# An Insight into Psychedelic Drugs in Schizophrenia

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Schizophrenia remains a serious chronic mental illness since its revelation more than a century ago by Dr. Emile Kraepelin. Despite the low prevalence, nearly 24 million people suffer from this disorder, which constitutes 1 in 300 people (0.32%) of the world's population and this rate is 1 in 222 people (0.45%) among adults. The symptoms of schizophrenia more often appear in the second or third decade of life, and disease occurrence is tied to a combination of factors such as genetic, socio-demographic, and environmental factor. Clinical schizophrenia is presented in two unique and distinct sets of symptomatology, which include 'positive' symptoms and 'negative' symptoms, and is also accompanied by significant impairment of cognitive functioning in one or more major areas. This may include an inability to execute work, interpersonal relations, or self-care, and there is also a failure to achieve the expected level of interpersonal, academic, or occupational functioning. According to the current Diagnostic and Statistical Manual for mental disorders-V (DSM-V), the positive symptoms of schizophrenia are delusions, hallucinations, disorganized speech, and behaviour; and the negative symptoms are diminished emotional expression or avolitio. These symptoms have been found to be chronically present once the disease starts, but generally the illness is marked as alternate signs of remission and exacerbation or partial remission or exacerbation. Some psychotic symptoms may be treated without the need for medication with proper human care, social support and care including electroconvulsive therapy.

psychedelics schizophrenia MDMA Psilocybin DMT

## 1. Introduction

### 1.1. Therapeutic Armamentarium for Schizophrenia

The first effective medication for treating psychotic symptoms was reserpine: an antihypertensive agent whose efficacy in schizophrenia was correlated to the reduction in synaptic dopamine release. The discovery of reserpine paved the way for the first antipsychotic medication, chlorpromazine in 1952 [1][2], which was originally synthesised as an anaesthetic agent [3]. The efficacy of chlorpromazine in treating acute psychotic symptoms and reducing relapses was confirmed by a large clinical one making it the first successful APD approved, which was in 1954 [4]. Soon a medley of other APDs followed, termed first-generation APDs, which shared similar modes of action, i.e., the blockade of dopamine $D_2$ receptors [1][5]. The first-generation APDs, although efficacious, produced significant side effects limiting their long-term use. Major adverse effects of the first-generation APDs were extrapyramidal symptoms such as acute movement disorders (e.g., dystonia, akathisia, tardive dyskinesia and so on), parkinsonian-like symptoms, and anticholinergic side effects. In addition, the first-generation APDs were found to

negatively affect some aspects of the disease such as weakening knowledge acquisition and cognition, and augmenting hostile behaviours, aggression, and suicidal tendencies [6][7][8]. It has also been reported that some dopamine blocking drugs themselves cause secondary negative and cognitive symptoms in schizophrenia patients [9][10]. Additionally, recurrence of psychotic symptoms has been reported after the withdrawal of some antipsychotic medications. In schizophrenia patients, the quality of life of the patient is greatly compromised due to the long-term exposure to such adverse effects of antipsychotic medications predisposing them to various illnesses such as cardiovascular, metabolic complications, sexual dysfunction, and heightening suicidal tendencies, which increases mortality [11][12][13][14][15][16][17]. The efficacy of all APDs is primarily associated with their action on post-synaptic dopamine $D_2$ receptors thereby preventing dopamine hyperactivity in the striatum. However, schizophrenia symptoms that are linked to low dopamine functioning in the prefrontal cortex and certain subcortical areas could not be treated adequately by the first-generation APDs. Additionally, in 2012, Demjaha et al. reported that antipsychotic medications did not elevate the dopamine synthesising capacity of dopaminergic neurons linked to the psychotic symptoms [18].

