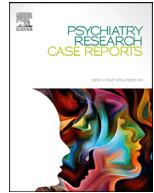




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# Late to respond, but early to relapse - An abnormal course of electroconvulsive therapy in treatment-resistant schizophrenia during times of COVID-19

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## 1. Introduction

Schizophrenia is a chronic mental disorder associated with significant functional disability and healthcare costs (Nucifora et al., 2019; Stenmark et al., 2020). Despite several pharmacologic treatment options, approximately 30% of patients do not respond to standard of care medications. These patients can be classified as suffering from treatment resistant schizophrenia (TRS), which is associated with greater health burdens (Nucifora et al., 2019; Chan et al., 2019). Electroconvulsive therapy (ECT) has been utilized in the treatment of schizophrenia since the 1930s and there is growing evidence for the use of ECT in augmenting antipsychotic pharmacotherapy among TRS patients (Nucifora et al., 2019; Chan et al., 2019). One recent blinded randomized control trial suggested that clozapine and ECT have synergistic effects on managing positive symptoms of schizophrenia (Petrides et al., 2015). Despite its potential, ECT remains significantly underutilized due to factors such as patient and provider stigma, negative media portrayal, excessive emphasis on side effects, legal restrictions, designation of ‘last resort’ status, and ill-defined or contradictory treatment guidelines (Kellner et al., 2020; Gergel, 2022; Griffiths and O’Neill-Kerr, 2019, Maixner et al., 2021). Recently, COVID-19 related disruptions have further hindered the accessibility of ECT treatments globally, prompting discussion that ECT should be considered an essential procedure (Ali et al., 2019).

There is also a need to better characterize ECT treatment parameters to understand and predict therapeutic responses (Chan et al., 2019). The current American Psychiatric Association (APA) Task force on ECT recommends treatment schedules consisting of two or three weekly sessions of ECT for patients with schizophrenia. APA guidelines recommend continuing treatment duration based on clinical judgment, although this individualization makes it difficult to predict when a therapeutic response is anticipated (American Psychiatric Association, 2002). While the rate of response and time course of ECT in depression has been characterized in multiple studies, only two similar studies have been reported for schizophrenia (Chan et al., 2019). The most recent study

demonstrated that TRS patients had the greatest reduction in positive symptoms between the third and sixth ECT sessions, with most patients responding in 12 sessions (Chan et al., 2019). Growing evidence has also suggested a role for maintenance ECT (M-ECT) following an acute ECT treatment course to prevent relapses frequency associated with TRS (Gangadhar and Thirhalli, 2010; Braga et al., 2019). However, there is currently no consensus regarding duration and frequency of this treatment among patients with schizophrenia.

Illustrating the complexity of the ECT time course, we present a unique case of a patient with TRS that responded significantly later than expected to her ECT regimen. Unfortunately, COVID-19 imposed quarantines and the involuntary nature of her treatment played a significant role in disrupting the patient’s clinical treatment. This treatment disruption resulted in an unanticipated abrupt clinical relapse. With this case as an example, we discuss potential challenges psychiatric teams may face in pursuing ECT, despite the indication for treatment.

Appropriate informed consent was obtained from the patient, patient’s family, and conservator of person for this case report.

## 2. Case presentation

A 37-year-old female with a previous diagnosis of schizoaffective disorder bipolar type; opioid use disorder, and stimulant use disorders initially presented to the Emergency Department stating her “mind was not working” after developing acute agitation and paranoia while living at a sober house. She reported experiencing ego-dystonic, command auditory hallucinations involving the devil telling her to kill herself and peers at the sober house. She cut herself superficially, tried to hang herself with a sheet, and was significantly preoccupied with suicidal thoughts. She was transferred to an inpatient psychiatric unit where she remained hospitalized for 1 year and 7 months. Due to the disabling nature of her symptoms, aggression, and treatment non-adherence during hospitalization, she was transferred to the author’s unit in a state Psychiatric Hospital. Her stay on prior units was significant for paranoia and multiple delusions. The content of these delusions varied on a

**Abbreviations:** ECT, Electro Convulsive Therapy; TRS, Treatment Resistant Schizophrenia; APA, American Psychiatric Association; CT, Computerized Tomography; MRI, Magnetic Resonance Imaging; COP, Conservator of Person; CBC, Complete Blood Count; CMP, Complete Metabolic Panel; EKG, Electrocardiogram; EEG, Electroencephalography; IM, Intra Muscular; RCT, Randomized Controlled Trial; BPRS, Brief Psychiatric Rating Scale; M-ECT, Maintenance Electro Convulsive Therapy.

