Proceedings of the 3rd International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/20/20230715

Application of different treatment methods for schizophrenia

Jinqi Hou[1, 3, †], Xinyi Li[2, †]

[1] Aulin College, Northeast Forestry University, Harbin, 150040, China
[2] The Affiliated International School of Shenzhen University, Shenzhen, 518066, China

[3] houjinqi2222 @nefu.edu.cn
[†] These authors contributed equally.

Abstract. Schizophrenia is a debilitating neurological and psychiatric disorder that can result in severe disability for those affected. The presence of this disorder can have far-reaching effects on all aspects of a person's life, affecting not only their personal and familial relationships, but also their social interactions, academic pursuits, and career prospects. Some individuals with schizophrenia may experience multiple cycles of symptom exacerbation and remission throughout their lifetime, with symptoms worsening and improving intermittently. However, for others, symptoms may progressively worsen over time and may even become increasingly severe, potentially persisting throughout their lifetime and significantly impacting their daily life and social relationships. As of today, most medications are still not perfect treatments for this disorder. And only a few, such as lumateperone, have shown initial success in improving and relieving patients' negative symptoms and cognitive dysfunction. In addition, psychological therapies are being developed, but therapists and psychiatrists are still limited in the number of treatments available. In the face of these unresolved challenges, different treatment methods have been conducted to evaluate investigational therapies, and new models are being constructed to study new pharmacological molecular therapeutic pathways. This research provides an overview of some of the current mainstream treatment strategies for schizophrenia and an outlook for the future.

Keywords: schizophrenia, treatments, mechanism.

1. Introduction

Schizophrenia is generally understood to be a serious mental illness characterized by abnormal reality interpretation [1]. It can produce unsettling symptoms and frequently runs in families. Symptoms could include having problems communicating with others and thinking coherently, as well as experiencing hallucinations, delusions, and profoundly disorganized thought and behavior that interfere with daily functioning. Early in adulthood, it frequently begins suddenly. Today, utilizing medicine merely helps to lessen the symptoms of schizophrenia rather than treating it completely. The major effects of schizophrenia are numerous. Patients may experience noises that no one else hears, voices that may criticize them or tell them they are useless or foolish. Also, they might inform the patients that someone is trying to hurt them or the people they care about, and they could advise them to act to defend themselves and the people they care about.

DOI: 10.54254/2753-8818/20/20230715

The brain is greatly impacted by schizophrenia. The schizophrenic brain exhibits a multitude of anomalies, according to brain scans and microscopic tissue research. The most common site of structural anomalies is the lateral ventricles of the cerebrum. Neuroimaging of individuals with schizophrenia exhibits enlarged versions of these cerebrospinal fluid-filled cavities encircling the brain. And distinct areas of the schizophrenic brain show a reduction of gray matter by as much as 25%. The term "gray matter" describes a number of brain regions that are involved in speech, memory, emotions, hearing, and sensory perception. Schizophrenia patients can experience extreme mood fluctuations that make it impossible for them to react appropriately to their environment. For instance, a person suffering from schizophrenia could appear pleased when others are upset. Moreover, schizophrenia raises the risk of chronic severe depression. What's worse is that sadness increases the likelihood of suicide in those with schizophrenia. Around 10% of persons with schizophrenia commit suicide, making suicide and schizophrenia both frequent. More memory and attention issues than those seen in schizophrenia without depression may also be present in those with schizophrenia plus depression.

Although the exact cause of the connection between sadness and schizophrenia is unknown, psychosis may have a role. In schizophrenia, hallucinations and delusions are the symptoms of psychosis. The perceptions of a sense—such as smell, touch, taste, hearing, or sight—that are not actually there are called hallucinations. Delusions are erroneous beliefs that people maintain despite contradictory facts. A hallucination may, for instance, be thinking the government is privy to the thoughts of the schizophrenic sufferer. There are a variety of therapy options available, and even after symptoms have subsided, it typically necessitates lifelong care. Psychosocial therapy and medication were typically used to treat schizophrenia, though hospitalization was occasionally necessary as well. Generally, a specialized psychiatrist in managing schizophrenia oversees the treatment process. To streamline the care, the therapeutic group might also involve a therapist, a social service specialist, a psychiatric nurse, and potentially a caseworker. Currently, treatments are limited, but can be divided into three categories: medication, brain stimulation, and psychotherapy. Antipsychotics are the preferred long-term treatment strategy for schizophrenia. All current treatments for schizophrenia are dopamine D2 receptor antagonists. These drugs are widely used because they can alleviate the favorable indications of schizophrenia, for example, perceptual aberrations as well as the constructive symptoms of schizophrenia, like sensory delusions. The constructive symptoms of schizophrenia, like sensory delusions, and delusions.

