PERSPECTIVE

Synergistic psychedelic - NMDAR modulator treatment for neuropsychiatric disorders

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Modern research data suggest a therapeutic role for serotonergic psychedelics in depression and other neuropsychiatric disorders, although psychotomimetic effects may limit their widespread utilization. Serotonergic psychedelics enhance neuroplasticity via serotonin 2 A receptors (5HT2AR) activation and complex serotonergic-glutamatergic interactions involving the ionotropic glutamate receptors, tropomyosin receptor kinase B (TrkB) and the mammalian target of rapamycin (mTOR). N-methyl-d-aspartate receptors (NMDAR) channel antagonists, i.e. ketamine, and glycine modulatory site full and partial agonists, i.e., D-serine (DSR) and D-cycloserine (DCS), share some of these mechanisms of action and have neuroplastic and antidepressant effects. Moreover, procognitive effects have been reported for DSR and DCS and 5HT2AR-NMDAR interactions modulate neuronal excitability in prefrontal cortex and represent a target for new antipsychotics. We hypothesize that the synchronous administration of a psychedelic and a NMDAR modulator may increase the therapeutic impact of each of the treatment components and allow for dose adjustments and improved safety. We propose to initially focus research on the acute concurrent administration of psilocybin and DSR or DCS in depression.

Molecular Psychiatry (2024) 29:146–152; https://doi.org/10.1038/s41380-023-02312-8

INTRODUCTION

A renaissance in human research with "classical" serotonergic psychedelics (SP) is in progress. Modern psychedelic treatment is being evaluated according to a clinical paradigm that includes 1–3 drug administrations over a few weeks, in the context of psychological support and environmental manipulation [1]. Initial data are promising and a potential role for SP is increasingly proposed for a wide array of psychiatric disorders including depression, anxiety disorders, addictions and even schizophrenia [2]. Such a wide therapeutic range may be explained by the proposed mechanisms of action of SP that include triggering of long-lasting, enhanced neuroplasticity in corticolimbic circuits [3]. Cardinal topics warranting further research are the potential upgrading of SP efficacy and the attenuation of unpleasant subjective reactions, suicidal ideation and self-injury events that are occasionally elicited by SP.

It is well established that the glutamate (GLU) N-methyl-D-aspartate receptors subtype (NMDAR) plays a critical role in neuroplasticity, meta-plasticity, long term potentiation (LTP), learning and memory [4]. Modulation of NMDAR-mediated neurotransmission has been the focus of intense research during the last decades culminating in the approval of the first "glutamatergic" antidepressant, esketamine. Moreover, antipsychotic and pro-cognitive effects may be produced by modulators acting at the glycine modulatory site (GMS) on the NMDAR NR1 subunit [5, 6] while, paradoxically, antidepressant effects have been reported with both NMDAR agonists and antagonists [7]. On the basis of existing molecular, animal and clinical data, we hypothesize that simultaneous administration of a SP and a NMDAR modulator may enhance the therapeutic effects of each treatment component, with reduced adverse reactions. This synergistic approach may potentially enhance the safety, efficacy and durability of clinical improvements across a range of neuropsychiatric conditions.

MOLECULAR MECHANISMS

Although SP do not have direct affinity for GLU receptors, glutamatergic neurotransmission plays a significant role in their overall downstream effects. The activation by SP of postsynaptic serotonin 2 A receptors (5HT2AR) on pyramidal neurons leads to a GLU-dependent increase in the activity of neurons in the frontal cortex, subsequently modulating prefrontal network activity [8, 9]. The 5HT2AR-dependent increase in extracellular GLU release may be experimentally reversed by antagonists of 5HT2AR, NMDAR (containing NR2B subunits) and α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid receptors (AMPAR) [10, 11]. The precise molecular pathways that modify neuroplasticity following 5HT2AR initial stimulation are not fully elucidated. The downstream signaling cascades involve ionotropic NMDAR and AMPAR and an increase in AMPAR/NMDAR ratios [12]. Available data suggest that the resulting AMPAR activation potentiates brain-derived neurotrophic factor-tropomyosin receptor kinase B (BDNF-TrkB) and mammalian target of rapamycin (mTOR) signaling, thus upregulating the expression of neuroplasticity-related genes and protein synthesis of synaptic components (e.g., via eukaryotic

