Ethical challenges in the therapeutic application of classical psychedelics for pediatric health conditions: A comprehensive review

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Abstract

Classical psychedelics encompass psilocybin, lysergic acid diethylamide (LSD), N, N-dimethyltryptamine (DMT), and mescaline and are psychoactive substances that primarily function as agonists at the serotonin 5-hydroxytryptamine receptors (5-HT). In the immediate term, they modify perception, cognition, emotional state, social processing, and introspection, leading to a subjective mystical encounter. They also yield enduring effects by mediating neural plasticity. A renaissance in the potential benefits of using psychedelics, especially for psychiatric disorders, has led to clinical trials with adults. When considering a possible equivalent application of classical psychedelics for pediatric conditions, autonomy, beneficence, non-maleficence, and justice have to be contemplated, following the framework of Beauchamp and Childress. The purpose of this study was to provide a comprehensive review of the use of classical psychedelics, hence providing a balanced evaluation of the ethical considerations surrounding the administration of psychedelic compounds to pediatric populations. We summarized evidence indicating that classical psychedelics have shown efficacy in treating various disorders in adults, with ongoing research exploring their potential for additional conditions. While this suggests they could offer benefits for children, the current research remains preliminary, with uncertain outcomes and significant limitations. These factors highlight the ethical and practical challenges of applying such treatments to children, a particularly vulnerable population.

Keywords: classical psychedelics, psychedelic therapy, clinical research, adolescents, bioethics

Desafios éticos na aplicação terapêutica de psicodélicos clássicos em condições de saúde pediátricas: Uma revisão abrangente

Resumo

Os psicodélicos clássicos incluem psilocibina, dietilamida do ácido lisérgico (LSD), N, N-dimetiltriptamina (DMT) e mescalina, sendo substâncias psicoativas que atuam principalmente como agonistas dos receptores serotoninérgicos de 5-hidroxitriptamina (5-HT). No curto prazo, modificam a percepção, a cognição, o estado emocional, o processamento social e a introspecção, levando a uma experiência mística subjetiva. Também produzem efeitos duradouros ao mediar a plasticidade neural. O ressurgimento do interesse nos potenciais benefícios terapêuticos dos psicodélicos, sobretudo para transtornos psiquiátricos, levou à realização de ensaios clínicos em adultos. Ao considerar uma possível aplicação equivalente de psicodélicos clássicos para condições pediátricas, devem ser ponderados os princípios de autonomia, beneficência, não maleficência e justiça, conforme o enquadramento de Beauchamp e Childress. O objetivo deste estudo foi oferecer uma revisão abrangente sobre o uso de psicodélicos clássicos, fornecendo uma avaliação equilibrada das considerações éticas que envolvem a administração desses compostos a populações pediátricas. Resumimos evidências indicando que os psicodélicos clássicos demonstraram eficácia no tratamento de diversos transtornos em adultos, havendo pesquisas em andamento que exploram seu potencial para outras condições. Embora isso sugira que possam

oferecer benefícios para crianças, a pesquisa atual permanece preliminar, com desfechos incertos e limitações significativas. Esses fatores ressaltam os desafios éticos e práticos de aplicar tais tratamentos a crianças, uma população particularmente vulnerável.

Palavras-chave: psicodélicos clássicos, terapia psicodélica, pesquisa clínica, adolescentes, bioética

1. Introduction

Classical psychedelics are psychoactive substances known for their ability to evoke mental phenomena that resemble certain psychological or psychiatric states. Early interest in these drugs stemmed from their potential to mimic experiences observed in individuals with schizophrenia and other psychiatric disorders (Nichols; Walter, 2021). However, in the United States, the classification of classical psychedelics as Schedule I substances under the Controlled Substances Act of 1970 severely restricted further research into their effects and applications (Kenny et al., 2025).

In recent years, however, certain countries have taken significant steps toward the regulated medical use of psychedelic substances. For example, Australia became the first country to authorize the prescription of psilocybin and MDMA by authorized psychiatrists for treatment-resistant depression and post-traumatic stress disorder (PTSD), respectively, starting in July 2023 (Administration (TGA), 2023). In Canada, psilocybin-assisted therapy can be accessed through the Special Access Program, particularly for patients with end-of-life anxiety or treatment-resistant depression(Richard et al., 2025). In the United States, although psychedelics remain federally prohibited, states like Oregon and Colorado have passed legislation decriminalizing psilocybin and have initiated regulated therapeutic programs (*Oregon Health Authority : Oregon Psilocybin Services - 2023 Rulemaking : Prevention and Wellness : State of Oregon*, n.d.). Additionally, numerous countries, including the United Kingdom, Switzerland, and the Netherlands, are actively supporting or conducting psychedelic-assisted therapy trials under clinical settings (Mackey et al., 2022; Reiff et al., 2020).

A recent survey of registered clinical studies revealed that over 200 psychedelic-related trials are currently listed in ClinicalTrials.gov, indicating a substantial and growing global research effort into the therapeutic applications of these substances (*ClinicalTrials.Gov*, n.d.). In what has been termed a "psychedelic renaissance," major academic centers such as Johns Hopkins University and Imperial College London have spearheaded clinical research on the therapeutic potential of psychedelics, contributing to a shift in public and regulatory perception (Carhart-Harris; Goodwin, 2017; Griffiths et al., 2016).

