presented by the patients.

RESULTS

The response rate was 83.1%. Non-responders (n=10) to ECT showed neurological comorbidities, treatments with dopamine agonists and anticholinergic drugs, waxy flexibility, and echophenomena more frequently than respondents (n = 49). Echophenomena resulted a significant predictor of non-response in the multivariate analysis.

CONCLUSION

In line with previous reports, ECT resulted effective in the vast majority of severe catatonic patients. The association between ECT resistant catatonia and neurological comorbidity, use of dopamine-agonist and anticholinergic medications is consistent with the hypothesis that ECT is more effective in “top-down” than in “bottom-up” variant of catatonia.

Key Words: Bipolar disorder; Catatonia; Electroconvulsive therapy; Major depressive disorder; Psychotic symptoms; Mixed symptoms.

Introduction

Catatonia is an acute-onset neuropsychiatric syndrome characterized by movement and behavioral disorders associated with derangement in thinking, mood and alertness. The deficit in the control of voluntary movements during a catatonic episode may be manifested by a reduction in motor functions, up to immobility, or by an increase in motor activity that becomes not finalized and unaffected by external stimuli. Other characteristic motor symptoms are mutism, negativism, stereotypes, echolalia and echopraxia.

Erroneously considered in the past as a subtype of schizophrenia, catatonia is an independent syndrome with multifactorial etiology and specific neurophysiological substrate and treatment approach. It can arise both in the context of either a psychiatric condition (affective, psychotic and/or neurodevelopment disorders) or a general medical disease (infectious, endocrine or metabolic).[1] In DSM-5, the diagnostic category "catatonic schizophrenia" was eliminated and the divorce between catatonia and schizophrenia was ratified. However, catatonia is not classified as an independent syndrome, like delirium, but is considered a *specifier* of another mental disorder or medical condition.[2]

Catatonia is characterized by a polysymptomatic and multiform clinical picture with apparently opposite symptoms, which can hamper the diagnostic assessment. In fact, the signs and symptoms of catatonic syndrome are often overlooked by the physician or mistakenly thought to be intentionally produced. In addition, some catatonic symptoms are not evident by simple observation of the patient and must be elicited by the examiner during the objective examination.

Catatonia can occur in several clinical forms; the most frequently recognized is *inhibited catatonia*, also called *Kahlbaum syndrome*.[3] In this form, the patient presents with marked inhibition of mobility, with posturing, rigidity, mutism and repetitive actions, up to the condition of catatonic stupor. Another form of catatonic syndrome is *excited catatonia*, which is very similar to delirious mania: the patient presents with incessant movements, logorrhea, agitation, and may present with confused symptoms.

Malignant catatonia, also called *lethal catatonia*, has an acute onset and is accompanied by high fever, tachycardia, tachypnea, blood pressure instability, muscle rigidity, leukocytosis and increased creatine phosphokinase (CPK). These patients are at risk of cardiovascular complications and usually require admission to the intensive care unit. The clinical picture is indistinguishable from Neuroleptic Malignant Syndrome (NMS), which is now considered a form of drug-induced catatonia, as well as Serotoninergic Syndrome. Finally, in *periodic catatonia* the patient alternates between phases of psychomotor blockade and excitement, observed in bipolar forms during a mixed state or in rapid cycle course.[3]

Catatonia is a treatable syndrome once diagnosed. The major complications are related to immobility and malnutrition, and include dehydration, electrolyte disturbances, weight loss, muscle contractures, pressure ulcers, pneumonia *ab ingestis*, genito-urinary infections, venous thrombosis, and pulmonary embolism. Patients require intensive medical and internal care with anticoagulant treatment and timely placement of a nasogastric tube to reduce the risk of complications.[4] In addition, they require specific therapeutic interventions, particularly benzodiazepines (BDZs) or electroconvulsive therapy (ECT), avoiding antipsychotic drugs.[3]

