Autism, youth suicide, and psychedelics: A review of the 21st century evidence

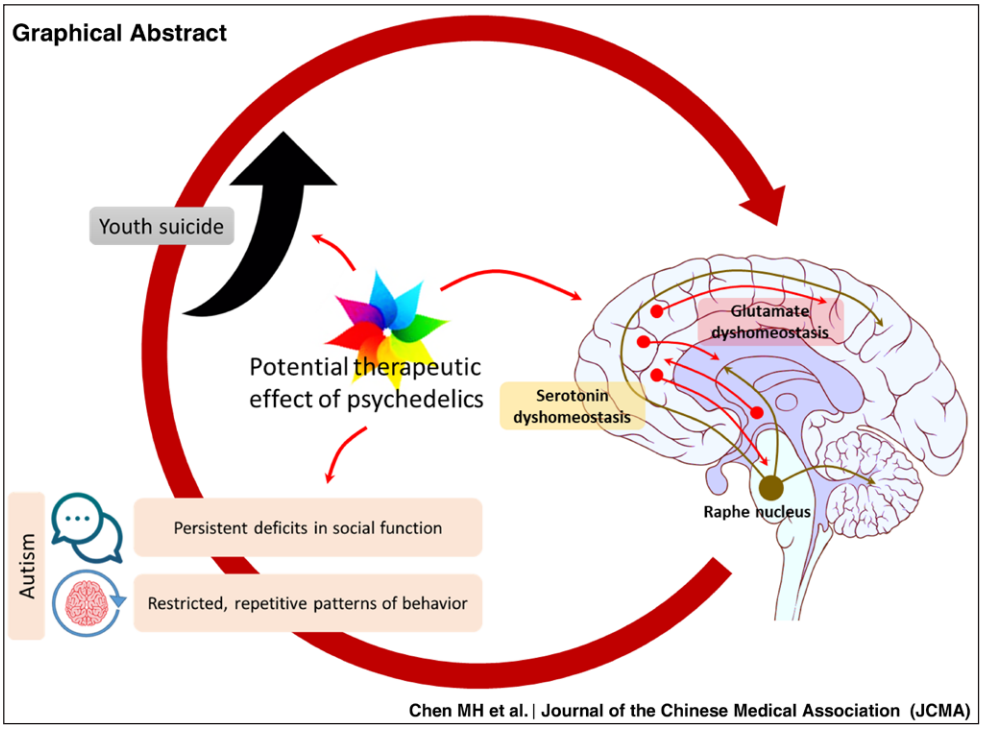
Mu-Hong Chen[a,b,*], Tung-Ping Su[a,b,c], Ju-Wei Hsu[a,b], Shih-Jen Tsai[a,b]

[a]Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]Faculty of Medicine, Division of Psychiatry, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [c]Department of Psychiatry, General Cheng Hsin Hospital, Taipei, Taiwan, ROC

Abstract

The concurrent rise in the prevalence of autism and youth suicide has drawn public health and professional attention. The renaissance of psychedelics in psychiatry occurred in the early 21st century and may suggest a hope for the therapeutic effect of psychedelics in autism and suicide. The psychedelics' molecular entities are the compounds that modulate the serotoninergic and glutamatergic systems, which play a crucial role in the pathomechanisms underlying autism and suicide. This systematic review comprehensively discussed the prevalence trends of autism and youth suicide globally and in Taiwan and discussed an association between autism and suicidality based on the 21st century clinical and preclinical literature. Furthermore, this review proposed a possible neurobiological connection between autism, suicide, and psychedelics. Finally, this review discussed the potential therapeutic applications of psychedelics in autism and youth suicide.

Keywords: 21st century; Autism; Psychedelics; Youth suicide



*Address correspondence. Dr Mu-Hong Chen, Department of Psychiatry, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: kremer7119@gmail.com (M.-H. Chen).

Conflicts of interest: Dr. Mu-Hong Chen, an editorial board member at Journal of the Chinese Medical Association, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2024) 87: 904-911.

Received July 11, 2024; accepted August 6, 2024.

doi: 10.1097/JCMA.0000000000001150

<z10.1097/JCMA.0000000000001150>

1. AUTISM IN THE 21ST CENTURY

Autism is a common, highly heritable, and heterogeneous neurodevelopmental condition that occurs in the very early stage of life and is characterized by persistent deficits in social communication and social interaction, as well as restricted, repetitive patterns of behavior, interests, or activities, with a male-to-female ratio of 3 to 4:1.[1–3] The economic burden, including annual direct medical, direct nonmedical, and productivity costs, of autism was at least $268 billion in 2015 and was estimated to be $461 billion in 2025 in the United States (U.S.).[4] Furthermore, the fact that autism is more common in males than in females may suggest the crucial influence of sex-linked factors at the genetic, endocrine, epigenetic, and environmental levels in the pathophysiology of autism.[1,2] Nonetheless, the precise pathophysiology of autism is still unknown, and its etiology seems to be multifaceted.

Studies on the prevalence of autism started in the 1960s and 1970s, with a relatively low prevalence estimated between ~50 and ~70 cases per 100 000 people.[5,6] Since 2012, 71 studies have published 99 estimates on autism prevalence, indicating a global prevalence that varies within and across regions, with a median prevalence of 100/10 000 (1%) ranging between 1.09/10 000 and 436.0/10 000.[7] According to the U.S. Centers for Disease Control and Prevention, autism affects one in 36 (2.8%) children aged 8 years, or approximately 4% of boys and 1% of girls in 2020.[8] Using the World Health Organization Global Burden of Diseases, Injuries, and Risk Factors Study data, Solmi et al[9] reported that the raw number of autistic individuals increased approximately from an estimate of 20 million in 1990 to over 28 million in 2019, corresponding to a relative increase of 39.3% in terms of the global prevalence of autism. In 2019, Taiwan's National Epidemiological Study of Child Mental Disorders demonstrated that the lifetime prevalence of autism is 1% (95% CI, 0.6-1.5) based on the diagnostic criteria of autism in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[10] Discrepancies in ethnic and socioeconomic factors may be associated with the difference in autism prevalence between the U.S. and Taiwan.[7] However, the exact mechanisms underlying such a prevalence difference would need further investigation.