Antipsychotic medication, for example, aripiprazole and others that were developed later were found to block dopamine $D_2$ receptors as well as serotonin receptors. Aripiprazole was reported as a partial agonist at dopamine $D_2$ receptors and as an antagonist at serotonin (5-hydroxytrptamine; 5-HT) 5-$HT_{1A}$ and 5-$HT_{2A}$ receptors. They were referred to as the second-generation APDs. The most commonly involved receptor target for the second-generation APDs, beside the dopamine receptors, was found to be the serotonin 5-$HT_{2A}$ receptors [19]. In the second-generation APDs, clozapine was the first APD with superior antipsychotic activities. It differed from the older, classical APDs in superiority of controlling positive as well as negative symptoms, preventing relapses, and also inducing negligible extrapyramidal side-effects [20][21][22]. The mode of action of clozapine was termed atypical because of its actions on multiple receptor sites, predominantly the dopamine D2 receptor blockade and also affinity for 5-HT, acetylcholine, and histamine receptors [13]. Clozapine binds strongly to dopamine D4 and serotonin 5-$HT_{2A}$ receptors and displays weak binding with dopamine $D_1$, $D_2$, and $D_3$ receptors. It has been reported that clozapine causes lesser risk of inducing extra-pyramidal symptoms, increasing prolactin levels and the induction of tardive dyskinesia upon long-term use. These actions of clozapine were associated with its weak binding to dopamine $D_2$ receptors and strong affinity to serotonin 5-$HT_{2A}$ receptors in the striatum [23][24]. The second-generation APDs, beside clozapine, included drugs such as amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, and zotepine. These drugs effectively managed schizophrenia patients who were unresponsive to the first-generation APDs [20]. Improvement in several schizophrenia indices such as anhedonia, avolition, reduced motivation and self-drive, learning and performance tests, depression, adherence, time to relapse, aggression, and suicidal tendencies were successfully achieved with the current APDs [25][26][27][28][29][30][31]. Schizophrenic patients require chronic or sometimes lifelong treatment with APDs, which predisposes the adverse consequences of APDs therapy. However, the use of second-generation ADPs demonstrated significant improvement in long term adverse consequences compared to first generation drugs. Despite the superiority of second-generation APDs, they were also reported to produce some harmful effects that negatively affected the therapeutic outcomes in schizophrenia.

These negative effects of second-generation APDs included the elevation of cardiometabolic abnormalities (for example, resistance to insulin, glucose intolerance, dyslipidaemia, raised blood pressure, and obesity), among others include life-threatening disorders such as myocarditis, agranulocytosis, and complications such as increased prolactin levels [32]. Additionally, the majority were suggested that the currently approved APDs mostly targeted schizophrenia symptoms as the primary intention to treat, therapeutically, and were largely similar in terms of efficacy [21][22][33][34][35]. Thus, the currently available APDs succeeded in lowering most of the aspects of schizophrenia pathology but functional outcomes in an appreciable number of patients have remained poor. Hence, even the newer APDs have somehow failed to achieve the desired therapeutic outcome. Additionally, sometimes the newer APDs were no better than the older APDs because many patients continue to suffer from schizophrenia symptoms and cognitive debilities. Despite the rapid advances in understanding the neuroscience of such neuropsychiatric illnesses, there remains a dearth of drug development activity in schizophrenia. The future APD development programs need to address the unmet goals and challenges of the present schizophrenia pharmacotherapy. The very first challenge in this context would be to find treatments for patients who are nonresponsive to the current schizophrenia medications [36][37][38]. Secondly, a disease modifying drug is the need of the hour, which could control subcortical dopamine levels and have improved outcomes on the course of schizophrenia [38]. In this regard, the recent development of a novel trace amine-associated receptor 1 target including the development of SEP-363856, a new non-dopamine $D_2$-receptor binding antipsychotic agent, suggest that meaningful therapeutic advances are taking place and are being pursued with more complex neurodevelopmental and molecular models [39][40][41]. Another recent development in this context is the therapeutic exploration of psychedelic compounds in a variety of neuropsychiatric disorders. Individualised treatment with psychedelic compounds has been suggested based on efficacy and tolerability of such medications. The clinical use of psychedelics is being seen as a paradigm shift in the treatment of neuropsychiatric diseases. Recently, patients who were treated with serotonergic psychedelic drugs reported early evidence that clinical psychedelics were efficacious and well tolerated in a range of psychiatric conditions [42] leading to an increase in advocacy for the controlled, clinical use of psychedelics including LSD and psilocybin [43]. Hence, psychedelics could be an excellent scientific tool for the development of novel drug molecules for a wide range of intractable neuropsychiatric disorders including schizophrenia, and particularly drug-resistant schizophrenia, and may constitute an exciting new treatment avenue in a health area with major unmet needs. Additionally, exploration of psychedelics would facilitate understanding of the serotonin–glutamate receptor hypotheses, as the serotonin–glutamate receptor complex is the target for both the psychedelic drug compounds as well as the atypical and glutamate classes of APDs [44][45]. A renaissance in the interest to learn the effects of psychedelics in the treatment of psychiatric disorders warrants a better understanding of the neurobiological mechanisms underlying the effects of psychedelics in schizophrenia [46]. This is an attempt to delve deep into neurobiological and neuropsychiatry mechanisms of psychedelics modelling vis-à-vis their role in future drug development in neuropsychiatric disorders including schizophrenia.

