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When Clozapine is Not Tolerated

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WHEN CLOZAPINE IS NOT TOLERATED

by

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Abstract

The case presented is focused on a 34 year old female diagnosed with paranoid schizophrenia. This patient had been on a number of antipsychotics without adequate relief of symptoms. She was subsequently prescribed clozapine. The clozapine initially helped alleviate her positive symptoms, but then caused her to break out in a systemic rash with continued titration. Therefore, the clozapine was discontinued and combined olanzapine and paliperidone were prescribed. The olanzapine and paliperidone combination was not specifically found in the literature review, but could be a focus of future studies. The literature review indicated that there are current combination, augmentation, and high-dose antipsychotic strategies available when clozapine is not tolerated. However, the evidence of efficacy varies significantly. More research is necessary to solidify efficacy and safety of such treatment strategies. There are novel treatment options in development with limited success at this point, but more research is necessary in this area. Substance abuse and level of compliance need to be identified before deeming medication ineffective. There may need to be a future focus beyond medications and more on balancing the entire biopsychosocial framework for adequate treatment response.

When Clozapine Is Not Tolerated

Background

Schizophrenia is a chronic psychiatric disorder with either persistent or fluctuating psychosis that exists with significant problems in social abilities (Stroup & Marder, 2018). Treatment-resistant schizophrenia can generally be defined as the presence of residual symptoms that are distressing and impair functioning despite multiple treatment attempts with various antipsychotics (Citrome, 2011). However, sometimes antipsychotics are not tolerated as opposed to being ineffective. Clozapine tends to not be tolerated as well as other atypical antipsychotics (Sagud, 2015).

The patient case presented is an example of this intolerability to an antipsychotic that was indeed effective for positive symptoms of schizophrenia. The patient had trialed many antipsychotics as both mono and combination therapy. The residual symptoms were always present enough to cause distress and impair her ability to function until she was placed on clozapine. The clozapine was effective at reducing positive symptoms of psychosis, but caused an allergic reaction resulting in a systemic rash. Literature is lacking for the reintroduction of clozapine to an individual who has experienced an allergic reaction (Choy, 2017). Therefore, the only clinically significant antipsychotic was not tolerated, which leads to the difficulties with treatment. There is a desperate need for a new psychotropic medication with at least equivalent efficacy as clozapine for intolerant cases (Choy, 2017).

Patients with schizophrenia respond more effectively to clozapine than other antipsychotics and it has been linked to reductions in psychiatric hospitalizations (Stroup, Gerhard, Crystal, Huang, & Olfson, 2016). However, roughly one out of five patients on

clozapine ends up discontinuing the medication due to undesirable or intolerable effects (Fazio et al., 2015). This highlights the clear need for new treatment interventions when patients do not adequately respond to antipsychotics, but also when intolerable to the "gold standard" clozapine.

As high as 40% of patients diagnosed with schizophrenia do not sufficiently respond to appropriate antipsychotic dosages (Lowe et al., 2017). Persons diagnosed with schizophrenia tend to live approximately 25 years less than the general population and mortality is reduced with adequate antipsychotic treatment for an average of a nine year period (Bryan, 2015). This risk decreases further with adequate use of clozapine (Bryan, 2015). The purpose of this paper is to identify beneficial alternatives, and to find novel treatments that are in current research and testing when intolerable to clozapine and not responsive to other treatment strategies.

Case Report

The case report is based on a 34 year old Caucasian female admitted to an inpatient psychiatric facility on an involuntary basis with a diagnosis of paranoid schizophrenia. This patient was brought to an ER by her twin brother as she was hallucinating, thought that angels and demons were talking to her, and told staff she was from another planet and was going to marry Jesus.

