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Therapeutic potential of classic and non-classic psychedelics in neurodevelopmental disorders: Opportunities and challenges

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ABSTRACT

Neurodevelopmental disorders (NDDs) comprise a heterogeneous group of conditions arising from altered brain development and leading to impairments in social, cognitive, emotional, and motor domains. Clinical manifestations are highly variable in severity and symptom profile, reflecting the complex and multifactorial etiology of NDDs. Available treatments are limited to early behavioral interventions, eventually combined with symptomatic pharmacotherapies, but remain largely unsatisfactory. Among possible new therapeutic strategies for NDDs, classic psychedelics, such as LSD or psilocybin, and non-classic psychedelics including ketamine have recently received interest due to their potential in enhancing neuroplasticity and restoring social and cognitive deficits. Classic psychedelics are a group of psychoactive substances sharing agonistic activity on serotonergic 5-HT2A receptors while ketamine is a dissociative anesthetic acting as N-methyl-D-aspartate (NMDA) receptor non-competitive antagonist. Although the literature about the potential of psychedelics in the treatment of NDDs is still scarce and heterogeneous, we revised here available clinical and preclinical data to discuss the opportunities and challenges associated with the use of these drugs in NDDs. We found that most of the evidence comes from small clinical studies on adult subjects mainly evaluating the therapeutic potential of low dose ketamine, while reports with classic psychedelics are scarce and primarily observational. Overall, despite further research being needed before any conclusions can be drawn regarding the efficacy and safety of classic and non-classic psychedelics in the management of NDDs, most findings are promising and report significant behavioral improvements especially in cognitive and social domains.

1. Neurobiological mechanisms of neurodevelopmental disorders and treatment approaches

Neurodevelopmental disorders (NDDs) are a group of conditions that affect brain development resulting in social, cognitive, emotional, and motor impairments [1]. NDDs typically manifest during early childhood although some of these disorders might occur at later stages of life [2]. According to the Diagnostic and Statistical Manual of Mental disorders (DSM-V), NDDs include intellectual disabilities, communication disorders, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), specific learning disorders, and neurodevelopmental motor disorders [3]. Rare genetic disorders, developmental and epileptic encephalopathies are considered NDDs as well [4,5]. Symptoms can be shared within different disorders although some might be more prominent in one condition compared to another and greatly vary in terms of severity, resulting in disease-specific symptomatology [6]. Common symptoms comprise difficulties with speech, language and communication, learning and memory impairments, altered motor skills, coordination and motor control, and behavioral dysfunctions in social and emotional domains. Importantly, comorbidity between two or

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more NDDs and co-occurrence with psychiatric conditions, including anxiety and depression, is often reported [7].

NDDs etiopathogenesis has been associated with a complex interaction between genetic factors and environmental determinants [8,9]. The study of inherited forms of NDDs has allowed the identification of multiple genetic pathogenetic factors which were associated with rare genetic NDDs [8,10]. Genes associated with NDD are involved in biological processes such as i) protein synthesis, with PI3K-mTOR pathway being one of the most affected; ii) transcriptional and epigenetic regulation of developmental genes; iii) alteration of synaptic proteins and synapse functions [8]. However, the genetic background seems not enough to entirely explain NDD etiology and progression because the same genotype is not always correlated with similar presence and severity of symptoms in all patients, resulting in subjects with very distinct clinical features. Indeed, several non-genomic environmental factors have been proposed to interact with genetic vulnerability contributing to NDD development [9]. Among them, epidemiological evidence has highlighted a role for pollution, endocrine disruptors, and stress exposure either during pregnancy or in the early phases of life [11–14]. Nonetheless, the exact molecular mechanisms underlying NDDs and how they participate in translating into functional and behavioral outcomes are still to be fully elucidated, while their knowledge would represent a pivotal step towards the development of better therapies.

To date, the treatment of NDDs is based on a combined approach of behavioral and pharmacological interventions. Timing is fundamental as early interventions were demonstrated to improve the developmental outcomes [15]. Behavioral treatments aim to improve social, communication, and adaptive skills to help patients to cope with daily challenges. Common approaches include Cognitive Behavioral Therapy (CBT) [16], which helps people identify and change negative thought patterns, and Applied Behavioral Analysis (ABA) [17], which uses positive reinforcement to help patients change their behavior. Other non-pharmacological approaches include play therapy where patients are taught to express feelings without the need to verbalize them [18] and family therapy where the whole family or caregivers are provided support and strategies to manage NDD patients [19]. Besides methodological differences, behavioral treatments aim to address NDD phenotypic dysfunctions and are used to obtain positive reinforcement and/or behavioral extinction to guarantee better quality of life and integration in daily social situations.

Although behavioral approaches are preferred, when symptoms are severe, pharmacological interventions may help in controlling some behavioral traits (see below). Unfortunately, there is no drug developed specifically for NDDs, thus limiting the efficacy of the interventions and introducing issues related to undesired side effects and patient compliance. Therefore, there is an urgent need for better pharmacological solutions able to treat NDDs in their clinical manifestations complexity and potentially addressing causative dysfunctional biological processes.

2. Pharmacological approaches to neurodevelopmental disorders

2.1. Conventional pharmacotherapy and its limitations

Conventional pharmacological treatment for NDDs exploits different classes of drugs used to alleviate some of the most severe behavioral symptoms [20].

Atypical antipsychotics can be used to alleviate irritability and aggression [21,22]. The second and third generation atypical antipsychotics, risperidone and aripiprazole respectively, are approved for ASDs and demonstrated to significantly reduce aggressive-related behaviors, thus favoring psychological assistance and simplifying daily routine [23,24]. Risperidone and aripiprazole demonstrate comparable efficacy and safety in managing irritability, aggression, and self-injury in children with ASD, but can cause significant side effects, most notably weight gain and increased appetite [25]. Other common side effects include drowsiness, fatigue, constipation, and changes in prolactin levels.

Hyperactivity and inattention are other frequent behavioral manifestations in children and adolescents with NDDs, especially in those suffering from ADHD. One pharmacological option to control these symptoms are stimulants of the central nervous system like methylphenidate or amphetamine [26]. These drugs increase levels of norepinephrine and dopamine, resulting in improved attention and reduced impulsivity in patients with ADHD. However, stimulants may induce cardiac side effects and may increase anxiety, as well as have abuse potential. An alternative is the alpha−2 adrenergic receptor agonist and hypotensive drug guanfacine that, besides its use in the treatment of hypertension, was shown to control catecholaminergic transmission in the prefrontal cortex and basal ganglia, improving the ADHD symptoms [27]. Guanfacine is typically chosen when stimulants fail to achieve therapeutic efficacy or are not tolerated.

Importantly, NDD patients often show obsessive/compulsive traits as well as anxiety and mood disbalance. Classic antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), can be effective in reducing anxiety and depressive states in NDDs [28] as well as repetitive behaviors, although this has been reported mostly when they are administered to adults rather than children/adolescents [29,30]. Conversely, SSRIs have limited success in treating core symptoms of NDDs and they may trigger behavioral activation, irritability, and hyperactivity [31].

Overall, the available pharmacotherapies might help in controlling some of the behavioral traits of NDDs and to improve the quality of life of patients and families. However, they come with not negligible side effects that limit their use, especially when administered in a vulnerable life period like childhood or adolescence. Moreover, none of the currently available drugs can target core etiopathological mechanisms of NDDs.

2.2. Emerging therapies

In recent years, thanks to recent technological advancements, gene therapy has been proposed for the treatment of monogenic forms of NDDs [32]. Different approaches might be used including delivering correct gene copies, silencing of dysfunctional causative genes with antisense oligonucleotides, or gene editing [32,33]. Although in most cases these therapies have been applied limitedly at preclinical level [32,34], some examples have shown promising results moving to clinical development.