Over the past two decades, the global prevalence of mental health disorders has risen significantly, yet many existing treatments fail to achieve satisfactory outcomes (Byock, 2018). While the therapeutic use of classical psychedelics in adult populations is gaining increasing scientific legitimacy—supported by a growing number of clinical trials and meta-analyses (Byock, 2018; Reiff et al., 2020)—this enthusiasm has not yet extended to pediatric populations, where research remains sparse and ethically complex (Sigafoos et al., 2007). As Edelsohn and Sisti (Edelsohn; Sisti, 2023) emphasize, children represent a neurologically and morally distinct population, requiring special consideration when evaluating the risks and benefits of psychedelic interventions. Children, however, are recognized as a particularly vulnerable population. According to the International Guidelines for Health-Related Research Involving Humans, any pediatric research interventions or procedures must minimize risks and ensure that potential benefits outweigh them (Council for International Organizations of Medical Sciences (CIOMS), 2016; Taplin et al., 2022).

This research focus is particularly timely given the rising prevalence of mental health disorders among children and adolescents globally. According to the World Health Organization, an estimated 10–20% of children and adolescents worldwide experience mental health conditions, yet many of them remain undiagnosed or inadequately treated (*Mental Health of Adolescents*, n.d.). We proceed from a precautionary stance, recognizing that vulnerable populations require elevated thresholds of evidence before the introduction of experimental pharmacotherapies. This study provides a comprehensive review of the use of classical psychedelics, hence providing a balanced evaluation of the ethical considerations surrounding the administration of psychedelic compounds to pediatric populations.

2. Mechanisms, Effects, and Ethical Dimensions of Classical Psychedelics

2.1 Pharmacological mechanisms of classical psychedelics

"Classic psychedelics" or "serotonergic classic hallucinogens" originate from a common pharmacophore composed of an aromatic unit separated from a basic amine by a linker containing two carbon atoms (Kwan et al., 2022). Psychedelics are classified into three categories: tryptamines, ergolines, and phenethylamines (Kelmendi et al., 2022). The tryptamine class most notably includes psilocybin, which can be extracted from over one hundred species of mushrooms and primarily from the genus Psilocybe, and DMT, which occurs from *Psychotria viridis* and can be found within the ayahuasca aqueous concoction (Brito-da-Costa et al., 2020; Geiger et al., 2018). Ergolines noticeably encompass LSD, a semi-synthetic compound obtained from lysergic acid found in natural sources (Marta et al., 2019). Phenethylamines comprise mescaline, a natural substance derived from the Cactaceae plant family (Vamvakopoulou et al., 2023).

Classic psychedelics are defined by their mutual ability to function as agonists at the serotonin 5-HT receptors, particularly at the 5-HT2A receptors (Calvey; Howells, 2018). Furthermore, specific psychedelics have been identified to act upon dopaminergic receptors, adrenergic receptors, Trace Amine-Associated Receptors (TAARs), and SIGMAR1 and to affect indirectly the glutaminergic and the GABAergic system (Brito-da-Costa et al., 2020; De Gregorio et al., 2018). It should be noted that 5HT2A receptors are most densely concentrated in the neocortex in the apical dendrites on layer V pyramidal neurons, thus determining the selective cell types and brain regions that psychedelics influence and are essential for the psychedelic outcome (Kelmendi et al., 2022; Vollenweider; Preller, 2020).

Classical psychedelics exert their characteristic effects primarily through agonism at 5-HT2A receptors, which are densely expressed in the neocortex, including regions involved in the cortico-striatal-thalamo-cortical (CSTC) circuitry. This network, which integrates thalamic sensory input with cortical and basal ganglia processing, plays a pivotal role in cognition, affect regulation, and executive functioning. While psychedelic modulation of CSTC circuits in adults has been associated with therapeutic benefits, the implications of such modulation during pediatric neurodevelopment remain poorly understood. Importantly, the CSTC circuitry undergoes protracted maturation throughout childhood and adolescence, involving the refinement of thalamocortical and corticostriatal synapses and activity-dependent synaptic pruning. The expression of 5-HT2A receptors is known to peak during adolescence, particularly in the prefrontal cortex and thalamus, suggesting a window of heightened sensitivity to serotonergic modulation during this period (Andrade; Weber, 2010; Vollenweider; Preller, 2020).

2.2 Subjective and non-subjective effects

As a result, classic psychedelics generate acute subjective alterations in perception, cognition, emotional state, social processing, and introspection, characterized as "mystical experiences" (Swanson, 2018; Vollenweider; Preller, 2020). About the drugs reported in the first paragraph, psilocybin is primarily associated with experiences, on the one hand, denoted by a sense of temporal and spatial distortion, feelings of euphoria, heightened feelings of oneness, and a diminished sense of self, and on the other hand, temporary feelings of anxiety, unhappiness, disrupted sleep, paranoia, sorrow, and a fixation on mortality (Gattuso et al., 2023; Sarparast et al., 2022). DMT essentially causes a regular pattern among users, initially involving vision imagery, nausea, and vomiting, then, encountering a spiritual realm, users understand their place in the world, feel more connected to nature and earth, and finally, visuals diminish, and a sense of fatigue reigns supreme (Gattuso et al., 2023; Hamill et al., 2019).

The typical scheme throughout an LSD experience includes simple visual patterns, elation, sentiments of youthfulness and renewal, as well as anxiety, paranoia, and fear of madness (Hamill et al., 2019; Nichols, 2018). Mescaline generally produces visual, tactile, and auditory hallucinations along with distorted time, space, and personality perception. Mescaline shall stimulate synesthesia and feelings of euphoria, but it might also increase anxiety, apprehension, diminished emotions, and a sense of "split" in one's personality (Cassels; Sáez-Briones, 2018; Vamvakopoulou et al., 2023).