## 1.2. Psychedelic Drugs in Schizophrenia

Psychedelics refer to a class of drugs that have hallucinogenic actions on the human brain and that, according to Jaffe, are defined as drug molecules with the ability to cause strong changes in perception, thought, and feeling in

human beings, which otherwise are not felt normally except in sleep or at times of religious invocations [47]. Previously, it was reported that serotonin agonists in the human brain behave as hallucinogens as they have a powerful influence on memory, learning, perception and emotion, causing momentary symptoms of psychosis [48]. The pharmacological actions of these compounds have been primarily attributed to their binding with and activation of serotonin 5-$HT_{2A}$ receptor subtypes in the brain. Psychedelic drugs have been reported to produce effects at the cellular and molecular levels in the brain, which probably explains their potential use in a number of etiologically varied psychiatric illnesses [49]. The administration of low, sub-hallucinogenic doses of psychedelics on a chronic, intermittent schedule is referred to as psychedelic microdosing, which is becoming increasingly prevalent among youths as it is believed to lower depression and anxiety and also improve cognitive function and promote social interaction [50][51][52]. In clinical ones, psychedelic compounds have been found to be well-tolerated and efficacious in regulated doses suggesting that they could open the gate to novel therapeutic approaches for treating various neurological illnesses including schizophrenia. Previously, it has been reported that psychedelic compounds could benefit patients suffering from various neurological disorders such as anxiety and resistant depression, substance use disorders, posttraumatic stress disorder, alcoholism and schizophrenia [48][53][54][55]. Additionally, psychedelics have been found to promote de-addiction to tobacco and alcohol, and treat some inflammatory conditions [54][55]. According to recent reports, medically supervised doses of psychedelic drugs are well-tolerated and there was no link of psychedelic drug use to adverse mental-health problems. On the contrary, people who used them reported fewer suicidal thoughts and felt better in several indices of anxiety and depression, which precedes the occurrence of schizophrenia [54][56]. By Hibicke et al., revealed that psychedelic compounds lowered depressive symptoms in a rodent model of depression suggesting that the therapeutic potential of classic psychedelics might be better than ketamine [57].

## 1.3. Psilocybin

Psilocybin (4-phosphoryloxy-*N*, *N* dimethyltryptamine) is a widely known contraband substance and occurs naturally as an indole alkaloid. In 2015, Hendricks and colleagues reported that psilocybin showed positive effects on mental health such as reduced psychological distress and suicidal feelings [56]. Preliminary findings of phase II clinical ones have suggested efficacy of psilocybin in conditions including obsessive compulsive disorder (OCD), depressive disorder, cancer-induced anxiety, and substance use disorders such as alcohol and tobacco [48]. In 2006, by Moreno and colleagues found that there was a greater reduction in OCD symptom following one or more sessions with psilocybin, which was administered at doses ranging from 25, 100, 200, and 300 µg/kg and given at an interval of 1 week. Additionally, patients mostly reported that they experienced relief even after psilocybin has left the body, beyond the 24 h assessment [58]. In the amygdala of the human brain, psilocybin has been reported to possess an inhibitory effect, which may explain the observed positive affective state with psilocybin use. In patients of drug resistant depression, a recent phase II clinical one reported that Hamilton Depression Rating Scale scores improved following treatment with psilocybin [59] indicating therapeutic efficacy in depression. Patients who have suffered from schizophrenia for a long time tend to develop depression, anxiety and substance use disorders, and develop other secondary illnesses that become challenging to treat besides the psychotic symptoms. Additionally, recently, psilocybin lowered suicidal tendencies, which are common in psychotic patients. Psilocybin has been reported to modulate the thoughts and behavioural patterns in individuals who are at risk of suicidal

behaviours. The mode of action of psilocybin is suggested to be the regulation of major pathways linked with suicidal behaviours which are affected by directly activating serotonin $5HT_{2A}$ receptors, and also, targeting the inflammatory and oxidative stress pathways leading to neuronal plasticity, and suppression of inflammation and increase in cognitive flexibility [60]. Recently, the FDA has dubbed psilocybin as a breakthrough medicine for the treatment of resistant depression [61]. Hence, future clinical ones involving psilocybin hold promise in the development of a novel drug for schizophrenia particularly for patients who develop suicidal behaviours and suicidal ideations.