For example, Angelman syndrome is caused by the deletion of the maternal UBE3A allele and ongoing clinical trials are exploring the therapeutic potential of investigational ASO, adeno-associated virus gene therapies, as well as a base editing strategy using mRNA-LNP (messenger RNA loaded lipid nanoparticles) to activate the paternal UBE3A gene [35–39]. Similarly, gene therapy approaches aimed at restoring SHANK3 gene haploinsufficiency are under evaluation in patients with Phelan-McDermid syndrome. Gene therapies raise great expectations, but their clinical efficacy in NDDs must still be demonstrated and the best time for administration determined. Moreover, a key concern regards the delivery into the brain, which represents an important challenge due to the physiological barrier represented by the blood-brain barrier, requiring the use of direct intracranial delivery and/or nanotherapeutics [40,41].

Another strategy that is showing promise is transcranial direct current stimulation (tDCS) [42]. tDCS is a non-invasive stimulation technique able to modulate neuronal activity and restore excitatory/inhibitory imbalance. This approach is currently under investigation both at preclinical and clinical levels in different NDDs including ASD and ADHD [43]. Recent evidence in ASD patients subjected to tDCS shows ameliorated verbal fluency and syntax as well as improvements in emotional processing and in different clinical scales

[44,45]. Similarly, ADHD patients demonstrated to benefit from tDCS by a reduction of inattention and hyperactivity and improvement of working memory performance [46,47]. One advantage of this technique is its relatively high safety profile with no serious adverse effects reported, even when administered at a young age [43]. Moreover, it seems to work well in combination with psychological interventions potentiating the positive effects. More studies using tDCS are needed to understand the long-term effects and to optimize protocols.

Regarding pharmacological treatments, various compounds are at different stages of preclinical and/or clinical development although with still mixed results and rarely showing significant improvements compared to conventional treatments. However, some have been successful as the synthetic analog of the N-terminal tripeptide of insulin-like growth factor 1 (IGF−1) known as glycine-proline-glutamate, trofinetide, which is the first drug approved by FDA for the treatment of Rett Syndrome (RTT) in pediatric and adult patients [48,49].

Another possible therapeutic approach is drug repurposing, which offers generally safer and faster drug development. Some examples are statins for their ability to reduce neuroinflammation and enhance synaptic function and neuronal survival [50], the antidiabetic drug metformin primarily used in ASD to manage weight gain caused by antipsychotic medications but under evaluation for its potential to treat core ASD behavioral symptoms [51], or the dissociative anesthetic ketamine.

Ketamine is a non-competitive NMDA receptor antagonist used in both human and veterinary surgical procedures since the 1960s. Importantly, ketamine has a high potential for abuse due to its fast-acting dissociative and euphoric effects which can cause high psychological dependence, rapid tolerance, and reinforcing properties. The study of its therapeutic potential has returned to the forefront in the last decade, following growing evidence of rapid antidepressant effects of low subanesthetic doses in treatment-resistant depressed patients (TRD) ([52,53]; see below for more details). This led to the approval of the intranasal formulation of the S-enantiomer in TRD and set the precedent for investigation into another class of psychoactive drugs, namely classic psychedelics. Indeed, after years of hiatus, classic psychedelics are now being studied again in the context of many adult psychiatric disorders including depression, post-traumatic stress disorder (PTSD), and substance-use disorders, where they are showing positive results in terms of efficacy and safety [54]. Moreover, their ability to promote neuroplasticity and rescue the behavioral alterations associated with these disorders make them interesting candidates also in NDDs in which dysfunctional plasticity processes play a key pathological role [55].

The aim of this narrative review is to provide an updated overview of the clinical evidence regarding the potential of classic and non-classic psychedelics in the treatment of NDDs and to describe the underlying putative neurobiological mechanisms as investigated in preclinical studies. Indeed, translational models of NDDs typically based on genetic mouse models are of help to better characterize the molecular basis of these diseases and etiopathogenetic mechanisms.

The information for this narrative review was collected by using the PubMed database, all literature available at the time of writing the review has been included in the text and organized by pathology.

3. Pharmacology of classic and non-classic psychedelics

Psychedelics are a heterogeneous family of natural and synthetic psychoactive compounds with different primary mechanisms but with the shared ability of producing altered states of consciousness. This family includes classic serotonergic psychedelics (e.g., lysergic acid diethylamide, LSD, psilocybin, and N,N-dimethyltryptamine, DMT) and non-classic psychedelics, including dissociative anesthetics (NMDA receptor antagonists) such as ketamine, entactogens/stimulants as 3,4-Methylenedioxymethamphetamine (MDMA), and antimuscarinic deliriants as scopolamine. Psychoactive brews can also fall in this definition, as for example, the DMT-containing ayahuasca. Recent decades have seen renewed scientific interest in classic and non-classic psychedelics due to their ability to modulate neuroplasticity, cognitive flexibility, and affective behaviors [56,57]. The theory that psychedelics open a window of plasticity is highly attractive for the management of pathological conditions with defective neuroplasticity such as NDDs [56] but, on the other hand, their intense subjective effects and abuse potential represent significant limitations.

3.1. Pharmacology of ketamine

Ketamine is a non-classic psychedelic with an arylcyclohexylamine structure and with a primary mechanism of action involving the non-competitive antagonism of glutamate NMDA receptors [58]. Ketamine has distinct psychoactive effects that are highly dose-dependent: while at medium-high doses (1–4.5 mg/kg i.v.) it has anesthetic properties with marked dissociative effects, lower subanesthetic doses (0.5 mg/kg i.v., 40-minutes infusion) are mildly dissociative and provide instead rapid and sustained antidepressant effects, as extensively demonstrated in Major Depressive Disorder (MDD) and TRD patients as well as in preclinical models [59]. Indeed, a single subanesthetic administration of ketamine was reported to induce antidepressant effects in TRD patients within hours which is also sustained for several days. In terms of mechanism of action, subanesthetic doses of ketamine were demonstrated to block NMDA receptors expressed on GABAergic inhibitory interneurons in corticolimbic brain areas resulting in the so-called disinhibition of glutamatergic excitatory neurons and subsequent enhancement of glutamate release in the synaptic cleft and activation of postsynaptic α-amino−3-hydroxy−5-methyl−4-isoxazolepropionic acid (AMPA) receptors leading to recruitment of BDNF/Trkb and downstream pathways linked with neuroplasticity and cells survival [60]. Beyond this action, ketamine also acts through postsynaptic and extrasynaptic NMDA receptors to control glutamate-dependent transmission and de-suppress protein synthesis associated with synaptic potentiation and strengthening [60], ultimately contributing to brain structural and functional changes associated with the antidepressant effect [61,62]. To overcome limited oral bioavailability, ketamine is usually administered intravenously as a racemic mixture of the two enantiomers S (+)- and R (-)-ketamine, reaching peak plasma concentrations in less than minutes and rapidly distributing to highly perfused tissues including the brain. Importantly, ketamine undergoes extensive hepatic metabolism that originates active metabolites like (2 R,6 R;2S,6S)-hydroxynorketamine ((2 R,6 R;2S,6S)-HNK) that have demonstrated antidepressant properties at preclinical level [63]. Indeed, despite a short half-life (2–4 h), that is prolonged for repetitive administrations regimens, the behavioral effects of ketamine persist for several days, suggesting that the metabolites might participate in the sustained antidepressant effects. Regarding side effects, while prolonged misuse of ketamine causes severe, dose-dependent organ toxicity and neurological deficits, antidepressant doses are typically well tolerated except for a transient and moderate increase in blood pressure and mild dissociative effects, which tend to tolerance with repeated administration [64]. Of note, the (S)-enantiomer of ketamine, namely esketamine, entered the market in 2019 as a nasal spray formulation for the management of TRD [65].