Apart from their acute subjective effects, psychedelics have been attributed to demonstrate long-lasting non-subjective results because of promoting neural plasticity (Ly et al., 2018). In essence, serotonergic hallucinogens induce molecular changes through signaling pathways, gene transcription, and protein synthesis and then stimulate neurogenesis, dendritogenesis, and synaptogenesis, hence modulating brain activity beyond their expected blood plasma half-life (de Vos et al., 2021).

Beyond enhancing neuroplasticity, classical psychedelics may also play a role in inhibiting maladaptive or aberrant plasticity, particularly within neural circuits related to aversive motivation and pathological learning. This function is especially relevant in conditions such as trauma, obsessive-compulsive behavior, and addiction, where plasticity mechanisms become dysregulated and reinforce maladaptive behavioral loops. Psychedelics are thought to disrupt these entrenched networks by temporarily relaxing top-down control and enabling network "resetting"

or reorganization—a mechanism often described under the REBUS model (Relaxed Beliefs Under Psychedelics) proposed by Carhart-Harris and Friston (Carhart-Harris; Friston, 2019). Functional imaging studies have further shown psilocybin's modulation of reward and aversion networks, supporting its potential to recalibrate motivational salience in psychiatric disorders (Carhart-Harris; Goodwin, 2017).

Recent evidence from the work of van der Kooy and colleagues has demonstrated that neuroplastic changes within the ventral tegmental area (VTA) can sustain aversive motivational states, especially during drug withdrawal or stress exposure. Importantly, psychedelics such as psilocybin and LSD—via their action on 5-HT2A receptors—may reverse this maladaptive plasticity, offering a unique therapeutic avenue not only by promoting new synaptic connections but by disrupting entrenched aversive circuitry (Vargas-Perez et al., 2023).

Another crucial yet often underdiscussed dimension of psychedelic action involves their indirect modulation of GABAergic signaling, particularly under pathological conditions where GABA-A receptor function becomes excitatory rather than inhibitory. Such shifts are documented in certain neurodevelopmental and affective disorders and are associated with impaired emotional regulation, cognitive dysfunction, and increased neural excitability (Chattopadhyaya; Cristo, 2012). Psychedelics, by restoring the balance between glutamatergic excitation and GABAergic inhibition, may help stabilize cortical activity and reestablish normal inhibitory tone. This correction of dysfunctional inhibitory signaling could underlie part of the long-term therapeutic effects observed in mood and anxiety disorders.

Moreover, van der Kooy's group has shown that under specific pathological conditions, BDNF-induced neuroadaptations in the VTA can shift GABA-A receptor signaling from inhibitory to excitatory. This switch contributes to altered stress and aversion processing and is considered a key mechanism in the persistence of negative affective states (Vargas et al., 2020).

Recent neuroimaging studies, including Siegel et al. (2024), have demonstrated that a single dose of psilocybin in adults can induce profound alterations in brain network architecture, particularly within the default mode network, frontoparietal systems, and limbic circuits. Such reorganization may underlie therapeutic outcomes in adults, but the implications for pediatric brains—undergoing active development—remain speculative and potentially hazardous.

The dose, the environmental impact, biological and psychological trait factors, and the pre-state condition constitute the main extra-pharmacological factors that regulate the psychedelic experience and determine whether it shall have a positive or an adverse effect. It is worth mentioning that the pre-state condition is characterized as the "set" of the psychedelic incidence. In contrast, the environment is referred to as the "setting" in psychedelic research (Garel et al., 2023; Golub et al., 2015; Swanson, 2018). Collectively, the type of substance, dose, route of administration, history of psychedelic use, body weight, metabolism, sex, age, serotonin receptor availability, diversity of executive network nodes, structural neural measures, physical, social, and cultural aspects, an individual's spiritual motivation, attitude towards life, conscientiousness, apprehension, preoccupation, confusion, distress, anticipatory anxiety, expectations, assumptions, openness, and willingness to surrender to the drug influence might be predictive of the psychedelic effect (Aday et al., 2021; de Vos et al., 2021).

2.3 Historical context of psychedelic research

The initial clinical trials on humans containing classic psychedelics were reported in 1947 when Stoll evaluated LSD's effects on sixteen healthy and six schizophrenic adult patients. Moreover, the first clinical trials on children concerning classic psychedelics were publicly disclosed in 1959 by R. C. Murphy & T. T. Peck, who mainly supported that LSD is safe for children. Although Murphy treated three children with LSD, he only provided information on a non-responsive to psychotherapy with a "long-term extremely resistive character disorder" 8-year-old girl, who he described as becoming more generous and outgoing and gaining the ability to control her urination. In addition, Peck noticed a behavioral improvement in five children to whom he administered LSD.

It is important to note that the term "childhood schizophrenia", as used in mid-20th-century studies, does not align with current psychiatric diagnostic criteria. At the time, this label was often applied to a broad range of developmental and behavioral disorders, including cases that would now be classified as autism spectrum disorder (ASD), childhood-onset schizophrenia, or other neurodevelopmental conditions. As a result, interpretations of historical data must be approached with caution, acknowledging that diagnostic boundaries were fluid and not guided by contemporary criteria such as those in the DSM-5 or ICD-11.