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Received: 9 July 2023 Revised: 17 October 2023 Accepted: 23 October 2023
Published online: 9 November 2023

elongation factor 2, eEF2), ultimately leading to rapid and long-lasting synaptogenesis [3, 9].

Highlighting the importance of glutamatergic transmission for antidepressant effects, similar mechanisms of action, involving NMDAR channel antagonism and AMPAR stimulation leading to neuroplastic synaptic and behavioral effects have been proposed for the dissociative anesthetic ketamine. Thus, while SP act indirectly on glutamatergic systems, the dissociative anesthetics, being NMDAR channel blockers, act directly on GLU ionotropic receptors. NMDAR antagonism has been associated with the dissociative effects of ketamine while serotonin receptors (5HTR) agonism is proposed as the main mediator of the psychoactive state induced by SP [8, 13].

Moreover, additional mechanisms and neurotransmitter systems may have a role in the generation of SP and ketamine clinical effects. Within the framework of this complex and evolving research field, recent findings implicate opioid systems, dopaminergic and GABAergic signaling [13] and the promotion of plasticity by direct binding of psychedelics to BDNF receptor TrkB [14]. Furthermore, it has been demonstrated that pro-hedonic, antidepressant-like effects of psilocybin in mice and concurrent strengthening of hippocampal excitatory synapses may be achieved in the context of prior administration of a 5-HT2A antagonist, suggesting that psychedelics may achieve their therapeutic effect by mechanisms other than direct stimulation of 5-HT2A receptors [12].

While enhanced neuroplasticity may contribute to the therapeutic effects of both SP and ketamine, the relationship between NMDAR modulation and depression is particularly complex. Not all NMDAR antagonists act as antidepressants. Furthermore, NMDAR full and partial agonists at GMS (e.g. D-serine (DSR), D-cycloserine (DCS), sarcosine), glycine transport inhibitors (sarcosine) and D-amino acid oxidase inhibitors (benzoate) have also shown antidepressant efficacy in animal models and clinical trials [6, 7, 15, 16]. These data raise the intriguing question regarding how NMDAR agonists and antagonists are both capable of having converging behavioral effects. It appears that AMPAR and BDNF/mTOR signaling and resulting neuroplastic changes are common downstream targets of both NMDAR agonists and antagonists. It is proposed that NMDAR antagonists, such as ketamine, inhibit the tonic activation of extra-synaptic NMDAR, resulting in activation of the mTOR signaling complex and protein synthesis. In contrast, NMDAR co-agonists, such as DSR, occupy unsaturated glycine sites on NMDAR, stimulating synaptic NMDAR and leading to LTP and antidepressant effects [7, 17].

In addition to neuroplasticity enhancement, SP and NMDAR modulators have in common anti- inflammatory and immune regulatory effects. Both 5HTR and NMDAR are expressed by a majority of immune tissues. SP such as psilocybin appear to produce strong anti-inflammatory effects by binding to 5HT2AR on immune cells while mixed results on markers of inflammation have been recently reviewed for ketamine [13]. Anti-inflammatory effects were also reported for DCS [18] and serine and glycine deprivation alters cellular metabolism and induces aberrant cytokine production in macrophages [19].

THE HYPOTHESIS

The above considerations lead us to hypothesize that concurrent administration of SP and NMDAR modulators may synergistically increase the therapeutic impact of each treatment component. An additional benefit could be a reduction in the dosage of each component, resulting in increased safety. It is widely presumed that SP efficacy requires psychedelic effects which are suggested to be dependent on 5HT2AR activation, mandate costly psychological support in specialized inpatient settings and present a significant barrier to SP widespread utilization. This drawback would be greatly reduced if the psychedelic response could be diminished without a significant reduction in clinical efficacy. We have obtained preclinical data indicating that combined SP-NMDAR modulator administration could achieve this objective, as envisaged by our hypothesis (See below).