3.2. Pharmacology of classic psychedelics and other non-classic psychedelics

Classic psychedelics comprise a variety of drugs ranging from tryptamines (e.g. psilocybin and its active metabolite psilocin, or DMT) to phenethylamines (e.g. mescaline) and ergolines (e.g. LSD) that share the ability to modulate the serotonergic system and primarily act as agonists on the 5-HT2A receptors, with different binding affinities also for 5-HT1A, 5-HT2B, 5-HT2C, 5-HT6, and 5-HT7 receptors [66]. The activation of 5-HT2A receptors is associated with the recruitment of specific intracellular cascades including the Gq/11, the β-arrestin−2, and the arachidonic acid pathways that ultimately lead to increased cell

activity, survival and maturation, and regulate gene expression of synaptic-relevant transcripts [67]. Classic psychedelics bind also to 5-HT2A receptors expressed on glutamatergic pyramidal neurons in the prefrontal cortex and neocortical areas resulting in an increase of their excitability, in turn modulating glutamate transmission and downstream plasticity pathways including the AMPA receptors-BDNF-TrkB-mTOR pathway [68,69]. Enhanced neuroplasticity is suggested to play a key role in the persistence of antidepressant, prosocial and procognitive effects associated with the acute administration of classic psychedelics [70]. Indeed, taking these drugs causes profound and transient subjective experiences within the first hours after administration (average Tmax, LSD: 1.38 h; psilocin: 2.2 h), which are driven by the activation of brain regions implicated in visual and perception integration and lead to extensive brain circuits rewiring [71–75]. Importantly, multiple clinical trials are investigating the therapeutic potential of such effects in different neuropsychiatric conditions, including MDD, TRD, anxiety, PTSD, and substance abuse disorders, with promising results emerging [76–79].

In clinical trials, classic psychedelics are usually administered orally in intervals of doses ranging from 1 mg to 50 mg for psilocybin and from 5 μg to 200 μg for LSD [80] and studies in humans have shown that the subjective psychedelic experience is dependent more on the 5-HT2A receptor occupancy rather than the dose of the psychedelic per se [81,82]. More studies implementing pharmacokinetic evaluations are warranted and will surely help better understand the temporal dynamics of the relationship between 5-HT2A receptor occupancy, plasma levels, and subjective experience, as well as its possible role in the sustained and therapeutically relevant behavioral effects of classic psychedelics.

Classic psychedelics are generally well-tolerated in controlled settings but can cause acute adverse effects including intense anxiety ("bad trips"), paranoia, confusion, dizziness, headaches, and increased blood pressure. Serious risks include prolonged psychosis, flashbacks, and dangerous behavior. While not physically addictive, they can cause, in rare cases, long-lasting distress or re-traumatization [83].

Differently, stimulants such as the amphetamine derivative MDMA (known in the illicit market as ecstasy) are considered non-classic psychedelics due to their ability to produce subjective experiences and neurometabolic effects, but with a different pharmacological profile than serotonergic psychedelics [84,85]. After oral administration of doses spanning from 50 mg to 180 mg they rapidly produce (Tmax approx. 2 h) strong prosocial effects characterized by increased sociability, empathy, and reduced anxiety, and are for this reason also referred to as entactogens [86], but they bind with low affinity to 5-HT2A receptors while exerting their activity interacting with the 5-HT transporter (SERT), the dopamine transporter (DAT), the norepinephrine transporter (NET), and directly stimulating monoamines release. Moreover, preclinical evidence has shown a critical role for oxytocin in MDMA-dependent reinforcement of adaptive social behaviors [87]. Importantly, MDMA presents a high risk of acute, dose-dependent systemic toxicity and fatalities, including serotonin syndrome, hyperthermia, seizures, and fatal cardiac arrhythmias. Common adverse effects are also dose-dependent and are related to sympathomimetic activation, with increased blood pressure and heart rate as well as decreased psychomotor performance [88].

Considering the limitation of using in therapy drugs with disperceptive properties and to limit the risk of acute physical adverse events, an alternative is the use of small sub-hallucinogenic doses of psychedelics, an approach termed "microdosing". Microdosing is defined as taking a small fraction of a full dose, often on a schedule over multiple days or weeks. Although there is no official standard for what constitutes a microdose, a commonly used measure is 10 % or less of the dose producing the full perception-altering effects [89,90]. Clinical evidence showed that microdoses of classical psychedelics may improve well-being, cognitive functions, and emotional processes and appear not to induce major acute perceptual changes or interfere with daily activities [91]. Nevertheless, little data is available regarding the long-term effects and safety of psychedelic microdosing and attention should be placed in considering possible side effects arising from chronic administration including dependence and heart valve toxicity [92]. Moreover, recent double-blind, placebo-controlled trials suggest that perceived benefits could be largely dependent on the placebo effect [93].

4. Classic and non-classic psychedelics in neurodevelopmental disorders: clinical and preclinical evidence

This section will detail clinical and preclinical evidence concerning the use of classic and non-classic psychedelics in different NDDs with the aim of discussing their therapeutic potential in this context. A choice among NDDs to discuss in this session has been made based on the availability of documented evidence of studies testing the therapeutic potential of these drugs reported in the literature.

4.1. Autism spectrum disorder

ASD is a pervasive and highly heterogeneous NDD characterized by persistent deficits in social interaction, dysfunction in language and communication, and repetitive patterns of behavior [3]. ASD is also commonly accompanied by significant psychiatric comorbidities including anxiety, depression, and/or trauma-related disorders, which contribute to functional impairment. ASD has a strong genetic basis involving hundreds of rare mutations, de novo mutations, and common variants, with heritability estimated between 80–90% [94]. Although diagnosis may occur later, symptoms typically emerge in early childhood in about 1 in 35–44 children with higher prevalence in males than females [95,96]. The prominent role of dysfunction in glutamatergic transmission and synaptic signaling in ASD [97,98] has motivated the initial studies of psychedelics and related agents as candidate interventions for ASD-related symptoms (as extensive reviews on the topic, please see [99–101]).

To date, clinical data regarding the use of psychedelics in ASD remain limited to case reports and studies on a few patients mainly using ketamine or MDMA, in addition to old studies with LSD (Table 1).

The only double-blind, placebo-controlled crossover pilot trial evaluating the therapeutic potential of ketamine failed to demonstrate any behavioral improvement [102]. This study involved 21 adolescents/young adults with ASD and low dose subanesthetic intranasal ketamine (30 mg and 50 mg) administered twice, one week apart, did not improve the primary measure of social withdrawal, with changes comparable to placebo. Ketamine was generally well tolerated with mild transient adverse effects (e.g., bad taste, dizziness, fatigue, headache, nausea) and low dissociation scores [102]. Despite the negative results, the authors suggested that the study was likely underpowered to detect clinically treatment effects, considering the placebo responses inherent in physician and parent reports. Rather than interpreting the findings as evidence of a lack of clinical improvements, they emphasized ketamine's safety profile in patients with ASD, recommending further clinical trials with ketamine in ASD patients.

Other evidence comes from case report studies, thus the limited sample size and lack of control must be taken into consideration in the interpretation of the results. A first study assessed repeated, self-administrated intranasal ketamine at escalating doses (20, 40, 60 mg) in a 29-year-old woman with ASD and severe psychiatric comorbidity, which resulted in rapid mood improvement and benefits in social interaction, together with decreased suicidal thoughts [103]. No significant adverse effects were recorded besides transient and mild sedation, dizziness and headache [103]. More recently, Özgen and Brink documented unsupervised sublingual self-administration of racemic ketamine (50–60 mg, 2–3 times/week for 10 weeks, with a 1-week break) in an ASD adult with TRD and chronic suicidal thoughts, resulting in marked mood improvement, mental flexibility, and reduced pessimism, without any reported adverse effects [104]. In a further study, intravenous ketamine with subsequent booster infusions were

Table 1
Clinical and preclinical evidence of the use of classic and non-classic psychedelics in ASD.