Such a significant increase in autism prevalence, from 50 to 70 cases per 100 000 people in the 1970s to ~1000/100 000 cases per 100 000 people in the 2020s, attracts public and professional attention in this decade (Fig. 1).[7,9] First, over decades, the diagnostic revisions to the DSM (DSM-III, DSM-III-TR, DSM-IV, DSM-IV-TR, and DSM-5) autism criteria reflect the conceptualization of autism over time, which means the definition of autism from the narrower version in the DSM-III/III-TR, to the broader version in the DSM-IV/IV-TR, and to the intermediate version in the DSM-5, and may partially explain this increase in autism prevalence.[11] Second, the increase in public and professional awareness of autism and improvements in earlier identification and easier accessibility to intervention services for autism are another possibility for this increase.[7,12–14] Third, accelerated modernity and technological innovations have led to an increase in social complicatedness and complexity over decades.[15] Using the 2003 to 2020 American Time Use Survey, Kannan and Veazie[16] discovered that, nationally, social isolation increased, social engagement with family and friends decreased, and companionship (shared leisure and recreation) decreased. In particular, they demonstrated that social engagement with friends and companionship plummeted for young Americans; men's social connectedness decline was steeper than for women.[16]

The DSM-5 autism criteria make an interesting but crucial statement: autistic symptoms must be present in the early developmental period, but they may not fully manifest until social demands exceed limited capacities or until learned strategies in later life mask them.[11] The 21st century, with its increased social complexity and complicated mix of reality and virtuality, presents social challenges for those with autistic traits.[15,17] There is evidence that the prevalence of autistic traits (the broader autism phenotype [BAP]) is stable in the population, with an estimate of 5% to 9%.[18,19] Dovgan and Villantis[18] used the Broad Autism Phenotype Questionnaire to examine the prevalence of BAP in young adults, and surprisingly found that 25.3% of the college-aged participants met BAP cutoffs, compared to previous estimates of only 5% to 9% of adult parents of neurotypical children and 14% to 23% of parents of autistic children.[18] Furthermore, the rise in social challenges and complexity caused by modern life may make people with autistic traits more likely to end up in a clinical setting for other nonautistic mental symptoms, such as anxiety, depression, and even suicidal behaviors.[2,20] Such a clinical scenario may lead to the acquisition of the autism diagnosis in those with autistic traits.

2. YOUTH SUICIDE IN THE 21ST CENTURY

Over the last 50 years, suicide rates have risen by 60% globally, and since 2020, suicide has been the cause of more than a million deaths.[21,22] The World Health Organization mortality database study of the young population (preadolescents, adolescents, and young adults) reported that the highest age-standardized

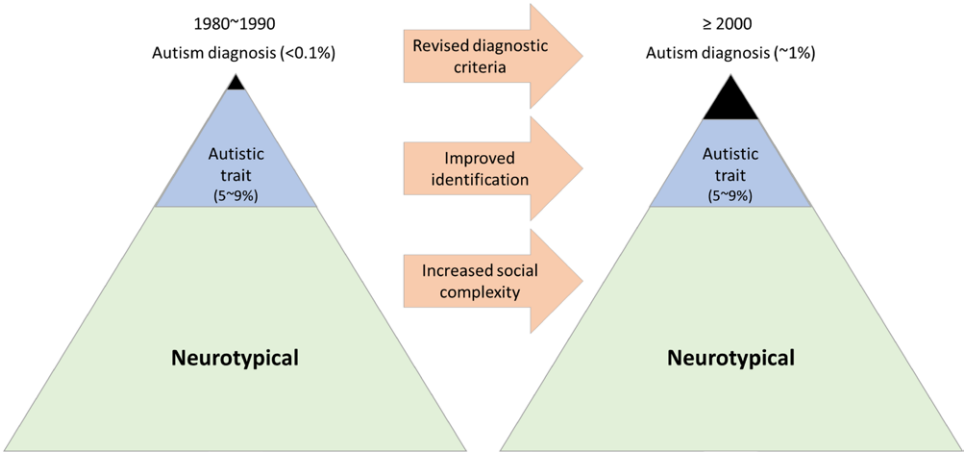


Fig. 1 Illustration of autism prevalence between 1980-1990 and ≥2000.

suicide rate was 15.5/100 000 males in the U.S., with an annual increase of 3.8% among males in 2009 to 2020 and 6.7% among females in 2007 to 2017.[22] Goto et al[23] further found that suicide rates among youth increased during the coronavirus disease 2019 (COVID-19) pandemic relative to prepandemic levels.

In Taiwan, suicide has become the second most prevalent cause of death for adolescents and young adults aged between 15 and 24 years, with the rate rising yearly from 4.0/100 000 in 2000 to 10.7/100 000 in 2022—doubling in only 20 years.[21,24] A time trend analysis for adolescent and young adult suicide between 1971 and 2019 in Taiwan revealed that youth suicide rates climbed 11.5% (95% CI, 5.2-18.1) annually between 2014 and 2019.[21] The increased trend in youth suicide between 2014 and 2019 may echo an upturn in divorce rates among females aged 40 to 59 years in 2014 and self-harm rates among youth aged 15 to 24 years in 2013.[21] In addition, between 2013 and 2016, there was an increase in the number of young people reporting insomnia and suicide ideation, plans, and attempts.[21] In 2013, a study of a nationally representative sample of 2835 Taiwanese college students demonstrated that approximately 12% and 9% of female and male students, respectively, had attempted suicide at least once in the preceding 12 months.[25]

Furthermore, Guo et al[26] examined the psychological disorders (psychological fragility) and suicide attempts in youths during the pre-COVID-19 and post-COVID-19 era in a Taiwan pediatric emergency department, and importantly displayed that in comparison to the prepandemic era (0.28%), the rate of psychological fragility rose throughout the pandemic period (0.4%) and the postpandemic period (0.8%). Additionally, they discovered a notable rise in suicidal attempts among young people, which went from 0.14% before COVID-19 and 0.25% during COVID-19 to 0.42% after COVID-19.[26] Youth suicide is definitely a public mental health crisis worldwide, including Taiwan.