A major focus of research over the past decade has been to determine the relative superiority of first- and second-generation antipsychotics. However, clozapine is the only medication that has an experimental basis for treating refractory patients, characterized by remarkable efficacy in addressing the positive symptoms exhibited by patients with refractory schizophrenia, while comparatively minimizing the incidence of extrapyramidal side effects when compared to other treatment modalities. This implies that this therapy not only effectively relieves the symptoms of patients but also significantly reduces the occurrence of adverse reactions. And there is evidence of its superiority over second-generation antipsychotics, but clozapine can cause adverse effects including those like neutropenia or granulocyte deficiency and cardiac complications, which in turn induce adverse effects like myocarditis or cardiomyopathy [2]. In addition, there is an ongoing debate on how to effectively and rationally select the use of first- or second-generation antipsychotics based on the actual situation, and whether to use them at all. On the other hand, the assessment of the effectiveness of the combination of antipsychotics with other drugs and effective enhancement methods are still inconclusive. Exploration is currently underway to investigate the potential uses of certain brain stimulation techniques in addressing specific mental disorders. These techniques include, but are not limited to, electroconvulsive therapy, repetitive transcranial magnetic stimulation, and deep brain stimulation. When dealing with mental illness that is unresponsive to conventional treatment methods, electroconvulsive therapy (ECT) is deemed as an efficacious intervention because it can quickly alleviate severe symptoms such as psychosis, hallucinations, and delusions. However, ECT has also been found to have some side effects, such as headache, nausea, and muscle spasms. Additionally, ECT may cause memory impairment as it affects the connections between neurons in the brain [3].

DOI: 10.54254/2753-8818/20/20230715

Therefore, regular assessment and monitoring are required for patients receiving ECT to ensure its safety and efficacy. Meanwhile, researchers are seeking other safer and more effective brain stimulation therapies to help treat patients with refractory mental illness. Whereas rTMS is considered a safer and non-invasive option. Studies have shown that a major advantage of rTMS is its effectiveness in alleviating persistent hallucinatory symptoms, such as auditory hallucinations (AH). Therefore, rTMS has been widely applied in the treatment of refractory psychiatric disorders and has achieved some clinical success. Nevertheless, its treatment in negative patients has not been substantially concluded. DBS is a potential new therapeutic strategy based on its potential for direct intracranial precision targeting to the brain while repairing specific circuitry circuits that may be disrupted in schizophrenia thereby potentially reducing the need for drugs. However, to date, there have been few clinical evaluations of it, and it is an invasive procedure compared to rTMS, which may have potential side effects such as the risk of hardware failure. Psychotherapy for psychosis has also been developed in response to non-pharmacological treatments. This can help patients address biased cognitive patterns and reassess psychotic symptoms, with psychotherapy targeting maladaptive family communication proving effective [4], and various psychosocial interventions have been shown to improve several aspects of social cognition [5]. Although psychotherapy may have the advantage of being able to reduce the use of medication and avoid the side effects and risks of brain surgery, it is worth noting that it requires an intensive amount of time to guide the patient, and the biggest difficulty is that this then requires the active cooperation of the patient. As a result, this research will analyze the different methods and mechanisms of action of treating schizophrenia.

