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# Psychedelics for treatment of negative symptoms and depressive symptoms in schizophrenia spectrum disorder: A narrative review☆

Michel Sabé [a,b,c,*], Paul Grof [d], Nathan B. Sackett [e,f], Sara Tai [g], Pamela Kryskow [h], Anya Bershad [i,j], Douglas Turkington [k], Matteo Buonarroti [l], Marco De Pieri [b,c], Pantelis Baniotopoulos [a], Mickael Eskinazi [c], Kerem Böge [m,n,o], Stefan Leucht [p,q], Federico Seragnoli [a], Léonice Furtado [a], Tatiana Aboulafia Brakha [a], Logos Curtis [b,c], Matthias Kirschner [b,c], Stefan Kaiser [b,c], Louise Penzenstadler [a,b], Daniele Zullino [a,b], Mikkel Højlund [r,s], Jade Gallo [t], Marco Solmi [t,u,v,w,x], Jacopo Sapienza [y,z], Marta Bosia [z,aa,ab], Joseph La Torre [ac,ad]

[a] Division of Addiction Psychiatry, Department of Psychiatry, University Hospitals of Geneva, 70, Grand-Pré, CH-1202, Geneva, Switzerland
[b] Faculty of Medicine, University of Geneva, Geneva, Switzerland
[c] Division of Adult Psychiatry, Department of Psychiatry, University Hospitals of Geneva, 2, Chemin du Petit-Bel-Air, CH-1226, Thonex, Switzerland
[d] Department of Psychiatry, University of Toronto, Toronto, ON, Canada
[e] Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA
[f] Center for Novel Therapeutics in Addiction Psychiatry, Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA
[g] Department of Clinical Psychology, School of Health Sciences, The University of Manchester, Manchester, UK
[h] Psychedelic-Assisted Therapy Post-Graduate Program, Health Sciences and Human Services, Vancouver Island University, Nanaimo, BC, Canada
[i] Department of Psychiatry and Biobehavioral Sciences, Jane and Terry Semel Institute for Neuroscience and Human Behavior, UCLA, Los Angeles, CA, USA
[j] VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA
[k] Early Intervention in Psychosis Service, Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, Gosforth, Newcastle Upon Tyne, NE3 3XT, UK
[l] Società Italiana di Medicina Psichedelica, Italy
[m] Department of Neuroscience and Psychiatry, Charité-Universitätsmedizin Berlin (corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin), Campus Charite Mitte, Berlin, Germany
[n] Department of Clinical Psychology and Psychotherapy, Medical University Brandenburg-Theodor Fontane, Neuruppin, Germany
[o] German Center of Mental Health (DZPG), Potsdam, Berlin, Germany
[p] Department of Psychiatry and Psychotherapy, TUM School of Medicine and Health, Technische Universität München, Munich, Germany
[q] German Center for Mental Health, Partner Site Munich/Augsburg, Munich, Germany
[r] Department of Psychiatry Aabenraa, Mental Health Services Region of Southern Denmark, Aabenraa, Denmark
[s] Department of Regional Health Research, University of Southern Denmark, Odense, Denmark
[t] Department of Psychiatry, University of Ottawa, Ottawa, Ontario, Canada
[u] Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany
[v] Department of Mental Health, The Ottawa Hospital, Ottawa, Ontario, Canada
[w] Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[x] School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[y] IRCCS San Raffaele Scientific Institute, 20127, Milan, Italy
[z] Department of Humanities and Life Sciences, University School for Advanced Studies IUSS, 27100, Pavia, Italy
[aa] School of Medicine, Vita-Salute San Raffaele University, 20132, Milan, Italy
[ab] Schizophrenia Research and Clinical Unit, IRCCS San Raffaele Scientific Institute, 20127, Milan, Italy
[ac] School of Psychology, University of Ottawa, Ottawa, ON, K1N 6N5, Canada
[ad] Department of Psychiatry and Behavioral Sciences, Center for Novel Therapeutics in Addiction Psychiatry, School of Medicine, University of Washington, Seattle, WA, 98104, USA

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* Corresponding author at: Division of Addiction Psychiatry, Department of Psychiatry, University Hospitals of Geneva, 70, Grand-Pré, CH-1202, Geneva, Switzerland.
*E-mail address:* michel.sabe@hug.ch (M. Sabé).

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ABSTRACT

Serotonergic psychedelics are re-emerging as therapeutic candidates across psychiatry, particularly for treatment-resistant depression. Their rapid and sustained antidepressant effects, alongside evidence for neuroplastic, dopaminergic, and glutamatergic modulation, have prompted interest in whether they could address depressive and negative symptoms in schizophrenia spectrum disorders (SSDs). This narrative review summarizes mechanistic, preclinical, and early clinical findings relevant to psychedelic use in SSDs.

Schizophrenia and major depressive disorder share disturbances in dopamine, glutamate, and neuroplasticity, and both involve large-scale network abnormalities. Schizophrenia is associated with widespread dysconnectivity, mesocortical hypodopaminergia, and striatal hyperdopaminergia linked to NMDA receptor hypofunction. Depression is characterized by fronto-limbic and default mode network hyperconnectivity, mesolimbic hypodopaminergia, and reduced cortical glutamatergic tone. Depressive symptoms within SSDs may reflect an intermediate phenotype combining depressive-like hyperconnectivity with schizophrenia-related global dysconnectivity, suggesting that psychedelics' capacity to transiently increase network flexibility and recalibrate maladaptive connectivity may be clinically relevant.

Preclinical studies show increased dendritic spine density, enhanced BDNF expression, restored reward sensitivity, and modulation of network dynamics after psychedelic administration. Clinically, uncontrolled exposure appears associated with increased psychosis-related presentations, whereas limited case reports suggest controlled administration may be tolerated in carefully selected, clinically stable individuals with SSDs. To date, only one early-phase trial (MDMA in schizophrenia) is ongoing, and no randomized trials have evaluated psilocybin or LSD in SSDs.

Overall, psychedelics are biologically and mechanistically plausible but remain unproven for depressive and negative symptoms in SSDs, which partially overlap. Carefully designed, safety-focused early-phase studies in clinically stable patients are therefore a prerequisite for broader clinical application.