3. PSYCHEDELICS IN THE 21ST CENTURY

The renaissance of psychedelics in psychiatry occurred in the early 21st century after a 30-year strict prohibition of psychedelics (ie, psilocybin, lysergic acid diethylamide [LSD]) as schedule I drugs due to the Controlled Substances Act, which was signed by President Nixon in 1970.[27,28]

Following the success of low-dose ketamine and esketamine, N-methyl-D-aspartate (NMDA) receptor antagonist anesthetic and dissociative drugs, in treating treatment-resistant depression (TRD) and suicidal symptoms in 2010s,[29–31] researchers initiated the pilot clinical trial of psilocybin, a 5-hydroxytryptamine (5-HT) receptor 2A agonist, for anxiety in patients with advanced-stage cancer in 2011.[32] Using a moderate dose (0.2 mg/kg) of psilocybin, Grob et al established the feasibility and safety of administering moderate doses of psilocybin to patients with advanced-stage cancer and anxiety.[32] They found a substantial decrease in anxiety at 1 and 3 months after treatment and a significant improvement in depressive symptoms at 6 months after treatment.[32] In the past decade, increasing evidence supports the beneficial role of psilocybin on mental health, such as anxiety, depression, hopelessness, demoralization, existential distress, and death anxiety, among patients with life-threatening cancer and those who were in end-of-life and palliative care.[28]

Given the preclinical evidence that both NMDA receptor antagonists (i.e. ketamine) and 5-HT_{2A} agonists (i.e. psilocybin) boost glutamate release in the pyramidal cells of the prefrontal cortex, Baumeister et al[33] hypothesized that those hallucinogens or psychedelics may exert an antidepressant effect. Kraehenmann et al[34] completed the phase 1 clinical trial of 0.16 mg/kg psilocybin vs placebo in 25 healthy volunteers in 2014. Using blood oxygen level-dependent functional magnetic resonance imaging to assess the amygdala reactivity to negative stimuli, they revealed that the amygdala responded less to negative stimuli after psilocybin than after a placebo and further discovered an association between the psilocybin-induced reduction in the amygdala's reactivity to negative stimuli and an increase in positive mood state.[34] Furthermore, the first open-label feasibility clinical trial of two oral doses of psilocybin (10 and 25 mg, 7 days apart) with psychological support for patients with TRD was published in 2016.[35] Carhart-Harris et al[35,36] reported that, relative to baseline, depressive and anxiety symptoms decreased significantly at 1 week and 3 months, as well as even 6 months, after high-dose (25 mg psilocybin) treatment, with fair tolerability and without serious or unexpected adverse events.

Five years later (2021), the first double-blind, randomized, controlled trial of psilocybin for TRD treatment was published.[37] In brief, 59 patients with TRD were randomly assigned to either the oral psilocybin or the oral escitalopram (a selective serotonin-reuptake inhibitor) groups.[37] In the psilocybin group, patients were given two doses of 25 mg psilocybin 3 weeks apart, along with a daily placebo for 6 weeks; in the escitalopram group, patients were given two doses of 1 mg psilocybin 3 weeks apart, along with a daily oral escitalopram for 6 weeks.[37] Researchers from the United Kingdom discovered that, using the 16-item Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR), treatment response (defined as a reduction in score of ≥50%) occurred in 70% of the patients in the psilocybin group and in 48% of those in the escitalopram group, with a similar profile of adverse effects between groups.[37] One month later, researchers from the U.S. validated their findings, favoring psilocybin over escitalopram in TRD.[38] Davis et al[38] reported that the QIDS-SR documented a rapid reduction in depression score from baseline to day 1 after session 1 of a single dose of 20 mg/70 kg psilocybin vs placebo (16.7 ± 3.5 vs 6.3 ± 4.4, $p < 0.001$), which remained statistically significantly decreased through the week 4 follow-up after session 2 of 30 mg/70 kg psilocybin vs placebo about 2 weeks apart from session 1. A meta-analysis of 436 adult participants with clinically significant symptoms of depression from seven clinical trials showed that psilocybin exerted a better antidepressant effect compared with comparator treatment.[39] They further suggested that only a moderate or high dose (20-25 mg) of psilocybin showed a sustained antidepressant effect, not a low dose (10-15 mg).[39] Yerubandi et al[40] further stated that the acute adverse effect profile, such as headache, nausea, anxiety, dizziness, and dissociation, of therapeutic single-dose psilocybin appeared to be tolerable and resolved within 48 hours. They found that psilocybin use was not associated with the risk of paranoia and transient thought disorder.[40]

In Australia,3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy for posttraumatic stress disorder (PTSD) has been legal since July 1, 2023, based on the findings from the phase 3 clinical trials that the decrease in the changes in Clinician-Administered PTSD Scale for DSM-5 score was –23.7 for MDMA-assisted therapy vs –14.8 for placebo with therapy ($p < 0.001$).[27,41–44] Australia is the first nation worldwide to allow the use of psychedelics in the treatment of severe psychiatric disorders, such as PTSD. The approval of MDMA-assisted therapy for PTSD in Australia may accelerate the research and clinical use of other psychedelics, especially psilocybin, in other severe psychiatric disorders, such as TRD, outside Australia in the near future.

4. AUTISM AND YOUTH SUICIDE IN THE 21ST CENTURY

Before 2000, there was unbelievably little research on the relationship between autism and suicide.[45] Hardan and Sahl[45] reported that suicidality was more often encountered in individuals with oppositional defiant disorder, affective disorders, and PTSD and less often in autistic individuals and those with severe/profound intellectual disability.