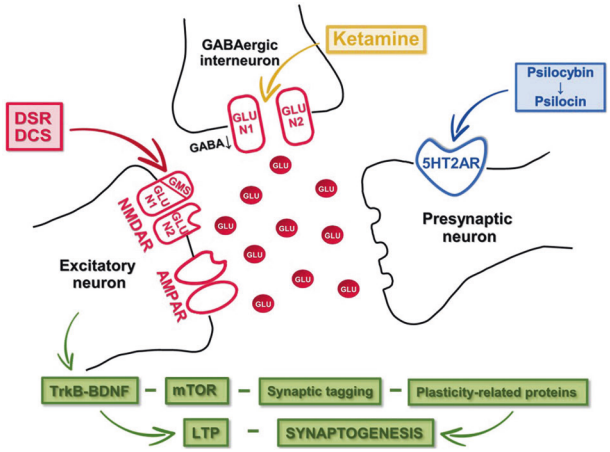

Fig. 1 Schematic representation of the hypothesized mechanisms of action of combined serotonergic psychedelic—NMDAR modulator treatment. Serotonergic psychedelics (SP, e.g., psilocybin) agonism at 5-hydroxitryptamine receptor 2A (5HT2AR) leads to glutamate (GLU) release and direct activation of glutamatergic ionotropic N-methyl-d-aspartate receptors (NMDAR) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR). Ketamine blocks NMDAR localized to gamma aminobutyric acid (GABA) ergic interneurons which leads to suppression of GABA tonic release and indirect disinhibition of excitatory neurons. Glycine modulatory site (GMS) agonists (e.g., D-serine (DSR), D-cycloserine (DCS)) lead to activation of synaptic NMDAR, trigger pathways leading to protein synthesis and synaptic plasticity and may also indirectly inhibit serotonergic function. The resulting increase in glutamatergic activity caused by SP, ketamine and GMS modulators produces downstream activation and signaling cascades involving brain-derived neurotrophic factor—tropomyosin receptor kinase B (BDNF-TrkB), mammalian target of rapamycin (mTOR), synaptic tagging and plasticity-related proteins, ultimately leading to long-term potentiation (LTP) and synaptogenesis.

In this context, it is noteworthy that the dissociative effects of ketamine are not required for its antidepressant impact and GMS agonists do not seem to have dissociative or psychedelic effects, suggesting that the psychoactive effects are not a prerequisite for molecular processes leading to enhanced neuroplasticity. Furthermore, 5HT2AR- NMDAR interactions are known to modulate neuronal excitability in prefrontal cortex and have been proposed as a target for antipsychotic drugs [20]. NMDAR blockade upregulates cortical 5HT2AR expression which is implicated in psychosis. While noncompetitive NMDAR antagonists appear to potentiate the activation of serotoninergic receptors [21], positive modulators of NMDAR could inhibit serotoninergic activation [22]. In mice, genetic depletion of the NMDAR NR1 subunit upregulates 5HT2AR leading to cortical hyperexcitability [23]. Overall, accumulating data suggest that combined SP-NMDAR modulator treatment may have safety and efficacy advantages (Fig. 1).

CANDIDATE COMPOUNDS

SP interact with a variety of serotonergic receptors ($5HT_{1A}$, $5HT_{1B}$, $5HT_{1D}$, $5HT_{1E}$, $5HT_{1F}$, $5HT_{2A}$, $5HT_{2B}$, $5HT_{2C}$, $5HT_4$, $5HT_5$ and $5HT_6$,) and, with less affinity, some non-serotonergic receptors (e.g., dopamine, kappa opioid and sigma receptors) [24]. The overlapping pharmacology of SP (i.e., $5HT_{2A}$ binding) was also demonstrated in a recent clinical trial that found that participants could not differentiate between the psychedelic experiences produced by LSD or psilocybin, except for their duration [25].

