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PERSPECTIVE

Could psychedelic drugs have a role in the treatment of schizophrenia? Rationale and strategy for safe implementation

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Schizophrenia is a widespread psychiatric disorder that affects 0.5–1.0% of the world's population and induces significant, long-term disability that exacts high personal and societal cost. Negative symptoms, which respond poorly to available antipsychotic drugs, are the primary cause of this disability. Association of negative symptoms with cortical atrophy and cell loss is widely reported. Psychedelic drugs are undergoing a significant renaissance in psychiatric disorders with efficacy reported in several conditions including depression, in individuals facing terminal cancer, posttraumatic stress disorder, and addiction. There is considerable evidence from preclinical studies and some support from human studies that psychedelics enhance neuroplasticity. In this Perspective, we consider the possibility that psychedelic drugs could have a role in treating cortical atrophy and cell loss in schizophrenia, and ameliorating the negative symptoms associated with these pathological manifestations. The foremost concern in treating schizophrenia patients with psychedelic drugs is induction or exacerbation of psychosis. We consider several strategies that could be implemented to mitigate the danger of psychotogenic effects and allow treatment of schizophrenia patients with psychedelics to be implemented. These include use of non-hallucinogenic derivatives, which are currently the focus of intense study, implementation of sub-psychedelic or microdosing, harnessing of entourage effects in extracts of psychedelic mushrooms, and blocking 5-HT2A receptor-mediated hallucinogenic effects. Preclinical studies that employ appropriate animal models are a prerequisite and clinical studies will need to be carefully designed on the basis of preclinical and translational data. Careful research in this area could significantly impact the treatment of one of the most severe and socially debilitating psychiatric disorders and open an exciting new frontier in psychopharmacology.

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INTRODUCTION

Schizophrenia affects 0.5–1.0% of the world's population with devastating consequences for affected individuals, their families, and society. It is the seventh most costly medical illness [1, 2], incurring an estimated yearly expense of over 102 billion USD worldwide [3]. In the European Union, the estimated prevalence of all psychotic disorders is around 1.2% and the incidence of schizophrenia is 15.2 per 100,000 persons [4]. The most prominent clinical features include hallucinations, delusions, and thought disorder. Thus, schizophrenia affects the most basic human processes of perception, emotion, and judgment [5]. These acutely occurring clinical features are termed positive symptoms. Schizophrenia patients also manifest negative symptoms which include impairments of volition, social functioning, and affect as well as deficits in cognition, specifically executive functions [6]. Current pharmacological treatments for schizophrenia are mainly effective against the acute manifestations of the illness (positive symptoms); considerably less so against the features that characterize the chronic phase (negative and cognitive symptoms) and are responsible for the major, long-term social and functional burden [7]. There is an urgent need to develop treatments for schizophrenia that significantly impact negative and cognitive features.

Psychedelic drugs induce characteristic changes in perception, cognition, and mood and are also termed hallucinogens or psychotomimetics because their perceptual effects resemble psychosis-like states [8]. Psychedelics encompass both natural and synthetic compounds. Naturally occurring psychedelics are of fungal, plant, and animal origin and are often termed entheogens because of their association with religious and spiritual uses over many centuries. Serotonergic psychedelics are the most widely used; they are termed serotonergic because of their action via serotonergic receptors, primarily but not exclusively of the 5-HT2A subtype. Serotonergic psychedelics include tryptamines, phenethylamines, and ergolines exemplified by psilocybin, mescaline, and lysergic acid diethylamide (LSD), respectively. Psilocybin and mescaline are naturally occurring entheogens while LSD is semi-synthetic. After being illegal for almost 50 years in most countries, psychedelics are now the focus of extensive research as potential treatments for a number of neuropsychiatric disorders including depression, posttraumatic stress disorder, and addiction [9, 10].

Schizophrenia is not a prominent focus in the current list of potential therapeutic targets for psychedelics. This is not surprising considering the hallucinogenic properties of these compounds. In fact, individuals with a personal or family history of

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psychosis are generally excluded from clinical trials of psychedelic compounds. Notwithstanding these significant reasons for caution, there are effects of psychedelics that render these compounds worthy of consideration in the treatment of schizophrenia, in particular when the disorder is characterized by prominent negative symptoms. This Perspective focuses on the potential role of psychedelics in the treatment of schizophrenia, on the patient groups most likely to benefit from them, on the significant risks, and on the steps that could be taken to avoid them. There is significant literature from the 1950s and 1960s on the use of psychedelics to treat schizophrenia. Notwithstanding their limitations, these studies provide interesting insights. In the absence of recent research, the intention of this Perspective is to re-open the topic for discussion with the aim of stimulating research that could ultimately allow schizophrenia patients to be safely and effectively treated with psychedelic drugs.

SCHIZOPHRENIA: THERAPEUTIC CHALLENGE OF NEGATIVE SYMPTOMS

The clinical presentation of schizophrenia encompasses symptoms that are divided into three dimensions: positive, negative, and cognitive. Negative symptoms, characterized by abnormalities of affect, volition, and social functioning, have a major impact on the quality of life of the affected individual. Differing from positive symptoms, negative symptoms are often associated with a limited response to pharmacotherapy. Like many common diseases, schizophrenia is multifactorial in origin. While its precise causes are unknown, epidemiological studies indicate it to be highly heritable (heritability score of ~0.8); yet its genetics is complex and likely modulated by numerous environmental factors [5]. Recent advances based on pharmacological studies, brain imaging analyses, and genetic research have indicated a central role for several neurotransmitters, including dopamine, glutamate, and serotonin, that may interact with neurodevelopmental defects reflecting disease-related genetic aberrations [2].

Public health challenge

After the onset of schizophrenia, usually in late adolescence or early adulthood, its severely disabling symptoms usually persist for life. Antipsychotic medications currently available are often only partially successful. Some patients are unresponsive to therapy, and suicide is a leading cause of premature death in schizophrenia patients [11, 12]. In fact, patients with schizophrenia spectrum disorders have significantly higher risk of premature death due to suicide and physical illness; their expected reduction in life expectancy is 10–20 years [13]. Current treatment for schizophrenia is largely symptomatic and only partially successful; therefore, the development of rational therapeutics, based on an understanding of the etiology and pathogenesis of schizophrenia, is imperative [5]. However, progress in schizophrenia has been slow, limited by phenotypic heterogeneity and lack of clear pathological lesions like those observed in classical neurodegenerative disorders [14].

Negative symptoms, what they are and why they are important

The identification of schizophrenia's negative symptoms dates to the earliest descriptions of Kraepelin and Bleuler, who both highlighted the central role of avolition in the phenomenology and course of this illness [15]. Negative symptoms include affective flattening, alogia, avolition, asociality, and anhedonia [16]. Factor analysis has isolated two separate but related subdomains—diminished expression (e.g., affective flattening), and amotivation (e.g., avolition/apathy) [17]. The distinction between positive and negative symptoms represented an important turning point in the conceptualization of schizophrenia. Although positive symptoms of schizophrenia are often adequately managed by antipsychotic medications, at least one-third of patients demonstrate persistent negative symptoms, which do not respond to currently available antipsychotic treatment [15]. Representing a distinct domain of the illness, several studies indicate that negative symptoms relate to worse symptomatic outcomes, continuous illness course, poorer global functioning, and lower likelihood of achieving recovery and clinical remission in the long term, ultimately suggesting that the unmet therapeutic challenge of negative symptoms may be crucial for the long-term outcome of schizophrenia [18].