2. Analysis of new treatment methods

The high relapse rate of patients after discontinuation of drugs is also significant. Therefore, long-term use of these drugs is necessary. However, it is not yet clear whether long-term treatment will cause changes in the dopamine system and pose a potential threat to patients. It is noteworthy that scant data supports the substantial enhancement of negative and cognitive symptoms through antipsychotic medications, unless they stem from favorable symptoms. Consequently, regarding the management of unfavorable and cognitive indications, other treatment options such as psychotherapy, social skills training, and vocational rehabilitation need to be explored. Whether to use a first- or second-generation antipsychotic is the key decision in the antipsychotic therapy of schizophrenia. Typically, the medical practitioner will select an atypical antipsychotic, which belongs to the category of second-generation antipsychotics. Owing to the potential side effects that can severely impede physical motion, Typically, conventional or typical antipsychotics, also known as first-generation antipsychotics, are not the first-line treatment for schizophrenia. However, those who do not respond to atypical antipsychotics, also called second-generation antipsychotics, may find relief from first-generation antipsychotics. And the pharmacological management of schizophrenia today is still based on the antipsychotic effect of chlorpromazine, a first-generation antipsychotic discovered by chance more than 50 years ago, but it has a high potential to cause extrapyramidal symptoms and delayed dyskinesia, and this phenomenon of causing dyskinesia is also a major differential feature of the first generation compared to second-generation antipsychotics like aripiprazole, olanzapine, asenapine, paliperidone and so on. All of that means suboptimal outcomes with medication remain common.

Pharmacotherapy remains the cornerstone of treatment for acute and long-term schizophrenia. Additionally, some more recent antipsychotic medications can sometimes help patients make a complete recovery from schizophrenia symptoms by reducing and controlling their symptoms. These medications are also known as atypical or second-generation antipsychotics. Because they are more recent than first-generation medications, they tend to have fewer adverse effects like habitual or unconscious movements like eye blinking. Aripiprazole is one such medication that can be very beneficial. This medication can help you feel less anxious, take an active role in daily life, and think more clearly and optimistically about yourself in addition to reducing hallucinations and enhancing concentration. Patients with certain mental disorders or emotional disorders typically take another medication (like schizophrenia and bipolar disorder). Also, more prominent is the second-generation

DOI: 10.54254/2753-8818/20/20230715

psychiatric drug called lumateperone, which has received its first global approval as a new agent for future schizophrenia [6]. Patients using it have observed fewer adverse reactions compared to placebo having significant superiority [7]. The ability to think more easily, feel less anxious, and engage in daily activities is the main benefit of using this type of drug. Additionally, it typically helps to lessen hallucinations and avoid extreme mood swings, though it may take a few weeks before you experience all of this medication's benefits. Both of these drug types can assist the brain in reestablishing the balance of specific natural substances due to their comparable mechanisms of action.

There are multiple models currently guiding the development of schizophrenia treatment. And in order to further improve the effectiveness of pharmacological treatments for schizophrenia, this requires the construction of new molecular models of neurodevelopment to carry out new therapeutic pathways. At present, in addition to conventional models like disrupted dopamine transmission and decreased activity of N-methyl-D-aspartate receptors in the glutamatergic system, excitability/ inhibition homeostasis, immune dysfunction and abnormal dendritic pruning, there are also new explorations like the one developed in 2020 for activators at trace amine-related receptor 1 and 5-hydroxytryptamine-ht1 receptors. What is remarkable in this trial is that these receptors showed in the initial phase 2 trial to be effective against negative symptoms and no significant neurological or metabolic adverse side effects occurred [8]. But unfortunately, there is no independent model that can perfectly elucidate the intrinsic connections of this complex disease.