Table 1. Characteristics of serotonergic psychedelics and NMDAR modulators.

	SP	Ketamine	D-Serine	D-cycloserine
Primary mechanism of action	5HT2AR agonist	NMDAR channel blocker	Obligatory co-agonist at NMDAR GMS	Partial agonist at NMDAR GMS
Cortical glutamate release	Increased	Increased	———	Increased
Affected receptors/ pathways	5HT2AR (intracellular ?) NMDAR AMPAR BDNF-Tr_KB mTOR eEF2	NMDAR (extrasynaptic ?) AMPAR BDNF-Tr_KB mTOR eEF2	NMDAR (intrasynaptic ?) AMPAR BDNF-Tr_KB mTOR 5HT2AR ?	NMDAR NR2A/B- partial agonist NR2C/D- full agonist AMPAR BDNF-Tr_KB 5HT2AR ?
Therapeutic effects	Antidepressant psychotherapy facilitation	Antidepressant	Antidepressant Anti-negative symptoms Procognitive	Antidepressant psychotherapy facilitation
Antidepressant effect time frame	Rapid acting	Rapid acting (within hours)	Unknown	Within 2-4 weeks
Administration millieu	Psychological support. Environmental manipulation	Stringent treatment environment	———	———
Limitations	Psychedelic trip. Abuse	Dissociative phenomena Abuse	Low oral bioavailability	Low NMDAR specificity Tachyphylaxis

SP Serotonergic psychedelics, *NMDAR* N-methyl-D-aspartate receptors, *5-HT2AR* 5-hydroxytriptamine 2A receptor, *GMS* Glycine modulatory site, *BDNF-TrKB* Brain- derived neurotrophic factor- tropomyosin receptor kinase B, *mTOR* Mammalian target of rapamycin, *eEF2* Eukaryotic elongation factor 2.

Although our line of thought conceptually envisages psychedelics in general, we propose to focus initially on psilocybin for which more extensive modern clinical research data is available.

In regard to NMDAR modulators, we propose primarily the evaluation of the prototypical full and partial GMS agonists DSR and DCS, respectively. NMDAR comprise a heterotetrameric complex of two obligatory GluN1 subunits with either two GluN2 subunits or a combination of GluN2 and GluN3 subunits. The GluN1 subunit has eight different isoforms owing to alternative splicing. GluN2 subunits and GluN3 subunits also have four (GluN2A-D) and two (GluN3A-B) variants, which are encoded by separate genes [26]. Activation of NMDAR uniquely requires occupancy of the GMS on GluN1, by either glycine or DSR, and binding of glutamate to its receptor on GluN2 in order to open the receptor-channel and permit calcium (Ca^{2+}) entry. Ca^{2+} induces a cascade of intracellular events that mediate local acute functional synaptic plasticity and changes in gene expression that promote long-term neural structural plasticity. Under glutamate over-stimulation conditions, unbalanced depolarization and Ca^{2+} influx may lead to neuronal damage and necrosis [27].

DSR and DCS have thus a different first-hit mechanism of action than SP and ketamine and have shown promise for indications other than depression (Table 1). Targeting the GMS is expected to have less adverse effects than targeting the glutamate site. Indeed, while the spatio-temporal patterns of NMDAR activity are largely controlled by phasic glutamate release at synaptic sites, it is generally assumed that glycine and DSR are tonically present at the synapse and therefore modulate the NMDAR response without inducing the toxicity linked to direct NMDAR activation [26, 27].

PSILOCYBIN

Psilocin, the active metabolite of psilocybin, is a potent agonist at most 5-HTR with affinities from 3 to 500 nM. In humans, the intensity of psilocybin -induced perceptual changes is correlated with 5HT2AR activation. Blocking 5-HT2A receptors significantly attenuates self-reported psychedelic-induced perceptual distortions [28].