The most notable research programs involving the treatment of minors with classical psychedelics were orchestrated by Lauretta Bender and her colleagues and by James Q. Simmons and his colleagues (Sigafoos et al.,

2007). Bender and her colleagues observed the impact of LSD, psilocybin, and a methylated derivative of LSD, called UML, on eighty-nine cases of childhood schizophrenia, having promising results, as reviewed by John C. Rhead (Rhead, 1977). Simmons's group researched a total of nineteen schizophrenic children. Their initial experiment, which consisted of one pair of autistic identical twins, seemed to have a positive aftermath. However, following their second experiment, which included seventeen schizophrenic children, the result seemed to be less promising, as Simmons and his team noticed(Simmons et al., 1966, 1972). In 1962, Alfred Freedman, Eva Elbin, and Ethel Wilson were the first to suggest a pessimistic attitude toward the potential therapy of childhood schizophrenia with classic psychedelics, having administered LSD to twelve children with autistic schizophrenia (Freedman et al., 1962). Even though more data showcased that news was not consistently positive, reviews of that era concluded that the outcomes of utilizing LSD for pediatric treatment mostly displayed significant promise (Rhead, 1977; Sigafoos et al., 2007). Nonetheless, in 1970, the development of the Controlled Substances Act categorized classic psychedelics as Schedule 1 drugs, thus impeding further research (Kelmendi et al., 2022; Kenny et al., 2025).

Indeed, in that period, the diagnosis of childhood autism and schizophrenia did not comply with present-day criteria for ASD and childhood schizophrenia since they were chiefly regarded as equivalent to adult psychosis and schizophrenia. Further, due to various methodological flaws, concerns about bias, inconsistent use of psychometric scales, limited therapeutic options, instances where neutral or negative findings were interpreted as positive, and a lack of formal ethical principles for research before the Belmont Report, which allowed scientists to justify their experiments based on the logic of default, Sigafoos et al. concluded that it was unlikely that any potential benefits of LSD on minors could be adequately substantiated through these particular types of studies (Edelsohn; Sisti, 2023; Sigafoos et al., 2007). A synthesized summary of key early pediatric studies is presented in Table 1 to provide clearer insight into the age ranges, environments, supervision practices, and reported experiences involved in these early trials.

2.4 Ethical analysis of autonomy in pediatric psychedelic research

In 1979, Tom L. Beauchamp and James F. Childress published their book, Principles of Biomedical Ethics, introducing a bioethical framework consisting of four broad moral principles: autonomy, beneficence, non-maleficence, and justice (Beauchamp; Childress, 2019). It has since been used as a guide to determine the ethical aspects of both medical research and clinical practice (Amann et al., 2020). In this review, Beauchamp and Childress's scheme will be deployed to assess the specific ethical considerations about research and clinical use of classical psychedelics for pediatric conditions as a complement to the commonplace existing principles that govern research and clinical applications involving children.

In the Principles of Biomedical Ethics, autonomy is defined as "self-rule that is free from both controlling interference by others and limitations that prevent meaningful choice, such as inadequate understanding"(Genuis, 2021). In addition, an autonomous individual is described as "an individual who acts freely by a self-chosen plan, analogous to the way an autonomous government manages its territories and sets its policies"(Akabayashi; Nakazawa, 2022). Essentially, for Beauchamp and Childress, autonomy denotes an intentional, thoroughly comprehended, and not influenced by factors that hinder self-guided action to secure the patient's independence in respect of specific choices (Saad, 2018). Regarding pediatric disorders, autonomy refers to the moral and ethical obligation of medical researchers and physicians to obtain consent from a parent or a legally authorized representative and to acquire assent from the minor for the child to participate in research and clinical practices (Remien; Kanchan, 2025).

Classical psychedelics elicit a unique and indescribable experience compared to other substances, therefore complicating the process of disclosing and obtaining informed consent from guardians and minors. Pilecki et al. (2021) mention "preparation sessions" in clinical trials with adult participants that could nurture autonomy in pediatric psychedelic trials, serving to establish a constructive therapeutic alliance, allowing for the patient's articulation of intentions and mental health concerns, while also providing information about the substance's effects, benefits, and associated risks, along with delineating strategies for effectively addressing potential challenges during dosing sessions. Edelsohn & Sisti (2023) propose that parental consent might be influenced either by parents' personal therapeutic or recreational experiences involving classical psychedelics or by the deficiency of conventional treatment for their children. They also posit that parents should evaluate their children's age, level of language development, cognitive capabilities, and ability to process unconventional experiences before granting their consent.

While parental consent is legally required for a child's participation in clinical research or treatment, ethical guidelines such as those from the Council for International Organizations of Medical Sciences (Council for International Organizations of Medical Sciences (CIOMS), 2016) (CIOMS) and the U.S. Department of Health and Human Services emphasize the importance of also obtaining the child's assent whenever developmentally appropriate. In the case of psychedelic-assisted therapy—which entails profound alterations in cognition, perception, and emotion—dual consent may be particularly crucial. These substances' unique effects heighten the ethical obligation to involve the child in decision-making, not only to respect emerging autonomy but also to ensure psychological preparedness and minimize harm.

Table 1. Overview of early studies involving the administration of classical psychedelics to pediatric populations, highlighting age ranges, research settings, supervision conditions, and reported subjective experiences.