Clinical evidence

Drug	Subjects	Sex	Design	Administration	Clinical Assessment	Adverse events	Ref
Ketamine	21 patients (14–29 yo) Weighed ≥ 50 kg	M/F	2-dose, randomized double-blind, placebo-controlled, cross-over pilot study	30 mg followed by 50 mg i.n. followed by two doses of matching placebo one week apart or vice versa	No statistical significance on ABC-SW (follow up at 1-day and 4-days), CGI-S, SRS or ADAMS scores after each dosing visit, and at the mid-point and final visits.	Mild transient: bad taste, dizziness, fatigue, headache, nausea, throat irritation	[102] X
Ketamine	1 patient (29 yo)	F	Case Report	Self-administered i.n. 20 mg on day 1; 40 mg on days 7, 14, 17, 21, 24, 27; 60 mg on days 30, 33, 37, 40, 42	Improved interaction, flexibility and tolerance of routine change, motivation and concentration and ↓ urge to purge and suicidal thoughts within 24 h after each self-administration	Transient sedation, dizziness, numbness of limbs and face, blurred vision, headache	[103] ✓
Ketamine	1 patient (adult)	M	Case Report	Self-administered sublingually 50–60 mg 2–3 times/week for 10 weeks, with a 1-week break at week 6	↑ Mood and mental flexibility and ↓ Pessimism during the first 4 weeks of self-medication and at 6 and 12 months of follow-up.	No adverse effects	[104] ✓
Ketamine	1 patient (29 yo)	M	Case Report	6 infusions i.v. (40 mg for the first infusion and +10 mg for each subsequent infusion), followed by 2 booster infusions (90 and 110 mg)	↓ anxiety (GAD−7), suicidality (CSSR-S), depression (PHQ−9) and Posttraumatic Stress (PCL−5) following the 6° infusion and the boosters.	No adverse effects	[105] ✓
MDMA	12 patients (≥ 21 yo) Three preparatory psychotherapy sessions	M/F	Randomized, double-blind, placebo-controlled pilot study	75–125 mg o.s.	At the primary endpoint (1 month after the 2° experimental session) and at the 6-month follow up: ↓ SAD symptoms (LSAS score) No increase in social anxiety ↑ Interpersonal interaction with family members	↑ moderate in blood pressure, heart rate, and temperature Transient anxiety and mild levels of suicidal ideation (first hour)	[106] ✓
LSD	14 autistic schizophrenic children (≤ 11 yo) Previous medications discontinued Social maturity quotient ≥ 32 and ≤ 60	M/F	Clinical treatment program	25 μg (i.m) 100 μg/weekly (o.s.), then 2–3 time/weekly and 6 times/weekly	After acute 25 μg i.m. administrations and over 6 weeks of an escalating oral dose (to 100 μg daily): ↑ High mood, playful, accepted contacts, habit patterning, physical condition ↓ aggressive behavior Better understood ordinary environmental stimuli ↑ plasma inorganic phosphate within an hour after parental dosing.	No major adverse events Disturbed anxious behavior (2 patients)	[107] ✓

Preclinical evidence

Drug	Animals	Sex	Model	Administration	Behavioral outcome	Molecular changes	Ref
MDMA CP−94,253	Mice (8–16 weeks)	M/F	*Sert-Cre*$^{+/-}$:16p11.2$^{flx/flx}$, *Cntnap2*$^{-/-}$, *Fmr1*$^{-/y,\ -/-}$, VPA mice, *Sert-Cre*$^{+/-}$:Arid1b$^{flx/+}$	Single dose CP−94,253 10 mg/kg (i.p.) Single dose MDMA 7.5 mg/kg (i.p.)	↑ Interaction time and social preference (three chamber test, juvenile interaction test) ↓ Hyperactivity (CP−94,253, in some lines) No changes in cognitive performance (NOR) (CP−94,253)		[108] ✓ X
LSD	Beagle dogs (1–2 yo)	M/F	*Shank3* Het, *Shank3* Homo	Single dose 7.5 μg/kg (i.m.)	↑ social interaction ↑ attention	↑ interbrain correlation (frontal and parietal regions) ↓ theta/beta ratio (only frontal region)	[110] ✓
LSD	Mice (12–24 months)	M	*Sert*$^{+/+}$, *Sert*$^{+/-}$	Single dose 0.32 mg/kg (i.p.)	↓ grooming duration ↑ head twitches ↑ tremors and backwards gait		[111] ✓ X

ABC-SW: Aberrant Behavior Checklist Social Withdraw, ADAMS: Anxiety, Depression and Mood scale, ASD: Autism spectrum disorder, BMI: Body mass index, CGI-S: Clinical Global Impression - Severity scale, C-SSRS: Columbia-Suicide Severity Rating Scale, F: females, FMR1: Fragile X Mental Retardation 1, GAD−7: General Anxiety Disorder−7, Het: heterozygous, Homo: homozygous, HTR: head twitch response, i.m.: intramuscular, i.n.: intranasal, i.p.: intraperitoneal, i.v.: intravenous, LSAS: Liebowitz Social Anxiety Scale, LSD: Lysergic acid diethylamide, M: males, MDMA: 3,4-methylenedioxymethamphetamine, NOR: Novel object recognition test, o.s.: per os, PCL−5: Posttraumatic Stress Disorder Checklist, PHQ−9: Patient Health Questionnaire, SAD: Seasonal affective disorder, SRS: Social responsiveness scale, yo: years old. Improvement in clinical outcomes and preclinical behavioral assessments is indicated with ✓; no improvement is indicated with X.

combined with psychotherapy to treat a 29-year-old man with bipolar disorder and ASD [105]. Given the patient suicidal ideation, high anxiety, and outbursts, he was recommended 6 initial ketamine intravenous infusions, in addition to psychotherapy, with a minimum interval of 48 h between sessions. For the first infusion, a standard of 40 mg intravenous ketamine dose was titrated by 10 mg for each infusion following. The 6th infusion ended at 90 mg of ketamine and was well tolerated. Further booster infusions were 90 mg and 110 mg, respectively. In line with other studies, the patient reported reductions in anxiety/suicidality and improved affective regulation without adverse effects [105].

Evidence on serotonergic compounds in ASD is preliminary and relies on a small randomized, double-blind, placebo-controlled pilot study evaluating MDMA-assisted psychotherapy in 12 ASD adults with marked to very severe social anxiety [106]. Oral MDMA (75–125 mg) during two 8-h psychotherapy sessions (60–90 min) was followed by improvement in Leibowitz social anxiety severity (LSAS) score at 1 month, with a signal for durability at follow-up. Adverse events were consistent with the acute sympathomimetic profile including moderate increase in blood pressure, heart rate, and temperature as well as transient anxiety and mild suicidal ideation observed within the first hour after the administration [106]. No long-term adverse effects were reported.

Finally, although with major methodological limitations, historical studies from the 1960s reported acute changes in affect or social engagement in a cohort of ASD children (14 children, 6–10.5 years) treated with a single intramuscular dose of 25 μg LSD, with variable reactions including anxious agitation and increased playful social contact [107]. However, given the outdated diagnostic framing, trial standards, and ethical context, these data are not readily generalizable to contemporary ASD studies.

Preclinically, studies on psychedelics in ASD are sparse and span both ASD models and related paradigms to assess social and repetitive/stereotyped behaviors. The most ASD-specific findings come from a mouse study showing that acute MDMA significantly rescued sociability deficits in juvenile interaction and three-chamber assay across four etiologically distinct ASD mouse models (homozygous genetic deletion of 16p11.2, homozygous single gene deletions of Cntnap2 and Fmr1, and prenatal valproate exposure), with 5-HT1B receptor dependent mechanisms [108].

For LSD, the available ASD related literature is still poor and combines mainly mechanistic work evaluating the prosocial effects in wild-type rodents [109] with a single study extended to an ASD canine model, in which Shank3 mutant beagle dogs receiving a single intramuscular LSD dose exhibited increased interbrain coupling and improved social-attentional electroencephalogram markers during human–dog interaction 24 h after administration [110]. Conversely, no effects on grooming behavior were observed in an ASD serotonergic mouse model (Sert+/−) treated with acute intraperitoneal LSD (0.32 mg/kg), suggesting no major changes in repetitive behaviors caused by LSD in this model [111].