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daily basis including: grandiose (“I have 40 houses”), paranoid (“I’m a New Britain cop and FBI undercover agent”; “I’m Escobar”), and somatic (“I’m 8 years old”; “I have 5 types of cancer”; “I am made of cocaine”; “I’m pregnant with triplets”). She claimed specific staff were her family members (Author 2 was her brother and uncle on two different occasions) or were going to adopt her. She was unable to participate in a reality based discharge plan, and would repeatedly state, “Just open the door and let me go to my home” (to the several mansions she owned) with her “8 children”.

The patient had an extensive past psychiatric history including several psychiatric hospitalizations, imprisonment, time in sober/halfway houses, and child protective services since her adolescence. She has a social history significant for trauma and family dysfunction including living in foster homes (from age 5 to 18), maternal death, and her sister-completing suicide. She had an extensive legal history with over 9 arrests and various charges including breach of peace and assault in the third degree. Furthermore, she had struggled with substance use including cocaine, heroin, and alcohol. While she did not have a history of drug overdose, she had lost all her teeth due to extensive substance use. Her concomitant medical conditions included obesity, asthma, and type 2 diabetes mellitus.

Our treatment team initially attempted numerous voluntary and involuntary trials of pharmacotherapy, including risperidone, ziprasidone, olanzapine, clozapine, paliperidone, asenapine, iloperidone and oxcarbazepine. However, despite treatment, there was no clinically significant reduction in positive symptoms. Given the patient’s treatment resistance, head CT and MRI were conducted to rule out organic causes of psychosis, which proved to be unrevealing. During these trials, she would also frequently refuse to take her medications due to paranoia that she was being poisoned. Her medication refusal was associated with severe aggression to the point where she physically assaulted a nurse. She was ultimately deemed incapable of giving informed consent in regards to psychiatric medication. Our treatment team noted that a trial of ECT was never considered during her three-year long course of clinical illness. She categorically refused to consider voluntary ECT, and the probate court deemed her incapable of consenting for ECT. Her conservator of person (COP) agreed for a trial of ECT and arrangements were made for treatment at the nearest available facility.

Appropriate medical and neurological evaluation performed prior to treatment included a CBC, CMP, EKG, EEG, and anesthesiology evaluation. Findings were unremarkable. The patient was tapered off Oxcarbazepine to ensure an effective seizure.

On examination of the patient’s mental status prior to ECT initiation, her speech was incomprehensible at times and affect was constricted. Her thought process became easily disorganized when questioned, and her thought content included somatic, grandiose, persecutory, and bizarre delusions. Her insight and judgment were both poor. She was unable to engage in consistent, reality based discussions of her treatment plan.

Right unilateral ECT was initially delivered with a pulse width between 0.3 and 0.5 ms at an initial frequency of 3 weekly sessions under general anesthesia. During this time, the patient continued on her psychiatric medications including clozapine 200 mg twice a day, paliperidone (Invega Sustenna) 234 mg IM every 28 days, and alprazolam 2 mg three times daily. Her alprazolam would be withheld in the morning before ECT and given on her return to the unit.

After receiving 14 sessions of ECT, the patient’s mental status remained similar to her previous baseline. Her speech was occasionally incomprehensible, and she continued to demonstrate a restricted affect. Her thought process remained disorganized as she demonstrated preoccupation with strongly fixed grandiose, paranoid, and bizarre delusions. She continued to lack insight and refused to engage in reality-based discussions regarding her potential discharge. Despite indicating the belief that she did not need ECT, she continued to comply with treatment sessions. To increase the time duration of effective seizures, ECT lead placement was also changed from right unilateral to bitemporal.

Involuntary ECT treatment duration was restricted to a maximum of 45 days due to state probate court limitations. Our treatment team utilized evidence of late response in literature, guidelines that recommend greater durations, and COVID-19 related interruptions to advocate successfully in court for additional treatment. Notably, after receiving 19 sessions of ECT, rapid and significant improvements were observed in the patient’s mental status. These included gradual insight into her psychiatric condition and increased cooperation with reality-based discharge planning. The patient was able to state her correct age, expressed interest in going to a group home in the city her biological father was living in, and conduct an in-person meeting with her father on the unit. On mental status examination, her speech was occasionally mumbled but mainly comprehensible. Her affect, while limited, demonstrated appropriate brightening on occasion and congruence to the content of discussion. Her tangentiality diminished, and her thought process became linear and goal oriented during conversation. She was able to appreciate inaccuracies in her perspective when challenged by the treatment team, and there was no evidence of fixed delusions. With respect to her cognitive state, she did exhibit transient confusion such as disorientation to the day of the week. Considering the overall benefits observed in her positive and negative symptoms, eight ECT sessions were continued at the same frequency. During this time, she became more receptive to addressing her substance use (she previously justified usage with somatic delusions of various cancer diagnoses). For the first time, she expressed interest in initiating Suboxone maintenance therapy.