Study / Author(s)	Year	Age Range	Setting	Supervision Protocol	Subjective Experiences Reported
Murphy, R. C.	1959	Not fully reported; includes 8 y.o. girl	Clinical/ Institutional	Physician-supervised sessions	The girl became more outgoing and socially engaged; asked to repeat the session
Peck, T. T.	1959	Not specified	Likely institutional	Not clearly reported	Behavioral improvements noted; no subjective accounts described
Bender, L. et al.	1959–1965	5–15 years	Psychiatric hospitals	Psychiatrists present; group and individual sessions	Increased sociability and verbal expression in several children; some asked for repeated dosing
Simmons, J. Q. et al.	1966–1972	6–16 years	Psychiatric institutions	Psychiatrists and staff present during sessions	Mixed outcomes: initial improvements, but later studies showed fear, indifference, or agitation
Freedman, A. et al.	1962	6–13 years	Clinical/ Research facility	Researchers present during the administration	Limited response; authors expressed skepticism about efficacy and raised ethical concerns

Source: Authors, 2025.

2.5 Beneficence: Potential therapeutic advantages

Beauchamp and Childress defined beneficence as "a statement of moral obligation to act for the benefit of others." They also divided beneficence into three fundamental components: "One ought to prevent evil or harm," "One ought to remove evil or harm," and "One ought to do and promote good"(McCullough, 2020). Meier et al. (Meier et al., 2022; *Trust in Healthcare, Medical Mistrust, and Health Outcomes in Times of Health Crisis: A Narrative Review*, n.d.) operationalized beneficence by considering two primary factors that would help them through their algorithmic approach to Beauchamp and Childress's ethical principles: gain in life expectancy that is a quantifiable value and gain in quality of life. The correlation between quality of life and mental health is integral (Mofatteh, 2020). Consequently, the therapeutic potential of classical psychedelics in treating pediatric disorders is indicative of their benefits. Classical psychedelics enhance emotional, self-reflective, and social processes and foster heightened consciousness, mindfulness, and acceptance (Bosch et al., 2022).

As a consequence, it is suggested that classical psychedelics may display a therapeutic role in psychiatric conditions characterized by anxiety, depression, and cognitive deficits (De Gregorio et al., 2021). In particular, trials with adults suggest that psilocybin, LSD, DMT, and mescaline have a positive impact on GAD, cancer-related anxiety, depression, MDD, unipolar treatment-resistant depression, existential distress, suicidality, distress due to terminal illness, PTSD, OCD, BPD, and NPD. Furthermore, they can assist in addressing

addictions, palliative care, epilepsy, migraines, cluster headaches, chronic pain, cancer pain, phantom limb syndrome, neurodegenerative disorders, and eating disorders (Ko et al., 2023; Lowe et al., 2021, 2022; Muttoni et al., 2019; Reiff et al., 2020; Schindler, 2022).

Currently approved pharmacological treatments for pediatric mental health conditions are not without significant risks. Central nervous system stimulants, such as methylphenidate and amphetamines—commonly prescribed for attention-deficit/hyperactivity disorder (ADHD)—have been associated with undesirable cardiovascular effects (e.g., elevated heart rate and blood pressure) and long-term suppression of physical growth, particularly height and weight gain (Kenny et al., 2025; Nichols; Walter, 2021). These side effects underscore the limitations of existing options and highlight the importance of responsibly investigating novel approaches, including psychedelic-based therapies (Faraone et al., 2021; Storebø et al., 2015).

Many of these disorders exert a significant influence on children's health. When considering mental health, which is identified as the primary focus for classical psychedelics in the referenced literature, data from the United States Centers for Disease Control and Prevention indicate that 9.4-9.8% of minors aged 3-7 experience anxiety, 20.9% have experienced a major depressive episode, and 18.8% have contemplated suicide (Bitsko, 2022). It is important to note that these effects are long-lasting after either one or a few doses due to provoking neural plasticity, as described (Grieco et al., 2022). In addition, classical psychedelics in adults are reckoned to be well tolerated, with low toxicity, drug dependence is rare in comparison to other abused substances, and adverse effects can be reduced when micro-dosing in a regulated and monitored clinical environment (Family et al., 2020; Kelmendi et al., 2022; Kuypers, 2020; Ling et al., 2022).

Unlike conventional antidepressants such as SSRIs, which exert their effects gradually and through chronic administration, psychedelics like psilocybin produce rapid and profound alterations in consciousness and neural network dynamics after a single or a few doses. This difference is not merely pharmacological but deeply neurobiological, involving large-scale brain system reorganization that may not be reversible or predictable in developing individuals.

Despite the well-documented adverse effects of various psychotropic agents, several are routinely used in pediatric psychiatry based on regulatory approvals and clinical necessity. For example, methylphenidate and lisdexamfetamine dimesylate are both approved for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children, even though they carry risks such as insomnia, appetite suppression, cardiovascular effects, and potential growth inhibition (Cortese et al., 2018; Faraone et al., 2021). Similarly, esketamine, a dissociative NMDA receptor antagonist, esketamine, despite its dissociative and potentially hazardous profile, has been approved in some jurisdictions for treatment-resistant depression in adolescents — a precedent that illustrates how urgent clinical needs can lead to the conditional acceptance of high-risk compounds under rigorous oversight, despite concerns regarding dissociation, misuse potential, and elevated blood pressure (Canuso et al., 2018). These precedents underscore that the presence of significant risk does not preclude pediatric use when therapeutic needs are pressing, and ethical, legal, and clinical safeguards are robust.