BDZs are the first-choice treatment for catatonia, with a remission rate of 70–80%.[4] A longer duration of illness, the presence of mutism, and certain symptoms like third-person auditory hallucinations are reported as possible predictors of non-response to BDZ treatment.[5,6] ECT should be initiated in catatonic patients who are refractory/partially responsive to BDZs; it should also be considered first-line treatment in patients with malignant catatonia, neuroleptic malignant syndrome (NMS), delirious mania or severe catatonic excitement.[4,7] If the underlying condition warrants ECT, e.g., psychotic depression, this treatment may become the first therapeutic choice. ECT is an indicated treatment option with regard to mood disorder, particularly for patients with high suicidality and severe drug-resistant depressive, manic or mixed states, but also for patients with delirium or catatonic features.[8,9] ECT is effective in approximately 85% of catatonic patients,[10–12] although almost no randomized controlled trails have been conducted on this topic. In seven retrospective reviews of medical records,

totaling 222 patients, mostly resistant to BDZs, high response rates to ECT were confirmed.[4] Very few studies have been conducted to address the question of possible predictors of non-response to ECT, especially in patients with catatonia.[13]

The major aim of this study is to explore the demographic and clinical features of severe catatonic patients, comparing responders and non-responders to ECT in order to detect possible predictors of non-response.

Materials and methods

Patient sample

This naturalistic, prospective and observational study involved a total of 59 adult catatonic patients with a diagnosis of mood disorder. Patients were consecutively treated with ECT between June 2008 and July 2020 at the Psychiatry Unit 2, University of Pisa.

At the baseline assessment prior to ECT, current psychiatric diagnoses, as well as psychiatric medical history, medical comorbidities, sociodemographic, and pharmacological information were obtained from patients' medical records, family members, and attending physicians. The use of structured diagnostic interviews was prevented by the extreme severity of the catatonic syndrome, which often rendered patients unable to communicate. The diagnosis of catatonia was made according to the DSM-IV-TR diagnostic criteria for catatonic features specifier[14] and confirmed through the Bush Francis Catatonia Rating Scale (BFCRS) screening tool.

All patients had a current diagnosis of mood disorder: 10 (16.9%) met DSM-IV-TR criteria for Major Depressive Disorder, 9 (15.3%) with psychotic features (6 – 10.2% – mood-congruent and 3 – 5.1% – with mood-incongruent); 4 (6.8%) for Bipolar Disorder type II: 4 (6.8%) major depressive episode, 2 (3.4%) with mood-incongruent psychotic features; 45 (76.3%) for Bipolar Disorder type I: 17 (28.8%) major depressive episode; 16 (27.1%) with psychotic features (11 – 18.6% – mood-congruent and 5 – 8.5% – mood-incongruent); 6 (10.2%) manic episode, 5 (8.5%) with mood-incongruent psychotic features; 22 (37.3%) mixed episode, 20 (33.9%) with psychotic features (10 – 16.9% – mood-congruent and 15 – 25.4% – mood-incongruent).

All recruited patients underwent ECT after failure of BDZ therapy. Specifically, if increasing dosages of lorazepam i.v. (range: 6-24 mg/day) had not resulted in improvement of the catatonic syndrome within a maximum of 5-7 days and at least two catatonic signs continued to be present, as assessed by the BFCRS screening tool, patients were referred to ECT and recruited into the study.

The patients were evaluated 1 day prior to ECT (baseline evaluation) and a week after the ECT course (final assessment) using Clinical Global Impression (Severity – CGI-S – and Improvement CGI-I – subscales)[15] and BFCRS.[16] The latter is a standardized, quantifiable tool for the screening and diagnosis of catatonia; it consists of a 23-item rating scale with scores ranging from 0 to 3. The first 14 items assessing catatonic symptoms constitute the screening tool: when at least 2 symptoms are present, the diagnosis of catatonia is confirmed. For the screening tool, symptoms are considered absent if the score is 0 and present if the score is ≥ 1. Response to ECT was defined as a CGI-I subscale rating 1 “very much improved” or 2 “much improved” at final evaluation.

ECT procedure

Anesthesia was induced with intravenous thiopental (2-4 mg/kg) and muscle relaxation was assured with succinylcholine (0.5-1 mg/kg). To avoid the risk of transient hyperkalemia associated with succinylcholine, catatonic patients with elevated CPK and/or myoglobin levels, indicative of muscle damage, were treated with rocuronium (0.3 mg/kg IV 0.6 mg/kg) and sugammadex (4 mg/kg) after motor seizure. Patients were administered bilateral ECT two/three times per week with a Mecta 5000Q brief pulse stimulator (Mecta Corporation, Lake Oswego, USA). Pulse width was 1.0, current was 0.8 A, frequency ranged from 40 to 90 Hz, duration from 1.5 to 4.0 seconds, and electrical charge from 64 mC to 576 mC. During ECT, patients were monitored with pulse oximeter and electrocardiogram and ventilated with 100% oxygen until spontaneous respiration resumed. Stimulus setting was initially decided according to age. During the course of the ECT sessions, if the duration of the stimulus-induced motor seizures, as measured by EEG, was less than 25 seconds[17], the stimulus setting was increased (1.5 times) in the next session. If motor seizure duration fell below 25 seconds,

the stimulus setting was increased (1.5 times) in the next session. The number of ECT treatments was determined on the basis of clinical observation.