4.2. Fragile X syndrome

Fragile X Syndrome (FXS) is a monogenic disorder considered the most common inherited cause of intellectual disability and one leading cause of ASD. This genetic condition arises from an excessive expansion of the CGG trinucleotide repeat (exceeding 200 copies) within the *FMR1* gene (coding for Fragile X Mental Retardation Protein, FMRP) located on the X chromosome, which by promoting DNA hypermethylation of *FMR1* results in transcriptional silencing and no FMRP expression [112]. The absence of FMRP leads to cellular dysfunctions that impair brain development and generate functional abnormalities, manifesting as physical and neurological symptoms that appear early in life [113,114]. From the clinical point of view, one Phase 2 clinical trial was initiated in Canada in 2023 to evaluate in a cohort of 10 adults diagnosed with FXS the effect of repeated 1.5 mg microdoses of psilocybin over a period of 28 days on improving memory performance and behavioral normalization [115] (Table 2). To date, the trial has been suspended and placed on indefinite hold due to required revisions of the protocol of exclusion criteria concerning concomitant medication [115]. To the best of our knowledge, no other clinical studies, neither observational nor randomized, testing psychedelics in FXS is currently ongoing.

From a preclinical perspective, different psilocybin microdosing regimens were investigated in a rat model of FXS based on the genetic deletion of *Fmr1* exon 8 (*Fmr1*-Δexon 8) [116]. The findings demonstrated dose-dependent mitigation of cognitive deficits in adolescent Sprague-Dawley *Fmr1*-Δexon 8 rats following both systemic and oral administration, across dosing ranges spanning 0.1–3 mg/kg. More recently, the same authors demonstrated that BDNF-TrkB signaling was necessary for the improvement of cognitive performance elicited by repeated microdosing of psilocybin (0.1 mg/kg per os, oral gavage) [117]. Conversely, the tryptamine-class psychedelic compound N, N-dipropyltryptamine was reported to completely prevent audiogenic seizures in juvenile *Fmr1* knockout (KO) mice, although this effect was observed only at 10 mg/kg and not at lower doses [118]. These findings contribute to the emerging hypothesis that serotonergic tryptamines may exert anticonvulsant and neuromodulatory properties in FXS yet highlight the necessity of dose-specific pharmacodynamic characterization.

4.3. Attention-Deficit/Hyperactivity Disorder

ADHD is a NDD characterized by persistent inattention, impulsivity, and hyperactivity, leading to significant functional impairment [119]. Diagnosis remains clinical and is based on observable behavioral symptoms, despite increasing insights into its genetic and neurobiological underpinnings. Studies indicate substantial heritability and involvement of genes regulating dopaminergic and noradrenergic modulation [120]. Neuroimaging approaches have revealed alterations in brain areas implicated in executive control, attention, and behavioral regulation [121–124].

Although some reports suggest potential benefits of psychedelics in ADHD, only one randomized controlled trial has been published to date [125] (Table 3). In this multicenter, double-blind, parallel-group, placebo-controlled study the effects of low-dose administration of LSD (27 patients) and placebo (26 patients) were compared over six weeks in adults aged 18–65 with moderate to severe ADHD. Both LSD and placebo groups exhibited overall symptom reduction, and low-dose LSD was not significantly different from placebo. LSD was physically and psychologically well tolerated in the controlled outpatient setting, with no serious adverse events or deaths, although minor adverse effects (headache, nausea, fatigue, insomnia, and visual disturbances) were more frequent in the LSD group than in the placebo group. Electrocardiogram parameters showed no differences between groups over time, and acute effects on blood pressure and heart rate were not significantly different. This study adopted a rather high microdose with the aim to increase the likelihood of detecting a positive response and efficacy. Nevertheless, being the only available double-blind study with LSD in ADHD, the authors do not feel like excluding that a lower dose or a different dosing interval could have yielded beneficial effects.

Other evidence comes from observational naturalistic prospective studies, based on following individuals who independently choose to self-administer psychedelic microdoses. In a prospective observational study involving 159 adults with severe ADHD, subjects engaged in microdosing (LSD or psilocybin) were compared with patients receiving standard pharmacotherapy (methylphenidate and amphetamines) [126]. The findings indicated that while both microdosing and conventional medication were equally effective in mitigating the primary symptoms of ADHD, the microdosing cohort reported a distinct advantage, showing marked improvements in emotional regulation relative to the standard pharmacotherapy group although without any improvement in empathy.

In a separate naturalistic prospective investigation, the same

Table 2
Clinical and preclinical evidence of the use of classic and non-classic psychedelics in FXS.

Clinical evidence

Drug	Subjects	Sex	Design	Administration	Clinical Assessment	Adverse events	Ref
Psilocybin	10 patients (18–50 yo) full *FMR1* mutation or other loss of function mutations; BMI > 18.3	M/F	Open label, single group interventional Phase 2 study	1.5 mg (o.s.) for 28 days	SUSPENDED-Indefinite hold due to protocol revisions relating to the exclusion criteria for concurrent medications		[115] X

Preclinical evidence

Drug	Animals	Sex	Model	Administration	Behavioral outcome	Molecular changes	Ref
Psilocybin	Sprague-Dawley rats (PND34–49)	M/F	*Fmr1*-Δexon 8	1 or 3 mg/kg (i.p.) 0.1 mg/kg (i.p) for 3 days 0.1 or 0.3 mg/kg (oral gavage) for 1 week	Improved discrimination index (NORT; 0.1 mg/kg i.p. and 0.1 or 0.3 mg/kg oral gavage)		[116] ✓
Psilocybin	Sprague-Dawley rats (PND34–44)	M	*Fmr1*-Δexon 8	0.1 mg/kg (oral gavage) for 2 weeks, every other day	At five days: improved discrimination index	↑ Bdnf, TrkB, pAkt (ser473) protein levels in the PFC	[117]
N,N-Dipropyltryptamine	Mice, juvenile (P23–25)	M/F	*Fmr1* KO	Single dose 3, 5.6, or 10 mg/kg (i.p.)	↓ audiogenic seizures Dose-dependent HTR		[118] ✓

Bdnf: brain-derived neurotrophic factor, BMI: Body Mass Index, F: females, FMR1: Fragile X Mental Retardation 1, HTR: head twitch response, KO: knock-out, i.p.: intraperitoneal, M: males, NORT: Novel object recognition test, pAkt: phosphorylated Akt, TrkB: tyrosine receptor kinase, yo: years old. Improvement in clinical outcomes and preclinical behavioral assessments is indicated with ✓; no improvement is indicated with X.

research group evaluated the self-initiated use of psychedelic microdosing among adults who reported having had experience with the following psychedelics: ayahuasca, DMT, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), LSD, novel lysergamides (e.g., 1P-LSD, ALD−52), psilocybin/psilocin (magic mushrooms, truffles), Salvia divinorum, ibogaine, or mescaline (e.g., san pedro, peyote), with ADHD for self-treatment purposes [127]. The study collected data at baseline, two and four weeks after, assessing the impact of microdosing on ADHD symptoms, overall well-being, and time perception. The results indicated significant subjective improvements in both ADHD symptomatology and well-being, while no changes were observed in time perception. Furthermore, the beneficial subjective effects on ADHD symptoms and well-being after four weeks of microdosing were found to be independent of conventional medication use or the presence of comorbidities [127]. Differently, self-medication with psychedelic microdosing in a group of adults diagnosed with ADHD was self-reported less effective than regular doses albeit still able to improve quality of life and reduce ADHD symptoms [128]. Although naturalistic studies offer insight into real-world consequences, they are markedly susceptible to placebo effects, expectancy biases, and selection bias.

Moreover, preliminary evidence includes an in-silico study exploring a ketamine–methylphenidate conjugate for the treatment of ADHD in comorbidity with major depressive disorder [129], though the authors highlight that preclinical and clinical validation is required. Unfortunately, to date no preclinical research with psychedelics has been reported.