## 1. Introduction

Accumulating evidence indicates that serotonergic psychedelics exert robust antidepressant effects, as demonstrated by rapid and sustained reductions in depressive symptoms across multiple clinical trials involving individuals with treatment-resistant depression (Perez et al., 2023; Ross et al., 2016). This resurgence of interest in psychedelics includes expansions beyond targeting individuals with treatment-resistant depression (Højlund et al., 2025). Post-traumatic stress disorder, anxiety, and substance use disorders are advancing rapidly, though no serotonergic psychedelic -such as psilocybin or lysergic acid diethylamide (LSD)- has yet received FDA approval for any psychiatric indication (Norring and Spigarelli, 2024). Notably, emerging research has begun to explore the application of serotonergic psychedelics for depressive symptoms comorbid with other disorders, such as neurodegenerative disorders (Bradley et al., 2025). In this open-label trial, individuals with Parkinson's disease—who are inherently at elevated risk for developing psychosis due to dopaminergic treatments—did not exhibit serious adverse events following psilocybin administration. No medical interventions were necessary to manage psilocybin-related effects, nor was there any observed exacerbation of psychotic symptoms. Similarly, Aaronson and colleagues investigated the safety and efficacy of psilocybin-assisted therapy in individuals with treatment-resistant depression and comorbid neurological conditions (Aaronson et al., 2024). Their open-label feasibility study propose that psilocybin, when administered under controlled clinical conditions with psychological support, was well tolerated and associated with significant reductions in depressive symptom severity. Importantly, participants did not experience worsening of potential psychotic symptoms. However, these populations differ fundamentally from individuals with SSD, in terms of psychosis vulnerability, and underlying disease mechanisms, and were systematically selected to exclude individuals at elevated risk for psychotic exacerbation; therefore, their findings cannot be directly extrapolated to SSD populations.

In parallel, a meta-analysis by Sabé et al. (2025a, 2025b) systematically reevaluated the risk of psychedelic-induced psychosis in both individuals without pre-existing psychotic disorders and those with SSD (Sabé et al., 2025a, 2025b). The findings indicate that, although low, there is a measurable 3.8% risk of positive symptom exacerbation in individuals with SSDs in uncontrolled trials. These findings indicate a measurable, though relatively low, risk of positive symptom exacerbation in SSDs in uncontrolled trials, underscoring the need for disorder-specific, safety-focused studies in carefully selected populations.

Subjective report of individuals with a diagnosis of SSDs, indicates that the use of psychedelic substances, even in non-medicalized setting and in absence of antipsychotics, does not seems to significantly exacerbate positive symptoms (La Torre et al., 2024). These individuals report positive experiences from psychedelic use, including personal growth, mystical experiences, and improved insight. A first case-report of psychedelic-assisted therapy in medical settings for individuals with SSDs has also been published (Sabé et al., 2025a). Indeed, within the specific context of SSD, there is a growing clinical interest in exploring serotonergic psychedelics as potential interventions for negative and depressive symptoms.

These symptom domains represent major unmet therapeutic needs and are often highly treatment-resistant in SSD (Helfer et al., 2016). Innovative treatments with antidepressant and pro-cognitive properties—such as serotonergic psychedelics—therefore constitute a promising avenue for future intervention. As such, a phase 1/2 clinical trial is currently underway at the University of California, Los Angeles, to assess the tolerability of 3,4-methylenedioxymethamphetamine (MDMA) in addressing social motivation deficits—a core negative symptom—in individuals with schizophrenia (NCT05770375).

Taken together, converging evidence from preclinical to early-phase human safety data and favorable risk–benefit evaluations, suggests that serotonergic psychedelics may hold promise as novel interventions for treatment-refractory negative and depressive symptoms in individuals with SSDs.

Accordingly, we propose to a narrative review, based on a previously published systematic review (Sabé et al., 2025b) to comprehensively map the psychedelic research in this domain, and identifying the milestones on the way of proposing psychedelic as adjunctive treatment for depressive and negative symptoms in stable individuals with SSDs.

## 2. Methods

This work was designed as a narrative review aimed at updating and expanding upon the findings of a previously published systematic review on the association between psychedelics and psychosis (Sabé et al., 2025b). The decision to adopt a narrative approach was motivated by

the emergence of new empirical evidence—particularly from recent clinical, translational, and mechanistic studies—that has not yet been systematically synthesized. Accordingly, study selection and thematic emphasis were guided by conceptual and clinical relevance rather than formal quantitative criteria, with particular focus on mechanistic plausibility, translational relevance to SSD, and safety considerations, including psychosis vulnerability and symptom exacerbation.

### 2.1. Search strategy

Two authors (MSa and ME) independently updated and expanded the previous search (Sabé et al., 2025b) to capture studies published from database inception through 1st November 2025. The search was guided by the PRISMA guidelines of the pre-registered protocol (CRD42023399591), which encompassed multiple electronic databases, including Embase, PubMed, PsyARTICLES, PsyINFO, and trial registries. Search terms and Boolean operators were tailored for each database, combining keywords and Medical Subject Headings (MeSH) related to psychedelics (e.g., "psilocybin", "lysergic acid diethylamide", "LSD", "DMT", "ayahuasca", "serotonergic psychedelics") and psychosis-related constructs (e.g., "psychosis", "psychotic disorders", "schizophrenia", "psychotic symptoms"). The complete list of search terms and search strings is provided in Table S1.

### 2.2. Eligibility criteria

Articles were considered if they (1) examined the relationship between classical serotonergic psychedelics and psychotic symptoms or SSD, (2) were peer-reviewed empirical studies, reviews, or meta-analyses, and (3) were published in English, French, Italian or German language. Studies focusing exclusively on non-serotonergic psychedelics (e.g., ketamine, PCP, salvinorin A) or case reports were excluded. Both human and relevant preclinical studies were considered to capture mechanistic and translational perspectives.

The examination of retained articles for this narrative review was conducted by two authors (MSa and ME), focusing on study design, participant characteristics, psychedelic agent, dosage, outcome measures related to psychosis or psychotic-like experiences, and safety outcomes. Discrepancies in study inclusion were resolved by discussion and, when necessary, consensus with a third reviewer.