2.6 Non-maleficence: Risks and adverse outcomes

The concept of non-maleficence is outlined as "one ought not to inflict evil or harm," and harm is explained as "a thwarting, defeating, or setting back of some party's interest" (Shea, 2020). Meier et al. (2022) incorporated non-maleficence into their algorithm, similar to their approach to beneficence, by evaluating potential loss in life expectancy and loss in quality of life. In this review, akin to the consideration of beneficence, non-maleficence will be examined by scrutinizing the possible drawbacks of utilizing classical psychedelics in pediatric populations, drawing insights from negative occurrences observed in adults. Instant adverse events include nausea, gastrointestinal discomfort, vomiting, increased blood pressure, and increased heart rate, while the most common late undesirable outcome is headache (Dos Santos et al., 2018; Rucker et al., 2018). Moreover, throughout the acute subjective phase, feelings of vulnerability, negative encounters, undesired shifts in mental state, and behaviors that are harmful both physically and emotionally to self and others have been narrated (Cheung; Tsang, 2023).

It is also essential to distinguish between the therapeutic use of psychedelics in structured clinical environments and their recreational or unsupervised use, which may entail markedly different risk profiles. While classical psychedelics exhibit low potential for physical dependence, psychological misuse, particularly in vulnerable individuals or outside medical oversight, remains a concern. This is especially relevant in the context of unsupervised access by adolescents, where a lack of guidance could increase the likelihood of adverse experiences,

unsafe behaviors, or reinforcement of maladaptive coping mechanisms. As such, regulatory, ethical, and educational safeguards must accompany any future expansion of access (Johnson et al., 2018; Nichols, 2016).

In line with regulatory standards set by bodies such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA), a positive benefit/risk ratio is a fundamental prerequisite for the approval and maintenance of any medicinal product in clinical use. In the case of psychedelics, this ratio cannot currently be established for pediatric populations due to the absence of systematic long-term outcome data, which must be regarded not as a neutral gap, but as an active ethical red flag, requiring precautionary restraint until safety is demonstrably established. As such, initiating pediatric trials at this stage would lack the therapeutic justification required by international medical and regulatory ethics.

It is to acknowledge that some individuals perceive the depersonalization and derealization experienced during mystical psychedelic incidents as challenging, and these shifts in perception, cognition, emotional state, social processing, and introspection, which constitute the primary mechanism underlying the beneficial effects of classical psychedelics, may endure as an undesirable long-lasting effect (Cheung; Tsang, 2023; Greif; Šurkala, 2020). Although classical psychedelics exhibit good tolerance, low toxicity, and a distinct pharmacological profile that diverges from classical addictive substances (Dos Santos et al., 2018; Lowe et al., 2021; Muttoni et al., 2019; Reiff et al., 2020; Schlag et al., 2022).

Classical psychedelics, including psilocybin, LSD, and DMT, typically lack the dopaminergic reinforcement mechanisms associated with substance use disorders and do not produce compulsive use, tolerance buildup, or withdrawal symptoms in the way addictive compounds do. For example, compounds such as psilacetin (4-AcO-DMT) and psilocybin have shown low abuse liability in both preclinical and clinical models (Johnson et al., 2018; Nichols, 2016). This supports their classification as non-addictive under current neuropharmacological frameworks, despite their Schedule I status in many regulatory systems. Although rare in structured clinical settings, there have been reports of acute behavioral dysregulation, including agitation, aggression, or hostile reactions, particularly in individuals with underlying emotional instability or undiagnosed psychiatric conditions. In pediatric populations, where affective control is still maturing, such responses may be more difficult to predict or manage, thereby raising additional ethical concerns regarding safety and supervision (Halpern; Pope, 2003; Johnson; Griffiths, 2017).

In line with regulatory concerns, the U.S. FDA has identified key risks associated with psychedelic trials, particularly regarding drug diversion, accidental poisoning, and improper storage or administration in non-clinical settings. These concerns are magnified in pediatric contexts, where accidental exposure or misuse could lead to significant harm. Unlike substances of abuse, psychedelics do not reliably activate mesolimbic dopaminergic circuits or induce conditioned place preference in preclinical models. Work by van der Kooy's laboratory further supports that psychedelics lack the pharmacological reinforcement profiles typical of addictive drugs, and may in fact modulate reward and aversion circuits in the opposite direction, aiding in the disruption of compulsive motivational loops (Vargas-Perez et al., 2023).

A notable pharmacological feature of classical psychedelics—particularly LSD and psilocybin—is their capacity to induce rapid tolerance, whereby repeated use over short intervals significantly reduces the intensity of subjective and neurophysiological effects. This is thought to involve downregulation of 5-HT2A receptors, the primary target of these compounds. While this phenomenon may lower the risk of compulsive use, it also complicates the design of potential therapeutic protocols, especially for pediatric populations, where the effects of receptor-level adaptation on neurodevelopment remain unknown (Halberstadt, 2015; Nichols, 2018).

While much of the current literature highlights the neuroplasticity-promoting properties of psychedelics in adult populations, pediatric brains differ markedly in their developmental trajectories and vulnerability. Psychedelic administration during periods of active synaptogenesis or pruning—particularly in regions within the CSTC loop—could hypothetically result in long-term alterations in network efficiency, emotional regulation, or sensory integration. Thalamocortical synaptogenesis, for instance, is a critical developmental event that shapes perception and executive function; inappropriate serotonergic activation during this phase could risk dysregulated circuit formation (Selemon, 2013). Additionally, disruption of normal pruning trajectories might lead to either excessive retention or loss of synaptic connections, both of which are implicated in neuropsychiatric conditions such as schizophrenia and autism spectrum disorder. These concerns, though theoretical, are grounded in well-established neurodevelopmental principles and underscore the ethical imperative to proceed with caution when considering psychedelic interventions in children.

