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The Ecstasy of Gold in Neurodiversity: Focus on the Use of Psychedelics in Autism Spectrum Disorder

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Abstract

Psychedelic drugs are serotonergic hallucinogens that can be divided into two types: naturally occurring (psilocybin, psilocin, and N,N-dimethyltryptamine) and synthetic (LSD, MDMA, 2,5-dimethoxy-4-iodoamphetamine, and ketamine). Psychedelics generally work on 5-hydroxytryptamine receptors and might be useful in cognitive enhancement, brain connectivity, neuroplasticity, and neuronal regeneration. These properties could be used in the pharmacological treatment of selected mental disorders. Autism spectrum disorders include a group of developmental disorders characterized by social communication issues, the presence of restricted interests as well as repetitive behaviors that impact the quality of life of patients and their caregivers. Currently, there are no authorized drugs for the treatment of the symptomatic features of ASD, but drugs are used for comorbid psychopathological aspects, but the efficacy and tolerability of such treatments are often questionable. Here, studies demonstrating the therapeutic utility of using psychedelic substances in autism are reported. These findings suggest a therapeutic potential of psychedelics for some aspects of symptoms associated with autism spectrum disorder.

Keywords: autism; autism spectrum disorder; psychedelics; psilocybin; MDMA; LSD; ketamine; esketamine

1. Introduction

The concept of intrinsic variation in neurocognitive functioning within human variability, described by the term neurodiversity, is gaining increasing social and clinical importance and relevance [1,2]. The concept of neurodiversity was initially coined in the 1990s within the autistic community [3], but the term appeared in print for the first time through the words of the journalist Harvey Blume: "Neurodiversity may be every bit as crucial for the human race as biodiversity is for life in general" [4]. The concept has subsequently expanded significantly to include numerous neurocognitive disorders such as attention deficit hyperactivity disorder (ADHD), dyslexia, learning disabilities (LD), and other neurodivergent conditions described as variations of the human brain rather than "illnesses" that need to be cured [5,6].

A common misconception about neurodiversity is equating it with disability. In literature, there are numerous definitions of disability, classified into several models, primarily medical, social, functional, and rights-based. The World Health Organization (WHO) defines disability within the International Classification of Functioning, Disability and Health (ICF) as: "an umbrella term for impairments, activity limitations, and participation restrictions, referring to the negative aspects of the interaction between an individual (with a health condition) and that individual's contextual factors (environmental and personal factors)" [7]. This definition reflects a biopsychosocial model, combining medical and social perspectives: disability is not just something "in the body", but emerges from how a health condition and the environment interact. On the other hand, neurodiversity is a concept that includes all neurological variations, both neurotypical and neurodivergent [8].

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About 15 to 20% of the global population is believed to have different types of neurodivergent conditions [9]. Although there are large variations between nations, the latest worldwide estimates of autism, ADHD, and dyslexia, respectively count 61.8 million people, over 84 million people, and about 700 million people globally [10–12].

Autism Spectrum Disorder (ASD) includes a group of developmental disabilities characterized by patterns of delay and deviance in the development of social, communicative, cognitive skills, and the presence of repetitive and stereotyped behaviours as well as restricted interests [12]. Core symptoms of ASD have varying effects on functioning in all spheres of life that persist even in adult life [13,14]. Indeed, 52% of kids with ASD reported communication challenges, 63% reporting social difficulties, and 85% having trouble in school [15]. In addition to core symptoms, people with ASD often have numerous medical and psychiatric comorbidities that worsen the quality of life of patients and their caregivers [16,17].

To date, the etiopathogenesis of autism has not been fully elucidated, but the scientific literature supports a multifactorial model that includes genetic, epigenetic, neurotransmitter, inflammatory, immunological, and environmental factors [18–23]. In recent years, the hypothesis of an altered modulation of excitatory and inhibitory systems in the etiopathogenesis of autism is gaining ground [24,25]. Particularly, the imbalance between glutamate and gamma-aminobutyric acid (GABA) is considered one of the primary neurobiological bases and neuropathophysiological mechanisms of ASD development [26]. Furthermore, the alteration of the serotonergic system seems to have a crucial role in the development of multiple forms of autism [27]. It is a critical neurotrophic factor during gestation, influencing neurogenesis, neuronal migration, and the maturation of synaptic connections [28]. Serotonergic-based treatments can improve functional abnormalities central to the clinical manifestations of autism [29].