## 3. Results

### 3.1. Psychedelics as "psychosis model"

In the 1960s, Wolbach and colleagues investigated the psychotomimetic effects of LSD and psilocybin in humans, documenting hallucinations, perceptual distortions, and altered thought processes (Wolbach et al., 1962). LSD was also already used in medical research in individuals with schizophrenia (Sabé et al., 2025b). These historical descriptions laid the foundation for the modern "psychotomimetic hypothesis" suggesting that psychedelic substances produce experiences that mimic or resemble symptoms of psychosis. Another author described the effects of serotonergic psychedelics such as mescaline, psilocybin, and LSD, which act through the serotonin 5-HT2A receptor (Halberstadt and Geyer, 2013; Vollenweider et al., 1998).

Although this model describes psychotomimetic effects similar to schizophrenia, while also promoting neural plasticity and network flexibility (Kometer et al., 2013; Vollenweider and Geyer, 2001), this model does not reproduce negative and cognitive symptoms with the same fidelity as the ketamine/PCP model of psychosis (Vollenweider et al., 1997).

For LSD, moderate to high-doses (100–200 μg per os) seem to be directly associated with the mesolimbic dopaminergic activity (De Gregorio et al., 2016b). At such doses, LSD also modulates the ventral tegmental area by stimulating dopamine D2 receptors, trace amine-associated receptor 1, and 5-HT2A receptors, leading to a decrease in dopamine firing activity, and producing psychosis-like symptoms: metamorphosis-like change in objects and faces, a metamorphic alteration of body contours, a change in body image, and intense (kaleidoscopic or scenic) visual imagery with transforming content, deficit in sensorimotor gating (De Gregorio et al., 2016a). This specific prodopaminergic effect of LSD (partial D2 agonist) has not been found for other serotoninergic psychedelics, in particular for psilocybin and DMT, which only indirectly increase dopamine via cortical-striatal circuit.

As such, serotonergic psychedelics are sought to induce widespread neuromodulatory changes through different mechanisms: 5-HT2A receptor activation and cortical excitation, neuroplasticity/synaptogenesis, and through indirect modulation of the dopamine system.

Indeed, psychedelics act as partial agonists at 5-HT2A receptors, especially in layer V pyramidal neurons in the prefrontal cortex (Vollenweider and Kometer, 2010). In rodent models, a single dose of psilocybin induces rapid (24 h) and persistent (1 month) growth of dendritic spines in the medial prefrontal cortex, increasing spine size and density by approximately 10% (Shao et al., 2021).

Other findings show increased glutamate release, enhanced neuronal oscillations, and cortical desynchronization, improving cognition and emotional reactivity (Carhart-Harris et al., 2012).

Psychedelics have also been shown to increase brain-derived neurotrophic factor (BDNF) levels and stimulate dendritic spine growth and synapse formation, particularly in the medial prefrontal cortex and hippocampus (Calder and Hasler, 2023; Ly et al., 2018). These changes may signal improved cognitive-emotional and motivational functioning, though this correlation and its translational significance remain unclear (de Vos et al., 2021). Psychedelics also display anti-inflammatory properties as found in cell and animal models of inflammation (Inserra et al., 2021).

Finally, although psilocybin does not directly agonize dopamine receptors, it appears to indirectly modulate mesocortical dopamine transmission via serotonergic and glutamatergic pathways (Vollenweider et al., 1998), potentially restoring motivational drive and reducing anhedonia (da Cruz et al., 2025). In rodent models, both psilocybin and LSD at low to moderate doses reopened the social reward learning critical period, for 2 to 3 weeks respectively, after administration session (Nardou et al., 2023). This period is described by users as the "afterglow", and may provide a window for cognitive plasticity, enabling patients to incorporate new insights and make lasting changes in their thinking patterns (Majić et al., 2015; Nardou et al., 2023).

### 3.2. Therapeutic potential of serotonergic psychedelics for depressive and negative symptoms

#### 3.2.1. Entanglement of depressive and negative symptoms

Negative symptoms—such as avolition, asociality, anhedonia, alogia and affective flattening—are significantly disabling and remain largely resistant to existing treatments. Similarly, the prevalence of major depressive disorders (MDD) is highly prevalent, affecting approximately 40% of individuals with SSD at all stages of their illness (Upthegrove et al., 2017). Negative symptoms can also be primary, considered as intrinsic to the disease, and secondary, as secondary to positive symptoms, medication side-effects, social deprivation, drug abuse, and, in particular, to depression (Kirschner et al., 2017).

The blurred boundary between negative and depressive symptoms in SSD—often referred to as an "entanglement"—is clinically meaningful (Table 1). Shared features include anhedonia, avolition, and social withdrawal (Galderisi et al., 2021a, 2021b; Kring and Barch, 2014), whereas depressive symptoms are more often associated with subjective distress, hopelessness, and mood reactivity, while primary negative symptoms tend to be persistent, emotionally neutral, and less state-dependent (Kirschner et al., 2017). (See Table 2.)

Depressive symptoms may exacerbate negative presentations and vice versa, complicating diagnosis and treatment. Of interest, depressive

**Table 1**
Clinical overlap and qualitative differences between negative and depressive symptoms.

| Symptom | Negative symptoms (schizophrenia) | Depressive symptoms (depression) |
|---|---|---|
| **Avolition** (loss of motivation) | Lack of initiation/ persistence in goal-directed activity; indifference | Loss of energy, psychomotor retardation, fatigue; linked to hopelessness |
| **Anhedonia** (loss of pleasure) | Reduced anticipatory pleasure (not looking forward to things) | Reduced consummatory pleasure (not enjoying things in the moment) |
| **Asociality** (social withdrawal) | Lack of interest in forming/ maintaining social bonds | Withdrawal due to low self-esteem, guilt, sadness, or loss of interest |
| **Affective flattening** (reduced emotional expression) | Blunted affect, poor eye contact, monotone speech, reduced gestures | Sad/flat expression, reduced reactivity, slowed responses, tearfulness possible |
| **Alogia** (poverty of speech/thought) | Reduced spontaneous speech, brief/empty replies, slowed thought generation | Slowed speech from psychomotor retardation; lack of initiative due to low mood |

symptoms occur in one-third of individuals with SSDs, with published prevalence estimates ranging from 5% to 83% (Helfer et al., 2016). Furthermore, when considering individuals with a minimum threshold for both depressive and negative symptoms, add-on antidepressants were more effective. Clinically, it is challenging to distinguish between primary negative symptoms, secondary negative symptoms due to depression, and depression without negative symptoms (Galderisi et al., 2021a, 2021b; Krynicki et al., 2018). Current evidence indicates that depressive symptoms can be reliably differentiated from the diminished expression dimension of negative symptoms (blunted affect, alogia), whereas the apathy dimension (avolition, anhedonia, and asociality) show substantially greater overlap with depression and therefore are challenging to distinguish (Kring and Barch, 2014).