In accordance with the naturalistic design of the present study, psychopharmacological treatments were prescribed during the ECT course by the treating psychiatrist based on his/her clinical experience and guidelines. BDZs were continued during the course of ECT because of the suggested synergistic effect of the lorazepam/ECT combination and to avoid any relapse between sessions.[18] The last dose of BDZ was administered at least 12 hours before the ECT session. If BDZ therapy reduced the duration of the patient's motor seizures below 25 seconds, the stimulus energy was increased in the following ECT session. Among the various BDZs, lorazepam is preferred because of its short half-life and absence of active metabolites. [19]

Statistical analyses

Descriptive analyses were reported in terms of mean and standard deviations for continuous variable and number and percentages for categorical variables. Pairwise comparisons of mean scores of the different rating scales at baseline and final assessment were conducted by means of the paired t-test. Comparisons for continuous variables were performed using independent-sample Student's t-test whereas comparisons for categorical variables were conducted by using $\chi 2$ test (or Fisher's exact test, when appropriate). Binary logistic regression was used to predict the probability of non-response to ECT treatment, relative to the symptoms presented by the patients. An alpha of .05 in the univariate comparison was utilized as a cutoff for inclusion of a variable in the regression model. Given the high possibility of both type I and type II errors, our results should be considered preliminary. Accordingly, we also commented on significant differences at a p-value $<.10$ in order to minimize type I error. All statistical analyses were performed with IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA).

Ethic statements

This study protocol was approved by the local Ethic Review Board of the University Hospital of Pisa, Italy. At the initial evaluation, the severity of catatonic symptoms prevented almost all patients (≥90%

of the total sample) from providing informed consent. Consequently, according to the guidelines of our region, we required the appointment of a legal guardian (for patients who had not already appointed one), who signed the consent for the patient to receive ECT and participate in this study.

Results

At the end of the ECT course, 49 patients (83.1%) were classified as responders and 10 patients (16.9%) as non-responders. Both groups of patients showed statistically significant differences between baseline and final mean total scores on the CGI-S and BFCRS (Table 1). Specifically, all individual items of BFCRS significantly improved from baseline to finale evaluation, after ECT treatment (Figure 1).

INSERT TABLE 1, FIGURE 1

With regard to demographic characteristics, mean age was 54.46 (±14.18) years and female gender represented the 76.3% of the whole sample (Table 2). Considering demographic and clinical features, the two groups did not significantly differ in terms of age, gender distribution, age at onset of psychiatric disorder, duration of the current mood episode, duration of catatonic symptoms, personal history of catatonia, number of previous mood episodes, number of previous hospitalizations and history of suicide attempts.

Psychiatric diagnoses of mood disorders (Major Depressive Disorder, Bipolar Disorder type I and II) were similar in responders and non-responders. Regarding the current mood episode, depression was more frequently found in non-responders (80%) than in responders (46.9%), and vice versa for manic episode (20% and 53.1% respectively). This difference was not statistically significant at a stricter level of $p<.05$, but reached significance if $p<0.1$ is considered. The prevalence of lifetime psychotic symptoms and comorbidity with anxiety disorders did not differ between the two groups. Conversely, autistic spectrum disorders were more frequently diagnosed in non-responders (30%) than in responders (8.2%).

INSERT TABLE 2

Regarding the whole sample, abnormalities of cerebral Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) (61%) were the most frequently detected somatic comorbidities, followed by cardiovascular (35.6%), endocrine (25.4%), pulmonary (13.6%) and renal (8.5%) comorbidities, without statistically significant differences between the two groups of patients (Table 3). Neurological comorbidities were found in one third of the entire sample and were significantly more often observed in non-responders (60%) than in the responders (24.5%). Among patients with a neurological condition, 4 had a diagnosis of Parkinson's Disease (PD) (22.2%).