Currently, there are no authorized drugs for the treatment of the core symptoms of ASD. On the other hand, in clinical practice, conventional psychotropic drugs are used for the management of psychopathological aspects or psychiatric comorbid conditions. Still, often there is poor efficacy and numerous side effects [30,31]. Only risperidone and aripiprazole are approved drugs for the treatment of irritability associated with ASD [32]. Polypharmacy is often used with the combinations of antipsychotics, antidepressants, anticonvulsants, stimulants, and adjunctive therapies, which increase the risk of pharmacokinetic interactions, adverse effects, and long-term metabolic burden [33,34]. For these reasons, the use of novel pharmacological treatments such as oxytocin, involved in social bonding and empathy, bumetanide, which modulates GABAergic inhibition, acetylcholinesterase inhibitors, and memantine could represent a viable alternative [35].

Additionally, there are numerous non-pharmacological treatments for clinical aspects associated with core symptoms of ASD, but they don't currently have enough data to be advised for widespread clinical usage, such as Deep Brain Stimulation, Microbiota-Transfer Therapy, food diets, anti-inflammatory treatments, and genetic therapies (for monogenic causes of ASD) [36–41].

Psychedelic drugs are a group of compounds that can produce profound changes in perception, cognition, and emotion. Classical psychedelics can be categorized into three primary classes based on their chemical structure: tryptamines, ergolines, and phenethylamines [42,43]. Tryptamines include compounds like psilocybin and N,N- dimethyltryptamine (DMT), phenethylamines include substances such as mescaline, and ergolines include lysergic acid diethylamide (LSD). In addition to classical psychedelics, there are other compounds considered psychedelics under a broader definition, such as 3,4-Methylenedioxymethamphetamine (MDMA), muscimol, scopolamine, ibogaine, phencyclidine, and ketamine. These compounds produce similar psychological effects of classical psychedelics, but with different mechanisms of action [44].

In the last few years, after about forty years of suspension of research due to illicit use and political pressure, the therapeutic use of psychedelic substances is finding a new interest in medicine, especially in psychiatry [45–49]. A recent meta-analysis showed that psilocybin, MDMA, LSD, and ayahuasca represent the psychedelics most studied in randomized controlled trials for psychiatric disorders [50]. Particularly, the strongest evidence was reported for the use, respectively, of

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psilocybin in the treatment of depression and MDMA for Post-Traumatic Stress Disorder (PTSD). On the other hand, LSD and ayahuasca showed little evidence for the treatment of alcohol use disorder and depression. Emerging evidence indicated promising anti-addictive effects of psilocybin, LSD, ayahuasca, and ibogaine for the treatment of Substance Use Disorders (SUDs) [51,52]. Moreover, in 2019, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved esketamine (the enantiomer of ketamine) for the treatment of patients with Treatment-Resistant Depression (TRD) [53].

Psilocybin, the prodrug of psilocin that represents the active metabolite, is a non-selective serotonin agonist with affinity at 5-HT2A, 5-HT2C, and 5-HT1A receptors, and represents the main psychoactive component of so-called 'magic mushrooms' [54]. The activation of cortical 5-HT2A receptors modulates the glutamatergic transmission and disinhibits pyramidal neurons, via GABAergic interneurons [55]. Psilocybin works by desynchronizing brain networks, reducing within-network connectivity, especially in the default mode network (DMN), with the strongest effects in DMN–hippocampus circuits, and increasing network connectivity and global integration [56,57]. The desynchronization of the DMN is especially important because of the increased activity and changed connectivity patterns in autistic individuals, linked to repetitive behaviors and difficulties with social communication. [58,59]. In rodents, psilocybin increases synaptic strength and neuroplasticity in the prefrontal cortex and hippocampus [60].

DMT, a 5-HT2A agonist, is the active component of ayahuasca, a hallucinogenic beverage with a historical role in spiritual practices [61]. This compound influences both ionotropic and metabotropic glutamate receptors, encompassing N-methyl-D-aspartate (NMDA) receptors, which in turn affects glutamate-mediated postsynaptic excitation [62]. Consequently, this postsynaptic excitation leads to an augmentation of global brain connectivity, especially within the functional connectivity of the DMN, frontoparietal control network, and salience network [63].