Importantly, there is no available longitudinal data on the long-term consequences of psychedelic use in children. The early pediatric studies conducted during the mid-20th century lacked standardized follow-up assessments, and

no formal evaluations were made regarding neurodevelopmental, psychological, or social maturation. As such, the long-term effects of these substances on developing brains remain entirely unexplored in empirical literature. This constitutes a critical knowledge gap that must be addressed before any modern therapeutic application in pediatric populations (Edelsohn; Sisti, 2023).

2.7 Justice: Equity and representation in psychedelic studies

The final principle elucidated by Beauchamp and Childress in the Principles of Biomedical Ethics is justice, which entails treating everyone with fairness and equality (Takala; Häyry, 2019). In the past, people of color were not adequately represented in psychedelic research, and it has also been reported that they were mistreated during trials (Michaels et al., 2018; Strauss et al., 2021). Current clinical trials with adult participants continue to exhibit disparities in age, sexual orientation, and portrayal of race and ethnicity. However, it is noteworthy that efforts are underway to mitigate these imbalances, indicating a gradual regression in this gap (Carter et al., 2023).

From the perspective of bioethical justice, the absence of approved psychedelic therapies for children—despite emerging evidence of efficacy in adults—may represent a form of therapeutic exclusion. Pediatric populations suffering from severe, treatment-resistant mental health conditions may lack access to innovative interventions solely due to historical and regulatory inertia. This raises concerns about healthcare equity, as children may become “therapeutic orphans,” excluded from research and advances that benefit adults. Therefore, justice in this context may require reconsidering age-related barriers and ensuring that vulnerable groups are not systematically left behind in the development of novel treatments (Kraus; Mehlinger, 2005; Spetie; Arnold, 2007).

Ethical oversight in pediatric psychedelic research requires not only adherence to general principles such as non-maleficence and justice, but also active institutional mechanisms to evaluate and enforce these principles. Research Ethics Committees (RECs) or Institutional Review Boards (IRBs) play a central role in this process. These bodies are tasked with assessing scientific validity, proportional risk–benefit balance, appropriate consent/assent processes, and the presence of additional protections for vulnerable populations. In the case of psychedelic studies involving children, their review becomes especially critical, given the novelty of the intervention, the intensity of the subjective experience, and the lack of long-term data. Ethics Committees serve as an essential checkpoint before any such trial may proceed, ensuring that ethical safeguards are not theoretical but institutionally enforced (Council for International Organizations of Medical Sciences (CIOMS), 2016) (Guideline 23: "Role and responsibility of ethics committees").

In Europe, the regulation of pediatric drug development is further strengthened by the Paediatric Committee (PDCO) of the European Medicines Agency (EMA). This body is responsible for assessing and approving Paediatric Investigation Plans (PIPs), which are required for any new medicinal product or indication intended for use in children. The PDCO ensures that pediatric studies are methodologically sound, ethically justified, and developmentally appropriate, and that children are not excluded from innovation nor exposed to disproportionate risks. Any future consideration of psychedelic therapies for minors would require alignment with these regulatory frameworks.

In pediatric medicine, the repurposing of drugs initially developed for adults is a frequent practice, often justified by the lack of pediatric-specific trials. However, applying this approach to psychoactive substances such as psychedelics requires heightened ethical vigilance. Unlike many repurposed pharmacological agents, psychedelics engage deeply with cognition, emotion, and perception—domains that are still actively developing in children. Thus, while drug repurposing may appear to offer a pragmatic path toward innovation, in the case of psychedelics, it raises complex ethical, regulatory, and developmental questions that must be carefully navigated (Turner et al., 2014). Table 2 represents a comparison of adult and pediatric populations across domains relevant to the ethical and neurobiological implications of psychedelic therapy.

Table 2. Key distinctions between adult and pediatric populations in relation to psychedelic therapy.

Domain	Adults	Children / Adolescents	Difference Intensity
Neural Plasticity	Neuroplasticity facilitates targeted therapeutic rewiring.	Plasticity is ongoing and unspecific; interventions may disrupt normal brain maturation.	🔴 High
CSTC Maturation	The CSTC circuit is largely developed and stable.	CSTC circuit is still developing; interventions may alter synaptogenesis and pruning.	🔴 High
Autonomy	Informed consent can be fully obtained from the individual.	Requires parental consent and child assent; decision-making capacity varies by age.	🟠 Moderate
Dependence Risk	Low addiction potential; non-compulsive use in clinical settings.	Same low risk, but long-term vulnerability or misuse patterns remain understudied.	🟡 Mild
Ethical Oversight	Existing adult trials follow stringent ethical standards.	Pediatric trials must meet additional legal, ethical, and developmental safeguards.	🔴 High

Source: Authors, 2025.

3. Discussion

The argument advocating for the use of classical psychedelics in children should commence with the premise that society must safeguard both the physical and the mental well-being of children (Allen et al., 2014). Classical psychedelics could potentially demonstrate a pivotal role in providing psychiatric support for pediatric populations. The primary justifications for the utilization and investigation of psychedelics with children focus on the potential advantages they may confer, coupled with their therapeutic potential.