In 2000, a small sample-size comparison study of psychopathology between 20 autistic adolescents and 20 adolescents with conduct disorder revealed that high levels of anxiety disorders were found in autistic adolescents; depression, suicidal ideation, emotional dysregulation, and defiance were found in both groups.[46] In 2011, a case report study by Spencer et al[47] brought attention to the unexpected diagnosis of autism in a suicidal adult in crisis, which further inspired clinicians and researchers to comprehensively clarify an association between autism and suicidality in the next decade, especially in young people. The second issue of the newly established flagship mental health journal, *Lancet Psychiatry*, published a landmark study on the relationship between autism and suicide in 2014, the year after the release of the DSM-5.[48] A retrospective clinical cohort study, involving 374 adults newly diagnosed with autism between 2004 and 2013, revealed that 243 (66%) of 367 respondents self-reported suicidal ideation, 127 (35%) of 365 respondents self-reported plans or attempts at suicide, and 116 (31%) of 368 respondents self-reported depression.[49] Autistic adults had an approximately 10 times higher risk of experiencing lifetime suicidal ideation than did individuals from a general United Kingdom population.[49]

Evidence further discovered that high suicide risk was particularly noted in autistic individuals without intellectual disability but not in those with intellectual disability.[50] A meta-analysis study of 48 186 autistic and BAP individuals demonstrated that pooled prevalence of suicidal ideation was 34.2%, suicide plans 21.9% (13.4-30.4), and suicidal attempts and behaviors 24.3%.[50] Surprisingly, Newell et al[50] found no difference in suicidality estimates between autistic and BAP individuals, which may suggest an independent effect of autism and BAP on suicidality. A genome-wide association study meta-analysis of suicide death and suicidal behaviors found that a single-nucleotide polymorphism rs73182688 in neuroligin 1 (NLGN1, encoding a member of a family of postsynaptic neuronal cell surface proteins) contributed to the genetic pathomechanisms underlying autism and suicidal behaviors.[51,52]

Using the medical and mortality database of the entire Taiwanese population (n = 29 253 529), our previous study examined the suicide risk between 45 398 autistic individuals and 181 592 age-/sex-matched nonautistic individuals and found that the risk of suicide was approximately four times higher in autistic individuals compared with nonautistic individuals.[53] The presence of comorbidities of attention deficit hyperactivity disorder (hazard ratio: 4.66), schizophrenia (4.32), bipolar disorder (6.46), and major depressive disorder (3.97) with autism was associated with substantially higher risks of suicide mortality.[53] Autistic individuals without intellectual disability, but not those with intellectual disability, had a higher risk of suicide than nonautistic individuals, which was compatible with Hirvikoski et al's results that the increase in the risk of suicide was the highest in autistic individuals who had no intellectual disability.[53,54]

5. SEROTONIN AND GLUTAMATE DYSHOMEOSTASIS IN AUTISM AND YOUTH SUICIDE: A POTENTIAL ROLE OF PSYCHEDELICS

Serotonin and glutamate dyshomeostasis are crucial pathomechanisms underlying autism and suicide, which may explain the possible therapeutic effect of psychedelics for suicide and autism (Fig. 2).[55–61] In an in vivo study using single-photon emission computed tomography on eight autistic adults and ten neurotypical nonautistic adults, it was found that autistic individuals had a significant decrease in cortical 5-HT_{2A} receptor binding in the total, anterior, and posterior cingulate; in the bilateral frontal and superior temporal cortices; and in the left parietal cortex.[59] Murphy et al[59] further showed that reduced receptor binding in the anterior and posterior cingulate cortex, as well as the right frontal cortex, was significantly related to abnormal social communication. A meta-analysis of 22 studies that compared blood 5-HT levels in autistic and nonautistic people displayed higher 5-HT levels in autistic people both in whole blood and in platelet-rich plasma compared with nonautistic people.[60] In addition, Spivak et al[57] revealed significantly lower levels of serotonin in platelet-poor plasma in autistic adults compared with non-autistic individuals. Furthermore, preclinical studies

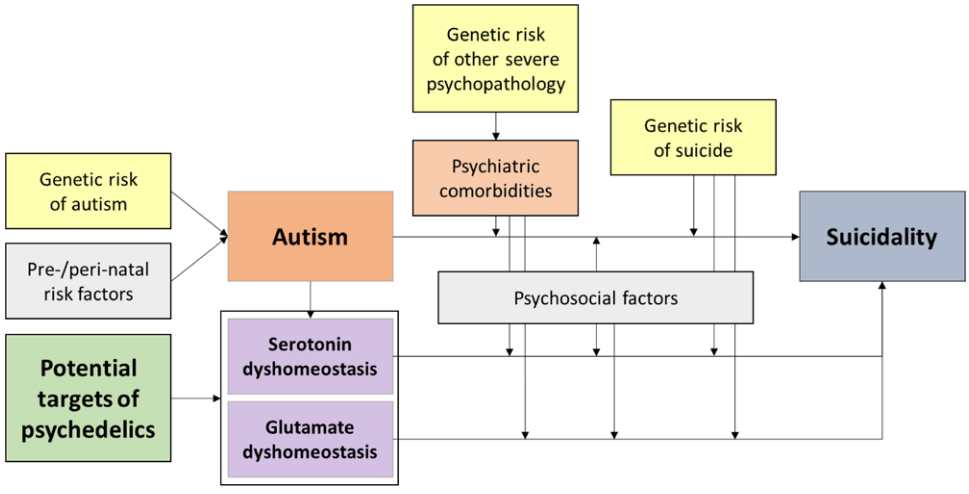


Fig. 2 Illustration of a link between autism, suicidality, and psychedelics.

revealed that transgenic mice expressing the 5-HT transporter (SERT) gene Ala56 variant exhibited enhanced 5-HT clearance rates and hyperserotonemia at the molecular level, as well as alterations in social function, communication, and repetitive behaviors at the behavioral level.[58,62]

Hollestein et al[63] reported that the glutamate gene-set was associated with total autism symptom severity scores on the Autism Diagnostic Observation Schedule-2 and the Autism Diagnostic Interview-Revised in autistic individuals aged 6 to 30 years. Using proton magnetic resonance spectroscopy (^{1}H-MRS) to examine glutamate and gamma-aminobutyric acid (GABA) levels in autistic adults, Horder et al[64] found that glutamate, but not GABA, concentration was reduced in the striatum in autistic individuals, with an association between reduced striatal glutamate levels and increased severity of social symptoms of autism. A metabolite quantitative trait loci analysis using whole-genome genotyping data from 1099 autistic and nonautistic people discovered that plasma glutamine levels were negatively correlated to the severity of restrictive and repetitive behaviors in autism.[65] Lee et al[65] further established a link between plasma glutamine levels and variants in the NLGN1 gene, a gene that encodes postsynaptic cell-adhesion molecules in excitatory neurons. The aforementioned findings provide strong support for the hypothesis that altered 5-HT and glutamate homeostasis can impact autism risk.