LSD acts as a potent agonist at 5-HT2A and 5-HT1A receptors, with additional partial activity at dopaminergic and adrenergic receptors, which is thought to contribute to broad alterations in sensory, cognitive, and affective processing [55]. LSD elevates glutamate and Brain-Derived Neurotrophic Factor (BDNF) levels and enhances NMDA mediated transmission [64,65], resulting in increased brain connectivity in subcortical regions such as the basal ganglia and thalamus and in cognitive regions involved in higher-order cognitive processes [66].

MDMA (also known as Ecstasy, Molly, Adam, Clarity, Lover's Speed, Peace) can produce acute psychological effects similar to those of classic hallucinogens (LSD), such as enhanced mood, increased intensity of emotions, increased sensory awareness and arousal, and derealization [67]. MDMA functions primarily as a monoamine-releasing agent, leading to increases in serotonin, norepinephrine, and dopamine [68]. Recently, Zimmermann et al. found that chronic MDMA enhanced excitatory activity in the striatum through an increase in glutamate and glutamine concentrations [69]. The substantial reduction in PTSD symptoms in patients treated with MDMA has led the FDA to call it a "breakthrough therapy" [70].

Ketamine is a racemic mixture derived from phencyclidine, composed of two enantiomers: R-ketamine and S-ketamine (also known as esketamine). Both compounds share the same mechanism of action, but esketamine exhibits approximately three- to fourfold higher affinity for NMDA receptors compared to its R-enantiomer [71]. Blockade of NMDA receptors leads to increased glutamate release, influenced by alfa-amino-3-idrossi-5-metil-4-isoxazolpropionato (AMPA) receptor antagonists or mGluR2 and mGluR3 agonists [72,73]. In the scientific literature, there are numerous studies on the efficacy of the application of ketamine beyond anesthesia, such as for the treatment of suicidal ideation, treatment-resistant depression, and alcohol use disorder [74–77].

As described above, the common mechanisms of action of the psychedelics are determined, through different neurobiological pathways, to increase serotonin and glutamate concentrations. Given the pathogenetic mechanism of altered excitatory/inhibitory balance in autism and the serotonergic hypothesis, psychedelics may be useful in treating the core symptoms of autism itself.

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2. Materials and Methods

A thorough literature search was carried out on major databases to find relevant studies for this paper. During the research phase, targeted queries focused on psychedelic drugs for autism spectrum disorders. The search used terms such as "psychedelic drugs," "psychedelics," "psilocybin," "MDMA," "LSD," "ketamine," "esketamine," and "autism," "autism spectrum disorder," "autistic."

Studies were included in the present paper if they reported on human clinical trials, observational studies, or case reports investigating the effects of the specified psychedelic substances on core symptoms or related behaviours in autism spectrum disorder.

3. Results

The literature search revealed that the psychedelic substances used for the possible treatment of core symptoms of autism are represented by LSD, psilocybin, MDMA, ketamine, and esketamine. No results were found for DMT, nor for clinical studies or animal models of ASD.

4. Discussion

Before the 1960s, children with autism (then diagnosed with juvenile schizophrenia) were considered incapable of acquiring new skills, a view later refuted by early rehabilitation interventions that used an operant discrimination paradigm [78–80]. Moreover, evidence-based treatments didn't exist, and neither biologic nor psychoanalytic treatments had yielded results. In the absence of therapeutic pathways, psychedelics were considered a novel and promising treatment.

4.1. LSD

LSD, UML (a methylated derivative of LSD), and psilocybin were the first psychedelic substances to be tested in children with infantile autism or schizophrenia, psychosis or emotional disorders in the United States, Europe, and Argentina [81–91] (see Table A1).

There were numerous positive aspects induced by psychedelic substances such as enhanced mood, sociability, and affectionate behaviour; increased emotional closeness, relatedness, and responsiveness to others, increased desire to communicate and interest in the surrounding environment, relief of perceptual hypersensitivity, improved speech and vocabulary, increased playfulness, smiling, and laughing; increased eye and face-gazing behaviour, decreased repetitive behaviours, and improved sleep patterns. On the other hand, some adverse effects were reported, such as rapid mood swings, ataxia, anxiety, "panic-like state", two episodes of seizures during, increased biting and pinching behaviour, aggressive behaviour, difficulty sleeping, and in one case, self-harming behaviour [92,93].