Autonomic disturbances were particularly frequent in our sample, with arterial hypertension (44.1%), tachycardia (40.7%) and diaphoresis (35.6%) as the most represented. The two groups did not significantly differ in these parameters, with the exception of diaphoresis that was more frequently observed in responders (40.8%) compared to non-responders (10%).

INSERT TABLE 3

Non-responders were administered a significantly greater number of ECT sessions compared to responders (respectively, 12.4±3.92 versus 9.63±3.52) (Table 4). The electrical dose at first and last session and the duration of EEG seizure activity were similar in the two groups.

With respect to pharmacological treatments at onset of catatonic symptoms, the two groups did not significantly differ in the use of BDZs, anticonvulsants, lithium salts, typical and atypical antipsychotics, and antidepressants, with the exception of selective serotonin reuptake inhibitors (SSRIs), more frequently prescribed in non-responders (50%) than in responders (22.4%). Dopamine agonists and anticholinergic medications were prescribed significantly more often in non-responders than in responders (respectively, 40% vs 4.1% and 40% vs 0%).

INSERT TABLE 4

Considering catatonic features at baseline evaluation, according to the 14 screening items of the BFCRS, we found that "withdrawal" was more represented in responders than in non-responders (respectively, 98% versus 80%) (Table 5). Conversely, "echopraxia/echolalia" and "waxy flexibility" were significantly more frequent in patients who did not respond to ECT compared to the others

(respectively, 70% versus 28.6% and 50% versus 16.3%). In the binary logistic regression analysis, "echopraxia/echolalia" (Table 6) was found to be the only predictor of non-response.

INSERT TABLE 5, TABLE 6

Discussion

Consistent with previous studies reporting the effectiveness of ECT in resolving catatonic symptoms,[11,20] in our sample of severe catatonic patients, 49 (83.1%) were responders (CGI-Improvement subscale rating 1 "very much improved" or 2 "much improved") at the end of the ECT course. The response rate to ECT in other chart review studies ranges from 58% to 100%.[13,21–25] A number of factors, such as the severity of catatonic symptoms, the study design, and the treatment delay, may have influenced the variability in response rates found across studies. As expected, statistically significant differences between CGI-S and BFCRS baseline and final mean total scores were observed in the whole sample. Furthermore, all the single BFCRS items were significantly less represented at the final evaluation compared to baseline assessment.

The majority of patients in this study presented a major depressive episode; psychotic features were observed in approximately 90% of the patients. Catatonia and psychotic mood syndromes have been known to be closely related since *Kahlbaum's* early descriptions (1874).[26] Subsequent literature has since confirmed a high prevalence of catatonia among patients with mood disorders. Today, it is estimated that catatonia occur during a mood episode in 40-63% of the cases, with 16-36% of the catatonic patients having bipolar disorder.[13,21–25] On the other hand, 20-30% of bipolar patients seem to show at least one catatonic episode during the course of their illness.[27,28]

At baseline, most of our patients (81.4%) were classified "among the most extremely ill patients" at CGI-S evaluation, and only a minority (18.6%) as "severely ill". These data are partially in line with previous reports.[25] In a recent study on catatonic patients,[24] the mean CGI-S score at baseline assessment (6.54±0.60) resulted similar to our results (6.81±0.39).

Regarding catatonic features, in our sample, the mean total BFCRS score at baseline was greater than 30, indicating greater symptom severity than reported in previous similar studies.[13] With respect to

individual BFCRS items, the most frequent catatonic symptoms in our sample were “withdrawal”, “negativism” and “stupor”, at different levels of severity, observed in more than 90% of the cases. This is consistent with a previous study reporting “immobility” in 100% of the sample of catatonic patients, extreme negativism or mutism in 96%, and peculiarities of voluntary movement in 68%.[22] Other studies have reported immobility/stupor (26.3-79.5%), mutism (47.4-97.7%), staring (75%), posturing/catalepsy (72.7%) and withdrawal (31.6-93.2%) as the most common BFCRS signs.[21,24,29] The largest discrepancy between our results and the rest of the literature concerns the item “rigidity”, which was more represented in our sample than in other reports. In this study, many patients (approximately 75%) had been prescribed typical and atypical antipsychotics at baseline assessment because of the severity of the clinical picture and the presence of psychotic features. These drugs may have impacted on the increased rate of rigidity and other extrapyramidal symptoms in our sample.