Due to confirmed COVID-19 cases, the psychiatric unit was placed on quarantine. During this time, the patient was unable to receive subsequent planned ECT treatments. This abrupt cessation in ECT therapy was associated with a rapid return to baseline mental status exam. After two weeks without ECT treatments, our patient essentially lost all the benefits of ECT and began to experience the same positive symptoms prior to ECT. Our treatment team attempted to approach the probate court again to reinstate ECT, but the patient began refusing her oral medications. This worsened her paranoia and aggression, resulting in her assaulting two patients on the unit and threatening several team members. Due to the significant risk of assault and other patients pressing legal charges, the patient was discharged to a forensic facility for stabilization and restoration.

### 3. Discussion

Given that ECT has been around for eight decades, it is remarkable that only a few studies have examined the speed of response to ECT among patients with TRS. These studies report variable findings. One prospective blinded RCT suggests a plateau in response to ECT occurring between 12 and 16 sessions (Petrides et al., 2015). A recent retrospective naturalistic study reported that among patients with TRS responsive to ECT, 80% responded within the first six sessions (Chan et al., 2019). Other studies in depression and schizophrenia typically describe a course of 6 to 12 treatments (National Institute for Health and Care Excellence, 2003). Here we present a patient with TRS and a significant response to ECT after a course of 19 sessions. This unusual delayed response to ECT demonstrates the challenge of predicting when clinical improvement might occur and the need for further characterization of the time course in TRS. Understanding the speed of response rate is significant for clinicians and patients to establish expectations and determine treatment duration in conjunction with continued clinical assessment and patient-centered decision-making. While the APA task force on ECT defers to clinical judgment for deciding the duration of ECT, there is considerable value in continued research to understand the mechanism of action of ECT in TRS in order to understand factors related to speed and likelihood of response (American Psychiatric Association, 2002). This information will allow for better stratification of treatment regimens to ensure patients receive an adequate course of ECT.

Despite remarkable improvement after receiving an extended course of ECT, the patient we describe had an equally noteworthy rapid relapse upon treatment cessation. Although ECT is an effective treatment in schizophrenia, relapse is frequent and may present in as many as 60% of patients after one year (Grover et al., 2019). One retrospective study found the median relapse free period after acute ECT therapy to be 21.5 months (Shibasaki et al., 2015). Although relapse is common within the first year, relapse within two weeks such as in our patient is atypical. Factors associated with a greater risk of relapse include a greater number of past psychotic episodes, higher Brief Psychiatric Rating Scale (BPRS) scores after acute ECT course, and higher number of ECT sessions (Grover et al., 2019). Given the extensive psychiatric history and longer ECT treatment course of our patient, these reported risk factors may suggest her greater likelihood for relapse. Interestingly, adjunctive mood stabilizer therapy was associated with a lower risk of relapse, which our patient did not receive (Grover et al., 2019). This was due to concern for complications with ECT as per the protocol of the ECT treatment facility. Tapering the ECT course has also been suggested to reduce relapse rate, and the abrupt nature of treatment discontinuation in our patient is another likely contributory factor for this acute decompensation (Kellner et al., 2020). For patients such as ours that may represent more intractable disease, there is limited but increasing data suggesting a benefit of M-ECT beyond the acute course (Braga et al., 2019, Grover et al., 2019). There is a lack of consensus regarding the duration, frequency, and benefit of M-ECT, which warrants further investigation for TRS patients.

Unfortunately, ECT treatment for our patient was abruptly discontinued due to COVID-19 related limitations. ECT was unavailable at the patient's primary psychiatric hospital. This presented a logistical challenge in arranging routine transportation, as the patient would threaten and assault transportation staff. This may explain the reluctance of prior treatment teams to consider ECT. The patient's continued aggression and refusal of treatment further complicated the primary team and ECT clinic's ability to coordinate and perform procedures respectively.

On several occasions, our patient was safely transported to the ECT site, only for ECT to not be performed due to her threatening ECT nurses and staff. The ECT site did not have the facilities or staff for physical restraint or administering medications. To confront these challenges, greater emphasis needs to be placed on recognizing ECT as an essential treatment in severe psychiatric illness. This includes providing ECT facilities with necessary resources to manage patients and promoting accessibility (Maixner et al., 2021). Recent preliminary work has suggested improved coordination of ECT sessions by multidisciplinary treatment teams utilizing checklists. This approach can strengthen communication and better delineate individual responsibilities (Mishra et al., 2021). Identification of additional strategies that improve provider confidence and patient assurance of ECT will be of considerable value.

#### 4. Conclusion

There is a need to further characterize the timing of anticipated ECT responses among TRS patients. For patients like ours, a prolonged treatment duration may be beneficial despite an initial lack of response in the first 16 sessions. Patients with more severe psychotic history and prior

treatments may also benefit from increased vigilance to provide regular treatment sessions maintained for longer durations due to an increased susceptibility for rapid relapse. Greater efforts are needed to enhance recognition of ECT as essential treatment, identify strategies to improve ECT care coordination, and reduce provider and patient stigma.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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