Importance of treating negative symptoms early in recent-onset patients to prevent the development of chronicity

Poor social functioning and disorganized symptoms are baseline risk factors that can be used to identify first-episode patients at risk for developing negative symptoms [19]. While resolution of positive symptoms, even in the early stages of schizophrenia, does not necessarily translate to functional recovery, the presence of prominent negative symptoms at baseline is one of the strongest predictors of poor outcome in first-episode patients [20]. Based on a relative pliancy of negative symptoms in recent-onset patients compared with increasing stability of these symptoms thereafter [21], early targeting of the negative dimension has been promoted as a critical measure to prevent long-term disability and maximize functional outcome [22].

Negative symptoms: present status of pharmacological treatment

The introduction of numerous "atypical" antipsychotics was accompanied by optimism that even primary negative symptoms could be diminished with this new class of medications. However, methodological issues and more recent effectiveness data have called into question the degree and scope of this benefit, which has been mostly limited to mitigation of secondary (i.e. iatrogenic, as in the case of extrapyramidal symptoms) negative symptoms [23]. Nonetheless, the importance of this domain has prompted the establishment of a focused National Institute of Mental Health (NIMH) Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative to enhance understanding of negative symptoms, and it has since become a routine to evaluate changes in negative symptoms in schizophrenia clinical trials [24]. In line with this approach, regulatory agencies such as the Food and Drug Administration have indicated that they will entertain approval of add-on treatments proven to be effective for negative symptoms [25]. Nonetheless, a recent meta-analysis of 168 randomized-controlled trials of interventions for negative symptoms in schizophrenia, which included numerous trials with add-on antidepressants and glutamatergic agents, concluded that while some statistically significant small-to-moderate effects on negative symptoms were evident, none reached the threshold for clinically significant improvement [26]. Overall, there is an urgent need for novel approaches to the treatment of negative symptoms in schizophrenia.

ASSOCIATION OF SCHIZOPHRENIA WITH NEURONAL DYSFUNCTION

Evidence from post-mortem studies

Autopsy evidence indicates that schizophrenia is associated with functional impairments in the neuropil that retard synaptic interactions and cellular support activities [27]. Most notable in the prefrontal cortex, the net result of such neuropil dysfunction may be impaired neural transmission, possibly worsened by structural abnormalities in relevant neural pathways. As for specific cell-type involvement, post-mortem studies have revealed reduced density of parvalbumin interneurons in the frontal cortex of patients with schizophrenia [28], accompanied by

moderate–large reductions in synaptic proteins [29], consistent with models that implicate synaptic loss in schizophrenia.

Evidence from imaging studies

Based on magnetic resonance imaging, widespread cortical thinning of the fronto-temporo-parietal region, sulcal flattening of the insula, and gyrification reduction of the frontal cortex have been observed in schizophrenia patients [30]. Accordingly, cortical thickness could have the potential in discriminating schizophrenia patients from healthy controls [31]. Notably, greater disease duration has been associated with reductions in grey matter volume beginning in the thalamus and progressing to the frontal lobe, and then to the temporal and occipital cortices [31]. Using causal network analysis, the thalamus has been shown to be the primary hub of the directional network and exhibited positive causal effects on the frontal, temporal, and occipital regions. Subsequently, frontal regions, which were identified to be transitional points, were shown to project causal effects on the occipital and temporal regions [32]. These data are consistent with gradual progression of grey matter abnormalities in schizophrenia and highlight the thalamus as a primary hub and the frontal regions as prominent nodes in the progressive brain atrophy that characterizes the disorder. As for white matter, widespread microstructural differences in schizophrenia have also been reported [33].

Early onset of structural changes and brain atrophy

Significant cortical thinning within cingulate, occipital, and frontopolar cortices has been reported in first-episode schizophrenia patients with little or no prior antipsychotic medication treatment [34]. Studies assessing patterns of age-related cortical thinning in schizophrenia have indicated that the reduction of cortical thickness might not be progressive over the course of the illness, consistent with the notion that pathological processes occur in a relatively limited period around the onset of the illness [35]. Notably, while longitudinal imaging indicated similar anatomical patterns of brain surface contraction in first-episode schizophrenia patients and healthy controls, surface contraction in the dorsal surfaces of the frontal lobe was significantly greater in patients, consistent with the notion that exaggerated progressive changes in first-episode patients may reflect an increased rate of synaptic pruning [36]. Beyond the cortex, baseline focal hippocampal atrophy has been shown to predict progression to syndromal psychosis [37], consistent with the emergence of atrophy at an early stage of the disorder in distinct subcortical regions. Finally, in relation to white matter, biophysical diffusion models demonstrated that altered fiber complexity is evident already in young–adult, medication-naïve patients [38].

Association with negative symptoms

The very nature of negative symptoms has implications regarding pathophysiology. Whereas positive symptoms are framed in the context of excess activity (e.g., hyperdopaminergia), negative symptoms, at least historically, have been conceptualized as reflecting a loss of functioning [39]. This position was central to the early work distinguishing positive and negative symptoms, where negative symptoms were associated with structural CNS changes. Indeed, in a study where the patient group was divided into three subgroups, consisting of patients with predominantly negative, disorganized, or paranoid symptoms, the negative symptoms subgroup showed the most extensive cortical thinning, whereas thinning in the other subgroups was focused on prefrontal and temporal cortical sub-regions, indicating a distinct and widespread structural deficit profile matching negative symptoms [40]. In another study based on an exceptionally large cohort, orbitofrontal cortex thickness was reported to be negatively associated with negative symptom severity after accounting for age, gender, and overall illness severity [41]. Employing a data-driven neuroimaging approach, another report revealed distinct patterns of cortical thinning in schizophrenia, with preserved cortical thickness linked to lower negative symptoms [42]. Considering that cognitive deficits often accompany negative symptoms, significant associations between lower processing speed and thinning of the frontal cortex and flattening of the parahippocampal gyrus have also been reported in schizophrenia [30]. Of note, cortical thinning of the frontal and temporo-parietal regions in patients with prominent negative symptoms has been reported in non-affective first-episode psychosis [43], indicating that in the context of negative symptoms, cortical atrophy tends to present in earlier disease stages. Subcortically, reductions in prefrontal white matter have also been associated with negative symptoms [44].

Current pharmacological approaches to treating negative symptoms and neuro-progressive changes

As negative symptoms have traditionally been associated with structural brain changes, it had been postulated that these features would not be amenable to pharmacotherapy in the same fashion as positive symptoms [45]. Moreover, most currently available drugs have limited effects on negative symptoms of schizophrenia that are not secondary to positive symptoms and to date no agent is approved by the FDA for the treatment of negative symptoms [46]. Tempering down earlier (premature) enthusiasm, overall, recent meta-analyses did not find the newer antipsychotics superior to their conventional counterparts in the treatment of negative symptoms, and the effect, in either case, was modest [26, 47].