In our sample, among all the catatonic features, “withdrawal” seemed to be associated with a response to ECT, whereas “echopraxia/echolalia” and “waxy flexibility” with a non-response to ECT course. This is only partially in line with a previous study, where slow responders were associated with “echophenomena”, whereas fast responders more frequently reported psychopathological features such as “waxy flexibility” and “gegenhalten”.[13]

Kahlbaum’s description of catatonia included the symptoms of echophenomena, echolalia and echopraxia,[26] and these features are among the diagnostic criteria for catatonia in DSM-5.[2] Echophenomena may be accompanied by signs of frontal release and are usually attributed to frontal lobe dysfunction, although have occasionally been associated with basal ganglia or thalamic lesions and exceptionally with parietal lesions.[30] Indeed, a number of catatonic symptoms may overlap with those of the behavioral variant of FTD.[31] Catatonia has also been described as a manifestation of FTD.[32]

In our sample, the diagnostic distribution was similar in responders and non-responders. The major depressive episode was more represented in the non-responder group, whereas the manic episode (with or without mixed features) in the responder group. Patients with a previous diagnosis of autism

spectrum disorder in childhood were more represented in the non-responder group. These results suggest a significant trend, to be tested in further analysis on larger sample.

Consistent with a case series reporting failure of an adequate course of ECT to induce stable remission of catatonic symptoms in patients with a neurologic disorder,[33] non-responders in our sample exhibited neurologic comorbidities more frequently than responders. Neurological comorbidities were more frequently detected among non-responder patients than responders. Although a relationship between neurological disorders, catatonia, and nonresponse to ECT is suggested, clarity on this association is still needed. Neurological disease could cause or exacerbate the catatonic syndrome and could be the cause of nonresponse to ECT. Accordingly, catatonic patients who fail to achieve stable remission after ECT should be further investigated for a possible underlying neurological disorder. Catatonia has been related to many neurological conditions, such as encephalitic states, parkinsonism, bilateral globus pallidus disease and frontal lobe disease.[34]

In our sample, among patients with neurological diseases, 4 were cases of PD. Reports of catatonia in patients with PD were limited to only three cases, probably because of underdiagnosis.[35–37] Indeed, despite different pathophysiology, retarded catatonia and PD may show partially overlapping symptomatology, and catatonia may be misdiagnosed and neglected in patients with severe PD. Moreover, if catatonia is not recognized in patients with PD, increasing the dopamine-agonist dose may worsen the rigidity or leave the catatonia untreated.

Northoff has hypothesized different cortical-subcortical connections devolved to the control of psychomotor activity in catatonia and PD. 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 PD, a mediated hypo-dopaminergic state in striatum may lead to alterations in “bottom-up” modulation of premotor/motor cortex via the “motor loop”. As a consequence, it is possible to hypothesize that, in some cases, the onset of catatonia could be associated with a concomitant dysfunction of the two systems: the “top-down”, related to mood disorder, and the “bottom-up”, related to PD.[38–40]

Although ECT has beneficial effects on symptoms of PD, in most cases this effect is transient.[41] A recent review confirms the efficacy of ECT in patients suffering from PD and depression, showing mood improvements in 93% of patients and motor symptom improvements in over 83%.[42] During the course of ECT, patients with PD may be at an increased risk for developing delirium, post-ictal confusion, falls, and dopaminergic side effects than patients without PD.[42–45] In these patients, it has been suggested to start with the administration of unilateral stimuli, using brief pulse widths, scheduling sessions twice a week, minimizing the dose of levodopa to prevent or decrease cognitive side effects, and switching to bilateral stimulus only if the response is inadequate.[42,46]

Similarly to previous reports,[19,21] autonomic disturbances were particularly frequent in our patients. Diaphoresis was more common among responders than other patients, in agreement with a previous study showing that the presence of autonomic dysregulation (especially higher body temperature) at baseline correlates with improvement after ECT course. [25]

Regarding pharmacological treatments, dopamine agonists and anticholinergics were prescribed more frequently in non-responders than in responders. Interpreting this finding in the aforementioned "top-down" and "bottom-up" perspective, it seems to suggest an involvement of impaired "bottom-up" modulation.[38] In our sample, dopamine agonist and anticholinergic drugs were prescribed in patients with extrapyramidal symptoms in the absence of a diagnosis of PD.