Low-dose ketamine's convincing effect against suicide may support the hypothesis of glutamate dyshomeostasis in suicide.[31,66,67] A postmortem brain study revealed increased expression of glutamatergic genes, including GRIN2B, GRIK3, and GRM2, in depressed patients with suicidality compared with those without.[68] Using ^{1}H-MRS to measure glutamate + glutamine (Glx) levels in the anterior cingulate cortex, Lewis et al[69] found higher Glx levels in depressed adolescents with suicidal ideation than those without suicidal ideation. They also reported a positive association between the intensity of suicidal ideation and Glx levels.[69] Davis et al[70] used positron emission tomography and ^{18}F-FPEB to quantify the metabotropic glutamate receptor type 5 (mGluR5) availability in patients with PTSD and observed an up-regulation in frontolimbic mGluR5 availability in patients with PTSD and suicidal ideation compared with those with PTSD without suicidal ideation.

Impaired serotonin neurotransmission is observed in the brains of suicide decedents and in the cerebrospinal fluid of nonfatal suicide attempters.[67] A postmortem brain study of adolescent suicide victims found significantly higher protein expression of 5-HT$_{2A}$ receptors in the prefrontal cortex and hippocampus compared to normal subjects.[71] They discovered that the prefrontal cortex of adolescent suicide victims showed higher protein expression of 5-HT$_{2A}$ receptors on pyramidal cells in cortical layer V but not in other cortical layers or the surrounding neuropil.[71] Anisman et al[72] found that suicide was associated with increased mRNA expression of 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors in the prefrontal cortex, increased mRNA expression of 5-HT$_{2A}$ receptors in the amygdala, and decreased mRNA expression of 5-HT$_{2C}$ receptors in the prefrontal cortex and amygdala. Mapping SERT, 5-HT$_{1A}$, and 5-HT$_{2A}$ receptor binding throughout the prefrontal cortex and in the anterior cingulate cortex postmortem, Underwood et al[73] demonstrated that suicide was associated with higher 5-HT$_{1A}$ binding, higher 5-HT$_{2A}$ binding, and lower SERT binding, and further indicated associations between childhood adversity and higher 5-HT$_{1A}$ and 5-HT$_{2A}$ binding.

The major pharmacological mechanisms of psychedelics involve the serotonergic and glutamatergic systems, which may imply that psychedelics have a potential role in autism and suicide.[27,74]

6. POTENTIAL ROLE OF PSYCHEDELICS IN AUTISM

Although humans have discovered psychedelics' potential impact on sociability for thousands of years, research on their application to autism may still be in its infancy.[74–76] Mason et al[77] reported the subacute effects of a single administration of psilocybin in a social setting on empathy (one of the autistic core symptoms), creative thinking, and subjective well-being in healthy volunteers. Simmons et al[78] first reported the potential role of 100 μg LSD in the modulation of autistic behaviors, such as increased eye-to-face contact and decreased repetitive behaviors during LSD sessions. Even if ethical and methodological flaws are obvious when seen through the prism of modern clinical and ethical research standards, findings from studies in the 1960s may imply the potential benefits of psychedelics in autistic children, including enhanced mood, sociability, and affectionate behaviors; increased emotional closeness, relatedness, and responsiveness to others; improved speech and vocabulary; increased eye and face-gazing behaviors; and decreased aggressive and repetitive behaviors.[74,79–82] However, between 1970 and 2010, there was almost no research regarding the application of psychedelics to autism.

In 2015, Danforth et al[83] proposed a new treatment model of MDMA-assisted therapy for social anxiety in autistic adults. The randomized, double-blind, placebo-controlled pilot clinical trial (n = 12, 8 in the MDMA [75-125 mg] group vs 4 in the placebo group) was completed in 2018 and found sustained (up to 6 months) improvement in social anxiety symptoms in autistic adults following MDMA-assisted psychotherapy.[84] They further indicated that autistic adult participants reported lasting transformation and healing from conditions (ie, psychological trauma and social anxiety) following the MDMA-assisted therapy.[85] An adult mouse study of a single intraperitoneal administration of various psychedelics discovered that, using the social reward-conditioned place preference assay, psilocybin, LSD, ketamine, and MDMA are able to reopen the critical period for social reward learning.[75] Nardou et al[75] further assessed the duration of the psychedelic open state across different psychedelics and demonstrated that the durations of the critical period open state induced by psychedelics in mice were 48 hours for ketamine, 2 weeks for psilocybin, 2 weeks for MDMA, and 3 weeks for LSD. Nardou et al's[75] findings may inspire clinicians and researchers to believe that psychedelics may be not only effective for accessory symptoms of autism, such as social anxiety and depression, but also for core symptoms of autism, including sociability and communication. However, in the 21st century, there has been no clinical trial investigating the potential therapeutic effect of psychedelics on the core symptoms of autism or in autistic children until now. Whether the psychedelics can really improve autism's core symptoms, namely sociability and restrictive and repetitive behaviors, will require further investigation using randomized, double-blind, placebo-controlled clinical trials with a large sample size.