## 1.4. LSD

LSD (lysergic acid diethylamide) is a semisynthetic ergot alkaloid [62][63] that was developed as a means of mind control by security agencies [64][65]. Its therapeutic dose range has been suggested to be between 100 and 200 µg, although it exhibits psychoactive effects at doses as low as 20 µg. Before the ban on psychedelics was imposed through a 1971 United Nation convention [66], many studies had already reported the benefits of LSD in several neurobehavioral conditions such as substance use disorder, pain, neurosis, and cancer-related anxiety, depression, and mood disorders, among others [67][68][69][70]. In a recent study, a 20 µg dose of LSD significantly improved tolerance time to cold (3 °C) water and reduced experience of pain and unpleasantness, subjectively [70] Additionally, a recent study reported that the administration of a 200 µg dose of LSD increased emotional empathy, which was attributed to an increase in oxytocin levels [71]. A clinical study reported a reduction in anxiety and increased quality of life following treatment with LSD for 12 months at a dose of 200 µg, and it was also found to be well-tolerated [72][73]. Further, a recent study suggested that oral administration of 5 µg, 10 µg, and 20 µg of LSD every fourth day over a 21-day period was safe and tolerated, and it is being explored for the treatment and prevention of Alzheimer's disease [74]. Another recent pilot study reported that the intake of LSD led to increased positive thinking in healthy human subjects [75], and augmented emotional responses to music [76].

## 1.5. MDMA

3,4-methylenedioxymethamphetamine (MDMA) was first synthesised in 1912. It is a derivative of methamphetamine and used as a middle agent in the synthesis of other chemical compounds [77]. It gained popularity as an 'Ecstasy medicine' before being banned as a controlled substance. MDMA exhibits pharmacological actions of both methamphetamine and mescaline. It is a strong releaser of catecholamine neurotransmitters through action at presynaptic reuptake sites, similar to the actions of methamphetamine. In addition, it has strong pre-synaptic serotonin releasing activities. $5\text{-}HT_{2A}$ receptor antagonists such as ketanserin have been found to diminish the subjective effects of MDMA similar to that observed with mescaline and other classic hallucinogens [78]. A recent randomized clinical trial (RCT) has shown efficacy of MDMA-assisted psychotherapy in severe post-traumatic stress disorder [79]. The findings of another RCT reported that MDMA-assisted therapy was highly efficacious and tolerable in patients with severe PTSD, including common comorbid neuropsychiatric disorders such as dissociation, depression, a history of alcohol and substance use disorders, and childhood trauma [80].

### 1.6. DMT

DMT possesses a similar molecular composition and affinity for binding to 5-$HT_{2A}$ receptors as psilocybin and LSD, but exhibits several different pharmacological actions [48][81][82]. DMT also binds to 5-$HT_{2C}$ and 5-$HT_{1A}$ receptors, which confers it with a variety of pharmacological actions. Some pharmacological actions of DMT have been linked to its binding to and activation of sigma-1 and trace-amine receptors, among others [83][84]. In 1965, Franzen and his colleague found the presence of DMT in the biological fluids of healthy individuals [85]. In 2012, Barker and colleagues found evidence from many that indicated the presence of DMT in the biological samples of both schizophrenia patients and control subjects who had never consumed it [86]. In animals, DMT was found to be present in the brain and pineal gland of rodents [87][88][89]. In 1999, Thompson and colleagues reported that indolethylamine-*N*-methyltransferase (INMT), the enzyme that produces DMT from tryptamine, has a ubiquitous presence in human organs such as lungs, thyroid, adrenal glands, placenta, skeletal muscle, heart, small intestine, stomach, pancreas, and lymph nodes [90]. According to a published report, DMT is responsible for neurocognitive activities such as consciousness and perception, particularly visual perception. It mediates neurocognitive activities through trace amine associated receptors [91]. Previously involving closely related synthetic DMT analogue have indicated that DMT could be used as an adjunctive psychotherapy for the treatment of alcohol addicts [92][93][94] and cancer diagnosis-induced anxiety [93][95][96][97]. DMT has also been found to modulate immune function and reduce inflammation by activation of sigma-1 receptor-mediated pathways [84][98]. In 2007, Heekeren and colleagues reported that DMT diminished the magnitude of the startle response in schizophrenia patients but not in healthy individuals [99]. DMT has helped in understanding the differences between psychosis caused by hallucinogenic compounds and those that occur naturally, and has also increased the understanding of organically occurring psychotic disorders and exhibited symptoms [100]. Recently, DMT has been found to be well-tolerated, providing ample opportunities to investigate the potential of DMT. Recently, it was proposed that DMT and other psychedelics could play substantial roles in the development, growth, maintenance, and repair of the brain [101].