We can also mention one historical and unique case from 1969 regarding the use of LSD in Tourette Syndrome [130], a chronic childhood-onset tic disorder persisting for at least one year and often associated with ADHD and obsessive-compulsive behavior features (Table 3). In the study, repeated LSD treatments in a 16-year-old adolescent appeared to improve the general state of the patient as well as the social impairment at 2-month follow-up, although prolonged hospitalization could also explain such changes [131].

Regarding preclinical evidence, no study investigating the therapeutic potential of classic and non-classic psychedelics in ADHD models is currently available in the literature.

4.4. *ADNP syndrome*

ADNP syndrome, also known as Helsmoortel-Van Der Aa syndrome, is a rare monogenic condition caused by mutations in the Activity-Dependent Neuroprotective Protein (ADNP) gene on chromosome 20q13.13. *ADNP* encodes for a crucial protein for brain function and neurodevelopment [132], modulating chromatin structure and gene transcription [133]. ADNP syndrome represents a leading cause of intellectual disability and developmental delay characterized by language and motor impairment (often with hypotonia and apraxia), hypotonia, congenital heart diseases, ASD features frequently combined with ADHD, hyperactivity, anxiety and sleep disturbances [134].

The potential therapeutic benefits of ketamine in ADNP syndrome were tested in an open-label study on ten children (6–12 years old) (Table 4) [135]. The authors reported good tolerability of a single subanesthetic ketamine infusion (0.5 mg/kg, 40 min), with transient and mild adverse events. Interestingly, one week after administration, caregiver- and clinician-rated behavioral measures converged in reporting consistent although heterogeneous improvements in social behavior, attention deficit and hyperactivity, restricted and repetitive behaviors [135]. The study also suggested the potential utility of electrophysiological measurement of auditory steady-state response and eye-tracking for clinical evaluation. In a subsequent complementary study, the same group investigated the longitudinal response to ketamine on the peripheral-blood transcriptome in the same cohort of patients, finding transient gene-expression responses enriched for immune/monocyte-related signatures immediately after ketamine infusion that returned towards baseline within days [136].

Table 3
Clinical and preclinical evidence of the use of classic and non-classic psychedelics in ADHD and Tourette syndrome.

Clinical evidence

Disorder	Drug	Subjects	Sex	Design	Administration	Clinical Assessment	Adverse events	Ref
ADHD	LSD	53 patients (18–65yo) Moderate-to-severe ADHD diagnosis (CGI-S and AISRS)	M/F	Double-blind, placebo-controlled, parallel-group phase 2 A randomized clinical trial	20 μg dissolved in 1 mL of alcohol solution, 20% (6 weeks/twice weekly)	Week 6 and Week 10 (follow-up): No significant improvement in ADHD symptoms	No serious adverse events (i.e. headache, nausea, fatigue, insomnia, visual alterations)	[125] X
ADHD	Psilocybin-containing mushrooms, novel lysergamides, LSD, ayahuasca	233 participants (≥ 18yo) CAARS-S:SV > 65	M/F	Online prospective naturalistic study	Self-initiated microdosing (722 mg psilocybin, 17.5 μg novel lysergamides, 12 μg LSD)	Week 4: Improved emotion regulation and partial improvement in cognitive and emotional empathy (vs. baseline) Week 2 and week 4: ↓ symptoms severity (CAARS:S-SV, IRI)		[126] ✓
ADHD	Psilocybin-containing mushrooms, novel lysergamides, LSD, ayahuasca	233 participants (≥ 18yo) CAARS-S:SV> 65	M/F	Online prospective naturalistic study	Self-initiated microdosing (722 mg psilocybin-containing mushrooms/truffles, 17.5 μg novel lysergamides, 12 μg LSD)	Week 2 and Week 4: ↓ symptoms severity (CAARS:S-SV) ↑ well-being (WHO−5) No changes in time perception (TRT) at 2 weeks and 4 weeks		[127] ✓
ADHD	Psychedelics	153 subjects (≥ 18yo) ADHD diagnosed by a physician	M/F	Online questionnaire for self-rated effectiveness of self-medication	Microdosing *vs.* regular doses	↑ quality of life Self-reported efficacy and symptoms disappearance (Retrospective study)		[128] ✓
Tourette Syndrome	LSD	1 patient (16yo)	M	Case Report	17 hallucinogenic administrations over 9 months	Week 8: Improvement in general state and social impairment		[129] ✓

Preclinical evidence

Disorder	Drug	Animals	Sex	Model	Administration	Behavioral outcome	Molecular changes	Ref
No data								

ADHD: Attention-deficit/hyperactivity disorder, AISRS: Adult ADHD Investigator Symptom Rating Scale, CAARS:S-SV: Conners Adult ADHD Rating Scales, CGI-S: Clinical Global Impression - Severity scale, F: females, IRI: Interpersonal reactivity index LSD: lysergic acid diethylamide, M: males, TRT: time reproduction task, yo: years old, WHO−5: World Health Organization-Five Well-Being Index, Ref: reference. Improvement in clinical outcomes and preclinical behavioral assessments is indicated with ✓; no improvement is indicated with X.

Table 4
Clinical and preclinical evidence of the use of classic and non-classic psychedelics in ADNP syndrome.

Clinical evidence

Drug	Subjects	Sex	Design	Administration	Clinical Assessment	Adverse events	Ref
Ketamine	10 patients (6–12 yo) Positive molecular genetic test; CGI-S $\geq$ 4; 4-weeks stable dose of medication	M/F	Open-label, single-dose	0.5 mg/kg (i.v.; 40 min single infusion)	Improvement in social (ABC, ADAMS), ADHD symptoms (ABC, ADAMS, Conners), restricted and repetitive behaviors (ADAMS, RBS-R) and sensory reactivity (SSP) at 1, 2, 4 weeks Improvement in Joint Attention Task Changes in gamma and beta neural oscillations in EEG	Well-tolerated; mild-to-moderate (elation/silliness, fatigue, aggression, anxiety)	[135] ✓
Ketamine	5–12 yo patients from [85]	M/F	Longitudinal biomarker study in trial participants	0.5 mg/kg (i.v.; 40 min single infusion)	Time-dependent transcriptomic changes in peripheral blood cells (RNA-seq)		[136]

Preclinical evidence

Drug	Animals	Sex	Model	Administration	Behavioral outcome	Molecular changes	Ref
No data.							

ABC: Activities-Specific Balance Confidence Scale, ADAMS: Anxiety, Depression and Mood Scale, ADHD: Attention-deficit/hyperactivity disorder, ADNP: Activity-Dependent Neuroprotective Protein, CGI-S: Clinical Global Impression - Severity scale, EEG: electroencephalogram, F: females, i.v.: intravenous, M: males, MBA: Motor Behavior Assessment, RBS-R: Repetitive Behavior Scale-Revised, SSP: Short sensory profile, yo: years old. Improvement in clinical outcomes and preclinical behavioral assessments is indicated with ✓; no improvement is indicated with X.

To date, to the best of our knowledge, no preclinical studies in ADNP models have tested the therapeutic potential of classic and non-classic psychedelics.

4.5. Rett syndrome

RTT is a rare, severe NDD that primarily affects girls with no effective therapies available. It typically manifests between 6 and 18 months of age with early neurological regression followed by loss of language and motor skills, cognitive deficit, increased susceptibility to seizures and stereotyped behaviors of the hands (e.g. wringing, clasping). The vast majority (>95%) of classic RTT cases are associated with mutations in the X-linked gene, encoding methyl-CpG-binding protein 2 (MECP2), a transcriptional protein that regulates gene expression and synaptic plasticity [137,138].

Evidence from post-mortem studies in RTT patients revealed an abnormal NMDA receptor expression and glutamatergic signaling in the frontal cortex, motivating research on NMDA receptor antagonists, including ketamine, as putative therapeutic drugs [139,140].