Case reports further illuminate this interplay. For example, a recent report describes a patient with schizoaffective disorder and treatment-resistant depressive and predominant negative symptoms, whose symptom burden was alleviated for many months following off-label psychedelic-assisted therapy (Sabé et al., 2025a).

This overlap suggests shared mechanisms that may underlie both SSD-related negative symptoms and depressive symptomatology. We thereafter develop pathophysiological mechanisms underlying both negative and depressive symptoms in individuals with SSD.

Considering the rapid and sustainable improvement of core depressive symptoms including anhedonia, hopelessness, and emotional numbing following psychedelic-assisted therapy (Griffiths et al., 2016; Perez et al., 2023), we propose that psychedelics may simultaneously alleviate both symptom clusters (Sabé et al., 2025a) by addressing their theoretical common neurobiological roots, such as promoting neuroplasticity, improving reward sensitivity (Bhandari et al., 2016; Nardou et al., 2023), and enhancing emotional and social processing (Maćkowiak, 2023). Nevertheless, at present, only isolated case reports and indirect translational data are available and should be interpreted as hypothesis-generating rather than confirmatory.

Furthermore, from a clinical and methodological standpoint, a rigorous distinction between primary and secondary negative symptoms constitutes the necessary first step for interpreting any putative therapeutic effects of psychedelics in SSDs. Without careful baseline characterization, improvements in negative symptom scores may primarily reflect secondary changes driven by antidepressant or psychological effects of psychedelic-assisted therapy, rather than a direct impact on primary negative symptoms. Future studies should therefore systematically assess the etiology of negative symptoms using validated instruments, combine negative symptom ratings with structured assessments of depression, and apply dimensional or mediation-based analytical approaches.

**Table 2**
Summary of the potential effect of psychedelics on depressive symptoms and negative symptoms for individuals with SSDs.

| SSD pathophysiology | Psychedelic mechanism | Potential clinical outcome |
|---|---|---|
| **↓ Mesocortical dopamine (PFC, caudate)** (Collo et al., 2020; Howes et al., 2017) | **Indirect dopaminergic modulation** via 5-HT₂A–glutamate interactions, which increase mesocortical/ mesostriatal DA tone ( Vollenweider and Kometer, 2010; Calder and Hasler, 2023; Martin et al., 2024) | **↓ Amotivation / avolition**, ↑ initiation of goal-directed behavior (de Vos et al., 2021) |
| **NMDA hypofunction and E/I imbalance** ( Moghaddam and Krystal, 2012; Li et al., 2024; Nakazawa and Sapkota, 2020) | **↑ Glutamatergic signaling** via 5-HT₂A activation ↑ Acute cortical excitation and presynaptic vesicle modulation (Carhart-Harris et al., 2012; Petrušková et al., 2025) | **↓ Anhedonia** **↑ Executive function and** improved reward sensitivity (da Cruz et al., 2025) |
| **↓ Neuroplasticity & impaired synaptic remodeling** (Bhandari et al., 2016) | **↑ BDNF, ↑ dendritic spine formation, ↑ PFC plasticity** (Ly et al., 2018; Shao et al., 2021; Calder and Hasler, 2023; Nardou et al., 2023) | **↑ Emotional flexibility** (enhanced adaptability to internal states) (Moujaes et al., 2025) |
| **DMN hypoconnectivity + poor network segregation in SSDs** ( Hu et al., 2017; Wang et al., 2015) | **Normalization of DMN dynamics**: ↓ rigid DMN states, ↑ flexibility, transient network "reset"( Carhart-Harris et al., 2017; Gattuso et al., 2023) | **↓ Asociality** (better engagement with internal and external cues) |
| **DMN hyperconnectivity in depressive states** ( Hamilton et al., 2015; Yan et al., 2019; Kumari et al., 2016; Gallucci et al., 2024) | **↓ DMN hypercoupling** (reduced ruminative self-referential loops) | **↓ Rumination** ↓ Negative self-focus (enhanced emotional clarity) |
| **Broad dysconnectivity in SSDs** (Dong et al., 2018; Yang et al., 2014) | **↑ Global network integration**, ↑ PFC–limbic synchrony, enhanced communication across large-scale networks ( Shao et al., 2021; Preller et al., 2019) | **↑ Cognitive–affective synchrony**, improved affective regulation and processing (Sapienza et al., 2023) |

### 3.2.2. *Clinical efficacy of antidepressant-add on*

Several meta-analyses have been published in the last decades on the efficacy of add-on antidepressants to concurrent antipsychotic treatments (Galling et al., 2018; Helfer et al., 2016; Singh et al., 2010; Tsapakis et al., 2024; Ulrich and Messer, 2021). Effect sizes in these meta-analyses ranged from small to medium, suggesting that while adjunctive antidepressant therapy can be beneficial, the improvements are modest, particularly on depressive symptoms.

Indeed, for depressive symptoms, a small beneficial effect was reported with a standardized mean difference (SMD) of −0.34 (95%CI: −0.58 to −0.09) (Helfer et al., 2016). For negative symptoms -without distinction of primary/secondary negative symptoms- a moderate beneficial effect was observed with an SMD of −0.58 (95%CI: −0.94 to −0.21). Importantly, this augmentation strategy was associated with a low risk of exacerbating psychosis, a minimal incidence of adverse effects, and was more pronounced for individuals with predominant

depressive symptoms.

Although evidence for antidepressant efficacy on depressive symptoms in SSDs is modest, they remain a commonly used and relatively low-risk add-on option given the lack of superior pharmacological alternatives (Galderisi et al., 2021a, 2021b).