7. POTENTIAL ROLE OF PSYCHEDELICS IN SUICIDE

Horton[86] reported that the mystical experience may function as a suicide preventive. As mentioned, ketamine and esketamine have been confirmed to exert rapid and sustained antisuicidal effects, which were only partially dependent on their antidepressant effects.[31,66,87–90] Chen et al[91] reported that, relative to the midazolam placebo, 0.5 mg/kg ketamine enhanced a positive thought against suicide among patients with TRD and suicidal ideation. Domany et al[92] further indicated that a single infusion of low-dose ketamine can alleviate hopelessness and the effects

persist for up to 3 days. Preclinical studies also revealed that ketamine can enhance resilience against stress and despair.[93,94] In addition, our previous study of 71 patients with TRD receiving either low-dose ketamine or normal saline placebo demonstrated that happiness during infusion, a positive psychedelic experience, was positively related to the antidepressant and antisuicidal effects of ketamine.[95]

Several trials have reported on the effect of classical psychedelics on suicidality, despite the lack of randomized, double-blind, placebo-controlled clinical trials designed to evaluate this effect.[96] Importantly, potential floor effects may occur in the condition of both patients with and without suicidality recruited because these trials have not specifically enrolled patients high in suicidality.[96] A crossover clinical trial of two psilocybin sessions (20 and 30 mg/70 kg, 2 weeks apart) in 24 patients with major depressive disorder showed inconsistent findings: before crossover, reductions in suicidal ideation in the psilocybin condition were not significantly greater than those in the wait-list condition, while after crossover, there was a significant decrease in suicidal ideation.[38] However, this clinical trial only included patients with low risk of suicide and moderately severe depression, which may confound the analysis of psilocybin in suicidality.[38] In addition, Carhart-Harris et al[36] also failed to find significant post-psilocybin reductions in suicidal ideation in a 6-month follow-up after Bonferroni correction. Interestingly, Zeifman et al[97] reported rapid (40, 80, and 180 minutes after administration) and sustained (2, 7, 14, and 21 days after administration) reductions in the suicide item of the Montgomery-Åsberg Depression Rating Scale (MADRS) following a single administration of ayahuasca. The estimated suicide item scores were 2.40 at baseline, 0.73 at 180 minutes postadministration, 0.53 at day 2 postadministration, and 0.33 at day 21 postadministration, respectively.[97] However, the small sample size (n = 15) and relatively low baseline suicidal symptoms (2.40 in the MADRS suicide item) limited the generalization of their findings.[97]

Finally, whether psychedelics may alleviate suicidal symptoms in patients at high suicide risk requires further randomized, double-blind, placebo-controlled clinical trials. Additionally, clinical trials specific to autistic individuals with suicidality may be necessary.

In conclusion, the rapid societal and technological changes, along with the unpredictable global pandemic, pose significant challenges for people in the 21st century. The prevalence of autism and youth suicide has increased in parallel, gaining public health and clinical attention. The 21st renaissance of psychedelics in psychiatry may motivate clinicians and researchers to clarify the pathomechanisms (i.e. serotonin and glutamate dyshomeostasis) underlying autism and suicidality, as well as to further develop novel medications that can help treat autism and suicide. However, the safety and efficacy of psychedelics for autism and suicide require more investigation and evidence.

ACKNOWLEDGMENTS

The study was supported by grant from Taipei Veterans General Hospital (V111C-010, V111C-040, V111C-029, V112C-033, V113C-010, V113C-011, V113C-039), Yen Tjing Ling Medical Foundation (CI-109-21, CI-109-22, CI-110-30, CI-113-30, CI-113-31, CI-113-32), Ministry of Science and Technology, Taiwan (MOST110-2314-B-075-026, MOST110-2314-B-075-024-MY3, MOST109-2314-B-010-050-MY3, MOST111-2314-B-075-014-MY2, MOST111-2314-B-075-013, NSTC111-2314-B-A49-089-MY2), Taipei, Taichung, Kaohsiung Veterans General Hospital, Tri-Service General Hospital, Academia Sinica Joint Research Program (VTA112-V1-6-1, VTA113-V1-5-1) and Veterans General Hospitals and University System of Taiwan Joint Research Program (VGHUST112-G1-8-1, VGHUST113-G1-8-1).

We thank Mr. I.-Fan Hu, MA (Courtauld Institute of Art, University of London; National Taiwan University) for the English editing.

REFERENCES

1. Lord C, Brugha TS, Charman T, Cusack J, Dumas G, Frazier T, et al. Autism spectrum disorder. *Nat Rev Dis Primers* 2020;6:5.
2. Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele J. Autism spectrum disorder. *Lancet* 2018;392:508–20.
3. Chen LC, Chen MH, Hsu JW, Huang KL, Bai YM, Chen TJ, et al. Association of parental depression with offspring attention deficit hyperactivity disorder and autism spectrum disorder: a nationwide birth cohort study. *J Affect Disord* 2020;277:109–14.
4. Leigh JP, Du J. Brief report: forecasting the economic burden of Autism in 2015 and 2025 in the United States. *J Autism Dev Disord* 2015;45:4135–9.
5. Talantseva OI, Romanova RS, Shurdova EM, Dolgorukova TA, Sologub PS, Titova OS, et al. The global prevalence of autism spectrum disorder: a three-level meta-analysis. *Front Psychiatry* 2023;14:1071181.
6. Wing L, Gould J. Severe impairments of social interaction and associated abnormalities in children: epidemiology and classification. *J Autism Dev Disord* 1979;9:11–29.
7. Zeidan J, Fombonne E, Scorah J, Ibrahim A, Durkin MS, Saxena S, et al. Global prevalence of autism: a systematic review update. *Autism Res* 2022;15:778–90.
8. Maenner MJ, Warren Z, Williams AR, Amoakohene E, Bakian AV, Bilder DA, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2020. *MMWR Surveill Summ* 2023;72:1–14.
9. Solmi M, Song M, Yon DK, Lee SW, Fombonne E, Kim MS, et al. Incidence, prevalence, and global burden of autism spectrum disorder from 1990 to 2019 across 204 countries. *Mol Psychiatry* 2022;27:4172–80.
10. Li G, Chen MH, Li G, Wu D, Lian C, Sun Q, et al. A longitudinal MRI study of amygdala and hippocampal subfields for infants with risk of autism. *Graph Learn Med Imaging* 2019;11849:164–71.
11. Rosen NE, Lord C, Volkmar FR. The diagnosis of autism: from Kanner to DSM-III to DSM-5 and beyond. *J Autism Dev Disord* 2021;51:4253–70.
12. Lai MC, Baron-Cohen S. Identifying the lost generation of adults with autism spectrum conditions. *Lancet Psychiatry* 2015;2:1013–27.
13. Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcin C, et al. Global prevalence of autism and other pervasive developmental disorders. *Autism Res* 2012;5:160–79.
14. Williams E, Thomas K, Sidebotham H, Emond A. Prevalence and characteristics of autistic spectrum disorders in the ALSPAC cohort. *Dev Med Child Neurol* 2008;50:672–7.
15. Wang X, Zhai F, Wang Y. Interplay between tradition and modernity: stress and coping experiences among parents of children with autism in Beijing, China. *Behav Sci (Basel)* 2023;13:814.
16. Kannan VD, Veazie PJ. US trends in social isolation, social engagement, and companionship – nationally and by age, sex, race/ethnicity, family income, and work hours, 2003-2020. *SSM Popul Health* 2023;21:101331.
17. Evans B. *The metamorphosis of Autism: a history of child development in Britain*. Manchester (UK); 2017.
18. Dovgan KN, Villanti KM. The prevalence of broad autism phenotype in young adults: the roles of genetic relationship to autism, gender, and academic major. *J Genet Psychol* 2021;182:174–81.
19. Lundstrom S, Reichenberg A, Anckarsater H, Lichtenstein P, Gillberg C. Autism phenotype versus registered diagnosis in Swedish children: prevalence trends over 10 years in general population samples. *BMJ* 2015;350:h1961.
20. Lai MC, Lombardo MV, Baron-Cohen S. Autism. *Lancet* 2014;383:896–910.
21. Chang YH, Lin CY, Liao SC, Chen YY, Shaw FF, Hsu CY, et al. Societal factors and psychological distress indicators associated with the recent rise in youth suicide in Taiwan: a time trend analysis. *Aust N Z J Psychiatry* 2023;57:537–49.