### 1.7. Mescaline

In 1896, Arthur Heffter isolated mescaline (3,4,5-trimethoxy-β-phenethylamine), which occurs in nature as a psychedelic compound, from *Lophophora williamsii* [102]. The pharmacological actions and adverse effects of mescaline have been reported to be comparable to LSD and psilocybin [103][104]. An early observational one was found mescaline to be well-tolerated and efficacious in substance use disorders, e.g., alcohol addiction [105], and recent data supported these findings. It was found that long-term users of mescaline elicited no impairment of cognition in comparison to the drug naive controls. In addition, the use of mescaline was found to cause significantly greater psychological well-being and general positive behaviours in comparison to controls [106].

## 2. Psychedelic Drug Models in Schizophrenia

### 2.1. Biomarkers of Neuropsychiatry and Their Association with Psychedelics Drugs

Biomarkers in neuropsychiatry are becoming immensely important and are playing a key role in facilitating diagnosis of the disorders, and the specific targeting of such biomarkers is helping in targeted treatments [107]. The findings of brain imaging ones have demonstrated an increase in the activation of neuronal structures involved in attention, reward perception, action selection, decision making and behaviour control following response to a drug therapy [108] in several brain regions [109][110][111], and altered neurochemicals in these brain areas was linked to drug craving [112]. Dopamine is a key neurotransmitter involved in various processes associated with cognition such as execution, decision-making, and planning, and also reinforces actions associated with reward and positive thinking [112]. Repetitive consumption of a drug leads to an increase in dopaminergic firing resulting in a rise in dopamine levels in brain areas such the anterior cingulate cortex, amygdala and nucleus accumbens [113][114]. Dopamine is also released along with glutamate in brain areas such as the nucleus accumbens, ventral tegmental area and prefrontal cortex associated with impulsivity, attentional, motivational and emotional processes following stimulus by addictive drugs. 5-HT is considered to be the regulator of emotion, stress and appetite, and is found to be increased in substance use disorders. Additionally, various neuropsychiatric symptoms such as anhedonia, dysphoria, depression, and anxiety during abstinence have been associated with altered metabolism of serotonin leading to triggering of drug seeking behaviours in human [114][115][116]. Further, in neuropsychiatric disorders, access to brain samples is particularly valuable; however, systematic investigations involving brain samples are limited because of the difficultly in monitoring the course of the disease. Functional neuroimaging techniques have been used for learning neuronal activities, alterations in local cerebral flow, energy metabolism and neurotransmitter receptor populations and function during the course of disease. However, they have failed to provide insights at the cellular biochemistry level and are limited due to their high economic costs. In this regard, in recent years, blood lymphocytes are increasingly being used as peripheral biomarkers for focusing on various diseases including neurological and psychiatric disorders because of the ease in sampling and isolation, and they also allow for daily monitoring of disease course [117]. It has been observed that the lymphocyte-mediated release of cytokines affects neuroendocrine and neurobehavioral responses including autonomic control. Furthermore, it was found that disruption of lymphocyte functions and metabolism leads to changes in neurotransmitters and the hypothalamic–pituitary–adrenal axis [118]. Hence, it was suggested that studies on lymphocyte gene expression in psychiatric patients who are at different stages of the disease could forecast alterations in neuronal activities in the brain. Additionally, this would help in characterising the mechanisms underlying the pathogenesis of the disease and in predicting the outcome of the pharmacological treatment. Lymphocytes obtained from the blood of psychiatric patients, such as schizophrenic and depressive patients, have been analysed for some proteins including c-fos, interleukins (IL) such as IL-2, IL-4, IL-6, and IL-10; nerve growth factor (NGF); and BDNF. Additionally, cannabinoid receptors, cholinergic receptors, γ-aminobutyric acid-A($GABA_A$) receptors, $\beta_2$ adrenergic receptors, glucocorticoid receptors, mineralocorticoid receptors, dopamine $D_3$ receptor, and 5-HT receptors have been analysed in lymphocytes from patients of schizophrenia and depression, suggesting that lymphocytes are important peripheral biomarkers [27][28][29][30][31][32][33][34].