#### 3.2.3. Dopaminergic hypofunction

The current evidence for dopaminergic contributions to negative and depressive symptoms in SSDs derives from a combination of human neuroimaging findings and mechanistic hypotheses primarily informed by preclinical and translational models, rather than from direct causal demonstrations in humans. Any proposed role of serotonergic psychedelics in modulating these pathways should therefore be regarded as theoretical and hypothesis-generating. Indeed, negative symptoms have been linked to putative mesocortical dopaminergic abnormalities, including reduced D1 receptor signaling and caudate dopamine hypoactivity, although these mechanisms remain largely hypothetical in humans (Collo et al., 2020). In contrast, PET studies consistently demonstrate increased striatal dopamine synthesis capacity, particularly in the dorsal striatum, indicating that dopaminergic dysfunction in schizophrenia is regionally heterogeneous rather than uniformly reduced - reduced cortical dopamine transmission has been associated with cognitive impairment- (Howes et al., 2017). while abnormalities in both cortical and subcortical circuits are thought to contribute to decreased motivation and diminished goal-directed behavior (avolition), as well as emotional blunting (affective flattening). Dopaminergic abnormalities may further arise secondary to cortical glutamatergic dysfunction, particularly NMDA receptor hypofunction, as demonstrated in phencyclidine- and ketamine-based schizophrenia-like models (Li et al., 2024).

A similar pattern of mesocortical dopaminergic dysregulation has been proposed in MDD, where reduced prefrontal dopamine signaling may contribute to anhedonia, psychomotor slowing, and cognitive rigidity (Belujon and Grace, 2017). Importantly, several neuroimaging studies suggest that depressive symptoms within SSDs may arise from additive or synergistic disruptions in mesocortical dopamine and fronto-limbic regulatory circuits, partially overlapping with MDD but embedded within broader schizophrenia-related network dysfunction. This convergence supports the view that mesocortical dopaminergic abnormalities constitute a shared mechanistic substrate for affective and motivational deficits across both disorders.

The overlap further suggests that, beyond ameliorating depressive symptoms (Perez et al., 2023), and potentially aspects of negative symptoms, interventions modulating mesocortical dopamine transmission may offer broader therapeutic benefit. Psychedelics—through transient increases in mesostriatal dopaminergic activity (Martin et al., 2024) and promotion of prefrontal cortical plasticity (Calder and Hasler, 2023) —represent one such avenue, with potential to influence both motivational and affective dimensions of psychopathology.

#### 3.2.4. Glutamate hypofunction and NMDA receptor deficiency

The glutamatergic dysfunction model of schizophrenia posits that NMDA receptor hypofunction—particularly on parvalbumin-positive GABAergic interneurons—disrupts the excitatory–inhibitory balance within cortical microcircuits (Howes et al., 2015). This cortical disinhibition contributes to cognitive disorganization, impaired executive functions, and reduced reward sensitivity, which are central to negative symptoms, most prominently anhedonia and, to a lesser extent, emotional withdrawal (da Cruz et al., 2025; Egerton et al., 2020; Moghaddam and Krystal, 2012).

In MDD, a distinct but partially overlapping pattern of glutamatergic dysregulation is observed. Reduced glutamate signaling and impaired synaptic plasticity in prefrontal and anterior cingulate regions have been linked to rumination, affective dysregulation, and treatment resistance (Murrough et al., 2017). The rapid antidepressant effects of ketamine—a non-competitive NMDA antagonist—highlight the importance of glutamatergic mechanisms in depressive symptomatology (Alnefeesi et al., 2022). However, the causal picture becomes more complex in schizophrenia. NMDA antagonists such as phencyclidine (PCP) and ketamine can induce schizophrenia-like symptom clusters, including positive symptoms (driven by mesolimbic dopamine excess following cortical disinhibition), negative symptoms (via prefrontal and hippocampal hypofunction and reduced mesocortical dopamine), and cognitive deficits arising from disrupted glutamate–GABA interactions (Li et al., 2024; Nakazawa and Sapkota, 2020). As a result, non-competitive NMDA receptor antagonists—despite their antidepressant efficacy—cannot be considered viable therapeutic candidates for SSD populations, as they pose substantial risk for exacerbating acute psychotic symptoms or inducing psychosis-like states.

By contrast, serotonergic psychedelics (e.g., psilocybin, LSD) modulate glutamatergic transmission primarily through 5-HT$_2$A receptor activation, rather than direct NMDA receptor blockade. Recent preclinical and molecular data demonstrate that psychedelics can rapidly alter presynaptic vesicle fusion, reduce readily releasable vesicle pools, and dampen calcium transients in cortical neurons (Petrušková et al., 2025), findings consistent with an acute recalibration of excitatory drive and short-term synaptic plasticity. These effects are best understood as state-dependent, transient reorganization of cortical glutamatergic signaling, rather than restoration or normalization of NMDA receptor function. Importantly, while such mechanisms provide theoretical and translational plausibility, there is currently no clinical evidence demonstrating that psychedelic-induced modulation of glutamatergic signaling translates into improvement of negative or depressive symptoms in SSDs, and these interpretations should therefore be regarded as hypothesis-generating.

Importantly, depressive symptoms in individuals with SSDs appear to arise from interacting disruptions in glutamate-mediated cortical regulation and fronto-limbic network dynamics, partially overlapping with the glutamatergic abnormalities observed in primary MDD but embedded within broader schizophrenia-related dysconnectivity. This convergence suggests that interventions capable of modulating cortical glutamatergic tone and enhancing synaptic plasticity—such as serotonergic psychedelics—may hold promise for alleviating both negative and depressive symptoms in this population.

#### 3.2.5. Serotonergic psychedelics and the modulation of large-scale brain networks

The Default Mode Network (DMN)—comprising the medial prefrontal cortex, posterior cingulate cortex, and precuneus—supports self-referential processing, autobiographical memory, and the construction of the internal narrative. In SSDs, intra-DMN connectivity is frequently reduced, particularly between the medial prefrontal and posterior cingulate cortices (Hu et al., 2017), alongside aberrant hyperconnectivity with non-DMN regions, reflecting impaired segregation and global network instability (Wang et al., 2015).

In major depression, by contrast, intra-DMN connectivity is typically increased, especially involving the subgenual anterior cingulate and medial prefrontal cortex (Yan et al., 2019). This hypercoupling is strongly associated with rumination and negatively valenced self-referential loops (Hamilton et al., 2015).