Only two clinical studies testing ketamine in small cohorts of RTT pediatric patients have been published to date, while most of the research has been limited to preclinical level (Table 5). In a randomized, placebo-controlled, cross-over trial, oral ketamine at low dosage (0.75–1.5 mg/kg) administered twice a day for 5 days in 6–12-year-old girls affected by RTT was safe and tolerable but with no difference in efficacy compared to placebo [141]. Another open-label phase 1 study conducted in a small group of three girls aged 5–10 years with RTT showed that a weekly intravenous dose of esketamine (0.25 mg/kg for 5 weeks) exerted variable improvements in mood and was well tolerated and considered safe [142]. These pilot studies suggest that efforts should be made to identify the appropriate dosage of esketamine based on pharmacokinetics parameters, to optimize the beneficial effects of esketamine without undesirable adverse effects.

Some preclinical studies have explored the effect of ketamine in *MeCP2*-KO mice, a validated RTT model that exhibits neurological features also observed in RTT patients.

In an early study, brain activity mapping revealed that acute treatment with a sub-anesthetic dose of ketamine fully rescued reduced forebrain c-Fos expression and behavioral dysfunctions in female *MeCP2* heterozygous mutant mice [143]. Accordingly, ketamine administered daily starting either early in development or at the onset of RTT phenotype in male *MeCP2*-KO mice was reported to improve motor performance and prolong lifespan without adverse side effects [144]. Ketamine also fully restored neuronal cortical connectivity, with the strongest evidence when treatment was started at the onset of symptoms. Interestingly, a single subanesthetic injection of ketamine rescued social deficits and reduced expression of synaptic molecules such as GluR1 and PSD95 in the dentate gyrus induced by hippocampal *MeCP2* knockdown in rats [145].

Finally, extracellular field recordings in hippocampal slices from wild-type and *Mecp2*-KO mice revealed that ketamine enhances the excitatory CA3-CA1 synaptic responses in a *MeCP2* independent manner, whereas leading to a reduction of the inhibitory transmission in both genotypes. Notably, the impaired neurotransmission in *MeCP2*-KO mice is restored by TrkB activation, underscoring a key role of BDNF-TrkB signaling in normalizing inhibitory balance in RTT [146].

5. Discussion and future perspectives

Classic and non-classic psychedelics are gaining renewed interest as potential treatments for various brain disorders, including not only MDD, PTSD, and substance use disorders, but also neurodegenerative, neurological, and neurodevelopmental conditions [66,147–150]. The enthusiasm about these molecules is justified by their potential of inducing rapid and long-lasting therapeutic actions, through mechanisms involving enhanced structural and functional neuroplasticity [56,57]. This appears particularly attractive from a therapeutic point of view because it gives the opportunity to correct neuropathological underpinnings in different neurological and psychiatric disorders. Although the main concern in the pharmacological use of psychedelics remains their abuse potential, they are generally well tolerated and clinical data demonstrates that classic and non-classic psychedelics cause only minor adverse physical effects when used as therapeutic drugs. Indeed, classic serotonergic psychedelics have low physiological toxicity and abuse potential and key aspects of setting, such as the safe environment and known medication origin and dose, are fundamentally controlled under clinical trial conditions, thus limiting the risk of bad trips [151,152]. Conversely, although non-classic psychedelics such as ketamine or MDMA are characterized by a high potential for toxicity, the low doses administered in therapy ensure a good safety profile and limit adverse effects and abuse risk [153,154].

To date, most of the literature aimed at exploring the therapeutic potential of classic and non-classic psychedelics in adult psychiatric illnesses [55], while the evidence regarding their potential interest in NDDs is still scarce. This is not surprising because NDDs carry a further challenge due to the early onset of the clinical condition and, while the

Table 5
Clinical and preclinical evidence of the use of classic and non-classic psychedelics in RTT syndrome.

Clinical evidence

Drug	Subjects	Sex	Design	Administration	Clinical Assessment	Adverse events	Ref
Ketamine	23 RTT patients 6–12 yo Confirmed pathogenic variant in *MECP2*	F	Double-blind, randomized, placebo-controlled, multi-center, sequential ascending dose cohort, cross-over study	0.75 or 1.5 mg/kg per dose (o.s.), twice daily/ 5 days + 5 days cross-over after 9 days wash-out	No clinical benefits in MBA, CGI-I, ClinDom, RSBQ, CSHQ, ParDom, RTT CIA at the end of each treatment (day 15 and 29), ParDom/CSHQ/RTT-CIA also mid-period on Day 8, 22, and 43. ↑ high frequency beta and gamma activity in the left frontal lobe (EEG) after the first dose of each treatment.	Mild-to-moderate (i.e. nausea); one grade III event (vomiting)	[141] ✓ X
Esketamine	3 patients (5–10 yo) Classic/typical RTT; No seizures for ≥ 8 weeks; positive medical evaluation	F	Single-arm, single-site, open-label, early phase 1 pilot study	0.25 mg/kg (i.v., 40-min infusion) for 5 weeks	Improvement in CGI-I, RSBQ, R-MBA by day 31 Improvement in posterior dominant rhythm (PDR) peak frequency during the 5 weeks of treatment. Improved moods, stereotypic hand behaviors, and hand functional use (medical observation) after each administration.	Mild transient (i.e. nausea)	[142] ✓

Preclinical evidence

Drug	Animals	Sex	Model	Administration	Behavioral outcome	Molecular changes	Ref
Ketamine	Mice	M/F	*Mecp2* KO (null); *Mecp2* Het	Single dose 8 mg/kg (i.p.)	Rescued prepulse inhibition of acoustic startle (*Mecp2* het)	↑ cFos in the prefrontal cortex (*Mecp2* null)	[143] ✓
Ketamine	Mice (P15 or P30)	M	*Mecp2* KO (null)	8 mg/kg (i.p) daily from P15–55 or 30–55	No changes in locomotor activity and prepulse inhibition response after a single administration. ↑ survival in both P15 and 30. ↑ motor performance (rotarod) evaluated at P45 (P15 treatment) and by P55 (P30 treatment). ↑ respiration (whole-body plethysmography) by P55 ↑ visual acuity at P45 and P55.	↓ PV immunofluorescence intensity ↑ neuronal activities and response reliability in visual cortex (in vivo extracellular recording)	[144] ✓ X
Ketamine	Sprague-Dawley rats (4 weeks)	M	VPA-injected; *Mecp2* KD (Dentate Gyrus)	Single dose 10 mg/kg (i.p.)	Rescued social deficit (three chamber test)	↑ PSD95, GluA1, Synapsin I mRNA (Dentate Gyrus)	[145] ✓
Ketamine	Mice (6–8 weeks)	M	*Mecp2* KO hippocampal slices	20 μM (bath perfusion) for 30 min		↑ acute and sustained potentiation of excitatory hippocampal signaling ↓ hippocampal fIPSP amplitude	[146]

ABC: Activities-Specific Balance Confidence Scale, ADAMS: Anxiety, Depression and Mood Scale, ADHD: Attention-deficit/hyperactivity disorder, ADNP: Activity-Dependent Neuroprotective Protein, CGI-I: Clinical Global Impression of Improvement, CIA: Rett syndrome Caregiver Burden Inventory Assessment, ClinDom: Clinician Domain Likert Scale, CSHQ: Child Sleep Health Questionnaire, EEG: electroencephalogram, F: females, fIPSP: field inhibitory postsynaptic potentials, Het: heterozygous, i.p.: intraperitoneal, i.v.: intravenous, KD: knock-down, KO: knock-out, M: males, MBA: Motor Behavior Assessment, o.s.: per os, ParDom: Parent Domain Likert Scale, PDR: posterior dominant rhythm, PSD95: post-synaptic density protein 95, PV: parvalbumin, R-MBA: Revised Motor Behavior Assessment RBS-R: Repetitive Behavior Scale-Revised, RTT: Rett syndrome, RTT CIA: Rett syndrome Caregiver Burden Inventory Assessment, RSBQ: Rett Syndrome Behavior Questionnaire, SSP: Short sensory profile, VPA: valproic acid, yo: years old. Improvement in clinical outcomes and preclinical behavioral assessments is indicated with ✓; no improvement is indicated with X.

dissociative properties and potential for abuse of these drugs raise significant ethical and regulatory challenges at any age, this concern is obviously more critical in pediatrics [155–157].

