Northeast Georgia Medical Center
GRADUATE MEDICAL EDUCATION

Medical Management of Treatment Resistant Schizophrenia and Decision-Making Mechanism for Clozapine: Case Report

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Learning Objectives

1. Define treatment resistant schizophrenia and how it is currently diagnosed
2. Recognize approved treatments and their associated side effects and monitoring
3. Identify key drivers and barriers in decision making
4. Discuss possible decision-making mechanism for clozapine

Academic Context

Definition: Treatment Resistant Schizophrenia (TRS), although not an official diagnosis, is minimally defined as persistent positive psychotic symptoms after at least two trials of antipsychotics at adequate dosage and duration with consistent medication adherence.[1]

Prevalence: Estimated that around 30% of patients with schizophrenia meet the criteria for TRS.[1]

Pathophysiology: Proposed hypotheses for TRS include dopamine super-sensitivity versus normodopaminergic etiology.[1]

1. **Dopamine super-sensitivity:** antipsychotics cause extended blocking of D2 receptors leading to increased sensitivity in those receptors, and thus intensifies psychotic symptoms during breakthrough episodes.[1]
2. **Normodopaminergic:** most likely increased glutamate concentrations.[1] Neuroimaging in TRS patients has shown decreased striatal dopamine synthesis, but increased glutamate levels in the anterior cortex.[2]

Treatment: Evidence shows clozapine is the superior and most efficacious treatment for TRS.[1]

Problem: Clozapine is associated with numerous dangerous side effects, such as agranulocytosis, seizures, myocarditis, and constipation that can lead to ileus and bowel ischemia.[4] These side effects and the continuous monitoring that is required for clozapine deters clinicians from starting it at the earlier recommended stages, leading to delayed treatment and worsened prognosis.[1]

Decision-making mechanisms problems:

1. There is discrepancy in the literature about the criteria for TRS.[1]
2. There is no decision-making algorithm to determine when clozapine should be initiated, and there are minimal designated clozapine clinics.
3. There is a Positive and Negative Syndrome Scale (PANSS) that is often used in literature to identify and quantify symptoms of psychosis.[6] However, no scaling is typically used in everyday practice.

Clinical Case

A 49-year-old white male with past medical history of schizophrenia and tobacco use disorder presented to the inpatient psychiatric unit with disorganized thought process and behavior with inability to participate in comprehensible conversation due to the severity of his psychosis. At admission he exhibited:

- disorientation x4
- disorganization in thought and behavior
- delusions
- response to internal stimuli
- restlessness
- thought process: flight of ideas, tangentiality, and moments of word salad

ROS: Unable to be obtained due to the severity of his psychosis.

Vitals and labs: His vitals were within normal ranges. His only abnormal lab values were a hemoglobin of 10.6 and a platelet count of 99,000.

Physical Exam: Disheveled and malodorous. He also displayed a shuffling gait and tardive dyskinesia in his right upper extremity and left lower extremity.

Management: The patient was started on Risperdal, but was transitioned to Haldol, Prolixin, and then Invega (Table 1). By day 19, discussion began about his resistance to medication and if he should be trialed on clozapine. To avoid the complexity of clozapine's side effects and monitoring, it was decided that he should restart Invega. This choice resulted in enough improvement in his thought disorganization to be discharged. However, it was noted that he was at high risk for readmission. The patient was ultimately readmitted six days later due to worsening hallucinations, disorganized behavior, and aggression.