22. Bertuccio P, Amerio A, Grande E, La Vecchia C, Costanza A, Aguglia A, et al. Global trends in youth suicide from 1990 to 2020: an analysis of data from the WHO mortality database. *eClinicalMedicine* 2024;70:102506.
23. Goto R, Okubo Y, Skokauskas N. Reasons and trends in youth's suicide rates during the COVID-19 pandemic. *Lancet Reg Health West Pac* 2022;27:100567.
24. Chen MH, Bai YM, Chen YS, Huang KL, Hsu JW, Su TP. Comorbidity of narcolepsy and schizophrenia in an adolescent patient. *J Chin Med Assoc* 2014;77:598–600.
25. Chou CH, Ko HC, Wu JY, Cheng CP. The prevalence of and psychosocial risks for suicide attempts in male and female college students in Taiwan. *Suicide Life Threat Behav* 2013;43:185–97.
26. Guo BC, Chen YJ, Huang WY, Lin MJ, Wu HP. Psychological disorders and suicide attempts in youths during the pre-COVID and post-COVID era in a Taiwan pediatric emergency department. *Front Psychol* 2023;14:1281806.
27. Reiff CM, Richman EE, Nemeroff CB, Carpenter LL, Widge AS, Rodriguez CI, et al; the Work Group on Biomarkers and Novel Treatments, a Division of the American Psychiatric Association Council of Research. Psychedelics and psychedelic-assisted psychotherapy. *Am J Psychiatry* 2020;177:391–410.
28. Nutt D, Crome I, Young AH. Is it now time to prepare psychiatry for a psychedelic future? *Br J Psychiatry* 2024;1:1–3.
29. Price RB, Kissel N, Baumeister A, Rohac R, Woody ML, Ballard ED, et al. International pooled patient-level meta-analysis of ketamine infusion for depression: in search of clinical moderators. *Mol Psychiatry* 2022;27:5096–112.
30. Su TP, Chen MH, Li CT, Lin WC, Hong CJ, Gueorguieva R, et al. Dose-related effects of adjunctive ketamine in Taiwanese patients with treatment-resistant depression. *Neuropsychopharmacology* 2017;42:2482–92.
31. Su TP, Li CT, Lin WC, Wu HJ, Tsai SJ, Bai YM, et al. A randomized, double-blind, midazolam-controlled trial of low-dose ketamine infusion in patients with treatment-resistant depression and prominent suicidal ideation. *Int J Neuropsychopharmacol* 2023;26:331–9.
32. Guo WB, Sun XL, Liu L, Xu Q, Wu RR, Liu ZN, et al. Disrupted regional homogeneity in treatment-resistant depression: a resting-state fMRI study. *Prog Neuropsychopharmacol Biol Psychiatry* 2011;35:1297–302.
33. Baumeister D, Barnes G, Giaroli G, Tracy D. Classical hallucinogens as antidepressants? A review of pharmacodynamics and putative clinical roles. *Ther Adv Psychopharmacol* 2014;4:156–69.
34. Kraehenmann R, Preller KH, Scheidegger M, Pokorny T, Bosch OG, Seifritz E, et al. Psilocybin-induced decrease in amygdala reactivity correlates with enhanced positive mood in healthy volunteers. *Biol Psychiatry* 2015;78:572–81.
35. Carhart-Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, Kaelen M, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry* 2016;3:619–27.
36. Carhart-Harris RL, Bolstridge M, Day CMJ, Rucker J, Watts R, Erritzoe DE, et al. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology (Berl)* 2018;235:399–408.
37. Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, et al. Trial of psilocybin versus escitalopram for depression. *N Engl J Med* 2021;384:1402–11.
38. Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, et al. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. *JAMA Psychiatry* 2021;78:481–9.
39. Metaxa AM, Clarke M. Efficacy of psilocybin for treating symptoms of depression: systematic review and meta-analysis. *BMJ* 2024;385:e078084.
40. Yerubandi A, Thomas JE, Bhuiya N, Harrington C, Villa Zapata L, Caballero J. Acute adverse effects of therapeutic doses of psilocybin: a systematic review and meta-analysis. *JAMA Netw Open* 2024;7:e245960.
41. Bedi G, Cotton SM, Guerin AA, Jackson HJ. MDMA-assisted psychotherapy for post-traumatic stress disorder: the devil is in the detail. *Aust N Z J Psychiatry* 2023;57:476–81.
42. Berger JJ, Fitzgerald PB. The prescription of psychedelic therapies in Australia and New Zealand: a brief survey of psychiatrists. *Australas Psychiatry* 2023;31:190–4.
43. Mellsop G, Ellis P. Re The prescription of psychedelic therapies in Australia and New Zealand: a brief survey of psychiatrists. *Australas Psychiatry* 2023;31:706.
44. Mitchell JM, Ot'alora GM, van der Kolk B, Shannon S, Bogenschutz M, Gelfand Y, et al. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. *Nat Med* 2023;29:2473–80.
45. Hardan A, Sahl R. Suicidal behavior in children and adolescents with developmental disorders. *Res Dev Disabil* 1999;20:287–96.