Nevertheless, a few considerations are warranted. In a meta-analysis of randomized, controlled, blinded, antipsychotic drug trials in patients with schizophrenia and predominant negative symptoms, low-dose amisulpride, which is approved for negative symptoms in a limited number of European countries, was the only antipsychotic superior to placebo in the treatment of negative symptoms; however, a reduction of depression was also observed making it difficult to assess whether the reduction in negative symptoms was secondary to depression improvement [48]. Significant differences and clinically relevant improvement in both negative symptoms and functional impairment were reported in favor of cariprazine, a dopamine D3-preferring D3/D2 receptor partial agonist and serotonin 5-HT1A receptor partial agonist, over risperidone, suggesting a clinically meaningful benefit for cariprazine in negative symptoms [49]. Importantly, a meta-review of available meta-analytic evidence aiming at elucidating the state-of-the-art for clozapine efficacy was recently published [50]. According to this research, clozapine appears to have superior effects on positive, negative, and overall symptoms and relapse rates in schizophrenia (treatment-resistant and non-treatment-resistant subpopulations) compared to first-generation antipsychotics and to pooled first/second generation antipsychotics in treatment-resistant schizophrenia. The relationship between these outcomes and the unique, wide range of highly complex effects that clozapine has on the brain remains to be elucidated. Clozapine is a relatively weak D2 receptor antagonist in the striatum with high affinity for D1, and antagonism for D3 and D4 receptors. In addition, clozapine has effects on the serotoninergic system, including 5HT2A receptors, effects on muscarinic M1 receptors and has been shown to modulate thalamocortical glutamatergic transmission [51]. It is highly likely that no single mechanism of action, but rather multifactorial interrelated effects may explain the unique clinical profile of clozapine. Given the considerable unmet medical need associated with negative symptoms, drug development is also active in this therapeutic area for agents with activity at different receptors including NMDA receptors, alpha 7 nicotinic receptors, 5HT2A, and sigma-2 receptors.

Notwithstanding the challenges in distinguishing negative and depressive symptoms clinically, a commentary based on an

extensive body of literature assessing the efficacy of antidepressants in the treatment of negative symptoms concluded that the evidence is not strong enough to support their use [52]. Ionotropic and metabotropic glutamatergic receptors, have been evaluated over the last two decades for the treatment of negative symptoms, providing ongoing (albeit limited) support for *d*-serine [53], alongside discouraging results for agents that act through glycine transporter 1 inhibitions [54] and mGluR2/3-positive allosteric modulation [55] and mixed results for NMDA receptor antagonists [56, 57]. Despite earlier hopes, targeting alpha-7 nicotinic neurotransmission did not improve negative symptoms of schizophrenia [58, 59]. With respect to attenuation of neuroinflammation associated with schizophrenia [60], and building on several lines of preclinical data demonstrating minocycline's potential to target dysfunctional glutamatergic, inflammatory, and oxidative stress pathways [61], it has been speculated that in conditions of hyperactive synaptic pruning, as implicated in schizophrenia, the inhibitory action of minocycline on microglia could offer an early neuroprotective intervention [62]. Indeed, an effect of minocycline on negative symptoms and on some cognitive domains has been shown in multiple, although relatively small, clinical trials [63], and more recently, treatment with high-dose minocycline led to improvements in cognitive scores and in negative symptoms, which were correlated with reduction in serum levels of interleukins 6 and 1β, indicating that minocycline's beneficial effects could be mediated via its inhibitory effects on microglial activation [64]. However, contrary to expectations, findings from a recent large randomized controlled trial that compared minocycline with placebo as an adjunctive treatment to usual antipsychotic treatment were largely negative [65]. Overall, it has been argued that these disappointing results do not necessarily mean that neuroinflammation in schizophrenia is not druggable [66], but rather reflect a pressing need to explore additional pathways that offer relevant neuroprotection.

Potential role of psychedelics

Given their increasingly reported effect to enhance neural plasticity (see below) and their reported effects on inflammatory processes [67, 68] it is possible that psychedelic drugs could have a role in treating cortical atrophy and cell loss in schizophrenia, and the negative symptoms associated with these pathological manifestations, provided that potential psychosis-inducing effects can be neutralized.

PSYCHEDELIC DRUGS AND SCHIZOPHRENIA: HISTORICAL PERSPECTIVES

Studies with psychedelic drugs in adult schizophrenia patients

The first trial of psychedelics in schizophrenia was conducted in 1947 by Stoll at the University of Zurich. He used escalating doses of LSD in six treatment-resistant patients, after studying the effects of LSD on 16 healthy volunteers. As compared to the healthy subjects, who responded to a 30 µg dose of LSD, schizophrenia patients required doses up to 130 µg to achieve an effect. The onset of the effect was protracted and the visual effects and euphoria were less pronounced as compared to those of the normal participants and different from the psychosis of the underlying disease. None of the patients had worsening of their disease and the authors speculated that repeat doses could lead to tolerance [69]. The study was expanded by Condrau [70], who examined seven volunteers, (junior physicians and the author himself), some of whom were blinded as to the day they received LSD in their morning coffee, and 30 psychiatric patients, most of them with schizophrenia. The expanded study confirmed the initial findings including the need for higher doses of up to 280 µg for achieving psychedelic effects in the patients, coupled with the emergence of weaker euphoric effects and a lower propensity for side effects such as nausea and headache. In a further study by Katzenellenbogen and Fang [71], the narcosynthesis and physiological effects of sodium amytal, methedrine and LSD were compared in the same 15 schizophrenia patients. LSD was given in doses ranging from 10 to 50 µg. Ventilation of emotions seemed to be more marked with LSD [72].

Although no clear therapeutic effects on core schizophrenia pathology were identified in these early studies [72], research continued during the 1950s and 60s when psychedelic drugs were often studied in conjunction with psychotherapy for a variety of psychiatric conditions including schizophrenia. The vast majority of schizophrenia trials, which studied the therapeutic effect of LSD in institutionalized patients in observational studies similar to the first studies conducted in Switzerland, reported similar findings. Most trials described the effect of various LSD dosages, ranging from 10 up to 500 µg, in schizophrenia patients and compared them to effects observed in healthy volunteers. Effects were assessed according to clinical judgment rather than unified criteria and findings were descriptive. These limitations also applied to studies testing the effects of other psychedelic substances, in which dosage varied considerably, ranging from 0.4 to 0.6 g of mescaline and 1 to 1.5 mg of DMT and often did not follow a predefined schedule. Some studies confirmed a diminished response to psychedelic drugs in schizophrenia patients with a need for higher doses to achieve an effect, while others observed either reversal of accustomed behavior or intensification of symptomatology and behavior patterns [72]. It was suggested that LSD and mescaline accentuated symptomatology in "acute" schizophrenia patients while "deteriorated schizophrenics" showed very little response. Abramson et al hypothesized that LSD facilitates "identification" of a schizophrenic patient with healthy volunteers in a group therapy setting and reported increased communication by patients after receiving LSD as compared to placebo [73].

Studies in autism and childhood schizophrenia

Several studies and case series reported the use of psychedelics in "schizophrenic autistic" children, who had exhausted all available treatment options. Psychedelics were hypothesized to stimulate maturation, to overcome defense mechanisms, and to make the patient more receptive to communication with others. Ages ranged from 5 to 15 years. The symptoms of the younger children were described as closer to classical autism while the symptoms of the older children more closely resembled adult schizophrenia. The children received one or more psychedelic agents according to various treatment schedules. LSD was the most commonly used drug in these studies. Psilocybin and UML-491, an experimental serotonin inhibitor, were used in a single report [74]. While all the studies observed some short-term improvements in speech and behavior, greater emotional responsiveness, increased positive mood, and decrease in compulsive ritualistic behavior, they all had severe limitations: patient populations were not homogenous, data were fragmented, criteria for drug effects and outcome were vague, and follow-up was inadequate [74, 75].