Day	Medication	Dosage	Response
1	Risperdal	1 mg BID	No changes
2	Risperdal	2 mg BID	Able to orient to self. No other changes
3	Risperdal	2 mg BID	No changes
4	Risperdal	2 mg BID	More redirectable. No other changes
5	Haldol	5 mg	No changes
6	Haldol	5 mg qam, 10 mg qhs	Increased paranoia with persecutory delusions. No other changes
7	Haldol	5mg qd/5mg q1300/10mg qhs	Diminished paranoia. No other changes
8	Haldol	5mg qd/5mg q1300/10mg qhs	No changes
9	Haldol	5mg qd/5mg q1300/10mg qhs	No changes
10	Haldol Prolixin	5 mg am 2.5 mg BID	No changes
11	Prolixin	2.5 mg qam, 5 mg qhs	Able to provide short answers such as "yes" before returning to incoherent, loose, and tangential thought
12	Prolixin	5 mg BID	No changes
13	Prolixin	5 mg BID	Worsening tardive dyskinesia. No other changes
14	Invega PO	3 mg qd	No changes
15	Invega PO	3 mg qd	No changes
16	Invega PO	6 mg qd	No changes
17	Invega PO	6 mg qd	No changes
18	Invega PO	9 mg qd	No changes
19	Invega PO Invega Sustenna	6 mg qd 234 mg	Slightly less disorganized and could answer more questions, but still exhibiting disorganized thoughts and behavior
20	Invega PO	6 mg qd	No changes
21	Invega PO	6 mg qd	No changes
22	Invega Sustenna	156 mg	Thought disorganization improved to believed baseline and prepared for discharge

Table 1: The patient's trials of antipsychotics with dosage and how the patient responded to each trial during his 22-day inpatient treatment.

Discussion

In this case, the patient failed multiple antipsychotic trials despite remaining adherent during his inpatient stay. He therefore is meeting criteria for TRS by the previously outlined definition.

Like many other patients with TRS, there was hesitancy regarding the risk versus benefit of starting this patient on clozapine.

These patients also face many challenges that further complicates clozapine treatment, seen in Figure 1.

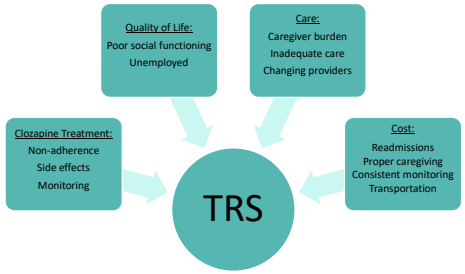

Figure 1: The challenges faced by patients with treatment resistant schizophrenia (TRS).

Discussion

Recommendations:

1. Clear and agreed-upon criteria be set forth for defining TRS, which will allow these patients to be identified and treated in a timely manner.
2. Implementing PANSS or a modified PANSS into everyday practice, which will allow for more accurate documentation and monitoring of treatment response even when providers are changed.
3. A treatment algorithm, which could help determine when it is appropriate to start clozapine, but also some next steps such as ECT if clozapine fails.
4. Increase the number of available clozapine clinics.

References

1. Kane JM, Agid O, Baldwin ML, et al. Clinical guidance on the identification and management of treatment-resistant schizophrenia. *J Clin Psychiatry.* 2019;80(2):18com12123
2. Nucifora FC Jr, Woznica E, Lee BJ, Cascella N, Sawa A. Treatment resistant schizophrenia: Clinical, biological, and therapeutic perspectives. *Neurobiol Dis.* 2019;131:104257. doi:10.1016/j.nbd.2018.08.016
3. McQueen G, Sendt KV, Gillespie A, et al. Changes in Brain Glutamate on Switching to Clozapine in Treatment-Resistant Schizophrenia. *Schizophr Bull.* 2021;47(3):662-671. doi:10.1093/schbul/sbaa156
4. De Berardis D, Rapini G, Olivieri L, et al. Safety of antipsychotics for the treatment of schizophrenia: a focus on the adverse effects of clozapine. Therapeutic Advances in Drug Safety. May 2018:237-256. doi:10.1177/2042098618756261
5. Mijovic, A., MacCabe, J.H. Clozapine-induced agranulocytosis. *Ann Hematol.* 2020;99:2477-2482. doi: 10.1007/s00277-020-04215-y
6. Keane Lim, Oon-Him Peh, Zixu Yang, Gurpreet Rekhi, Attilio Rapisarda, Yuen-Mei See, Nur Amirah Abdul Rashid, Mei-San Ang, Sara-Ann Lee, Kang Sim, Hailiang Huang, Todd Lencz, Jimmy Lee, Max Lam. Large-scale evaluation of the Positive and Negative Syndrome Scale (PANSS) symptom architecture in schizophrenia. *Asian Journal of Psychiatry.* 2021;62:102732. doi:10.1016/j.ajp.2021.102732