Importantly, both disorders are now understood to involve broad network-level abnormalities, including dysfunctional interactions among DMN, salience, and fronto-parietal control networks (Cheng et al., 2016; Kaiser et al., 2015; Dong et al., 2018).

Emerging neuroimaging data suggest that depressive symptoms within SSDs may reflect a hybrid connectivity phenotype: elements of DMN hyperconnectivity typically observed in MDD, superimposed on the more widespread dysconnectivity characteristic of schizophrenia. Specifically, SSD patients with comorbid depression show increased DMN–fronto-limbic coupling relative to SSD patients without depression (Kumari et al., 2016; Li et al., 2024; Gallucci et al., 2024/2025), partially resembling MDD patterns of ACC–mPFC hyperconnectivity. Yet

these changes remain embedded within the broader thalamo-cortical and sensory–perceptual dysconnectivity that typifies schizophrenia (Dong et al., 2018; Yang et al., 2014; Kaufmann et al., 2015). Cross-disorder meta-analytic work supports this view, showing overlapping affective-network alterations with MDD but more extensive disruptions in SSDs (Crossley et al., 2016; Sha et al., 2019). This intermediate phenotype highlights why depression in SSDs does not simply mirror primary MDD and may respond to interventions targeting large-scale network flexibility. Serotonergic psychedelics appear to modulate these dysfunctional architectures by disrupting rigid DMN states and inducing a transient period of increased global integration, during which network boundaries become more flexible (Gattuso et al., 2023).

Within the Entropic Brain and REBUS frameworks, psychedelics increase neural entropy and relax high-level priors, enabling more adaptive patterns of within- and between-network connectivity to emerge (Carhart-Harris et al., 2014; Carhart-Harris and Friston, 2019; Moujaes et al., 2025).

Neuroimaging evidence in depression aligns with this model: clinical improvement following psychedelic administration correlates with restored prefrontal–limbic communication, normalization of amygdala responsivity, and reductions in hyperstable DMN-driven network states (Carhart-Harris et al., 2017). Complementary effective-connectivity studies show that LSD reduces top-down constraints and enhances bottom-up signaling, supporting a shift toward more dynamic and flexible processing modes (Preller et al., 2019). Given that individuals with SSDs and comorbid depression exhibit both depressive-style hyperconnectivity and SSD-related hypoconnectivity, psychedelics may uniquely address this dual disturbance by temporarily reorganizing large-scale network dynamics. By restoring functional connectivity across DMN–FPN–salience interactions and reducing pathological self-focus, these agents may help alleviate depressive symptoms and potentially aspects of negative symptoms, which have been linked to rigid and under-engaged cortical network states (Sapienza et al., 2023).

This framework—centered on the capacity of psychedelics to transiently enhance network flexibility—thus offers a mechanistic bridge between disorders characterized by excessive rigidity (e.g., MDD) and those marked by dysconnectivity and reduced integration (e.g., SSD), supporting their investigation in SSD populations with comorbid depressive symptoms.

## 4. Psychedelics in stabilized psychosis: a case for chronic-stage application

### 4.1. Currently eligible population

Given the hypothetical potential of psychedelics to exacerbate existing or residual positive symptoms, as well as the relatively high risk of transition from psychedelic-induced psychosis to a chronic psychotic disorder (Sabé et al., 2025b; Sapienza et al., 2025), certain precautions are warranted. Although recent studies have suggested that the risk of transition to SSDs following hallucinogens use may be lower than previously estimated, approximately 3.9% (Myran et al., 2025), compared to 13% in the meta-analysis by Sabé et al., we advocate for a conservative and highly selective approach when defining eligible subpopulations for early trials. Specifically, inclusion of individuals with SSDs should focus on chronic forms characterized by a predominance of negative and/or depressive symptoms (Table 3). Only patients in a stable phase of chronic SSDs, who present with treatment-resistant depressive and/or negative symptoms should be considered for inclusion. Individuals who have not achieved clinical remission of positive symptoms (i.e., any PANSS positive subscale item >4) should be excluded (Andreasen et al., 2005).

Furthermore, certain SSD diagnoses—such as delusional disorder, and schizotypal personality disorder—should not currently be considered due to the heightened sensitivity of these conditions in early-phase psychedelic trials, which mainly limits the eligible diagnosis to individuals with schizophrenia and in particular with schizo-affective disorders.

Eligible participants should meet the commonly accepted criteria for treatment-resistant depression and persistent negative symptoms. Treatment-resistant depression is characterized by having previously completed adequate options of at least two distinct classes of antidepressant medications administered at therapeutic dosages and durations, in combination with a minimum effective dose of a second- or third-generation antipsychotic (McIntyre et al., 2023). Persistent negative symptoms are clinically relevant negative symptoms that can be primary or secondary negative symptoms, that have not responded to treatment for a minimum of 6 months, interfere with normal role functioning, and persist during periods of clinical stability (Correll and Schooler, 2020). In cases where a first-generation antipsychotic is prescribed, a switch to a second- or third-generation agent should first be attempted, given the potential mood-dampening and sedative effects associated with first-generation compounds (Solmi et al., 2017).

Conversely, individuals at high risk for transition to chronic psychosis such as those with a personal or family history of psychotic disorders, those identified as being at clinical high risk, or individuals with a history of first-episode psychosis should continue to be excluded from psychedelic interventions. Current evidence indicates that such individuals possess an elevated vulnerability to transitioning into a chronic psychotic state. Although age should not serve as a strict exclusion criterion, younger individuals may be more susceptible to psychedelic-related adverse effects (Simonsson et al., 2024), and chronic SSDs predominantly occur in individuals over 25 years of age (Solmi et al., 2022).