Decline of psychedelic research

Psychedelic research declined due to tighter regulation of pharmaceutical drug development in 1963 following the thalidomide tragedy. Earlier observations of effectiveness could not be reproduced in formal randomized placebo-controlled trials, which had become the gold standard [76, 77]. By 1965, Sandoz no longer provided LSD for research, as the company became concerned with the reputational risks associated with over-exuberant advocacy for nonmedical use of psychedelics and media coverage of "bad trips", accidental deaths, suicides, and psychoses. The lack of pharmaceutical drug supply coupled with the 1970 US Controlled Substances Act whereby psychedelics became Schedule 1 drugs with the

termination of all publicly funded research, heralded an over 30-year hiatus in psychedelics research [78].

Insights from the historical studies

Design limitations of the historical studies, the subjective nature of the evaluations, and lack of follow-up hamper the ability to draw any firm conclusions as to the potential effectiveness of psychedelics in schizophrenia. Schizophrenia patients and healthy volunteers were reported to react differently to psychedelic compounds. The overwhelming majority of studies of psychedelics in schizophrenia were conducted with LSD. Today, there is greater understanding of the complex pharmacodynamics of the various psychedelic compounds coupled with a growing appreciation that these compounds interact with multiple receptors and transporters in the brain and can bring about a wide range of trophic changes. Whether the neuroplastic attributes of psychedelics have therapeutic use in schizophrenia, in particular to counter negative symptoms, remains to be demonstrated. The studies of Bender in older autistic children with schizophrenia-like symptoms, strongly reminiscent of negative symptoms as presently defined, raise interesting possibilities. It is also noteworthy that in adult schizophrenia patients, exacerbation of psychosis was not consistently observed with so-called retarded patients showing very little response. These observations suggest that there may be a place for the judicious use of psychedelics in patients with schizophrenia, particularly those with negative symptoms. How to avoid potential exacerbation of psychotic symptoms while defining a schedule to alleviate negative symptoms without inducing tolerance remains a central challenge.

HALLUCINOGENIC EFFECTS OF PSYCHEDELIC DRUGS

Definition and clinical effects of hallucinogens

The term, hallucinogen, highlights just one aspect attributed to a class of drugs used by mankind for millennia. Beyond eliciting profound changes in perception, these agents have striking effects on consciousness, mood, and psychological wellbeing. Many psychedelic substances exert their hallucinogenic effect through 5-HT2 serotonergic receptors, a receptor subfamily that comprises three subtypes—5-HT2A, 5-HT2B, and 5-HT2C [79]. Although the psychedelic drugs LSD, psilocybin, and mescaline are derived from structurally distinct chemical entities, their hallucinogenic effect is similar [80, 81] and primarily mediated through 5-HT2A receptors [82]. Indeed, a widespread definition of a hallucinogenic substance is “an agent that binds to 5-HT2A receptors and alters thought, perception and mood, without inducing addiction, memory impairment or delirium” [83]. All serotonergic psychedelics induce an altered state of consciousness [84–86], including three core dimensions as indicated by the Aussergewöhnliche Psychische Zustände questionnaire: *oceanic boundlessness* (OB), representing a pleasant state of depersonalization and derealization; *anxious ego dissolution* (AED), representing dysphoric effects of altered consciousness such as ego disintegration, loss of self-control, anxiety, thought disorder, and delusions; and *visionary restructuralization* (VR), representing visual hallucinations and perceptual illusions [87]. Converging data derived from both human and animal studies indicate that the 5-HT2A antagonist, ketanserin, blocks the hallucinogenic effect of serotonergic psychedelics in humans and the behavioral effects in rodents are considered to be proxies of human psychedelic effects [84, 88–90]. In addition to blocking the hallucinogenic effects of serotonergic psychedelics, 5-HT2A antagonists are also reported to block the effects of these drugs on synaptic plasticity [91, 92].

Psychedelic drugs as a model for schizophrenia

In humans, as well as in translational animal models, serotonergic psychedelic drugs induce symptoms resembling the positive symptoms of schizophrenia [88, 93, 94], including deficits in prepulse inhibition (PPI) and altered acoustic startle response [95], whereas non-competitive NMDA receptor antagonists such as ketamine and PCP, especially when administered (sub) chronically, can also model the negative and cognitive symptoms that are characteristic of schizophrenia [96–100]. Psilocybin, LSD, and mescaline all model psychosis in non-schizophrenic humans, which closely resembles the early stage of schizophrenia [101, 102] and also in laboratory animals [103, 104]. Interestingly, although serotonergic psychedelic drugs evoke psychotic-like phenotypes, these symptoms are attenuated by serotonergic but not by dopaminergic antagonists such as haloperidol suggesting that psychedelic-induced psychosis is mediated via serotonergic rather than dopaminergic pathway [88], and also that imbalanced 5-HT2A signaling play a role in schizophrenia, and hence may serve as a target for treatment of the disease.

Psychedelics and etiological theories of schizophrenia

Because hallucinations represent a core feature of schizophrenia, it has been argued that not only can psychedelic agents model schizophrenia but there might also be a more direct link between schizophrenia and hallucinogens. Some studies have indicated that individuals manifesting long-term psychosis secondary to psychedelic drug (ab)use share phenomenology and trajectory with schizophrenia patients, consistent with the model of psychedelic drug psychosis representing a drug-induced (variant of) schizophrenia [105–109]. These similarities led to the hypothesis that there is an endogenous substance similar to psychedelic agents within the brains of schizophrenia patients that induces the disease [110]. This hypothesis has never been validated, yet pursuit of the hallucinogen–schizophrenia connection has not been exhausted.

Do psychedelic drugs exacerbate schizophrenia?

There is limited evidence that in vulnerable subjects, with predisposition to mental illness, psychedelic agents such as LSD may induce psychosis characterized by panic, mistrust, impaired reasoning, and delusions of grandeur [111] instead of the overall pleasant experience usually associated with the use of psychedelic agents. Studies have indicated that in subjects who have relatives with a schizophrenia diagnosis, LSD is more likely to induce psychotic symptoms [106, 112], while in subjects without a psychiatric history or family history, paranoid features manifested in the Rorschach test could predict psychotic experience during LSD exposure [113]. It has also been suggested that psychedelic drugs such as LSD could lead to psychosis by interacting with a premorbid schizophrenia vulnerability [114]; consistent with these observations, antipsychotic drugs such as haloperidol and chlorpromazine have been found effective in the treatment of psychedelic-induced psychosis [115]. In this line, in a recent review, the authors found that features common to LSD psychosis and schizophrenia were that both experiences were related to a reduced integration and stability of functional networks, as well as to a distorted anti-correlation between resting-state and task-positive networks. Furthermore, both experiences were afforded a strong metaphysical meaning [116]. Nonetheless, extending older reports noting differences between psychedelic-associated psychosis and schizophrenia [117], the same recent review [116] also highlighted various crucial differences. For instance, schizophrenic hallucinations are often characterized by associative network over-activation, are mostly auditory in nature, and are detailed, concrete, and well-anchored in space [118], whereas psychedelic hallucinations are mostly visual, and linked to 5-HT2A and primary visual cortex over-activation [119], varying from simple and mostly geometric hallucinations to complex hallucinations containing ordinary and extraordinary entities [120]. Although psychedelic hallucinations can be very vivid, reality testing normally remains intact [121] and discriminates the hallucinations from everyday

perception. Schizophrenic hallucinations, in contrast, occur in the context of defective reality testing. Consistent with these reports, a recent large population study did not find consumption of psychedelic drugs such as psilocybin, LSD, and mescaline to be associated with suicidal behavior or with psychiatric disorders such as depression, anxiety, and schizophrenia [122, 123].