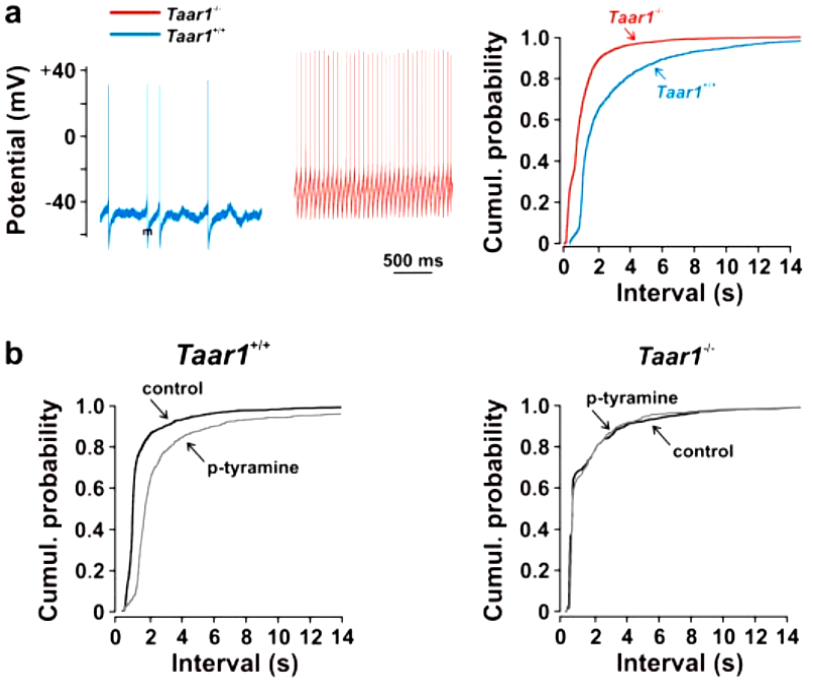

Figure 1. Electrophysiological analysis of dopaminergic neurons in the ventral tegmental zone of Taar1 knockout and wild-type littermates born mice [9].

The development of a number of other rather non-baroreceptor antagonists is also under investigation. For example, some pathogenic pathways of excitatory/inhibitory balance in regions such as hippocampus have been mastered by the insight of SCZ circuitry. It was found that by compensating the loss of parvalbumin (PV) interneurons, it may be one of the effective ways to repair hippocampal disorders and alleviate SCZ symptoms. For other targets, on the one hand it has been proposed that the stimulation of trace amine-associated receptor 1, namely TAAR1, can modulate presynaptic dopamine synthesis capacity [9], as shown in Figure 1. In addition to direct activation, TAAR1 may also exert antipsychotic effects by modulating the D2 receptor-mediated signaling pathway via the creation of heterodimers in conjunction with D2 receptors. The formation of TAAR1-D2 receptor heterodimers can influence neurotransmitter release and neuronal excitability, and may

DOI: 10.54254/2753-8818/20/20230715

mediate the therapeutic effects of drugs. Although TAAR1 is considered an important target in the treatment of antipsychotic drugs, its detailed mechanism still requires further investigation [10]. Conversely, research indicates that nicotine may have a positive impact on the behavioral and neurophysiological abnormalities induced by rat's treatment. Specifically, nicotine has been demonstrated to ameliorate symptoms of anxiety and depression, and enhance motor and cognitive function, and also boost the activity of neurons in the prefrontal cortex and hippocampus of rats that received MAM treatment. These discoveries imply that nicotine has the potential to be a therapeutic remedy for schizophrenia and other linked ailments. However, the exact mechanism of nicotine still needs further research [11], it may have a therapeutic effect on neurological recovery. And combined with the large amount of evidence on the dysfunction of the cholinergic system in the SCZ suggests that the activation of cholinergic receptors may serve as a new attempt in the future [12], as shown in Figure 2. All these findings demonstrate some new ideas of receptor modification for the future treatment of SCZ.

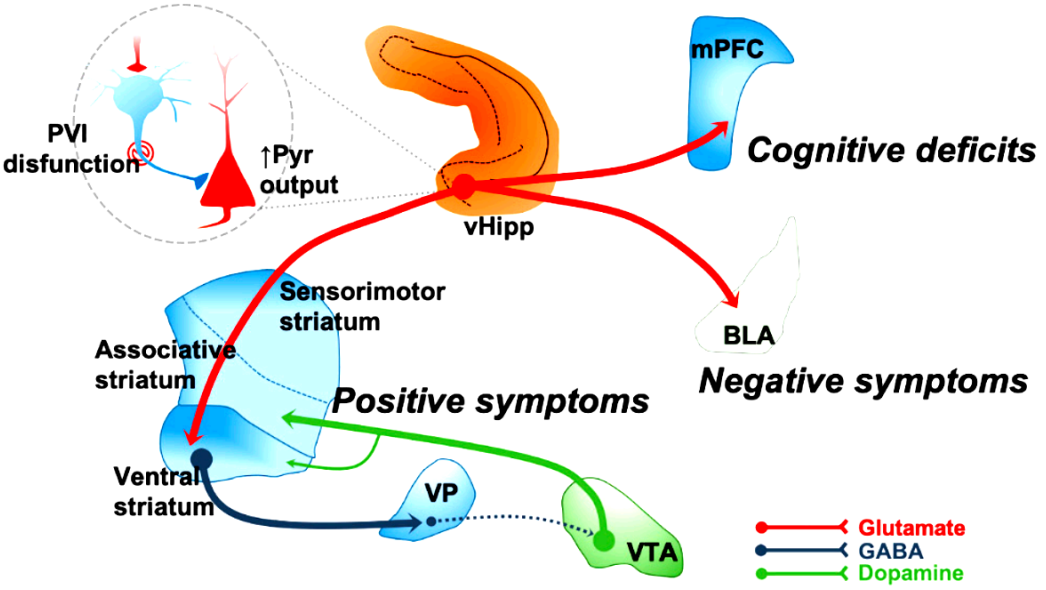

Figure 2. The anterior limbic hippocampus in humans [12].