This patient was originally diagnosed with paranoid schizophrenia in 2003. There was not a known history of suicide attempts, self-harm, or violent behavior. She had a known history of multiple inpatient admissions due to positive symptoms of schizophrenia, which were primarily spiritual delusions with auditory hallucinations. There were known antipsychotic trials of the patient on ziprasidone, quetiapine, aripiprazole, and perphenazine. The exact dosage of these medications was uncertain. This patient has a known history of substance abuse, which

included methamphetamine use in 2004, LSD use in 2010, mushroom use twice, cocaine use twice, and daily marijuana abuse until 2014. She denied alcohol use, but later admitted to quick ingestion of four to five 5.9% alcohol content beers nightly, which could explain the Alanine Transaminase (ALT) mild elevation of 126 IU/L. Laboratory testing was otherwise unremarkable with a negative urine toxicology screen.

The patient's medical history included asthma with recurrent bronchitis, but the patient does have a history of smoking a pack of cigarettes per day. The patient's family history was negative for mental illness, substance abuse, and suicide attempts/completions. The patient reported a good childhood. She reported being a slow learner, but did complete high-school. The patient has never been married and has no kids. She is on disability for mental illness and has not worked since being diagnosed in 2003. She did get a DUI in 2003 and has gotten caught stealing a few times. The patient does not have a history of mania, OCD, panic attacks, eating disorders, or PTSD.

The patient was switched to olanzapine while inpatient. The olanzapine was titrated up to 30 mg daily. There were very minute improvements in the patient's positive symptoms. Clozapine was added and olanzapine was tapered with the ultimate goal of clozapine monotherapy. Clozapine was the next choice, because she lacked adequate response to olanzapine and the other four antipsychotics mentioned earlier. The patient was started on 25 mg of clozapine and once titrated up to 75mg she broke out in a systemic rash that was very painful and pruritic to the patient. The patient had experienced significant reductions in positive symptoms prior to breaking out in the rash.

The patient had also not been sleeping, which warranted the addition of temazepam 15 mg at bedtime with a repeat PRN dose. The patient didn't sleep due to the psychosis, but the positive symptoms of psychosis could not be adequately managed. Paliperidone was then added to the regimen and the olanzapine was simultaneously tapered. Eventually the patient was on 10 mg of olanzapine and 9 mg of paliperidone at bedtime. There was improvement in positive symptoms of schizophrenia with this combination. However, the improvement was not yet to a tolerable level and was still not as effective as the clozapine monotherapy.

The patient denied noncompliance with treatment regimen prior to admission, but it was not completely ruled out. Therefore, the target of treatment was aimed at developing a combination medication regimen to diminish the positive symptoms of psychosis. Initiation of paliperidone palmitate long-acting injection was attempted, but she was completely resistant to the injections. The combination of paliperidone palmitate IM injection and olanzapine PO would have been ideal, because at least the paliperidone would have still been providing some coverage in the event of noncompliance with PO medication.

Limitations include not being able to prove the level of medication compliance and not knowing the exact dosage of prior antipsychotic trials. However, she remained compliant with olanzapine at 30 mg a day monotherapy and olanzapine 10mg in combination with paliperidone 9mg in a controlled environment with limited efficacy. Also, the extent in which the alcohol consumption has affected the efficacy of the treatment regimen is unknown.

Literature Review

The literature was reviewed to identify current and prospective treatment options to adequately treat the positive symptoms of schizophrenia when clozapine is not tolerated and

other atypical antipsychotics have been deemed ineffective as monotherapy. More treatment strategies need to be developed as greater than 50% of patients that have treatment resistant schizophrenia are also unable to tolerate or do not respond to clozapine (Sagud, 2015). Some literature was also reviewed for treatment alternatives when medication noncompliance and/or substance abuse is the culprit of inadequate treatment response to antipsychotics as these potential problems have not been completely ruled out in this case.