Hallucinogen persisting perception disorder (HPPD)

HPPD is a nonpsychotic disorder, consisting of recurring perceptual disturbances that were previously experienced under hallucinogens use but ceased after the intoxication subsided, in the absence of current intoxication and without an alternative diagnosis that better explains the condition such as anatomical lesion, infection, neurodegenerative disease, or mental disorder such as schizophrenia [124]. HPPD is categorized into two subtypes: HPPD type I and HPPD type II. HPPD type I refers to short-term flashbacks for the original intoxication, that might provoke unpleasant feelings but does not induce considerable distress and/or impairments affecting social, occupational, or personal areas of life [125]. HPPD type II refers to long-term, irreversible/very slowly reversible, severely impairing distortions often leading to considerable distress and functional impairment [126]. The prevalence of HPPD type I is higher than HPPD type II, with 5–50% of hallucinogen users reporting flashbacks of the hallucinogenic trip to some extent, whereas ~4.2 of the hallucinogen users are estimated to experience HPPD type II to some extent [127]. It is important to note that although high rates of hallucinogen users may develop HPPD type I, they might not be diagnosed as HPPD cases according to the DSM-V criteria, as HPPD diagnosis requires that the symptoms induce severe distress/impairment. Hallucinogenic drugs differ in their tendency to induce HPPD. LSD is the most common hallucinogenic that is associated with HPPD, and the severity of the symptoms is positively correlated with number of occurrences of LSD use [127]. Psilocybin was also associated with HPPD, but only in combination with other drugs [128].

A concern regarding psychedelic use in schizophrenia patients is that they might have higher tendency to develop HPPD, as they are prone to hallucinations. Interestingly, schizophrenia patients who also suffer from HPPD have lower negative symptoms score and lower general psychopathology scores, compared to schizophrenia patients without HPPD [124]. Moreover, although hallucinations are present both in schizophrenia and HPPD, the nature of hallucinations is different in the two pathologies, and have different etiology [129].

Implications for the treatment of schizophrenia

Recent findings which do not indicate overt hypersensitivity of schizophrenia patients to classic hallucinogen-associated psychosis are in stark contrast to the reported hypersensitivity of schizophrenia patients to non-psychedelic psychotomimetics. Amphetamine typically elicits overt psychosis via stimulation of mesostriatal dopamine pathways. Increases in both psychotic symptoms and in amphetamine-induced synaptic dopamine concentrations were larger among schizophrenia patients compared to controls [130, 131]. Mirroring the amphetamine data, an exaggerated psychotomimetic response in schizophrenia subjects was also reported with sub-anesthetic doses of the N-methyl-D-aspartate (NMDA) antagonist ketamine, which produced marked psychotic symptoms that were strikingly reminiscent of the subjects' symptoms during active episodes of their illness [132]. Taken together, these data indicate that in schizophrenia patients, psychedelic agents may be less likely to provoke symptom exacerbation than has been thought, and this favorable profile differs markedly from that elicited by "classical" psychotomimetic agents that modulate dopaminergic and glutamatergic transmission. Based on the above, it would seem possible to consider cautious use of psychedelic agents in schizophrenia if steps are taken to mitigate potential exacerbation of positive symptoms. Such caution should include all research participants in psychedelic studies with a family history of schizophrenia.

NEUROPLASTIC EFFECTS OF PSYCHEDELIC DRUGS

Psychoplastogens and their effects

Neuroplasticity is defined as the ability of the nervous system to respond to internal and external stimuli through re-modulation of its physical structure and functional connections [133, 134]. Because of their unusually robust abilities to produce rapid and long-lasting changes in neural plasticity, compounds that have these effects, such as ketamine and psychedelics, have recently been termed psychoplastogens—a suggested new class of therapeutic agents [135]. Classic psychedelics act on 5-HT2A receptors which are expressed on glutamatergic pyramidal cells [136, 137]. Through stimulation of the 5-HT2A receptor, psychedelics activate intracellular signaling pathways such as PLC, PLA, and Src [138, 139]. Psychedelics also produce modification of neuronal and synaptic plasticity through signaling pathways such as the mammalian target of rapamycin and BDNF-NTRK2 [140–142], with growing evidence that psychedelics promote structural and functional plasticity of synapses [142–144]. Reports suggest that the beneficial effects of psychoplastogens can last for months following a single administration, and these compounds have demonstrated suggestive efficacy across a range of neuropsychiatric disorders including depression, PTSD, and addiction [145–148]. Furthermore, psychedelics have been shown to have potent anti-inflammatory properties and given their affinity for the 5-HT2A receptor, may represent a unique anti-inflammatory agent targeted to brain tissue [67].

Evidence for induction of neurogenesis in preclinical studies

Neurogenesis is thought to be a crucial step to achieve antidepressant outcomes in animal models, and its blockade leads to the development of depressive-like behavior, making it a critical mediator of stress resilience and susceptibility [149, 150]. Psilocybin has been shown to induce a biphasic hippocampal neurogenesis response, with low dose (0.1 mg/kg) producing subtle neurogenesis increase and high dose (1.0 mg/kg) significantly decreasing neurogenesis [92]. Psilocybin activates 5-HT-2A receptors and stimulates neurogenesis through brain-derived neurotrophic factor (BDNF) expression in the neocortex but appears to consistently inhibit the same process in the hippocampus in a rat model [151]. In rat cortical neuronal cultures and drosophila larvae, LSD promoted neurogenesis and synaptogenesis in a dose-dependent manner, suggesting an important cross-species evolutionary pathway for this effect, and indicating that there may be an optimal dose for harnessing the effect [142].

Evidence for neural plasticity in preclinical studies

Psychoplastogens are suggested to be a relatively new class of fast-acting therapeutics, capable of rapidly promoting structural and functional neural plasticity. Psychoplastogenic compounds including ketamine, LSD, N, N dimethyltryptamine (DMT), and 2,5-dimethoxy-4-iodoamphetamine (DOI) increase dendritic arbor complexity, promote dendritic spine growth, and stimulate synapse formation. Besides depression, ketamine has shown promise for treating PTSD [148] and heroin addiction [149]. Animal models have shown that the therapeutic effect of ketamine stems from its ability to promote the growth of dendritic spines, increase the synthesis of synaptic proteins, and strengthen synaptic responses [141, 152, 153]. Sub-anesthetic doses of ketamine elevated in vivo extracellular cortico-striatal glutamate levels and firing rates of pyramidal neurons in the medial prefrontal cortex [143, 154, 155], while increasing spine density and synaptic plasticity markers such as synapsin 1, postsynaptic and density protein 95 in stress-exposed rats [156].

Low-dose ketamine also increased hippocampal AMPA/NMDA receptor density ratio in a preclinical MDD model [157].