Current research indicates that when individuals are exposed to stressful stimuli, a series of biochemical changes occur, with one major biochemical change being the occurrence of oxidative stress. Oxidative stress is the result of an imbalance in cellular redox reactions caused by the overproduction of reactive oxygen species, which can affect the function of antioxidant mechanisms. This imbalance may result in a range of diseases, including cardiovascular disease, neurodegenerative diseases, and cancer, among others. Therefore, further investigation into the mechanisms of oxidative stress and its relationship with diseases is of crucial importance for developing new therapeutic strategies and preventative measures. There is considerable evidence to indicate that oxidative stress (OS) is heavily involved in the onset of different disorders affecting the central nervous system. It is commonly acknowledged that OS is a key factor in the pathogenesis of schizophrenia. [13]. The interference of various external factors disrupts the natural regulatory mechanisms of transcription factors that are sensitive to redox reactions, non-coding RNA, and epigenetic mechanisms, leading to disrupted gene expression. The disruptions can also result in metabolic irregularities, which can worsen mitochondrial performance and result in atypical neural growth as well as dysregulated myelin formation. Overall, these disturbances could potentially have a substantial impact on the initiation and advancement of disorders within the central nervous system. However, it is inconclusive whether it is the main cause of the disease. Therefore, one of the important therapeutic avenues is the development of drugs based on the correction of oxidative homeostasis.

DOI: 10.54254/2753-8818/20/20230715

Both typical and atypical antipsychotics have shown significant improvements in redox homeostasis in schizophrenia. Therefore, additional antioxidant treatment can have a beneficial effect on redox balance thereby improving the mental status of schizophrenic patients and achieving remission. However, research has found that both typical and atypical antipsychotic drugs can have a positive impact on promoting oxidative status in patients with different types of schizophrenia. This suggests that these drugs can be effective treatments for schizophrenia, regardless of the patient's type [14].

And relevant human research has indicated that antipsychotics contribute to oxidative stress [15]. Furthermore, with prolonged treatment, the use of both typical and atypical antipsychotic drugs can cause disruptions in oxidative homeostasis through the promotion of oxidative processes, with the result that their antioxidant efficiency is insufficient. Some potential transcription factor-targeting drugs can act as activators to dysregulate the corresponding redox-sensitive transcription factors (e.g., Nrf2, FoxO) and contribute to the normalization of redox homeostasis. However, the consequences are not known, and even small changes in oxidative homeostasis can have serious consequences.

With regard of the psychotherapy, individual counseling is the first line of treatment for schizophrenia. A mental health professional such as a therapist or psychiatrist can guide the patient in managing their thoughts and behaviors during therapy sessions. The patient can acquire greater insight into their condition and its impact, as well as develop the ability to differentiate between genuine and distorted information. It may also aid them in managing their daily lives. Find out more about the various forms of counseling. Schizophrenia is frequently treated with cognitive enhancement treatment (CET), also known as cognitive remediation. By improving their ability to identify social cues and triggers, and enhancing their focus, memory, and cognitive organization, patients can benefit from this type of therapy. It is usually associated with group therapy sessions and computer-based cognitive training. Coordinated specialty care (CSC) can be used if a person is having their first incident of psychosis. It tries to involve the family when feasible and involves medication, psychological therapies, social and employment services. By catching the illness early on, this treatment aims to alter the course and prognosis of the condition. And the best long-term outcome will be achieved by patients with schizophrenia who receive this type of treatment at an early period.