Potential Current Treatment Options

Clozapine is often considered the gold standard antipsychotic for treatment resistant schizophrenia. Clinicians are put in a difficult situation when multiple atypical antipsychotics have been ineffective in conjunction with an allergy or intolerance to clozapine (Choy, 2017). Switching antipsychotics due to intolerable side-effects has displayed effectiveness (Stroup & Marder, 2018). Whereas, changing antipsychotics due to lack of effectiveness has shown limited benefit unless switching to clozapine (Stroup & Marder, 2018). There is some evidence supporting the use of combining antipsychotics and augmenting them with electroconvulsive therapy (Choy, 2017). However, augmentation should be restricted to those who should be on clozapine, but cannot tolerate it (Kane, Kishimoto, & Correll, 2018).

Patients with predominately auditory hallucinations are recommended to augment treatment with repetitive transcranial magnetic stimulation (Kane et al., 2018). Electroconvulsive therapy (ECT) is recommended if positive symptoms other than auditory hallucinations exist or if repetitive transcranial magnetic stimulation is either unsuccessful or not available (Kane et al., 2018). Augmentation with topiramate, lamotrigine, or aspirin to an antipsychotic is a possibility in the event that ECT and rTMS are unsuccessful or unavailable, but results are mixed due to a

lack of studies (Kane et al., 2018). Choy (2017) supports the use of high-dose aripiprazole monotherapy and high-dose quetiapine monotherapy. The case presented by Choy (2017) discussed a female with treatment resistant schizophrenia and intolerance to clozapine who was adequately controlled on high-dose quetiapine with minimal residual positive symptoms of psychosis.

In addition, the use of very high-dose atypical antipsychotics is a potential option (Batail et al., 2014). Very high-dose olanzapine has been utilized since the end of the 20th century and has been considered an acceptable option for the patients who cannot tolerate clozapine. There are four random double-blind clinical trials on the use of olanzapine at doses between 25-45 mg/day and three of the four concluded that this dose of olanzapine is equally effective as clozapine dosed between 100-600 mg/day. It was concluded that high-dose olanzapine was well tolerated at doses between 25-60 mg/day. A case report of a patient with treatment-resistant schizophrenia and a patient with clozapine induced agranulocytosis were put on olanzapine doses above 60 mg/day. Both had beneficial results with good tolerance except for a 10 kg gain in weight for one of the patients. This study concluded that more research needs to be conducted on the tolerance and response of very high-dose olanzapine for treatment resistant and clozapine intolerant schizophrenia. Further research may also open the window for testing additional atypical antipsychotics at very high-doses for the same issue at hand.

Zink and Englisch (2012) reported that amisulpride or sulpiride can be augmented to clozapine or olanzapine when the psychotic symptoms have not adequately subsided with monotherapy. Amisulpride is an atypical antipsychotic and sulpiride is a typical antipsychotic. The addition of sulpiride has shown to be superior to amisulpride in specifically decreasing positive symptoms when olanzapine or clozapine are unsuccessful as monotherapy. This

augmentation strategy helps supplement the weak D2 antagonistic effects of clozapine and olanzapine. This medication combination has not been intensively studied in trials, but has shown benefit in case studies, open trials, and a randomized control trial. This has resulted in its use in practice. Therefore, the utilization of olanzapine with either amisulpride or sulpiride could be utilized when clozapine is not tolerated.

The utilization of aripiprazole in combination with ECT has also shown beneficial results in treatment-resistant schizophrenia when clozapine is unable to be used due to a prolonged QTc interval (Nordin & Othman, 2018). The case presents a 30-year old male with treatment-resistant schizophrenia who had to have clozapine discontinued due to prolonged QTc. The patient was then started on 15mg of aripiprazole with improvements, but was readmitted two weeks later due to psychotic behavior. The patient then began an acute series of 12 ECTs in addition to the 15mg of aripiprazole and the patient had significant improvement in symptoms. However, this patient was lost to follow-up after only a couple maintenance ECT treatments, which impedes understanding of the long-term effects. This case provides evidence that antipsychotic and ECT combination therapy may improve psychotic symptoms in a treatment-resistant patient with schizophrenia who is unable to take clozapine.