The article by Rolo et al. is the only one to report poor efficacy of LSD use in a 12-year-old schizophrenic child. Behavioural side effects such as catatonic states (bizarre postures, waxy flexibility of the arms) and loss of appetite until the drug wore off were also reported [87].

As stated by Sigafoos et al., " the initial era of LSD experimentation ended where it had begun, with pessimism for the drug's potential in the treatment of autism" [94]. Since 1974, no additional studies on LSD for autism have been published. The clinical relevance of these studies seems mostly historical. This is mainly due to serious flaws in their methods, such as small sample sizes, lack of control groups, inconsistent dosing, and subjective outcome measures. It is unlikely that LSD-related substances will be used for therapeutic purposes for children with ASD in the future due to ethical concerns and the risk of adverse events. Indeed, it should not be underestimated that the risk of psychedelic-induced psychosis, especially in people with ASD, in whom the prevalence of schizophrenia is significantly higher than in neurotypical individuals [95,96]. Moreover, today, there is a growing body of evidence of the effectiveness of various rehabilitative interventions addressing core features of ASD and fundamental in managing behavioural aspects and teaching new skills to children with ASD [97–100].

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Recently, Aaron Paul Orsini published a book entitled "Autism on Acid" become a cornerstone of the "Autistic Psychedelic Community" [101]. In his book, Orsini described how LSD and later psilocybin helped him connect his inner world with the social world around him. He referred to the experience as a "new way of seeing," which enabled him to notice social cues and emotional details he had previously missed or found overwhelming. Orsini's self-experimentation led to the idea of "LSD-Assisted Immersion Therapy." In this approach, low to moderate doses (20-50 micrograms) were used not for a full trip, but to promote social learning and break rigid behaviour patterns in real-time. While these accounts are anecdotal, they have provided a basis for researchers to explore how psychedelics might aid in social reward learning and reopen critical periods for social adaptation [102].

4.2. Psilocybin

The positive outcomes observed in various neuropsychiatric disorders with psilocybin use, such as increased cognitive and emotional flexibility, behavioural regulation, and prosocial attitudes, have led to speculation about its possible use in ASD [103,104]. Moreover, in a rat model of ASD and Fragile X syndrome (a monogenic cause of ASD), the administration of psilocybin normalized the aberrant cognitive performance [105], improved novel object recognition memory [106], and rescued the social behavioural abnormalities [107].

In the literature, two papers of interest for the present study are present. The studies reported the use of psilocybin in people with ASD and comorbid conditions, such as depression, and aphantasia [108,109].

Psilocybin was used to treat psychological problems like cognitive inflexibility, heightened fear, or disruptive behaviors, and to provide support for social difficulties and the inability to create mental images (aphantasia). Using psilocybin led to increased empathy and emotional expression, as well as a reduction in symptoms associated with their condition or comorbidities [108,109]. For the first time, the girl with aphantasia experienced vivid mental imagery and the ability to manipulate images in her mind [109]. These effects persisted long after the acute drug effects had subsided, showing continued increases in mental imagery vividness scores, aligning with research on psilocybin's effects on brain connectivity and neuroplasticity [110].

A narrative literature review published in 2021 explored the therapeutic potential of psilocybin for the treatment of treatment-resistant anorexia nervosa [111]. Considering the common symptomatic characteristics between anorexia nervosa and autism, the authors propose a possible use of psilocybin in the treatment of the core symptoms of autism.

The recent Psilocybin in Adults with and without ASD (PSILAUT) study used psilocybin as a tool to investigate whether brain systems are differently regulated by serotonin in autistic individuals compared to controls [112]. Through the use of multimodal techniques to detect changes in brain function (functional magnetic resonance imaging, electroencephalography, magnetic resonance spectroscopy), the study has demonstrated for the first time the peculiar neurobiological functioning of the autistic mind.

