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Combined Antipsychotics and Electroconvulsive Therapy in an Acutely Psychotic Patient with Treatment-resistant Schizophrenia

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ABSTRACT *~ Treatment of patients with Treatment-resistant Schizophrenia (TRS), who fail to respond to multiple antipsychotic trials, including clozapine (CLZ), is challenging. Several alternative strategies are reported in studies, one of which includes augmenting antipsychotics (AP) with Electroconvulsive therapy (ECT). We discuss a case of an acutely psychotic patient with TRS who responded effectively and sustained remission to this strategy which was ECT combined with two AP, CLZ and aripiprazole. Notable improvement in clinical and cognitive outcomes was seen with just five right unilateral ECT sessions, CLZ titrated up to 62.5 mg/d and aripiprazole 20 mg/d with no adverse effects. Nine days into the psychiatric hospitalization, patient had decreased total scores on the Positive and Negative Syndrome Scale by 44% and an improved score on the St. Louis University Mental Status Exam by increasing from 3 to 22. This case report suggests that a subgroup of patients with TRS could benefit from a trial of adjunct ECT combined with AP to achieve a rapid alleviation of positive and negative symptoms which allows patients to have greater functional stability.* Psychopharmacology Bulletin. *2017;47(2):57–62.*

Introduction

With a global prevalence of 1% and significant functional impairment, schizophrenia is a disabling disease.[1] Complicating this further is the heterogeneity among patient presentations, course of illness and treatment responses. Despite treatment with at least two adequate trials of antipsychotics (AP), 10%–30% of patients do not respond to treatment with AP and meet criteria for Treatment-resistant Schizophrenia (TRS).[2,3] Clozapine (CLZ) is recognized as the most effective AP medication for TRS, but a subgroup of 40%–70% fail to see an improvement with CLZ or require its suspension due to adverse effects such as neutropenia.[4] These patients often struggle with debilitating symptoms and face

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a higher degree of functional and social disability.[5] Adjunct treatment strategies have been investigated, one of which is augmenting CLZ with Electroconvulsive therapy (ECT).[6] There is some preliminary evidence suggesting the safety and efficacy of CLZ augmentation with ECT (CLZ + ECT) in TRS.[7] Here we report a case of a 38 year-old female with TRS who responded effectively and sustained remission to this treatment strategy combining AP (i.e. CLZ + aripiprazole) with ECT.

Case Presentation

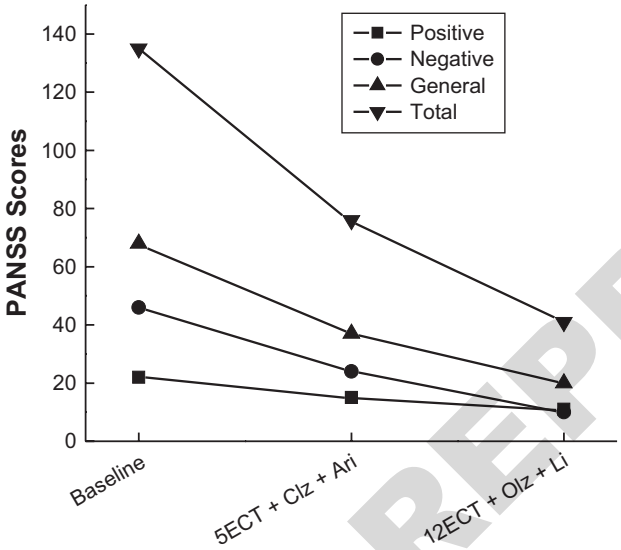
A 38 yrs. old Caucasian female presented to a local emergency room with a 2 week history of psychotic symptoms and cognitive impairment secondary to psychosis. Patient was diagnosed with TRS and has a history of Cannabis, Alcohol and Cocaine use disorder, but was in sustained remission for over 18 years under the care of assertive community treatment team (ACTT). One month prior to her presentation, she failed a second re-challenge with CLZ which was discontinued due to mild neutropenia with an Absolute Neutrophil Count (ANC) of 1400 μL (Normal range ANC 1500 μL in the general population). Patient was switched to aripiprazole (Ari) and titrated up to 20 mg/d and lorazepam 0.5 mg/d. However, this transition did not yield adequate control of symptoms. Following her admission, the Positive and Negative Syndrome scale (PANSS) was administered and she scored 135 out of 210, with prominent negative symptoms (Figure 1). Her acute cognitive impairment, as assessed by the St. Louis University Mental Status (SLUMS) exam was a total of 3. She had no significant past medical history or any active use of substances. After medical clearance, she agreed to a voluntary psychiatric hospitalization.

Patient's previous psychiatric admission was nearly 16 years ago, when she was first diagnosed with Schizophrenia at age 22. Since then, she had trials of quetiapine, risperidone, olanzapine and ziprasidone at adequate doses and duration before meeting criteria for TRS. For 9 years, she remained in partial remission on the most effective combination of AP, including CLZ 800 mg/d and ziprasidone 320 mg/d, along with bupropion XL 150 mg/d, clonazepam 1.5 mg/d and risperidone 3 mg/d as needed. Routine monthly blood draws were within normal limits for 8.5 years until bimonthly ANC monitoring was warranted. Six months later, a dramatic decrease in ANC was noted over two weeks (2100 μL to 1700 μL) warranting biweekly blood draws. She declined this level of monitoring and CLZ was discontinued at age 37.