A retrospective analysis concluded that the long-acting injectable paliperidone palmitate may be an acceptable substitute to clozapine for patients who continue to smoke cigarettes after stabilization on clozapine and discharge from the hospital (Tomko, Ahmed, Kuntz, & Zick, 2016). The authors did not specify whether the patients were treatment resistant, but clozapine is typically only prescribed in resistant cases. It is known that the clozapine was effective as in the focal case of this paper. The retrospective study over three years showed that the patients administered the paliperidone palmitate injectable and the patients administered PO clozapine all

had very similar data in regards to admission, discharge, readmission, and demographics. However, the patients administered the paliperidone palmitate had a significant reduction in readmissions in comparison to the clozapine. This evidence supports the use paliperidone palmitate in place of clozapine, but further research is necessary.

The use of vortioxetine and lurasidone as combination therapy has been utilized in schizophrenia when clozapine was not tolerated due to side-effects (Lowe et al., 2017). The case report focused on three cases of treatment-resistant schizophrenia in which there was significant improvement in cognition and positive symptoms of schizophrenia with the use of vortioxetine and lurasidone. The report indicates that the vortioxetine is likely to have a large impact in the combination as two of the three patients were already taking lurasidone without much benefit on psychotic symptoms. It was noted that persistent use of vortioxetine shares some of the pharmacological actions as clozapine and that lurasidone shares dopamine 2 (D2) and serotonin 2A (5-HT 2A) antagonism with clozapine. It was recognized that this is a case report, which could lead to skewed results due to potentially uncontrolled factors. However, the patients in the case did have significant improvement in cognition and psychotic symptoms with this medication combination. More research in the future on this combination could offer a beneficial alternative to clozapine when it is not tolerated by the patient with schizophrenia.

The inadequate response to multiple antipsychotics prior to the clozapine intolerance may have been due to noncompliance and/or substance abuse as opposed to lack of effectiveness. It is crucial to be cognizant of noncompliance, partial compliance, and/or substance abuse as any of these could play a role in poor response to treatment (Citrome, 2011). Noncompliance can typically be ruled out by the utilization of a long acting injectable (Dold & Leucht, 2014).

Noncompliance could also be ruled out through a controlled environment such as a prolonged inpatient stay.

Co-occurring substance abuse and schizophrenia are associated with poor treatment outcomes and noncompliance (Campbell, Caroff, & Mann, 2018). Substance abuse by a patient with schizophrenia can make psychotic symptoms worse due to the specific properties of the substance or by causing decreased blood levels of the antipsychotics. Patients with schizophrenia that are noncompliant and abuse substances are recommended to be treated with a long-acting injectable antipsychotic. There is some evidence that certain antipsychotics can actually decrease substance use, but the evidence is too inconsistent and limited to recommend one antipsychotic over another in these situations. The authors reported that research evidence is minimal, but through clinical experience they concluded that naltrexone can be safely and effectively utilized with an antipsychotic for co-occurring schizophrenia with alcohol abuse.

Potential Future Treatment Options

Current treatment for schizophrenia is based on the dopamine hypothesis. It suggests that the dopaminergic system is imbalanced in various regions of the brain, which leads to the positive symptoms, negative symptoms, and cognitive decline (Kantrowitz & Javitt, 2011). All of the currently available frontline antipsychotics block the dopamine 2 (D2) receptors (Mouchlianitis et al., 2015). Roughly one-third of patients diagnosed with schizophrenia show minimal response to the frontline antipsychotic medications even though there is adequate D2 antagonistic action (Mouchlianitis et al., 2015). Ironically, clozapine is typically effective in treatment resistant cases despite a weak D2 blockade. This has led to an increase in research

efforts to discover potential alternative pathophysiologic mechanisms responsible for treatment resistant schizophrenia.