A complex interplay between serotonergic and glutamatergic systems in prefrontal circuits may underlie the therapeutic effects of psilocybin [29]. Psilocin has been reported to induce changes in neuroplasticity, including neurogenesis, mediated through TrkB, mTOR and 5HT2AR signaling pathways [29, 30]. Systemic administration of psilocybin has been shown to increase BDNF production in the hippocampus [31]. Furthermore, the increase in neurogenesis was accompanied by extinction of conditioned fear related behaviors [32].

Recent studies with psilocybin suggest significant benefits in major depressive disorder for 1-2 psilocybin (~25 mg) administration sessions [33, 34]. Nevertheless, psilocybin -induced alterations in perception and potential suicide risk [35] represent significant drawbacks that could be diminished by coadministration of a compound that allows for a reduced psilocybin dose or attenuated psilocybin -induced psychedelic effects, while preserving the neuroplastic efficacy.

D-SERINE

DSR is an endogenous obligatory NMDAR co-agonist at the NR1 subunit-located GMS that does not bind to other known targets [36]. In rodents, an acute DSR dose led to antidepressant effects in animal models of depression, similarly to a single dose of ketamine [37, 38]. The antidepressant effects of a single high dose of DSR were found to be mediated by rapid AMPAR- induced mTOR signaling and increased BDNF levels [37]. These DSR actions are blocked in NR1-knock out mice [38]. Reduced immobility in the forced swim test and reduced latency to feed in the novelty-suppressed feeding test were also observed in mice chronically fed with DSR or when DSR synthetizing enzyme, serine racemase, was over-expressed [39].

It is well established that DSR administration results in increased extra—and intracellular brain DSR levels and can enable LTP and/or reverse age-related deficits in LTP expression and learning performance [40, 41]. In mice, administration of 50 mg/kg DSR intraperitoneally for 8 consecutive days increased hippocampal cell proliferation, the density of neural stem cells and the survival of newborn neurons [42]. An acute DSR dose reduced feelings of anxiety and sadness and improved cognitive scores in healthy volunteers [43]. DSR seems to be involved in cognitive impairments in normal aging and dementia and overall, a cognitive enhancer role has been suggested for this amino acid [41].

Clinical trials indicate that DSR (30–120 mg/kg/day) added to ongoing treatment with non-clozapine antipsychotics may result in significant symptom improvements in chronic schizophrenia patients, most significantly in the negative symptom cluster [6, 15]. Meta-analyses indicate that additional dysfunction domains e.g. depression and cognitive symptoms are also affected by DSR [44, 45]. More recent investigations suggest the use of DSR pharmacotherapy in conjunction with some form of cognitive remediation such as computerized cognitive retraining or auditory cognitive remediation [46].

DSR-induced nephrotoxicity has been reported in rats but not in any other species. Even in rats, DSR-related tubular necrosis is dose dependent and reversible; and does not appear to be present at doses producing an acute Cmax of <2000 nmol/ml [47, 48]. In contrast, the acute Cmax of DSR 120 mg/kg, the highest dose tested in humans, is ~500 nmol/ml [48]. Across all published DSR human studies, including ~500 DSR receivers, only one person has been reported to have abnormal renal values that fully resolved within a few days of stopping treatment [49].

Despite its excellent safety profile, a major challenge to DSR use is low oral bioavailability. Orally administered DSR is substantially catabolized by D-amino acid oxidase [27, 40] diminishing its bioavailability and necessitating the administration of gram level doses. In view of this limitation, the ideal dosage and mode of administration of DSR may involve the synchronous administration of compounds with overlapping mechanisms of action.

