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Therapizing Schizophrenia Therapies: How the Unmet Needs of TRS Patients Highlights the Need for Alternatives

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ABSTRACT

Schizophrenia is a disorder of which there is no known cause right now. The most researched theory is that there are increased levels of dopamine in the brain. Schizophrenia is generally treated with antipsychotics targeting the dopamine system to reduce the patient's positive and cognitive symptoms. These medications do not effectively treat schizophrenia for all patients, so more research into alternative therapeutics is necessary. Treatment-resistant schizophrenia (TRS) occurs when patients don't respond to the treatment they've been put on. Patients with TRS are at a higher risk of suicide or substance abuse as well as unemployment. Healthcare costs are also much higher for TRS patients than those with schizophrenia. As for treatment, if other medication for TRS patients does not aid in reducing their symptoms then clozapine is prescribed. Clozapine can reduce the risk of a relapse in symptoms, the risk of suicide, and the craving of substances. Combining antipsychotics can also be helpful in treatment. Some patients, however, do not respond to any of these treatments. This could be due to the treatment all targeting dopamine receptors as that is the widely studied cause of schizophrenia. Getting treatment for the patients who don't respond to the existing ones means that there should be more exploring into the different causes of schizophrenia.

Introduction

Schizophrenia is a psychotic disorder characterized by increased levels of dopamine in certain brain regions, according to the dopamine hypothesis. Dopaminergic dysfunction occurs in the striatum. The striatum acts as the center point for processing information in the brain and dysfunction occurs in the nigrostriatal pathways (Patel et al., 2014; Robert A. McChutcheon et al., 2019). There is another theory, the serotonin hypothesis, that proposes a dysfunction of serotonin receptors in a patient. Essentially, there is an overdrive of serotonin in the cerebral cortex (Arnold E. Eggers, 2013). In addition to serotonin and dopamine, there are also other theories involving acetylcholine, glutamate, and inflammation suggesting anomalies in other areas of a patient's brain. This paper focuses on second generation antipsychotics (SGA) that target dopaminergic dysfunction (Jibson, 2023; Yang & Tsai, 2017). There is no known cause of schizophrenia currently, however experts have deduced that the environment that a patient was raised in has a large influence on the illness (Patel et al., 2014). Studies have indicated that growing up as a minority, in areas with heavy drug use, or in urbanized places may contribute to the development of schizophrenia. Trauma from abuse and neglect can also play a role (Os et al., 2010). Additionally, there are genetic factors that raise the chances of someone having schizophrenia. Copy number variants (CNVs) are regions in which a genome is repeated and it increases the risk of schizophrenia along with individual common risk alleles (Rutten et al., 2014).

There are multiple symptoms of schizophrenia and they are separated into positive, negative, and cognitive symptoms (Patel et al., 2014). Positive symptoms are categorized by psychotic behaviors that wouldn't be seen in a person who did not have schizophrenia. Usually, this means hallucination or delusions. These are the symptoms that are most prevalent and therefore the ones that most likely come to mind when people think of schizophrenia (Patel et

al., 2014). Negative symptoms are disturbances in the emotional processing and thought patterns of a patient. This could show itself in different ways, such as avoiding interactions with loved ones or disregarding personal needs. Negative symptoms can lead to a patient developing depression, anxiety, or anhedonia, which is the inability to experience pleasure. It can also lead to avolition, or the lack of motivation, or lethargy, which is the lack of energy (Correll, et al. 2020; Patel et al., 2014). They can also cause a patient to become an insomniac. The last category of symptoms is cognitive. Cognitive symptoms disturb communications like the ability to organize and express thoughts coherently. In order to be classified as cognitive symptoms they have to be severe to the point where another individual would notice them. This manifests as disorganized speech or erratic actions (Carbon & Correll, 2014).

There have been many advances in the treatment for schizophrenia, however these interventions are often insufficient for patients, especially those with TRS. In fact, about 30% of schizophrenic patients have been shown to have insufficient treatment (Patel et al., 2014). This paper reviews the current therapeutic options for schizophrenia and investigates alternative therapeutic strategies that may be more effective for patients.

Treatment

Treatment for schizophrenia is largely targeted toward depleting the excess of dopamine in one's brain to make it more balanced (Patel et al., 2014). Treatment methods for schizophrenia include types of therapy and antipsychotics. The most common therapy is cognitive behavior therapy (CBT). CBT aims to reduce some of a patient's negative or cognitive symptoms by offering family therapy or exercises that allow them to cope with their symptoms (Chein & Kip, 2013 & Turkingston et al., 2004). It isn't ideal to use therapy on its own as antipsychotics have a better effect on a patient's positive symptoms, but using it alongside prescribed medications aids the treatment of negative or cognitive symptoms (Turkingston et al., 2006). More often, patients use antipsychotics to treat their schizophrenia. This is because therapy has been insufficient in treating positive symptoms as it is meant to focus on negative symptoms (Turkington et al., 2006) and antipsychotics not only reduce positive symptoms but also reduce the risk of a patient's symptoms relapsing (Csernansky & Schuchart, 2002).