Psychedelic compounds such as LSD, DMT, and DOI promote dendritic branching and/or increase spine/synapse number both in cultured cortical neurons and in vivo [141]. Like ketamine, 24 h after administration, a single intra-peritoneal injection of DMT, increased dendritic spine density as well as the frequency and amplitude of spontaneous excitatory postsynaptic currents in the rat PFC. DMT (10 mg/kg) produced positive effects in behavioral tests relevant to depression and PTSD in rats [145]. In rat models, 5-HT2A receptor activation using mid-dose psilocybin (0.13 mg/kg) enhanced both prospective and retrospective learning, with lesser effects seen at a lower dose (0.06 mg/kg) [158, 159]. Consecutive daily dosing diminished benefits, and in older rodents learning was further enhanced by an enriched environment [158]. Additionally, it has been reported that a single dose of psychedelics such as 4-bromo-3,6-dimethoxybenzocyclobuten-1-yl) methylamine (TCB-2) and DMT facilitated the extinction of cued fear memory in mice and rats [160]. Notably, using models of behavioral despair or passivity such as the forced swim test, it has been suggested that a single administration of psilocybin or LSD produced long-lasting (up to 5 weeks) antidepressant-like effects in rats [161].

Evidence for synaptic plasticity in human studies

While clinical studies indicate a therapeutic potential for psychedelics in various psychiatric disorders, evidence of psychedelic effects on neuroplasticity in humans is still scarce. A single, low dose of LSD (5, 10, and 20 µg) administered to healthy volunteers ($n = 24$) resulted in increased serum BDNF levels compared to placebo 6 h after treatment [162]. In another cross-over study, in healthy participants ($n = 18$) who received a single dose of LSD (25, 50, 100, and 200 µg) over six sessions, with 10 days in-between administrations, plasma BDNF levels were dose dependently elevated compared with placebo [163].

Potential importance of neuroplastic effects in the treatment of negative symptoms of schizophrenia

As reviewed in previous sections, there is a well-supported association between negative symptoms in schizophrenia patients and cortical atrophy. It is thus reasonable to consider that treatments, such as psychedelics, which promote neuroplastic processes that include neurogenesis and synaptic plasticity, could have a role in treating schizophrenia, particularly those patients with negative symptoms of relatively recent onset. Realizing this potential clinically would depend on the implementation of strategies to reduce the potential of psychedelic compounds to worsen the positive features of the illness.

POTENTIAL STRATEGIES TO AVOID PSYCHOTOGENIC EFFECTS OF PSYCHEDELIC DRUGS WHILE RETAINING NEUROPLASTIC EFFECTS

In this section, we consider strategies that could be implemented to harness the neuroplastic effects of psychedelics while avoiding potential psychotogenic effects.

Non-hallucinogenic derivatives

At the doses used to treat psychiatric disorders, all psychedelic drugs induce the striking constellation of psychological effects that is termed the "trip". This constellation of effects requires careful observation of the patient for up to 24 h after treatment. It is widely held that the trip, occurring in the context of carefully monitored set and setting, is the key therapeutic component of the treatment [164]. On the other hand, there is growing support for the view that non-hallucinogenic psychedelic analogs that do not induce a trip but do induce neuroplastic effects, could be a therapeutic option that is both accessible and effective [135]. A novel compound derived from the psychedelic drug, ibogaine, but lacking its toxic and hallucinogenic effects, has been found to rapidly reverse the effects of stress in mice and to have potential antidepressant effects as well as anti-addictive properties as evidenced by reduction of alcohol and heroin seeking [165]. This compound induced structural and functional neuroplasticity in mice without enhancing the head twitch response, a well-established rodent analog of psychedelic potency [165]. Further structure-based studies from a different group of investigators have demonstrated several 5-HT2AR β-arrestin–biased agonists that displayed antidepressant-like activity in mice but without hallucinogenic effects [166]. Non-hallucinogenic psychedelic derivatives that have neuroplastic effects could offer an ideal approach for treating schizophrenia with psychedelic agents.

Sub-psychedelic dosing

Currently, the doses used in clinical studies with psilocybin are ~20–25 mg per 70 kg adult, selected to elicit clearly discernible, subjectively experienced effects on perception, cognition, and mood. Treatments are often performed in a context termed "psychedelic-assisted psychotherapy" in which the subjective effects of the drug are considered a prerequisite for effective treatment or under conditions of close observation and support of the patient without formal psychotherapy. It is possible that psychedelic drugs exert effects on brain function at doses that do not induce striking subjective effects. The public health implications are enormous because of the lower intensity of patient care that would be required and consequently reduced costs. Preliminary support is provided by a small, uncontrolled clinical study of OCD in which doses of psilocybin that did not induce psychedelic effects reduced symptom severity [167]. Further support comes from the widely used practice of microdosing in which doses of psilocybin that are only a fraction (one tenth or less) of the psychedelic dose are taken by individuals in a non-medicinal context. While results are not consistent and comprehensive studies are lacking, there is evidence that microdosing may have positive effects on mood, creative processes, and energy [168, 169]. In a recent large internet-based study psilocybin was the most frequently microdosed psychedelic agent. The self-selected microdosers reported health-related motivations and lower levels of anxiety and depression compared to non-microdosers [170]. In a preclinical study, Cameron et al. [145, 171] reported that chronic, intermittent microdoses of DMT induced an antidepressant-like phenotype and enhanced fear extinction in rats as well as increasing dendritic spine density, while Higgins et al. [171] reported that low doses of psilocybin enhanced motivation and attention in poor-performing rats.

Psychedelic microdosing is regarded by informal convention as 10% of the dose that elicits definitive psychedelic effects in the average adult. The upper limit for a microdose of psilocybin is 2.0–2.5 mg [172]. If such doses could be given to schizophrenia patients without eliciting psychotic effects, their potential efficacy could be determined particularly in alleviating negative symptoms. At low doses that do not elicit significant subjective effects (higher than microdoses but nevertheless sub-psychedelic), it would seem likely that a course of treatment of at least 10 days would be needed rather than single administration. Exploratory studies will be needed to determine tolerability of treatment and, in the absence of psychotogenic effects, the appropriate dosing regimen.

Harnessing entourage effects of psychedelic mushrooms and other naturally occurring psychedelics

Anecdotal reports suggest a discernible difference between the effects of chemically synthesized psilocybin and those of psychedelic mushrooms and also differences among the effects of different mushroom strains. These reports are consistent with the observations of Gartz [173] regarding the effects of the

mushroom, Inocybe aeruginascens (high in aeruginascin content) as compared to the effects of mushrooms with a high psilocybin and psilocin content. Gartz [173] observed an increased mood-enhancing effect of the mushrooms high in aeruginascin content as compared to those high in psilocybin. These observations led Gartz [173] to propose an "entourage effect" of psychedelic mushrooms whereby additional components of the mushroom extract enhance the effect of psilocybin. (It should be noted that negative entourage effects are also possible in the form of enhanced adverse effects). Entourage effects were originally suggested in the context of cannabis research where it was proposed that additional components of cannabis extract may modify the effect of tetrahydrocannabinol and reduce its psychoactive effects [174, 175]. A preclinical study that is relevant in this context compared the effects of an extract from Psilocybe argentipes to pure psilocybin on marble-burying behavior in mice, a translational model of obsessive-compulsive disorder. Psilocybin mushroom extract was more effective reducing marble burying than pure psilocybin at the same dose [176], supporting an entourage effect of the mushroom-derived preparation. Further evidence for a psychedelic mushroom entourage effect was provided by Zhuk et al. [177] showing that psilocybin mushroom extracts were significantly more potent inducing HTR than the same dose of pure psilocin, the active metabolite of psilocybin.