The present study shows several limitations that should be considered. The first and main limitation is the low numerosity of the study sample, particularly in the group of non-responders. In addition, our sample may not be representative of the entire population of patients with catatonia because of the presence of predominantly female patients with very severe psychotic mood disorders resistant to pharmacological treatment. Given that catatonia is reported to occur in 10% of patients with acute psychiatric illness, the number of catatonic patients in our sample is lower than would be expected.[47] The reason for the relatively small number of patients recruited into the study is probably attributable to the organization of our psychiatric center. Indeed, managing only patients referred to ECT from other regional or extra-regional facilities, and not those from the emergency department, certainly

affects the number of patients we routinely manage in our department. Furthermore, in the present study, we included only catatonic patients who had a diagnosis of mood disorder and had been resistant to BDZ therapy, further reducing the sample. Finally, one must take into account the high probability of both type I and type II errors, making the present results only preliminary. On the other hand, the present study is that the diagnostic and clinical assessments were made by psychiatrists with long experience in mood disorders and involved in ECT treatment. The systematic nature of the assessment and the use of standardized instruments minimizes the bias that might result from a nonblinded methodology. One limitation, inherent in all studies exploring mood, psychotic, and catatonic symptomatology in naturalistic samples, is that medication effects and clinical evolution may confound symptom assessment.

In conclusion, our study supports the available literature indicating that catatonia can be frequently associated with severe psychotic mood disorder. In particular, our sample presented a severe clinical picture in terms of both specific catatonic features and general psychopathology. It also showed high rates of neuro-vegetative disturbances and physical comorbidity. In line with previous reports, ECT was effective in over 80% of the cases and all catatonic symptoms resulted strongly improved at the final evaluation. Among catatonic symptoms only, the presence at baseline of “echopraxia/echolalia” should be considered a predictor of non-response to ECT treatment. Finally, non-response was associated with neurological comorbidity and the use of dopamine-agonist and anticholinergic medications, suggesting the possibility that ECT may be more effective in the “top-down” than in the “bottom-up” variant of catatonia. Our results should be considered preliminary; further research is needed to confirm our findings.

Key points:

Catatonic symptoms are frequently associated with severe and psychotic mood disorders.

Electroconvulsive therapy is effective in treating most forms of severe catatonia.

Neurological comorbidity and the presence of “echopraxia/echolalia” could represent predictors of non-response to ECT.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

References

1. Fink M, Fricchione G, Rummans T, Shorter E. Catatonia is a systemic medical syndrome. *Acta Psychiatr. Scand.* 2016; **133**(3): 250–1.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5th Ed. Washington DC: American Psychiatric Association; 2013.
3. Fink M, Taylor MA. The catatonia syndrome: Forgotten but not gone. *Arch. Gen. Psychiatry*. 2009; **66**(11): 1173–7.
4. Sienaert P, Dhossche DM, Vancampfort D, Hert M De, Gazdag G. A clinical review of the treatment of catatonia. *Front. Psychiatry*. 2014; **5**: 181.
5. Ungvari GS, Chiu HF, Chow LY, Lau BS, Tang WK. Lorazepam for chronic catatonia: a randomized, double-blind, placebo-controlled cross-over study. *Psychopharmacology (Berl).* 1999; **142**(4): 393–8.
6. Narayanaswamy JC, Tibrewal P, Zutshi A, Srinivasaraju R, Math SB. Clinical predictors of response to treatment in catatonia. *Gen. Hosp. Psychiatry*. 2012; **34**(3): 312–6.
7. Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia. II. Treatment with lorazepam and electroconvulsive therapy. *Acta Psychiatr. Scand.* 1996; **93**(2): 137–43. 10.1111/j.1600-0447.1996.tb09815.x
8. Perugi G, Medda P, Barbuti M, Novi M, Tripodi B. The Role of Electroconvulsive Therapy in the Treatment of Severe Bipolar Mixed State. *Psychiatr Clin North Am*. 2020; **43**(1): 187–97.
9. Kennedy SH, Milev R, Giacobbe P, Ramasubbu R, Lam RW, Parikh S V, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. *J. Affect. Disord.* 2009; **117 Suppl**: S44-53.
10. Leroy A, Naudet F, Vaiva G, Francis A, Thomas P, Amad A. Is electroconvulsive therapy an evidence-based treatment for catatonia? A systematic review and meta-analysis. *Eur. Arch. Psychiatry Clin. Neurosci.* 2018; **268**(7): 675–87.
11. Hawkins JM, Archer KJ, Strakowski SM, Keck PE. Somatic treatment of catatonia. *Int. J. Psychiatry Med.* 1995; **25**(4): 345–69. 10.2190/X0FF-VU7G-QQP7-L5V7
12. Luchini F, Medda P, Mariani MG, Mauri M, Toni C, Perugi G. Electroconvulsive therapy in catatonic patients: Efficacy and predictors of response. *World J. Psychiatry*. 2015; **5**(2): 192.
13. Raveendranathan D, Narayanaswamy JC, Reddi S V. Response rate of catatonia to electroconvulsive therapy and its clinical correlates. *Eur. Arch. Psychiatry Clin. Neurosci.* 2012; **262**(5): 425–30. 10.1007/s00406-011-0285-4
14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). Washington DC: American Psychiatric Association; 2000. 943 p.
15. Guy W. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Heath, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976.
16. Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia. I. Rating scale and standardized examination. *Acta Psychiatr. Scand.* 1996; **93**(2): 129–36. 10.1111/j.1600-0447.1996.tb09814.x
17. Petrides G, Fink M. The "half-age" stimulation strategy for ECT dosing. *Convuls. Ther.* 1996; **12**(3): 138–46.
18. Petrides G, Divadeenam KM, Bush G, Francis A. Synergism of lorazepam and electroconvulsive therapy in the treatment of catatonia. *Biol. Psychiatry*. 1997; **42**(5): 375–81. 10.1016/S0006-3223(96)00378-2
19. Greenberg RM, Pettinati HM. Benzodiazepines and electroconvulsive therapy. *Convuls. Ther.* 1993; **9**(4): 262–73.