There are two types of antipsychotics, first generation and SGAs. SGAs additionally have more of an affinity for dopamine receptors compared to first generation antipsychotics (FGAs) (Chokhawala et al., 2023, Jibson, 2023). This results in SGAs being more commonly prescribed for patients as they have a higher efficacy than FGAs. A difference in the two drugs is that FGAs or typical antipsychotics, have effects that relate more with a patient's motor functions (Zhang et al., 2013). SGAs, or atypical antipsychotics, result in the worsening of a patient's cardiometabolic health.

The most common antipsychotic used in treatment is clozapine. Clozapine is a SGA that is the most effective in patients with schizophrenia. Clozapine produced positive responses in about 30% of patients that used it (Fakra & Azorin, 2012). However, the drug is still underused. In the United States, only about 10-20% of patients are eligible to be prescribed it (Bogers et al., 2016). This could be due to the fact that the drug has a high risk of effects that could be dangerous to patients. Therefore, the determination of the dosage as well as when a patient can start using the medication is always calculated by clinical trials of the treatment (Yuen et al., 2021, Griffiths et al., 2021).

One of the most prevalent effects of clozapine is weight gain. Significant weight gain is a concern for schizophrenic patients because it increases inflammation and inflammatory proteins in cells. This is not safe as it increases their chances of a psychotic relapse. Additional effects caused by clozapine are hyperglycemia, hypertension, and dyslipidemia. When prescribed to children with schizophrenia, the side effects are still the same. However, the rate of side effects was higher in children than adults, but according to Sporn, et al. (2007), that is not related to the clozapine dosage or concentration. Generally, clozapine is used among schizophrenic patients who have TRS.

Treatment-Resistant Schizophrenia

TRS occurs when a patient's positive symptoms persist despite receiving non-clozapine treatment (Kane et al., 2019). Within TRS is clozapine-resistant schizophrenia which involves a patient not responding to the antipsychotic clozapine. There is also ECT-resistant schizophrenia which is when a patient does not respond to electroconvulsive therapy, a practice that is generally reserved for the most severe cases of schizophrenia (Leiknes et al., 2012; Kane et al., 2019). When classifying a TRS diagnosis, the biggest factor to consider is if the patient responds to treatment at the beginning of their diagnosis. This can't be the only determining factor because patients can develop a resistance to antipsychotics after having been on them for years. Therefore, a set of clinical guidelines was created by a group called Treatment Response and Resistance in Psychosis, or TRIPP, that more efficiently allowed patients with TRS to be diagnosed (Howes et al., 2016). These guidelines are separated into the severity and duration of symptoms, how functional the patient is, if the patient has previously been responsive, the dosage of their prescription, and number of antipsychotics that they have been given (Howes et al., 2016).

Patients with TRS also generally have a poorer quality of life as they do not respond to treatments intended to reduce their positive symptoms. They have higher rates of unemployment and often do not do well in social settings (Lasevoli et al., 2016; Roth et al., 2003). Not only this, but healthcare costs for TRS patients are much higher than they are for other patients. The antipsychotics themselves are priced lower than the average drug, but hospitalization costs are significantly more for TRS patients than they are for the general United States population (Kennedy et al., 2014). TRS patients also have to spend more time hospitalized than patients with non-TRS schizophrenia. The healthcare cost for a schizophrenic patient in total monthly is roughly $1,806 and reportedly six-fold higher in TRS patients (James et al., 2014), whereas the healthcare cost of a non TRS schizophrenic patient is roughly $419 (Fitch et al., 2014). On top of this, TRS patients have much higher rates of alcohol and substance abuse and smoking as well as suicidal ideation (Kennedy et al., 2014).

Current Treatment of TRS

As of right now, clozapine is the only effective antipsychotic used to treat TRS as it has proven to be the best at reducing TRS patients' symptoms (Patel et al., 2014). However, TRS patients are usually only eligible to use clozapine after the first antipsychotics they were prescribed did not work and positive symptoms persist (Vita et al., 2019; Kim et al., 2020). Considering the severity of the side effects, clozapine is typically a last resort for patients. However, sometimes TRS is not recognized and so a patient would have to wait to be put on clozapine. The amount of time varies, but it's averaged at 3.9 years (Howes et al., 2012). According to Yoshimura, et al. (2017), the patients who experienced a shorter delay before they started the treatment generally responded better to it as well. As previously mentioned, sometimes TRS is not noticed, causing a delay in the start of treatment. Different studies have different ways to define treatment resistance, and thus the guidelines on determining whether a patient has TRS or not are vague. This leads to treatment delays and potential misdiagnoses.