Standard exclusion criteria commonly applied in psychedelic clinical trials should also be maintained, including the absence of a current or recent (within the past six months) substance use disorder and the absence of any history of suicidality. Furthermore, the potential for psychedelics to precipitate manic episode, particularly among individuals at risk for bipolar I disorder, remains a topic of ongoing debate

**Table 3**
Recommended criteria for psychedelic-assisted therapy in individuals with SSDs.

| |
|---|
| **Inclusion criteria** |
| -A chronic diagnosis of schizophrenia, or schizoaffective disorder |
| -Treatment-resistant depressive and/or negative symptoms |
| -Clinical stability for at least 6 months, with no changes in medication over the past 6 months (PANSS-P items <4) |
| **Exclusion criteria** |
| -Individuals with a history of first-episode psychosis |
| -Individuals identified at clinical high risk |
| -Individuals with a schizophreniform disorder |
| -Individuals with a delusional disorder |
| -Individuals with a paranoid personality disorder |
| -Individuals with a history of mania or mania-induced disorder |
| -Individuals with a personal history or a current substance use disorder |
| -Individuals with a personal history of suicidality |

(Morton et al., 2023). Given the robust antidepressant effects observed with psychedelic compounds, individuals with a history of manic episodes should currently be excluded from such studies.

### 4.2. Substance, set and setting

#### 4.2.1. The substance

Careful selection of the compound, dosing strategy, and therapeutic environment is essential to ensure both safety and clinical validity. Accordingly, the use of LSD should be limited to doses below 120 μg, as higher doses are associated with increased pro-dopaminergic activity, potentially elevating the risk of psychotic exacerbation. This recommendation aligns with the mechanistic findings of Preller et al. (2019), who demonstrated that LSD induces alterations in thalamocortical connectivity. Such alterations can disrupt normal sensory gating and lead to cortical overload, resulting in sensory flooding, cognitive disorganization, and ego dissolution—phenomena that resemble both psychedelic and psychotic experiences (Preller et al., 2019).

Given these considerations, psilocybin currently represents the preferred psychedelic agent for individuals with SSDs. Psilocybin exhibits a more predictable pharmacokinetic profile, a shorter duration of action, and a comparatively lower risk of dopaminergic stimulation. Although the optimal dose for individuals with SSDs remains unknown, studies in treatment-resistant depression have identified higher doses (e.g., 36 mg) as most effective (Perez et al., 2023). This finding is consistent with early investigations suggesting that individuals with SSDs may respond more robustly to higher doses of psychedelics (Anastasopoulos and Photiades, 1962; Belsanti, 1952; Condrau, 1949).

In contrast, MDMA is associated with a significantly greater burden of adverse effects, including cardiovascular stimulation, anxiety, agitation, and the well-characterized post-acute "comedown" (Straumann et al., 2025), though it remains a promising candidate for enhancing social connectedness in individuals with SSDs, in particular when considering MDMA impacts on oxytocin (Zierhut et al., 2024).

*N*,*N*-Dimethyltryptamine (DMT) also represents a promising compound for investigation in SSDs, primarily due to its very short duration of action and rapid pharmacokinetic clearance, which may enhance safety and manageability in clinical settings (Chaves et al., 2024). When administered intravenously or via inhalation, DMT typically lasts less than 30 min, potentially reducing overall exposure to altered states and limiting the risk of prolonged dysregulation. However, despite its brevity, the subjective intensity of the DMT experience is often markedly higher, characterized by profound perceptual distortions and ego dissolution. These properties underscore the need for additional controlled trials to mitigate the risk of psychological distress or destabilization in vulnerable populations such as individuals with SSDs.

Regarding ongoing antipsychotic treatment, it should preferably be maintained throughout psychedelic interventions to prevent acute withdrawal symptoms or rebound of the underlying condition. While antipsychotic agents -particularly second- and third-generation compounds- may attenuate or block the acute subjective effects of psychedelics via 5-HT2A receptor antagonism, this does not necessarily preclude the emergence of delayed antidepressant or anxiolytic effects in the subsequent days or weeks. Clinical emphasis should therefore remain on post-acute therapeutic outcomes rather than on the intensity of the acute psychedelic experience.

This rationale aligns with the ongoing investigation by Husain et al. (2023), who are empirically testing whether the therapeutic efficacy of psilocybin can be maintained even when the subjective psychedelic experience is pharmacologically suppressed through concurrent 5-$HT_2$A receptor blockade—thereby directly addressing whether the psychedelic experience itself is necessary for clinical benefit (Husain et al., 2023). Similarly, non-hallucinogenic analogues of LSD are currently under development as potential therapeutic agents designed to preserve the molecular antidepressant properties of classical psychedelics while minimizing perceptual alterations (Agrawal et al., 2025; Lewis et al., 2023). However, their efficacy in treating depressive symptoms remains unproven, and further controlled studies are needed to determine whether the hallucinogenic experience itself constitutes a necessary component of therapeutic action.

#### 4.2.2. The set and the setting

The therapeutic environment should be carefully structured to optimize safety and minimize psychological stress (Murphy et al., 2021). Ideally, the setting should be neutral, low-stimulation, and predictable, reducing the risk of sensory overload, suggestibility, or anxiety during the acute psychedelic experience. One-to-one supervision and using a one trained therapist who has prior experience of care among individuals with SSDs is strongly recommended to provide continuous support, monitor affective responses, and intervene promptly if distress arises. Beyond physical surroundings, the psychological "set" of the participant, including expectations, mood, and mindset prior to dosing, should be actively managed through preparatory sessions. Notably, the risks associated with psychedelic administration in SSD populations appear to escalate in unsupervised or emergency-department contexts, rather than in controlled research settings, underscoring the critical interplay of both set and setting in ensuring safety, containment, and potential therapeutic benefit.

### 4.3. Current ongoing trials

To the best of our knowledge, only one clinical trial has been registered investigating the safety of psychedelic compounds in individuals with SSDs. The "Tolerability of MDMA in Schizophrenia" study (NCT05770375) is an open-label, ascending-dose trial conducted at the University of California, Los Angeles. This trial is designed to evaluate the safety and tolerability of 3,4-methylenedioxymethamphetamine (MDMA) in clinically stable adults with a diagnosis of schizophrenia. The protocol includes three within-subject sessions with escalating doses (40 mg, 80 mg, and 120 mg), with close monitoring of psychotic symptomatology 24 h after each administration. Primary endpoints assess the emergence or worsening of positive symptoms- specifically disorganized speech, delusions, or hallucinations -while secondary objectives explore potential effects on social motivation and negative symptoms. In this trial, participants are required to have demonstrated clinical stability for at least six months without recent hospitalization or medication changes. The study is promising and represents a first-in-human investigation of MDMA in this population and will provide crucial preliminary data on safety parameters and tolerability thresholds for future psychedelic research in schizophrenia.