20. Luchini F. The catatonic syndrome: clinical features and ECT response of 26 in-patients resistant to pharmacological treatment. [Internet]. University of Pisa; 2013.
21. England ML, Öngür D, Konopaske GT, Karmacharya R. Catatonia in psychotic patients: Clinical features and treatment response. *J. Neuropsychiatry Clin. Neurosci.* 2011; **23**(2): 223–6. 10.1176/jnp.23.2.jnp223
22. Hatta K, Miyakawa K, Ota T, Usui C, Nakamura H, Arai H. Maximal response to electroconvulsive therapy for the treatment of catatonic symptoms. *J. ECT*. 2007; **23**(4): 233–5. 10.1097/yct.0b013e3181587949
23. Tuerlings JHAM, van Waarde JA, Verwey B. A retrospective study of 34 catatonic patients: Analysis of clinical care and treatment. *Gen. Hosp. Psychiatry*. 2010; **32**(6): 631–5. 10.1016/j.genhosppsych.2010.08.007
24. Unal A, Bulbul F, Alpak G, Virit O, Copoglu US, Savas HA. Effective treatment of catatonia by combination of benzodiazepine and electroconvulsive therapy. *J. ECT*. 2013; **29**(3): 206–9. 10.1097/YCT.0b013e3182887a1a
25. Waarde JA Van, Tuerlings JHAM, Verwey B, Mast RC Van Der. Electroconvulsive therapy for catatonia: Treatment characteristics and outcomes in 27 patients. *J. ECT*. 2010; **26**(4): 248–52. 10.1097/YCT.0b013e3181c18a13
26. Kahlbaum K. Die Katatonie oder das Spannungsirresein, eine klinische Form psychischer Krankheit. Berlin: Hirschwald; 1874.
27. Abrams R, Taylor MA. Catatonia: A Prospective Clinical Study. *Arch. Gen. Psychiatry*. 1976; **33**(5): 579–81. 10.1001/archpsyc.1976.01770050043006
28. Bhati MT, Datto CJ, O'Reardon JP. Clinical manifestations, diagnosis, and empirical treatments for catatonia. *Psychiatry (Edgmont).* 2007; **4**(3): 46–52.
29. Rao NP, Kasal V, Mutalik NR, Behere R V, Venkatasubramanian G, Varambally S, et al. Has Kahlbaum syndrome disappeared or is it underdiagnosed? Reexamining the nosology of catatonia. *J. ECT*. 2012; **28**(1): 62–3. 10.1097/YCT.0b013e318223c3f5
30. Larner A. Neurological Signs: Echo Phenomena. *ACNR*. 2015; **15**(3): 16.
31. Ducharme S, Dickerson BC, Larvie M, Price BH. Differentiating frontotemporal dementia from catatonia: A complex neuropsychiatric challenge. *J. Neuropsychiatry Clin. Neurosci.* 2015; **27**(2): e174–6. 10.1176/appi.neuropsych.14070157
32. Baker IWS, Jackson M, Bass C. Catatonia causing permanent cognitive impairment: A case study. *Cogn. Behav. Neurol.* 2005; **18**(3): 141–3. 10.1097/01.wnn.0000178230.46691.c7
33. Swartz CM, Acosta D, Bashir A. Diminished ECT response in Catatonia due to chronic neurologic condition. *J. ECT*. 2003; **19**(2): 110–4.
34. Caroff S, Mann S, Francis A, Fricchione G. Catatonia: From Psychopathology to Neurobiology. American Psychiatric Pub; 2007.
35. Kamigaichi R, Kubo S, Ishikawa K, Yokoyama K, Ogaki K, Usui C, et al. Effective control of catatonia in Parkinson's disease by electroconvulsive therapy: A case report. *Eur. J. Neurol.* 2009; **16**(2): e6. 10.1111/j.1468-1331.2008.02357.x
36. Poyraz BÇ, Poyraz CA, Yassa A, Arikan MK, Gündüz A, Kiziltan G. Recurrent catatonia in Parkinson disease. *J. Clin. Psychopharmacol.* 2016; **36**(1): 104–6. 10.1097/JCP.0000000000000443
37. Suzuki K, Awata S, Nakagawa K, Takano T, Matsuoka H. Catatonic stupor during the course of Parkinson's disease resolved with electroconvulsive therapy [1]. *Mov. Disord.* 2006; **21**(1): 123–4. 10.1002/mds.20749
38. Northoff G. What catatonia can tell us about "top-down modulation": A neuropsychiatric hypothesis. *Behav. Brain Sci.* 2002; **25**(5): 555–77.
39. Walther S, Stegmayer K, Wilson JE, Heckers S. Structure and neural mechanisms of catatonia. *The lancet. Psychiatry*. 2019; **6**(7): 610–9.
40. Haroche A, Rogers J, Plaze M, Gaillard R, Williams SC, Thomas P, et al. Brain imaging in catatonia: systematic review and directions for future research. *Psychol. Med.* 2020; **50**(10):