Psilocybin is also gaining recognition for its ability to create long-lasting structural and functional changes in the brain. This includes the growth of new dendritic spines and the strengthening of synaptic connections, a process known as psychoplastogenesis [113,114]. In autism, where synaptic pruning and connectivity may not follow typical patterns, promoting plasticity offers a significant therapeutic opportunity.

Researchers are now concentrating on how psilocybin can ease the psychological rigidity and ongoing distress that come from navigating a world designed for neurotypical minds. Discovering that psychological flexibility plays a key role in therapeutic success suggests that psilocybin could help foster a more adaptive and resilient self-concept in autistic individuals [115].

4.3. MDMA

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An early proponent of the potential use of MDMA as a supplementary treatment for autism was Riedlinger (1985), but restrictions on MDMA at that time greatly limited research [116].

In 2013, Danforth published a dissertation reporting the subjective experiences of autistic adults with MDMA/Ecstasy, summarized in a paper published in 2019 [117,118]. The study used an online survey to collect data from 100 participants across 13 countries, followed by qualitative interviews with 24 of those participants. While this approach provided valuable insights, it introduced selection bias and potential inaccuracies due to self-reporting, limiting how widely the findings can be applied. Participants reported significant reductions in social anxiety and increased feelings of social connectedness. Particularly, 86% of respondents claimed, "Ease of Communication", 91% reported "Increased Feelings of Empathy/Connectedness" as a result of using MDMA or ecstasy. In the MDA/ecstasy experience group, 72% of people reported "more comfort in social settings", 78% "feeling at ease in my own body", and 77% "easier than usual to talk to others".

In 2018, following the publication in 2016 of a study protocol, Danforth et al. published a randomized, double-blind, placebo-controlled pilot study on MDMA-assisted psychotherapy with autistic adults [119,120]. The findings showed potential therapeutic benefits, including stronger social connections, feelings of love and companionship, heightened confidence in school, work, friendships, and romantic relationships, increased comfort with eye contact, a better ability to express emotions verbally, and improved social functioning [119,120]. Improvements in social anxiety, assessed with the Leibowitz Social Anxiety Scale (LSAS), were significantly greater in the MDMA group [120].

Given the increased risk of developing social anxiety in people with ASD, the above findings appear to be of considerable interest [121,122].

Confirming the positive effects of MDMA on anxiety symptoms, a recent pilot study showed promising results of using MDMA assisted therapy in the management of social anxiety in non-autistic individuals [123].

A central pillar of the research into MDMA for autism is the drug's capacity to induce the release of oxytocin [124]. Oxytocin plays a vital role in social bonding, trust, and recognizing positive social signals, which are often impaired in ASD due to lower oxytocin levels or signalling deficits [125]. Functional MRI studies show that MDMA reduces activity in the amygdala in response to threatening faces while boosting activity in the ventromedial prefrontal cortex [126,127]. Lowering subjective fear and sensitivity to social rejection would help autistic individuals stay emotionally engaged during social interactions, which could reduce the avoidance behaviours that characterize social anxiety disorder.

Furthermore, MDMA use resulted in greater improvements than methamphetamine in affective touch and visual attention to emotionally expressive faces [128]. Given that people with autistic traits find emotional contact less pleasurable than healthy controls [129,130], MDMA could be used in the future to improve this aspect.

Overall, current evidence indicates that MDMA-assisted therapy may reduce social anxiety in a small group of autistic adults, likely improving social interaction and boosting sociability. However, there isn't enough high-quality clinical evidence to claim that it consistently improves overall social interactions across ASD populations.

When considering the use of psychedelics in therapy, various treatment settings must be explored. A "neurodiversity-affirming" approach to psychedelic therapy acknowledges that the "set and setting" should be tailored to meet the sensory and communication needs of autistic individuals [131,132]. This includes: a) preventing sensory overload by using weighted blankets, adjustable lighting, and high-quality noise-cancelling headphones, b) providing communication support by recognizing that participants may become non-verbal during peak effects and ensuring that therapists are trained in alternative communication methods, and c) offering specialized integration to help participants understand their experiences in a way that honours their unique neurology rather than trying to fit their insights into a neurotypical framework.

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Additionally, it is crucial to ethically involve the autistic community in designing these trials. This helps avoid pathologizing autistic traits and ensures that the research benefits the individuals involved [133,134].