3. Conclusion

In the face of suboptimal treatment with traditional first- and second-generation antipsychotics, challenges related to patient noncompliance and significant adverse drug reactions, new neurodevelopmental molecular models need to be constructed to find and replace the traditional dopamine D2 receptor inhibitory pathway. Research directions such as TAAR1 and cholinergic receptors are of great interest for the future. Meanwhile, for the oxidative stress theory, the development of drugs based on the repair of oxidative homeostasis in patients is also one of the important therapeutic pathways in the future, such as the development of targeted drugs related to redox-sensitive transcription factors. Although the effect of drug development guided by relevant research models is uncertain, it is believed that there will be new breakthroughs in the future with the exploration of crossover pathways in combination with other models. As for the exploration of brain stimulation therapies, although there is interest in potential new treatment strategies like DBS, these approaches require active patient cooperation for better evaluation, so there are still a lot of dissenting views expressing some concerns about this. Therefore, the treatment of schizophrenia still faces serious challenges, and although various classical therapies are still inadequate, they are still effective in alleviating the spread of the disease to some extent.

References

[1] Lehman, A. F., Lieberman, J. A., Dixon, L. B., McGlashan, T. H., Miller, A. L., Perkins, D. O., Kreyenbuhl, J., American Psychiatric Association, & Steering Committee on Practice Guidelines (2004). Practice guideline for the treatment of patients with schizophrenia, second edition. The American journal of psychiatry, 161(2 Suppl), 1–56.

[2] Marder, S. R. and Cannon, T. D., "Schizophrenia," The New England journal of medicine 381, 1753–1761 (2019).
[3] Gu, X., Zheng, W., Guo, T., Ungvari, G. S., Chiu, H. F. K., Cao, X., D'Arcy, C., Meng, X., Ning, Y. and Xiang, Y., "Electroconvulsive Therapy for Agitation in Schizophrenia: Metaanalysis of Randomized Controlled Trials," Shanghai archives of psychiatry 29, 1–14 (2017).
[4] Hooley J. M., "Expressed emotion and relapse of psychopathology," Annual review of clinical psychology 3, 329–352 (2007).
[5] Fiszdon, J. M. and Reddy, L. F., "Review of social cognitive treatments for psychosis," Clinical psychology review 32, 724–740 (2012).
[6] Kumar, B., Kuhad, A. and Kuhad, A., "Lumateperone: a new treatment approach for neuropsychiatric disorders," Drugs of today 54, 713–719 (2018).
[7] Syed, A. B. and Brašić, J. R., "The role of lumateperone in the treatment of schizophrenia," Therapeutic advances in psychopharmacology 11, 20451253211034019 (2021).
[8] Koblan, K. S., Kent, J., Hopkins, S. C., Krystal, J. H., Cheng, H., Goldman, R. and Loebel, A., "A Non-D2-Receptor-Binding Drug for the Treatment of Schizophrenia," The New England journal of medicine 382, 1497–1506 (2020).
[9] Lindemann, L., Meyer, C. A., Jeanneau, K., Bradaia, A., Ozmen, L., Bluethmann, H., Bettler, B., Wettstein, J. G., Borroni, E., Moreau, J. L. and Hoener, M. C., "Trace amine-associated receptor 1 modulates dopaminergic activity," The Journal of pharmacology and experimental therapeutics 324, 948–956 (2008).
[10] Espinoza, S., Masri, B., Salahpour, A. and Gainetdinov, R. R., "BRET approaches to characterize dopamine and TAAR1 receptor pharmacology and signaling," Methods in molecular biology 964, 107–122 (2013).
[11] Weeks, J. J., Grace, A. A. and Sved, A. F., "Nicotine Administration Normalizes Behavioral and Neurophysiological Perturbations in the MAM Rodent Model of Schizophrenia," The international journal of neuropsychopharmacology 24, 979–987 (2021).
[12] Gomes, F. V. and Grace, A. A., "Beyond Dopamine Receptor Antagonism: New Targets for Schizophrenia Treatment and Prevention," International journal of molecular sciences 22, 4467 (2021).
[13] Perkins, D. O., Jeffries, C. D. and Do, K. Q., "Potential Roles of Redox Dysregulation in the Development of Schizophrenia," Biological psychiatry 88, 326–336 (2020).
[14] Zhang, X. Y., Tan, Y. L., Cao, L. Y., Wu, G. Y., Xu, Q., Shen, Y. and Zhou, D. F., "Antioxidant enzymes and lipid peroxidation in different forms of schizophrenia treated with typical and atypical antipsychotics," Schizophrenia research 81, 291–300 (2006).
[15] Upthegrove, R. and Khandaker, G. M., "Cytokines, Oxidative Stress and Cellular Markers of Inflammation in Schizophrenia," Current topics in behavioral neurosciences 44, 49–66(2020).