Genomic biomarkers have also been used to learn normal biologic and/or pathogenic processes, including pharmacotherapeutic responses. These biomarkers are measurable features of deoxyribonucleic acid (DNA) and/or ribonucleic acid (RNA), such as single nucleotide polymorphisms (SNPs), variability of short sequence

repeats, haplotypes, deletions or insertions of (a) single nucleotide (s), copy number variations and cytogenetic rearrangements (translocations, duplications, deletions, or inversions) (45). The use of genetic techniques allowed the analysis of candidate genes, genome-wide and polygenetic risk score analysis to understand multiple psychiatric disorders including schizophrenia (46, 47). In 2019, Wu et al., reported that an SNP in the gene expressing a protein known as glutamate decarboxylase-like protein-1, was linked with the response to lithium in Chinese bipolar disorder patients [119]. An SNP has been also been associated with immune disturbances in bipolar disease patients, leading to increases in the levels of total T cells, CD4+ T cells, activated B cells and monocytes. Therefore, alterations in the number of immune cells may serve as a biomarker for diagnosis, disease progression, and response to therapy in patients with bipolar disorder. Another class of biomarker in neuropsychiatry are the transcriptomic biomarkers, which have potential for understanding the biology of psychiatric disorders. A transcriptome is the full range of messenger RNA, or mRNA, molecules expressed by an organism. The term “transcriptome” can also be used to describe the array of mRNA transcripts produced in a particular cell or tissue type, alternatively it is a complete set of all RNA molecules present in a single cell or in a cell population at a particular developmental stage or physiological condition [120]. The findings of transcriptomics studies have suggested that the therapeutic responses to antidepressants is linked to changes in the expression of certain genes such as matrix metallopeptidase 28 and K × DL motif-containing protein-1. Hodgkin et al. observed that efficacy of nortriptyline in patients of depression was linked to changes in genes responsible for synthesising these proteins [121]. The findings on RNA have led to the identification of biomarkers of suicide. The postmortem analysis of the brain areas, particularly the dorsolateral prefrontal cortex and the anterior cingulate cortex (ACC), of depressive patients who committed suicide found altered RNA editing on the cyclic nucleotide phosphodiesterase (PDE), particularly PDE8A, involved in the hydroxylation of cyclic adenosine monophosphate and cyclic guanosine monophosphate. These alterations have been proposed to be a potential biomarker of risk for attempting suicide in patients with depressive symptoms (68). MicroRNA-124 (miR-124) and microRNA-181 (miR-181) were found to be upregulated in the blood samples of females with cocaine addiction, and have been proposed as potential biomarkers for cocaine use disorder [122].

Proteomics is another valuable technique for identifying potential biomarkers for psychiatric disorders. This technique commonly uses blood, plasma or serum including cerebrospinal fluid (CSF) as biological samples for diagnostic purposes in clinical practice, and are easy to obtain [123]. In 2015, Nascimento and Daniel Martins-de-Souza reported that proteomics could help understand the biochemical processes of schizophrenia at the cellular and tissue levels by identifying proteins expressed predominantly in the brain tissue [124]. In 2018, Comes at al., identified alterations in specific proteins in patients with schizophrenia using proteomic ones, and suggested that these proteins could act as potential biomarkers for schizophrenia as they play key roles in relevant pathophysiological, biochemical and neurochemical processes [124][125]. In 2018, Xu et al., reported that one of these proteins was zinc finger protein 729. They found that the expression of zinc finger protein 729 was significantly lower in psychiatric patients in comparison to healthy people [126]. In 2019, Rodrigues-Amorim et al., reported that the levels of specific proteins including glia maturation factor beta, BDNF, and Rab3 GTPase activating protein catalytic subunit (RAB3GAP1) were significantly reduced in the plasma of schizophrenia patients. These proteins were presented as promising biomarkers for this psychiatric disorder [127]. Other potential

biomarkers reported for certain psychiatric and neurodegenerative disorders including major depression, anorexia nervosa, bipolar disorders and so on, have been found to be acetyl-L-carnitine and neurofilaments light chains [128][129][130]. Lately, a number have identified potential metabolomics biomarkers in different psychiatric diseases including schizophrenia and bipolar disorder [131][132], suggesting that metabolomics could be a promising tool for developing precision medicine in psychiatry [132].

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