4.4. Ketamine and Esketamine

Interest in ketamine and esketamine use for the treatment of core symptoms of autism comes from their effects on NMDA glutamate receptors and neuroplasticity. Several ASD models showed NMDA receptor dysfunction; both excessive and reduced NMDA activity can produce autistic-like behaviours, and correcting this can normalize social and repetitive behaviours [135,136]. Ketamine is thought to help reset and tune the altered NMDA receptor functions. By silencing hyperactive neurons and activating quiet ones, ketamine may reorganize functional networks into a more homeostatic state [137]. In a maternal separation model, ketamine improved sociability indices and reduced repetitive marble-burying while normalizing NMDA-pathway gene expression [138].

About ketamine and esketamine use in people with ASD, a total of six studies eligible for this review have been found during the search phase [139–144]. A further study was also found of the use of ketamine in children with Activity-dependent neuroprotective protein (ADNP) syndrome, a condition with clinical features very similar to ASD [145].

The placebo-controlled, randomized, pilot study by Wink et al. [139] showed that ketamine was relatively well tolerated with only mild adverse effects and was safe to use in adolescents and young adults. On the other hand, no statistically significant improvements were reported after ketamine treatment for Clinical Global Inventory—Severity (CGI-S), Aberrant Behaviour Checklist (ABC), Social Responsiveness Scale (SRS), and Anxiety Depression and Mood Scale (ADAMS) scores [139].

Case reports utilized ketamine and esketamine in the treatment of comorbid conditions in autistic people: major depressive disorder, treatment-resistant depression, anorexia nervosa, and obsessive-compulsive disorder. All studies reported improvements in clinical conditions [139–144]. Particularly, for the core aspects of autism, improved autism related symptoms, increased social cognition, and an easier ability to socialize with others. On the other hand, while the effect on core social cognition was described as mild, the impact on their quality of life and depressive symptoms was profound. It should be emphasized that, although ketamine does not alter the primary neuroanatomy of autism, it significantly reduces the symptom burden that often isolates autistic individuals from society.

The use of ketamine in the treatment of ADNP syndrome was associated with notable improvement in a variety of domains such as social behaviour, attention deficit and hyperactivity, restricted and repetitive behaviours, and sensory sensitivities [145].

A recent review of the scientific literature has proposed a possible neurobiological connection between autism, suicide, and psychedelics and their potential therapeutic applications in autism and youth suicide. In fact, in the United Kingdom, statistics report that autistic adults have a risk of having suicidal ideations approximately 10 times higher than the general population [146]. Furthermore, the risk of suicide is particularly high in autistic individuals without intellectual disability and in the presence of comorbidities such as depression, ADHD, schizophrenia, or bipolar disorder [147,148].

In 2016, Kastner et al. published a case report about core symptoms improvement in an adolescent with severe autism, bipolar disorder, and obsessive-compulsive disorder who underwent anaesthesia with propofol and ketamine for dental surgery. Immediately upon recovery, the parents report that their child began speaking in full sentences and making eye contact. This behaviour lasted for approximately 36 hours and quickly waned [149].

Finally, in paediatric emergency settings, intranasal ketamine is increasingly preferred to midazolam for children with ASD. Indeed, unlike midazolam, which can cause paradoxical reactions such as hyperactivity and agitation in children with developmental delay, ketamine preserves airway reflexes and provides reliable anxiolysis and analgesia [150].

The studies considered suggest that ketamine can acutely improve autism related behaviours, but this remains experimental, with unknown long-term safety and efficacy. The evidence is very

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limited and, at present, ketamine should only be considered within carefully monitored research trials, not as routine treatment for autism.

4.5. Summary

While clinical research is still developing, surveys of the autistic community offer insights into how common and impactful psychedelic use is. A survey of 233 autistic individuals showed a significant decrease in psychological distress [151]. Among those who reported mental health benefits, the most frequently mentioned issues were anxiety disorders (76.9%), mood disorders (56.5%), and PTSD (40.1%). However, participants also faced challenges. About 43.4% said the experience was moderately psychologically challenging, and 19.3% found it highly challenging.