In the present narrative review, we presented available clinical and preclinical studies evaluating the therapeutic potential of classic and non-classic psychedelics in different NDDs and found that, despite some promising data, current evidence remains preliminary and inconsistent. Indeed, most of the findings come from case reports, studies on small patient populations, or even naturalistic studies, often without placebo control and with a single-dose design. The psychedelics used, the dose, and the treatment design are variable as well. Importantly, due to the lack of knowledge about the specific risks of psychedelics in pediatric populations, only a few clinical studies have been conducted in children, mainly involving microdosing, while hallucinogenic doses have been primarily investigated in young adults with NDDs. In this context, an important unresolved issue concerns the dosage thresholds for observable therapeutic effects without inducing any significant adverse effect, because the inconsistency of the results also derives from the variability of the treatment protocols, which use different psychedelics, dosages, and administration frequency. However, all the available literature converge on confirming the safety of classical and non-classical psychedelics in different NDDs, with no severe reactions and only minor and transient adverse effects. This is particularly relevant and highlighted also in randomized studies reporting no therapeutic effects of psychedelics [106,125,141]. Indeed, considering the pilot nature of most of the studies and the limits of the scales used for assessing behavioral improvements, the authors tend to give more value to safety assessment in their reports than to the evaluation of therapeutic benefits.

On the other hand, we found only a few preclinical studies in animal models of NDDs, which instead could be crucial to provide translational evidence and to clarify possible mechanisms of action of psychedelics. The use of translational animal models could indeed provide useful information, especially regarding dosage determination, treatment protocol, and long-term efficacy and safety.

Despite the limitations of the published literature, to summarize available data, we built Sankey diagrams combining the results of the studies reported in the tables (Fig. 1). We observed that clinical evidence is more abundant than preclinical evidence, with a total of 15 and 9 studies, respectively. Of note, 7 out of the 15 clinical studies involved 10 or less subjects and, among them, 4 studies are represented by case

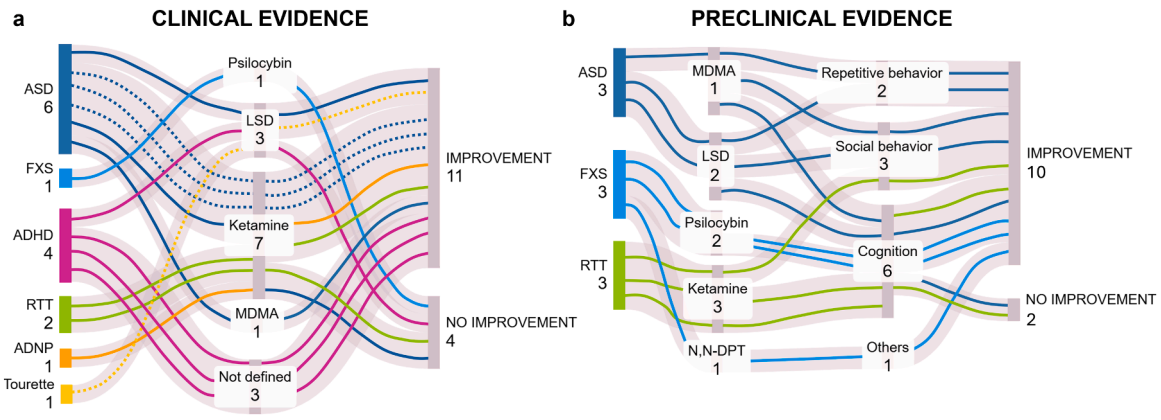


Fig. 1. Sankey diagram of the outcome of clinical and preclinical use of ketamine and classic psychedelics in NDDs. (**a**) The graph shows the overall outcome of the clinical use of ketamine and classic psychedelics in NDDs as reported in the available literature and revised in the main text. Nodes on the left represent the number of studies for each specific NDD in which psychedelics were tested. Nodes in the center represent which and how many times a psychedelic drug was used in the studies. The nodes on the right show the number of studies in which improvement or no improvement was observed at the clinical assessment. The width of the edges corresponds to the increase in number. Thinner edges were color-coded based on NDD and allow visualization of which drugs were used for a specific NDD and how many articles reported successful or unsuccessful effects of the use of psychedelics in NDDs; (**b**) The graph shows the overall outcome of the preclinical use of ketamine and classic psychedelics in translational models of NDDs. Nodes on the left represent the number of studies for each specific NDD in which psychedelics were tested. Nodes in the center represent which and how many times a psychedelic drug was used in the studies and the number of studies in which improvement or no improvement was observed in the specific behavioral domain tested in behavioral tests. The nodes on the right show the number of studies in which improvement or no improvement was observed at the behavioral assessment. The width of the edges corresponds to the increase in number. Thinner edges were color-coded based on NDD and allowed visualization of which drugs were used for a specific NDD and how many articles reported successful or unsuccessful effects of the use of psychedelics in NDDs. For clinical evidence, dashed lines were used to identify case reports based on one patient. The graph was created with SankeyMATIC.com. Methodological details are reported as Supplementary Material. ADHD: attention-deficit/hyperactivity disorder, ADNP: Activity-Dependent Neuroprotective Protein, ASD: autism spectrum disorder, FXS: fragile X syndrome, LSD: lysergic acid diethylamide, MDMA: 3,4-methylenedioxymethamphetamine, N,N-DPT: N,N-dipropyltryptamine, RTT: Rett syndrome.

reports based on one patient, thus limiting the strength of the reported clinical outcome. Moreover, clinical studies were mainly focused on ASD and ADHD and primarily tested low dose ketamine and LSD as therapeutic drugs (Fig. 1a), while preclinical studies are limited to models of ASD, RTT, and FXS, evaluating the effects of different psychedelics (Fig. 1b). This suggests that preclinical evaluations are sparser and more preliminary, while replication studies are largely missing. Conversely, the clinical approach, although heterogeneous from a methodological point of view, has focused more on specific conditions and therefore presents some preliminary confirmations. Overall, most of the clinical and preclinical data converge to support specific behavioral improvements, particularly in domains related to repetitive and social behaviors. This strongly supports the need for further studies to understand the therapeutic potential and safety of psychedelics in NDDs. Larger, sex-balanced and randomized controlled trials with standardized outcomes and robust safety monitoring are required. Importantly, the rapid advances of psychedelic research in psychiatric disorders could be of help in providing a standardization of the protocols and more evidence about safety and behavioral domains of efficacy.

6. Conclusions

NDDs are a heterogeneous group of disorders with broad defects in cognitive, motor, psychiatric and social domains. Psychedelics, due to their ability to promote brain plasticity in cortical regions, represent a fascinating therapeutic potential, possibly inducing rapid and long-lasting therapeutic effects. Although preliminary efforts provide promising indications, the available clinical research remains unfortunately in its early stages and lacks definitive efficacy or safety conclusions. We believe that further studies are needed, particularly at the preclinical level, to help identify critical mechanisms of action and safety concerns. This would be crucial for the translational prediction of advantages and disadvantages in the use of psychedelics in NDDs. A crucial point would be the identification of the threshold doses and protocol of administration (single vs repeated doses) required to induce a therapeutic outcome without the induction of significant adverse effects. We believe that translational animal models, and particularly the ones based on genetic variants associated with NDDs in patients, represent a valuable source for the experimental evaluation of the therapeutic potential of classic and non-classic psychedelics.

CRediT authorship contribution statement

Mattia Giovenzana: Writing – original draft. **Stefano Spinosa:** Writing – original draft. **Noemi Nicosia:** Writing – original draft. **Jessica Mingardi:** Writing – review & editing, Writing – original draft, Supervision. **Laura Musazzi:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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Supplementary Materials

Methods for the generation of Sankey diagrams.

Declaration of Competing Interest

The authors declare that the research was conducted without any commercial or financial relationship that could be construed as a potential conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2026.108366.

Data availability

No data was used for the research described in the article.

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