D-CYCLOSERINE

DCS (synonyms: Cycloserine; C3H6N2O2; D-4-Amino-3-isoxazolidin;d-Oxamycin; Seromycin) is a *Streptomyces*-isolated broad-spectrum antibiotic approved for tuberculosis (TB) treatment, used since the 1950's, usually at 500–1000 g/day regimens, in millions of individuals. DCS is a structural analogue of d-alanine and belongs to the core second line treatment group C listed by WHO guidelines for treatment of multi-drug and extensively-drug resistant-TB (MDR/XDR-TB). Given its activity and lack of reported resistance in strains infecting humans, DCS has been called "the cornerstone option" for treating drug resistant TB cases [50]. This feature makes DCS the only antibiotic that has been used in humans for almost seven decades that has evaded resistance selection in bacterial populations [51, 52]. Although associated in early reports with detrimental neuropsychiatric effects, no propensity for addiction, abuse, or frontal brain region neurotoxicity, that have been reported with direct NMDAR channel blockers, have been associated with DCS [53, 54].

The discovery of an agonist role for DCS at GMS in the 1980's led to the characterization of its impact on the facilitation of cortical neuroplasticity [55]. In a variety of brain injury animal models, it was shown that DCS can reverse synaptic plasticity alterations via improved LTP, restored BDNF levels and AMPAR-related effects and increased dendritic spine density [56–58].

In animal models, DCS enhances extinction of conditioned fear, a form of learning that represents a valid preclinical model of NMDAR-depedent exposure-based therapy [59, 60]. DCS also shows efficacy in preclinical models of deficient fear extinction after stress [61], REM sleep deprivation [62] and alcohol withdrawal [63], as well as in mutant mice harboring the BDNF Val66Met polymorphism that is associated with increased susceptibility to neuropsychiatric disorders [64]. In humans, treatment with DCS administered in conjunction with cognitive behavioral therapy (CBT) sessions, enhances the efficacy of exposure therapy for various forms of maladaptive fear, including social anxiety, obsessive-compulsive disorder and panic disorder [65, 66]. Interestingly, in humans with anxiety disorders. DCS treatment is associated mainly with a faster rate of improvement rather than a better overall outcome [55, 67]. Moreover, most trials reporting positive results administered only a small dose (50–250 mg) of DCS in conjunction with 3-5 exposure sessions [67].

DCS antidepressant effects in tuberculosis patients were noted already in the 1950's [68]. More recently, high-dose add-on DCS was shown to safely relieve treatment resistant depression (TRD), with therapeutic effects evident 2–4 weeks after treatment initiation and no associated psychotic or dissociative side effects [69]. In healthy volunteers, administration of 1000 mg DCS resulted in acute increases in brain GLU plus glutamine levels [70] and in high-frequency EEG oscillations [71] similarly to ketamine, but devoid of its psychotomimetic effects. An open label study suggested a potential role of DCS in the maintenance of the antidepressant effect of a single dose of ketamine in patients with bipolar depression [72]. A therapeutic benefit of DCS maintenance treatment has been demonstrated for TRD patients who respond to ketamine infusion but have a residual suicidal risk [73]. Since DCS is a weak partial agonist at GluN2A- and GluN2B-containing receptors, with greater agonist efficacy at GluN2C and GluN2D-containing receptors [74, 75], it has been suggested that DCS may preferentially facilitate or inhibit NMDAR subtypes and high dose DCS may attenuate executive cognitive deficits associated with suicide risk [73].

DCS limitations include its low specificity for different NR2 subunits and tachyphylaxis. Furthermore, dose-timing in relation to exposure therapy sessions remains to be established [53, 65]. Newer approaches explore the efficacy of dual treatment combining DCS with other treatments, such as neuropeptides [76] or transcranial magnetic stimulation [77].

CLINICAL RESEARCH CONSIDERATIONS

The accumulating animal models and clinical data regarding NMDAR modulators and SP effects indicate that their combined use may be relevant for major unmet medical needs such as treatment—resistant schizophrenia and depression. While a randomized double-blind, placebo-controlled, parallel-arm design remains the gold standard in the clinical development stage, the utility of testing the proposed combined treatment versus an active control (e.g., stand-alone psilocybin) should be pondered.