Another extensive online survey of 261 autistic adults provided a detailed look at the real-world use of these substances [152]. The survey revealed that 69.7% of respondents had used psychedelics, with psilocybin mushrooms being the most common choice. Most experiences took place at home (63.9%) or in nature (33.3%), and 91% rated their experience as moderately or highly meaningful. The participants generally viewed psychedelics positively, with 77.8% expressing a willingness to try them in a clinical setting. Crucially, the survey found that highly meaningful experiences and higher doses were correlated with longer-lasting mental health improvements. On the other hand, approximately 20% of participants reported undesirable effects, highlighting that psilocybin is not a universal solution and requires careful patient screening [152].

The studies considered in this paper examine the historical, present, and likely future frontiers of using psychedelics in the treatment of core symptoms of autism. Considering the psychoplastogenic capabilities of the substances taken into consideration, some studies are of notable clinical relevance but burdened by important limitations. In fact, most of them are case reports, a few are randomized controlled trials, and the overall sample size is still too small to draw clear conclusions. Longitudinal studies are needed to test the real efficacy even in the long term and to monitor any adverse events in autistic people already at risk of comorbid psychopathological and medical conditions.

There can be numerous side effects resulting from the use of psychedelic substances, even when used for therapeutic purposes [153]. Few studies reported adverse effects, and in any case, they were mild. Generally, psychedelics were well-tolerated. Psychedelic-related adverse events in autistic people are often similar to those seen in neurotypical populations, such as anxiety or confusion. Still, scientific literature suggests that they may interact specifically with autism traits, leading to different or more intense experiences, including “bad trips” (intense fear, anxiety, and paranoia, potentially leading to lasting psychological distress), increases in aggressive behaviours, and dissociative and psychotic states [154]. Furthermore, for individuals with a history of seizures or severe cardiovascular issues, the physical strain of a psychedelic experience poses additional risks [153].

In the end, a significant research perspective is the development of non-hallucinogenic psychedelic analogs, often called psychoplastogens, which promote neuroplasticity and therapeutic benefits without inducing characteristic subjective hallucinatory effects [155,156]. These compounds could represent a new and interesting, hopefully viable, therapeutic frontier for autism spectrum disorders.

5. Conclusions

Current research does not support psychedelics as an established or routine treatment for autism. There is interesting early evidence and a solid theoretical basis, but human data in autistic individuals are limited, of low quality, and carry significant risks. The safety profiles of these substances differ. MDMA shows promise for social anxiety in controlled settings, while ketamine’s use in ASD requires more investigation into its specific risks and benefits beyond its effects on depression. Use should be limited to carefully designed clinical trials.

Currently, standard behavioural and pharmacological approaches remain the evidence-based options. Future research should prioritize identifying specific psychedelic molecules, such as MDMA

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for social communication challenges, psilocybin for cognitive rigidity or ketamine for autism related behaviours, that show the most promise for particular ASD phenotypes. New frontiers are represented by psychoplastogenic compounds. Furthermore, rigorous ethical frameworks are crucial for any studies involving pediatric populations, given the unique vulnerabilities and developmental considerations.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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Abbreviations

The following abbreviations are used in this manuscript:

ASD	Autism Spectrum Disorder
ADHD	Attention Deficit Hyperactivity Disorder
LD	Learning Disability
WHO	World Health Organization
ICF	International Classification of Functioning
GABA	Gamma-aminobutyric acid
LSD	Lysergic acid diethylamide
UML	Methylated derivative of LSD
MDMA	3,4-Methylenedioxymethamphetamine
DMT	N,N- dimethyltryptamine
SUDs	Substance Use Disorders
PTSD	Post Traumatic Stress Disorder
TRD	Treatment-Resistant Depression
EMA	European Medicines Agency
FDA	Food and Drug Administration
DMN	Default Mode Network
NMDA	N-methyl-D-aspartate
AMPA	Alfa-amino-3-idrossi-5-metil-4-isoxazolpropionato
BDNF	Brain-Derived Neurotrophic Factor
ADNP	Activity-dependent neuroprotective protein
LSAS	Leibowitz Social Anxiety Scale
CGI-S	Clinical Global Inventory—Severity
ABC	Aberrant Behaviour Checklist
SRS	Social Responsiveness Scale
ADAMS	Anxiety Depression and Mood Scale

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