Over that next year, multiple combinations of AP were attempted, and she had periods of non-compliance with medications. Later, she was adamant about being on a single AP; hence a second CLZ trial was

FIGURE 1

Positive and Negative Syndrome Scale (PANSS) was used to measure patient's response to combined treatments at the 3 time points: baseline, following 5 right unilateral ECTs and following 12 right unilateral ECTs



Abbreviations: Olz, olanzapine; Li, lithium; Ari, Aripiprazole.

started and titrated up to 800 mg/d, as monotherapy for 4 months, only to be suspended again due to mild neutropenia (ANC 1400 μL). It was this second CLZ discontinuation and replacement with Ari 20 mg/d that led to this current ER visit. Given the gravity of her presentation, she was re-challenged with her third CLZ trial started at 25 mg/d, and continued on Ari 20 mg/d.

Clinicians recognized the urgent necessity to alleviate symptoms, so they obtained consent from patient's mother to implement treatment with right unilateral ECT combined with two AP (CLZ + Ari). In just 9 days, patient had a significant clinical improvement with five right unilateral ECT sessions as adjunct to CLZ, titrated up slowly from 25 to 62.5 mg/d, while being maintained on Ari 20 mg/d with stable ANC counts at 2510 μL. Rating scales also correlated with this improvement: PANSS score decreased by 44% (total, and a more prominent reduction in negative than positive (47.8% vs. 32%) was noted. The SLUMS total score increased from 3 to 22, indicating the rapid response to this combined treatment. Noting her improvement, patient declined any further ECT, which was granted as she had medical decision capacity.

Slow titration of the third CLZ trial continued due to past history of neutropenia, though further improvement was slight and gradual

compared to the five ECT treatments. By the end of 34 days of hospitalization, patient's CLZ was titrated up to 200 mg/d, but required immediate discontinuation after ANC dropped to 1410 μL. CLZ was replaced with Olanzapine (Olz) 10 mg/d and within three days of this transition, ANC improved to 2100 μL. Given the prolonged hospitalization, her notable clinical and cognitive improvement, she requested to be discharged. With close ACTT weekly out-patient follow-up and patient being at her baseline mentation with non-bothersome hallucinations, she was deemed stable for discharge under her family's care on the following medications: Ari 20 mg/d, Olz 10 mg/d and mirtazapine 15 mg/d.

Four months later, patient discontinued Ari due to akathisia and lithium (1200 mg/d) was added to stabilize her mood. She has continued to decline any further re-challenges with CLZ to date due to her previous experiences. Eight months after the discharge from the hospital, she agreed to maintenance ECT and received 12 right unilateral treatments to target persistent positive symptoms, while being on the aforementioned doses of Lithium, Olz, and mirtazapine. Not only does she remain in partial remission to date, she has not required any further hospitalizations in over two years.

Discussion

Treatment of TRS is challenging. A staggering 40%–70% of TRS patients fails to respond to CLZ or is unable to tolerate it due to adverse effects leaving clinicians with the difficult task of finding alternate treatment strategies.[4,8] This subgroup faces insurmountable disabilities, has higher annual medical costs, and is often subject to frequent and prolonged hospitalizations compared to the non-TRS patients.[9,10] Multiple adjunct treatments to AP have been studied, including ECT. Current indications for the use of ECT in Schizophrenia are: prior response to ECT, ineffective pharmacotherapy and as second line for TRS.[11] Current data regarding this combined strategy stems mainly from case reports and open labeled trials, with limited information about implementing CLZ + ECT in patients who previously could not tolerate CLZ due to developing neutropenia, like the patient in this report.[12] Our case serves as an example for the safety and efficacy of this treatment strategy in TRS, especially with predominant negative symptoms.

In this reported case, clinicians required consideration of several factors in determining this patient's suitability for treatment with combined AP (CLZ + Ari) with ECT, including a past history of non-compliance with frequent blood draws, uncertainty over reinitiating a third CLZ trial in a patient who failed it twice due to neutropenia, her tolerance of this combined therapy and balancing her autonomy, beneficence and

non-maleficence given limited decision making capacity on admission. Based on a higher benefit versus risk ratio, the gravity of clinical presentation and lack of her capacity, informed consent was obtained from the patient's mother. Compared to the average ECT sessions for treatment of major depression, TRS patients likely need a higher number of treatments, with one systematic review finding the average to be 11.3 (range 4–20).[12,13] However, our patient achieved good results with just five right unilateral sessions, further supporting the growing evidence on the safety and effectiveness of this combined treatment strategy. Her rapid shift in symptoms correlated with improved total scores on SLUMS. Psychopathology as assessed by the PANSS also reflected her good response as seen by a decrease in all sub-scales, especially with the highest change in negative symptoms by 47.8% (Figure 1). This is significant as most previous studies found that severity rating scales saw higher reductions in positive symptoms with either little to no change or worsening of the negative symptoms in TRS with combination of CLZ + ECT.[14–16] There are likely multiple factors that may contribute to different observations between our case and others. This could include a much higher degree of illness severity prior to treatment, tools to assess severity changes (PANSS vs. other scales), combining specific AP like CLZ + Ari, frequency and type of ECT, patients' age and duration of psychotic episode.[12,17]

Conclusion

The combination of AP (CLZ + Ari) with adjunct ECT is safe and effective in improving prominent negative and cognitive symptoms in patients with TRS. This case report suggests that a subgroup of patients with TRS could benefit from a trial of adjunct ECT combined with AP to achieve a rapid alleviation of positive and negative symptoms which allows patients to have greater functional stability. Clinicians should consider this treatment option when managing patients with TRS. ✤

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