Sometimes, before being put on clozapine, patients will receive either a higher dosage of their medication or switch to a different antipsychotic. In order to receive a higher dosage of the antipsychotic, it would need to be increased over time as to slowly ease the patient into the new prescription (Dold & Leucht, 2014). Other antipsychotics that patients currently use are olanzapine and risperidone. Like clozapine, olanzapine reduces positive symptoms and it has a similar level of efficacy (Bitter et al., 2004 & Buchanan et al., 2005). Buchanan et al. (2005) suggested that olanzapine's efficacy is not greater than other medications. Olanzapine is an SGA and has side effects like weight gain, hyperglycemia, and insulin signaling, although they are less evident than they are with different antipsychotics (Bitter et al., 2004; Buchanan et al., 2005; Townsend et al., 2018). Risperidone is also an SGA but it differs from clozapine more than olanzapine does. They are both effective in treating TRS, but according to a study conducted by Bondolfi, et al. (1998), risperidone went into effect much quicker than clozapine. Between the two, olanzapine seems

to be the preferred (Heres et al., 2006). However, switching to different antipsychotics often does not make too large of a difference in the treatment process (Luecht et al., 2015; Dold & Laucht, 2014).

Clozapine also aids in treating some negative symptoms of TRS, albeit not as well as it treats positive and cognitive effects. This is a factor that makes it more desirable for patients. It reduces the risk of suicide along with lowering aggression (Farooq & Taylor, 2018). It also reduces the craving for substances. This in turn reduces the likelihood of a relapse of substances happening (Brunette et al., 2006). In terms of dosage, TRS patients who are younger have a higher dosage than patients who are older, and if the patient shows a reduction in symptoms then the dosage would be slowly decreased (Dold & Leucht, 2014).

In addition to all these treatments, some TRS patients are administered two antipsychotics at once. This is known as pharmacological combination treatment and it has proven to work well to treat patients, especially when clozapine is combined with them (Dold & Leucht, 2014; Pandarakalam, 2019). Combination treatment could be a great alternative to antipsychotic monotherapy, although antipsychotic monotherapy is more common. There is another form of combining treatments called augmentation treatment which involves combining two drugs that are in different classes (Muscatello et al., 2014). For example, combining an antipsychotic with a mood stabilizer or antidepressant. However, there is not much evidence on the use of this strategy and it is not commonly practiced. Patients will be taken off of both combination treatment and augmentation treatment if they show inefficacy (Dold & Leucht, 2014; Muscatello et al., 2014; Pandarakalam, 2019).

Discussion

While clozapine is extremely effective in treating TRS patients that respond to it, about 30% of TRS patients can't be treated with it as it is not effective in reducing symptoms (Meltzer, 1997). This is likely due to the fact that current therapeutics largely target dopamine receptors despite there being other contributors beyond dopamine dysregulation that may underlie schizophrenia. There is not much known about TRS and its causes or even schizophrenia and its causes, so it is often not clear what to target when treating patients. Schizophrenic patients are often treated in a uniform way despite potentially having different causes of their disorder. Because the dopamine hypothesis is the most widely studied, it drives the therapeutics for schizophrenia. Some patients may not respond to treatment because their disorder has imbalances in other areas like serotonin or glutamate. Therefore, there should be alternate treatments that target more areas of ailment.

The serotonin hypothesis, as previously mentioned, is when serotonin receptors in a person's brain dysfunction. Drugs that target it could largely reduce symptoms in patients that have more serotonin dysfunction compared to dopamine. These include risperidone, olanzapine, sertindole, and quetiapine. All of these are similar to clozapine, however they block serotonin much more efficiently than clozapine does (Meltzer, 1999). Combining drugs that have more of an affinity towards dopamine with drugs that have an affinity for serotonin could treat a broader range of symptoms (Tancredi & Kleven, 2011).

There is another potential cause of schizophrenia that doesn't involve neurotransmitters but rather the immune system and its dysregulation. Autoimmunity leads to a loss of immune tolerance which can cause autoimmune diseases such as chronic inflammation or tissue injury (Tauber, 2015). According to Rogers and Goldsmith (2014), autoantibodies had been found in a group of schizophrenic patients. It's unclear whether these autoantibodies were a response to treatment or a cause of the disease. In order to treat this complex system, antibiotics like minocycline are effective as well as azithromycin and cycloserine. The last two, however, had mixed results when tested (Severance et al., 2018). Additionally, anti-inflammatories are used to lessen inflammation. Autoantibody clearance requires immunosuppression; autoantibodies already produced will be degraded naturally and the immunosuppression prevents more from being made (Severance et al., 2018).

All in all, there are many patients who could benefit from having treatment that more specifically targets the cause of their schizophrenia, as there are many more causes than the ones that most people get treated for. Schizophrenia patients and TRS patients are often treated as a group rather than individual people, though everyone's

diagnosis is different and requires different types of treatments. To answer the research question, the treatments currently in use work perfectly efficiently in people who respond to them, but there are many patients for whom current treatment options do not work. Helping this significant population of patients, roughly 70% of people diagnosed with schizophrenia (Patel et al., 2014), requires the development of novel therapeutics. Ideally, these novel therapeutics should address imbalances in various or multiple neurotransmitters, including dopamine (McChutcheon et al., 2019), serotonin (Eggers, 2013), acetylcholine (Higley & Picciotto, 2014), and glutamate (Coyle, 2006).

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