These observations raise the possibility that additional components found in naturally derived extracts containing psychedelic compounds may modify the effects of the principal component in a way that possibly reduces its psychedelic effects and enhances its therapeutic action. If such entourage effects were demonstrable in preclinical studies, they could be tested in humans and if proven, provide a basis for clinical studies in schizophrenia patients.

Blocking 5-HT2A receptor-mediated hallucinogenic effects

It is well established that the 5-HT2A receptor mediates the psychedelic effect of serotonergic psychedelics such as mescaline, LSD, and psilocybin. Two 5-HT2A receptor antagonists, ketanserin (5-HT2A/2C antagonist) and risperidone (5-HT2A/D2 antagonist), were shown to block the psychedelic effects of psilocybin represented in the VR (visionary restructuralization), OB (oceanic boundlessness), and AED (anxious ego dissolution) dimensions in human subjects [88, 178, 179]. Moreover, the response to psilocybin is positively correlated with the level of 5-HT2A receptor occupancy [180]. 5-HT2A receptor antagonists were also demonstrated to block the psychedelic effects of mescaline [89, 181] and LSD [90, 182, 183] in human subjects and in laboratory animals. Activation of 5-HT2A receptors underlies visual hallucinations via altered visual-evoked cortical response, increasing cortical excitability [183], activating GABAergic interneurons in the piriform cortex [184], and inhibiting spontaneous activity in the locus coeruleus [185]. Various 5-HT2A receptor antagonists were demonstrated to block these hallucinogenic effects [13, 14]. 5-HT2A receptors in the prefrontal cortex seem to mediate the inhibition of psychedelics on startle habituation [186] and PPI [90], whereas 5-HT2A receptor antagonists reverse these effects [95, 186].

Head-twitch response (HTR), a rapid side-to-side rotational head movement evoked in rodents by 5-HT2A agonists [187, 188], is completely blocked by selective 5-HT2A antagonists [189], and is absent in 5-HT2A knock out mice [190]. HTR was originally reported in mice following administration of the serotonin precursor 5-hydroxytryptophan [191], and later following administration of various serotonergic hallucinogens [192, 193]. Because of this specificity, HTR has been widely accepted as an animal behavioral assay of 5-HT2A activation, and particularly of assessment of hallucinogen-like effects; absence of HTR is regarded as absence of hallucinogenic effect. This approach created a framework for testing the therapeutic potential of serotonergic psychedelics while blocking their hallucinogenic properties. Following a study that demonstrated a persistent antidepressant-like effect of a single injection of LSD or psilocybin [161], another recent study tested the effect of a single psilocybin injection on anhedonic behaviors induced by a chronic multimodal stress protocol. Psilocybin had an anti-anhedonic effect, restoring preference for hedonic stimuli 24–48 h following administration and evoking marked HTR in the treated mice. Pretreatment with the 5-HT2A/2C antagonist ketanserin attenuated HTR, but not the anti-anhedonic effect of psilocybin [194]. 5-HT2A antagonism also did not abolish the beneficial effect of psilocybin on dendritic spine growth in the prefrontal cortex of the mice [194, 195], a hallmark of antidepressant effect. Psilocybin was also demonstrated to inhibit marble burying in mice, a repetitive behavior considered an animal model of obsessive-compulsive disorder (OCD) [176, 196]. Psilocybin attenuation of marble burying was not blocked by a 5-HT2A antagonist [196], suggesting that psilocybin might effectively treat OCD without relying on its hallucinogenic activity. Furthermore, these findings raise the possibility that 5HT2A receptors, and thus psychedelic responses, may not be required for a therapeutic response to psilocybin [194], which may be, at least partially, dependent upon downstream psilocybin effects on additional neurotransmission systems and enzymatic pathways.

In summary, the enhancing effects of serotonergic psychedelics on neural plasticity [194, 195, 197], fear extinction [92] and antidepressant effect suggest that psychedelics might prove beneficial in treating the cognitive and negative symptoms of schizophrenia. However, although psychedelics rarely induce prolonged psychosis [198] and their hallucinogenic effect is distinguished from schizophrenic hallucinations [118–120], schizophrenic patients are considered at greater risk for adverse effects of serotonergic psychedelics. An approach that might be taken to achieve the possible therapeutic effect of psychedelics in treating negative and cognitive symptoms of schizophrenia (other than using lower, sub-psychedelic, non-hallucinogenic doses) would be to use a full dose of psychedelic in the presence of 5-HT2A antagonists. The results obtained in animal studies indicating that the antidepressant and anti-compulsive effects of psychedelics, along with their effect on synaptic plasticity, are preserved in the context of 5-HT2A antagonist treatment, suggest that such an approach might be applicable to schizophrenia.

CRITICAL QUESTIONS FOR PRECLINICAL STUDIES

Based on the data discussed above, psychedelic agents may have benefits on the negative and cognitive symptoms of schizophrenia. It is necessary to test the effects of psychedelic agents in translational preclinical models before testing the effects in clinical studies. However, using translational models raises several critical questions. Until now, most clinical applications of psychedelic agents have been in the context of psychotherapy [9]. The contribution of psychotherapy to the beneficial effect of psychedelic agents might be by providing a supportive framework that enables the patient to channel and process the psychedelic experience to achieve a therapeutic breakthrough [199]. Psychotherapy is unique to mankind, hence there is no translational model of psychotherapy.

However, administration of psychedelic agents only in the context of psychotherapy imposes severe limitations due to low accessibility of psychedelic-assisted therapy. Proving psychedelic agents beneficial in translational models will enable an affordable, more widespread application of psychedelic-assisted therapy to patients who cannot access full psychotherapy. Moreover, preclinical models can be used to test the beneficial effect of sub-psychedelic doses, as well as the effect of psychedelic doses with and without co-application of a 5-HT2A antagonist that can further extend the therapeutic use of psychedelic agent.

Testing the effect of psychedelic agents in the context of the negative and cognitive symptoms of schizophrenia requires a careful selection of the translational model, in regard to both face and predictive validity and the means to distinguish between the effects of schizophrenia model and the effects of the psychedelic agent. Translational models of schizophrenia fit into four categories: lesion, genetic, developmental, and drug-induced models [200]. Among developmental models, maternal immune activation models are designed to mimic the effect of maternal viral infections and are known to induce increased sensitivity to amphetamine-induced hyperlocomotion [201] and disruption of PPI [202, 203], that models positive symptoms, along with cognitive and social deficits [203–205] and working memory impairments [205, 206]. Several studies have demonstrated that effects of maternal immune activation are reversed by clozapine treatment [201, 207], indicating predictive validity of the model.

Genetic models often replicate changes in mRNA and proteins that are identified in genetic studies of schizophrenia. Among these models are DISC1 mutations, inducing subtle PPI deficiency and hyperlocomotion [208, 209], representing the positive symptoms and reversed by antipsychotic drugs [210]. Some DISC1 models have also demonstrated reduced sociability of the mutant mice [208], increased anxiety, and a depressive phenotype [209]. Another study demonstrated that a combination of DISC1 mutation with maternal immune activation yields a stronger, more pronounced phenotype [203]. Both genetic and developmental models are based on manipulations that affect early development, whereas the schizophrenia-like symptoms are tested in the adult mouse. The temporal separation of manipulation and the evoked phenotype, containing analogs for both positive and negative symptoms make these models good candidates to test the effects of psychedelic agents in the context of schizophrenia.