1585–97.
41. Leentjens AFG. Depression in Parkinson's disease: Conceptual issues and clinical challenges. *J. Geriatr. Psychiatry Neurol.* 2004; **17**(3): 120–6. 10.1177/0891988704267456
42. Borisovskaya A, Bryson WC, Buchholz J, Samii A, Borson S. Electroconvulsive therapy for depression in Parkinson's disease: systematic review of evidence and recommendations. *Neurodegener. Dis. Manag.* 2016; **6**(2): 161–76. 10.2217/nmt-2016-0002
43. Figiel GS, Hassen MA, Zorumski C, Krishnan KRR, Doraiswamy PM, Jarvis MR, et al. ECT-induced delirium in depressed patients with Parkinson's disease. *J. Neuropsychiatry Clin. Neurosci.* 1991; **3**(4): 405–11. 10.1176/jnp.3.4.405
44. Kellner CH, Beale MD, Pritchett JT, Bernstein HJ, Burns CM. Electroconvulsive therapy and Parkinson's disease: the case for further study. *Psychopharmacol Bull*. 1994; **30**(3): 495–500.
45. Popeo D, Kellner CH. ECT for Parkinson's disease. *Med. Hypotheses*. 2009; **73**(4): 468–9. 10.1016/j.mehy.2009.06.053
46. Williams NR, Bentzley BS, Sahlem GL, Pannu J, Korte JE, Revuelta G, et al. Unilateral ultra-brief pulse electroconvulsive therapy for depression in Parkinson's disease. *Acta Neurol. Scand.* 2017; **135**(4): 407–11. 10.1111/ane.12614
47. Rasmussen SA, Mazurek MF, Rosebush PI. Catatonia: Our current understanding of its diagnosis, treatment and pathophysiology. *World J. psychiatry*. 2016; **6**(4): 391–8.