### 4.4. Ethics and clinical perspectives

The proposal to use psychedelics in individuals with SSDs—particularly those burdened by depressive or negative symptoms—raises significant ethical dilemmas. Given the heightened sensitivity of individuals with SSDs to psychoactive compounds, any discussion of potential therapeutic benefit must be balanced against a systematic consideration of adverse effects, including anxiety, mood or dissociative symptoms, perceptual destabilization, and the risk of acute psychotic symptom exacerbation, which remain the principal safety concerns in this population. On one hand, negative and depressive symptoms in individuals with SSDs are among the most treatment-resistant and debilitating aspects of the illness, and preliminary evidence suggests that serotonergic psychedelics may offer therapeutic potential. On the other hand, these compounds are known to have psychotomimetic effects, posing a theoretical—if not mostly speculative—risk of symptom exacerbation, destabilization, or relapse in this vulnerable population. Clinicians therefore face a tension between beneficence—providing a potentially novel treatment—and non-maleficence—avoiding serious harm.

Issues of informed consent and justice further complicate the ethical

landscape. Individuals with SSDs may have impaired decisional capacity, and the unpredictable nature of psychedelic experiences heightens this concern. Ensuring genuinely informed and sustained consent is thus ethically essential. At the same time, systematically excluding this population from research risks perpetuating therapeutic neglect. Psychostimulants, which carry a higher risk of precipitating psychotic exacerbation or transition from high-risk states to chronic psychosis, have nonetheless been prescribed to this population for decades.

Research suggests that, when combined with antipsychotics and appropriate monitoring, these risks can be minimized. Specific subgroups, such as individuals with predominant negative symptoms, may derive substantial benefits, including fewer hospital admissions, reduced antipsychotic dose (Rohde et al., 2018), and even lower mortality rates (Luykx et al., 2025). Thus, the debate over prescribing psychostimulants in SSDs is influenced not only by clinical risk but also by stigma surrounding psychedelic use.

Ethical trial design will require strict safeguards -such as screening for clinical stability, independent consent monitoring, and intensive follow-up- alongside incremental research strategies that prioritize mechanistic and safety evidence before widespread clinical application. Ultimately, the exploration of psychedelics in SSD underscores the need for humility and caution: potential benefits must be carefully weighed against substantial risks, with patient protection remaining paramount.

Finally, emerging hypotheses suggest that microdosing psychedelics could offer novel therapeutic avenues for individuals with SSDs, particularly through mechanisms related to synaptic plasticity. Sapienza and colleagues have proposed that repeated, low sub-perceptual doses might help restore synaptic density, potentially mitigating network dysfunction and improving cognitive deficits in individuals with SSDs (Sapienza et al., 2025). This idea aligns with broader interest in microdosing, as summarized by Polito and Liknaitzky (Polito and Liknaitzky, 2022), whose systematic review of research from 1955 to 2021 reported preliminary signals of cognitive and mood benefits associated with low-dose psychedelics. However, the review also emphasized significant methodological limitations, including reliance on self-selected samples, expectancy effects, absence of placebo controls, and short follow-up periods. Importantly, no robust evidence exists regarding long-term outcomes, neural structural changes, or sustained functional improvements. In individuals with SSDs, these uncertainties are especially critical, as microdosing could expose patients to meaningful adverse effects without demonstrable therapeutic benefit. Thus, while microdosing remains an intriguing theoretical avenue, there is currently no solid proof that it is effective or safe in this population.

## 5. Conclusion

Serotonergic psychedelics represent an emerging research avenue for addressing depressive and negative symptoms in SSDs, supported by converging mechanistic models and limited observational evidence. However, current data are insufficient to support clinical application, and any therapeutic promise must be interpreted within the context of substantial safety concerns and unresolved mechanistic uncertainty.

Future research should therefore proceed through safety-prioritized early-phase clinical trials, designed primarily to assess tolerability, acute psychotic symptom exacerbation, and feasibility in carefully selected, clinically stable individuals with SSDs. Such studies should employ conservative dosing strategies, maintain antipsychotic treatment, and include intensive short- and medium-term monitoring.

Only if acceptable safety profiles are established should RCTs be considered, with rigorous differentiation between primary and secondary negative symptoms, standardized assessment of depressive outcomes, and systematic adverse-event reporting. Precise patient selection—excluding individuals with active positive symptoms, first-episode psychosis, or bipolar vulnerability—will be critical to minimize risk and ensure interpretability.

At present, serotonergic psychedelics should be regarded as hypothesis-generating investigational tools rather than therapeutic options in SSDs. Carefully staged, methodologically rigorous studies are essential to determine whether this approach is feasible, ethically justified, and clinically meaningful.

## CRediT authorship contribution statement

**Michel Sabé:** Writing – original draft, Methodology, Conceptualization. **Paul Grof:** Writing – review & editing. **Nathan B. Sackett:** Writing – review & editing. **Sara Tai:** Writing – review & editing. **Pamela Kryskow:** Writing – review & editing. **Anya Bershad:** Writing – review & editing. **Douglas Turkington:** Writing – review & editing. **Matteo Buonarroti:** Writing – review & editing. **Marco De Pieri:** Writing – review & editing. **Pantelis Baniotopoulos:** Writing – review & editing. **Mickael Eskinazi:** Writing – review & editing. **Kerem Böge:** Writing – review & editing. **Stefan Leucht:** Writing – review & editing. **Federico Seragnoli:** Writing – review & editing. **Léonice Furtado:** Writing – review & editing. **Tatiana Aboulafia Brakha:** Writing – review & editing. **Logos Curtis:** Writing – review & editing. **Matthias Kirschner:** Writing – review & editing. **Stefan Kaiser:** Writing – review & editing. **Louise Penzenstadler:** Writing – review & editing. **Daniele Zullino:** Writing – review & editing. **Mikkel Højlund:** Writing – review & editing. **Jade Gallo:** Writing – review & editing. **Marco Solmi:** Writing – review & editing. **Jacopo Sapienza:** Writing – review & editing. **Marta Bosia:** Writing – review & editing. **Joseph La Torre:** Writing – original draft.

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