Among available pharmacological models many are based on non-competitive NMDA receptor antagonists such as phencyclidine (PCP), MK801, and ketamine. PCP and ketamine are known to induce hallucinations and delusions [211, 212], as well as cognitive impairment and social withdrawal [213]. Mouse models of PCP [214], MK801 [215] and ketamine [216] all induce translational phenotypes of positive, negative, and cognitive symptoms. However, these models present special challenges as a framework for testing the beneficial effect psychedelic agents. First, because the phenotype induced is sometimes short lasting [207]. The second challenge is more complicated, originating from the effect of some of the NMDA antagonists such as ketamine on neurogenesis and synaptic plasticity [217], as well as antidepressant activity [218], potentially making the effects of psychedelic agent and ketamine on neural plasticity indistinguishable.

Overall, a well-chosen animal model for schizophrenia provides a powerful framework for testing the beneficial effects of psychedelic agents on the negative symptoms, and possible interactions with positive symptoms.

CRITICAL ISSUES IN THE DESIGN OF CLINICAL STUDIES

The number of clinical studies with psychedelic drugs is increasing at a rapid rate. The clinical strategies implemented in these trials vary but may generally be classified under one of four treatment models as defined by Bogenschutz [219].

Psychedelic model

This is currently the most common clinical treatment model. This model employs high doses of classic psychedelics and one or very few administrations of the drug. Underlying the treatment is the assumption that a single "peak" psychedelic experience can produce rapid, pronounced, and permanent psychological change. This form of psychedelic administration is frequently combined with psychotherapy of low intensity or psychological support without a specific therapeutic component.

Psycholytic model

In this model, lower but not sub-perceptual doses of the psychedelic drug are employed. There are a larger number of treatment sessions generally combined with psychotherapy. In this type of treatment, the psychedelic drug is seen as facilitating the psychotherapy as compared to the high dose model where the psychedelic-induced experience is seen as the instrument of therapeutic effect.

Microdosing model

In this model small, repeated doses of a psychedelic drug are taken daily, every second day or a few times a week for varying periods of time. Classically a microdose is defined as 10% of the psychedelic dose. This would be 0 2.5 mg for psilocybin, 25 mg of which induces significant psychedelic effects in a 70 kg person. Subjective effects of psychedelic microdoses are mild or not noticeable. Thus far there is little evidence to support therapeutic effects of microdoses although a possible clinical role is frequently suggested. Under this heading low psychedelic doses that induce minimal acute psychological effects should be considered. Such a dose would be less than 10mg of psilocybin for a 70 kg person and could be termed sub-psychedelic although not sub-perceptual.

Neuromodulation model

The emphasis in this model is on the neurobiological changes induced by the psychedelic drugs and not on their subjective effects which are considered side effects or epiphenomena. The view underlying this model is that neuroplastic changes induced by psychedelics are responsible for their therapeutic action and the psychological effects are redundant. This approach underlies the development of non-psychedelic ibogaine derivatives described in "*Potential strategies to avoid psychotogenic effects of psychedelic drugs while retainingneuroplastic effects*" as well as other approaches described there to reduce or eliminate psychedelic effects while retaining neuroplastic effects. One strategy supported by two influential preclinical publications [194, 195] is to eliminate the acute psychological effects of psychedelic drugs by concurrent administration of a 5-HT2A antagonist; according to this approach neuroplastic effects are ostensibly mediated by other pathways and would thus not be affected by 5-HT2A receptor blockade.

Administration of psychedelic drugs to schizophrenia patients is a clinical step that requires extreme caution given the history of these compounds as psychotomimetics and hallucinogens (reviewed in "*Psychedelic drugs and schizophrenia: historical perspectives*", See Table 1). In this context, it is interesting to note that in the many studies of psychedelic administration to young patients with autism and schizophrenia performed in the 1950s and 1960s (reviewed in "*Psychedelic drugs and schizophrenia: historical perspectives*") exacerbation of psychosis was not a consistent observation. In fact, improvements were observed in symptom domains that would be defined today as negative symptoms.

Nevertheless, administration of psychedelic doses of psychedelic drugs to patients with schizophrenia would clearly be a hazardous undertaking and is not recommended here. Such doses could be considered if the drug is administered in conjunction with a 5-HT2A antagonist as discussed above. Microdoses of psychedelics are an option that could be considered. Use of sub-psychedelic doses that may induce some perceptual effects but not a full-blown trip could also be a therapeutic option under carefully controlled conditions. These options would be of particular interest when the psychedelic substance used is an

Table 1. Pros and Cons of Psychedelic Treatment in Schizophrenia.

Patient characteristics	Brain mechanism	Pros of psychedelic treatment	Cons of psychedelic treatment
Schizophrenia patients suffering mostly from positive symptoms and low negative symptoms score	Mostly mesolimbic circuits [220]	May alleviate anxiety without sedative effect. Decrease negative mood and increase positive mood [221] Decrease appetite [222] – may counteract weight gain induced by antipsychotics.	If psychedelic doses are used, risk of a "bad trip" that will increase anxiety. Risk of evoking psychotic episode. Risk of evoking HPPD.
Schizophrenia patients with high negative symptoms score	Mesocortical circuits, prefrontal cortex [223]	Same as above. Additionally: Increasing prefrontal cortex function and connectivity [195]. Reduction of amygdala response to negative emotional stimuli [221].	Same as above
Early onset schizophrenia patients	Thalamocortical abnormalities [224]	Same as above. Additionally: Enhancement activity and connectivity of thalamocortical circuits [94]	Same as above
Schizophrenia patients with cognitive abnormalities and reduced cognitive flexibility	Dorsolateral prefrontal cortex [225]	Enhanced cognitive and neural flexibility [226].	Same as above

entheogen that is administered in conjunction with additional entourage molecules that could enhance its therapeutic effects. As discussed in the preceding sections, neuroplastic effects could be of pivotal importance in treating negative symptoms in schizophrenia. Therefore, novel chemical entities derived from psychedelic drugs that retain the neuroplastic effects of these compounds without the trip-inducing properties could be of unique therapeutic value.

CONCLUSIONS

Exploring a potential role for psychedelics in the treatment of schizophrenia is intriguing and highly challenging. Patients with recent onset disease that is characterized by prominent negative symptoms would be prominent candidates for such treatment. These patients are highly resistant to currently available treatments. In this population the potential of psychedelics to induce neurogenesis and synaptic plasticity is a highly desirable characteristic given the association of negative symptoms with cortical atrophy. Considerable research is required at the preclinical level to establish whether psychedelic treatment regimens under consideration have the potential to exacerbate psychosis and whether they are effective in negative symptom models. Treatments that do not have the potential to induce psychosis and are effective in alleviating negative symptom-like features should be tested in appropriately designed phase 1 studies. Careful research in this area could have a significant impact on the treatment of one of the most severe and socially debilitating psychiatric disorders and is an exciting new frontier in psychopharmacology.

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Conceptualization: BL, GW, AL, UHL. *Literature Search and Synthesis*: GW, SS, KB, LL, TL, UHL, AL, BL. *Writing and Revision*: GW, SS, KB, LL, TL, UHL, AL, BL. All authors read and approved the final version of the manuscript.

COMPETING INTERESTS

LL is an equity partner in Back of the Yards Algae Sciences. BL is a consultant to Back of the Yards Algae Sciences. The other authors declare no competing interests.

ADDITIONAL INFORMATION

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