The initial investigation of psilocybin + DSR or + DCS in TRD should employ standard treatment-resistance inclusion criteria and prototypical symptom scales scoring and should asses an acute administration of the combined investigational compound, alongside psychological support. However, more adequate instruments may be necessary for detection of early meaningful changes [78–80]. Clinical as well as laboratory (e.g., inflammation markers) assessments should be performed. Overall, it is recommended to include durability assessments under double-blind conditions for a minimum of 6 weeks and follow-up collection of blinded data for at least 3 months [78].

The issue of treatment frequency should be addressed from early stages of intervention development. Stand-alone as well as add-on administration to an already on-going fixed dose treatment with a selective serotonin reuptake inhibitor (SSRI) should be considered. For psilocybin, it was recently suggested that the efficacy findings within such an add-on research paradigm are similar to those in studies in which antidepressant withdrawal was performed prior to psilocybin administration [81].

In the initial trials, is seems appropriate to exclude participants experiencing a major comorbid psychotic disorder or suicide risk. Potentially, when the efficacy and side effects profile of the combined intervention are better appreciated, depressed patients with marked severity and/or suicidal ideation/behaviors may become treatment candidates. Until then, careful monitoring of psychotomimetic effects and suicidal ideation should be applied. Experimental intervention discontinuation and "rescue" psychotherapeutic and/or antipsychotic 5HT2AR antagonist drug treatment should be implemented when necessary.

Regarding the synchronous use of SP with ketamine/esketamine, although mechanistically attractive, it may carry an increased risk of suicidality, abuse, dissociative and psychotic phenomena that warrants prior in-depth preclinical evaluation.

CONCLUSIONS AND FURTHER DIRECTIONS

Molecular underpinnings, not yet fully elucidated, and accumulating clinical research data suggest that synchronous SP-GMS modulator treatment may have efficacy and safety advantages. We propose to initially focus on psilocybin -DSR and/or psilocybin -DCS acute administration for TRD. These combination treatments should subsequently be assessed for additional neuropsychiatric disorders.

Preclinical studies performed in our laboratory have examined the effects of psilocybin-DSR and psilocybin-DCS synchronous administration on the head twitch response (a rodent correlate of human psychedelic effects) and MK-801 induced hyperactivity (a putative model for acute antipsychotic effects) in mice and have found attenuation of these behavioral markers by the combined treatment [82]. The psychotropic compounds were all administered at doses equivalent to meaningful therapeutic dosages. These findings suggest potential reduction of both psychedelic and psychotic-like effects and warrant investigation in human studies.

Further preclinical studies in established rodent models of depression and schizophrenia are indicated. The correlation between the behavioral effects induced by these treatment regimens and markers of neuroplasticity should be examined specifically seeking an additive effect. Subsequent work should establish the optimal psilocybin, DSR and DCS doses to be employed within the framework of a synergistic treatment paradigm. Ultimately, randomized controlled clinical trials are the key test to our hypothesis and pivotally required for demonstrating the envisaged efficacy and safety superiority of the combined treatment.

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ACKNOWLEDGEMENTS

Hadassah BrainLabs - Center for Psychedelic Research (https://cfpr.brainlabs.org.il/) was established with the support of Negev Labs.

AUTHOR CONTRIBUTIONS

UH and BL have jointly put forward and conceptualized the hypotheses and concepts presented in this paper and prepared the manuscript

COMPETING INTERESTS

UH is inventor in patents and patent applications for the use of NMDAR modulators in depression, autoimmune encephalopathies, inflammatory disorders and in conjunction with psychedelics in neuropsychiatric disorders. BL is inventor on a patent application for the use of NMDAR modulators in conjunction with psychedelics in neuropsychiatric disorders.

ADDITIONAL INFORMATION

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