There is now a glutamate model of schizophrenia, which indicates that the N-methyl-D-aspartate (NMDA) glutamate receptor has a role in the disorder (Mouchlianitis et al., 2015). The role of glutamate in schizophrenia is supported by the effects of the NMDA receptor antagonist ketamine and phencyclidine (PCP). Ketamine can cause symptoms in a healthy individual that mimics the positive, negative, and cognitive symptoms of a person with schizophrenia (Ashton & Todd, 2011). PCP eliminates the ability of glutamate to bind to the NMDA receptor, which causes symptomology similar to schizophrenia (Kantrowitz & Javitt, 2011). This further strengthens the correlation between glutamate dysfunction and schizophrenia pathology (Kantrowitz & Javitt, 2011). However, the glutamine and dopamine systems are very intertwined, which means that the improvement in symptoms may still be from dopaminergic changes influenced by glutamate (Ashton & Todd, 2011). Theoretically, there would need to be treatments created to increase the functionality of glutamate since the culprit of symptoms is through decreased ability of glutamate to exert its action (Kantrowitz & Javitt, 2011).

The metabotropic glutamate receptors have been discussed in research. These receptors are presynaptic and are responsible for controlling glutamate release from the synapse (Kantrowitz & Javitt, 2011). The metabotropic glutamate receptors type 2 and 3 (mGluR2/3) decrease the release of glutamate from the presynaptic terminals (Kantrowitz & Javitt, 2011). Therefore, an agonistic clinical compound known as LY-2140023 was in development to target these receptors and did show improvements in symptoms, but has since been removed from continued research and development (Stahl & Muntner, 2013). The metabotropic subtype 5

(mGluR5) has since been identified and is currently in the developmental process (Kantrowitz & Javitt, 2011).

Cuomo et al. (2018) reported that there may be a connection between schizophrenia and changes in immune function. The authors indicated that the gastrointestinal flora may have an impact on inflammation, which could be contributing to the resistance to usual antipsychotic treatment. The authors think probiotics or the development of other medications could target and treat this inflammation, which would lead to improvement in schizophrenia symptoms. However, the authors reported that there is still a lot of research and testing to be completed to determine if aiming treatments at the GI flora and associated inflammation is a viable treatment option.

Mandolini et al. (2018) reported that cannabidiol (CBD) may possess an antipsychotic effect in schizophrenia through actions on the endocannabinoid system and specific blockade of the cannabinoid type 1 receptor. GABA and glutamate regulation in the presynaptic terminal and normalized neuronal dopamine transmission may result from a boost in endocannabinoids (Gururajan & Malone, 2016). Cannabidiol was not initially known to have dopaminergic properties. Seeman (2016) studied the effects of CBD as an antipsychotic and found that it likely has partial agonist properties for the D2 receptor similar to the antipsychotic aripiprazole. The evidence shows that CBD may have a place in psychiatry for the treatment of schizophrenia. However, more research and placebo-controlled randomized clinical studies need to be conducted before determining it to be a therapeutic option (Mandolini et al., 2018).

Implications

There is still a level of doubt as to which antipsychotic should be utilized when clozapine treatment is not tolerated (Dold & Leucht, 2014). Fortunately, there are multiple

pharmacological treatment options available when an individual is unable to tolerate or is resistant to clozapine, but with low to moderate evidence of success (Sagud, 2015). There have not been consistent results from randomized controlled trials in support of combining antipsychotics or augmenting with other medications (Citrome, 2011). The beneficial evidence that is available in regards to combination, augmentation, and high-dose antipsychotics should be considered when options have been exhausted and clozapine intolerance is a factor. However, the risks and benefits of each case would need to be closely evaluated before moving forward due to the lack of concrete evidence.

Dunlop and Brandon (2015) indicate that the phase 2 and 3 study results have been quite unsuccessful for the future novel treatment options that go beyond the dopamine hypothesis. It is important to learn from these novel studies to assist in future research and clinical trials for medication development (Dunlop & Brandon, 2015). The focus tends to be on medications, but there may need to be more emphasis on stabilizing the biopsychosocial framework in conjunction with advancements in medications. Persistent poor living environment, lack of community support, and financial deficiencies may be impacting outcomes of treatment more than once thought (Sagud, 2015).

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