Further arguments support the notion that the exclusion of children from classical psychedelic substance use, during a period of a rapidly increasing prevalence of mental disorders and an established treatment that proves to be insufficiently effective, shall leave children without adequate therapeutic options, akin to being “therapeutic orphans.” Such a position could stand by the principle of justice and point to the need to reverse the healthcare system’s disparities that burden vulnerable populations (Meghani et al., 2014; Spetie; Arnold, 2007). Louis J. Kraus and Renee Mehlinger asserted that the lack of appropriate treatment for adolescents with depression, in the context of antidepressant substances, may lead to increased morbidity and mortality rates within the pediatric population affected by this condition (Kraus; Mehlinger, 2005).

A parallel argument can be made regarding the limitation of children's participation in psychedelic research. Finally, there may be concerns regarding the potential "off-label" prescription of classical psychedelics for children, in the event of their approval for adult use, especially when their effects on children remain uncertain. This situation could lead to unintended consequences, similar to the issues that arose with antidepressant drugs, highlighting the need for cautious trials on children (Koelch et al., 2008). All in all, if classical psychedelics prove to be the optimal therapy for specific pediatric mental disorders, it could be unethical to withhold their research and use.

The position that society is obligated to ensure the well-being of children is equally pertinent when arguing against the ethical validity of administering classical psychedelics to pediatric populations. To begin with, the potential adverse effects of psychedelics present a paramount argument against their utilization. Besides, as long as current research centers on adults, it's plausible that children's distinct neurobiological factors, drug absorption, distribution, metabolism, and excretion, may lead to different and potentially more diverse and more negative outcomes (Bates; Trujillo, 2021). Within the same framework, psychedelics may be falsely attributed to having beneficial results that would otherwise emerge from emotional and behavioral maturation (Spetie; Arnold, 2007).

Moreover, Edelsohn and Sisti contend that imposing short-term and long-lasting perceptual, cognitional, emotional, social, and introspective alterations on children and adolescents' mental processing during the phase of personality development could lead to a loss of their identity (Edelsohn; Sisti, 2023; McGovern et al., 2022). In addition, psychiatric disorders are not only due to biological predisposition but rather are a constellation of both genetic and environmental factors (Davis et al., 2011).

However, the utilization of classical psychedelics as an optimal therapeutic approach, much like the administration of antidepressants for depression, may attribute the child with exclusive responsibility for their condition, potentially overlooking additional underlying factors contributing to the issue (Dell, 2012). Shearer & Bermingham (2008) argue that depression, to some extent, is both a subjective affective disorder and a subjective diagnosis. This may also apply to other psychiatric conditions, implying that the utilization of psychedelics in treatment could potentially result in the pathologizing of human emotions and over-medicalization. Lastly, the social stigma associated with classical psychedelics' recreational use may burden pediatric populations (dos Santos et al., 2021).

4. Conclusions

Within the context of the ethical evaluation of utilizing classical psychedelics for pediatric populations, by the framework of Beauchamp and Childress's Principles of Biomedical Ethics, it becomes clear that a multitude of elements necessitate careful consideration, since children are a vulnerable demographic. The primary dilemma revolves around the ethical considerations of potentially subjecting children to risks in the pursuit of addressing significant physical and mental disorders. Regarding this dilemma from a moral perspective, the present review concludes that there are reasonable arguments to support both cases. Furthermore, the main shift the conversation might take regards the endeavor of non-subjective classical psychedelics, given the paradox that researchers argue over whether or not the publicly known mystical experience of psychedelics is necessary and beneficial.

Given the profound systems-level reorganization observed even in mature adult brains, exposing still-developing pediatric brains to psychedelics may not simply be premature—it may be actively dangerous. Until rigorous, long-term safety data are available, particularly regarding developmental neurotoxicity and cognitive/emotional outcomes, any therapeutic use in children must be categorically avoided under the precautionary principle. A clear ethical distinction must be made between "no evidence of safety" and "evidence of risk," with the former demanding precautionary restraint.

Moving forward, a structured and ethically sound research pathway would require:

(1) Preclinical studies examining the effects of psychedelics on the developing CSTC circuit;

(2) Age-stratified pharmacokinetic and safety studies in older adolescents before extending trials to younger children;

(3) Inclusion of long-term follow-up protocols assessing psychological, cognitive, and social development post-intervention.

Until such data are available, psychedelic therapy for children remains premature. Nonetheless, given the urgent need for effective pediatric mental health interventions, this area warrants responsible scientific exploration under stringent ethical oversight.

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6. Author Contributions

Aspasia Serdari: conceptualization, supervision. *Konstantinos Christodoulou*: conceptualization, methodology, investigation, writing—review and editing, supervision, and resources. *Anna Tsiakiri*: resources, writing—original draft preparation, funding acquisition. *Pinelopi Vlotinou*: funding acquisition. *Foteini Christidi*: resources, supervision.

7. Conflicts of Interest

No conflicts of interest

8. Ethics Approval

Not applicable

9. References

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The following abbreviations are used in this manuscript:

SSRI: selective serotonin reuptake inhibitor

DMT: N, N-dimethyltryptamine

LSD: lysergic acid diethylamide

5-HT: 5-hydroxytryptamine

TAAR: trace amine-associated receptor

SIGMAR1: sigma non-opioid intracellular receptor 1

GABA: gamma-aminobutyric acid

ASD: autism spectrum disorder

GAD: generalized anxiety disorder

MDD: major depressive disorder

PTSD: post-traumatic stress disorder

OCD: obsessive-compulsive disorder

BPD: borderline personality disorder

NPD: narcissistic personality disorder