46. Green J, Gilchrist A, Burton D, Cox A. Social and psychiatric functioning in adolescents with Asperger syndrome compared with conduct disorder. *J Autism Dev Disord* 2000;30:279–93.
47. Spencer L, Lyketsos CG, Samstad E, Dokey A, Rostov D, Chisolm MS. A suicidal adult in crisis: an unexpected diagnosis of autism spectrum disorder. *Am J Psychiatry* 2011;168:890–2.
48. Kato K, Mikami K, Akama F, Yamada K, Maehara M, Kimoto K, et al. Clinical features of suicide attempts in adults with autism spectrum disorders. *Gen Hosp Psychiatry* 2013;35:50–3.
49. Cassidy S, Bradley P, Robinson J, Allison C, McHugh M, Baron-Cohen S. Suicidal ideation and suicide plans or attempts in adults with Asperger's syndrome attending a specialist diagnostic clinic: a clinical cohort study. *Lancet Psychiatry* 2014;1:142–7.
50. Newell V, Phillips L, Jones C, Townsend E, Richards C, Cassidy S. A systematic review and meta-analysis of suicidality in autistic and possibly autistic people without co-occurring intellectual disability. *Mol Autism* 2023;14:12.
51. Li QS, Shabalin AA, DiBlasi E, Gopal S, Canuso CM, FinnGen ISGC, et al. Genome-wide association study meta-analysis of suicide death and suicidal behavior. *Mol Psychiatry* 2023;28:891–900.
52. Tian C, Paskus JD, Fingleton E, Roche KW, Herring BE. Autism spectrum disorder/intellectual disability-associated mutations in trio disrupt neuroligin 1-mediated synaptogenesis. *J Neurosci* 2021;41:7768–78.
53. Tsai SJ, Chang WH, Cheng CM, Liang CS, Bai YM, Hsu JW, et al. All-cause mortality and suicide mortality in autistic individuals: an entire population longitudinal study in Taiwan. *Autism* 2023;27:2496–506.
54. Hirvikoski T, Boman M, Chen Q, D'Onofrio BM, Mittendorfer-Rutz E, Lichtenstein P, et al. Individual risk and familial liability for suicide attempt and suicide in autism: a population-based study. *Psychol Med* 2020;50:1463–74.
55. Canal CE. Serotonergic psychedelics: experimental approaches for assessing mechanisms of action. *Handb Exp Pharmacol* 2018;252:227–60.
56. Devlin B, Cook EH Jr, Coon H, Dawson G, Grigorenko EL, McMahon W, et al; CPEA Genetics Network. Autism and the serotonin transporter: the long and short of it. *Mol Psychiatry* 2005;10:1110–6.
57. Spivak B, Golubchik P, Mozes T, Vered Y, Nechmad A, Weizman A, et al. Low platelet-poor plasma levels of serotonin in adult autistic patients. *Neuropsychobiology* 2004;50:157–60.
58. Muller CL, Anacker AMJ, Veenstra-VanderWeele J. The serotonin system in autism spectrum disorder: from biomarker to animal models. *Neuroscience* 2016;321:24–41.
59. Murphy DG, Daly E, Schmitz N, Toal F, Murphy K, Curran S, et al. Cortical serotonin 5-HT2A receptor binding and social communication in adults with Asperger's syndrome: an in vivo SPECT study. *Am J Psychiatry* 2006;163:934–6.
60. Gabriele S, Sacco R, Persico AM. Blood serotonin levels in autism spectrum disorder: a systematic review and meta-analysis. *Eur Neuropsychopharmacol* 2014;24:919–29.
61. Hamed NO, Al-Ayadhi L, Osman MA, Elkhawad AO, Qasem H, Al-Marshoud M, et al. Understanding the roles of glutamine synthetase, glutaminase, and glutamate decarboxylase autoantibodies in imbalanced excitatory/inhibitory neurotransmission as etiological mechanisms of autism. *Psychiatry Clin Neurosci* 2018;72:362–73.
62. Veenstra-VanderWeele J, Muller CL, Iwamoto H, Sauer JE, Owens WA, Shah CR, et al. Autism gene variant causes hyperserotonemia, serotonin receptor hypersensitivity, social impairment and repetitive behavior. *Proc Natl Acad Sci U S A* 2012;109:5469–74.
63. Hollestein V, Poelmans G, Forde NJ, Beckmann CF, Ecker C, Mann C, et al. Excitatory/inhibitory imbalance in autism: the role of glutamate and GABA gene-sets in symptoms and cortical brain structure. *Transl Psychiatry* 2023;13:18.
64. Horder J, Petrinovic MM, Mendez MA, Bruns A, Takumi T, Spooren WB, et al. Glutamate and GABA in autism spectrum disorder-a translational magnetic resonance spectroscopy study in man and rodent models. *Transl Psychiatry* 2018;8:106.
65. Lee IH, Walker DI, Lin Y, Smith MR, Mandl KD, Jones DP, et al. Association between neuroligin-1 polymorphism and plasma glutamine

levels in individuals with autism spectrum disorder. *eBioMedicine* 2023;95:104746.
66. Lin WC, Su TP, Li CT, Tsai SJ, Tu PC, Bai YM, et al. Current suicide risk, but not lifetime history of attempted suicide, predicts treatment response to low-dose ketamine infusion: post hoc analysis of adjunctive ketamine study of Taiwanese patients with treatment-resistant depression. *Exp Clin Psychopharmacol* 2023;32:84–9.
67. van Heeringen K, Mann JJ. The neurobiology of suicide. *Lancet Psychiatry* 2014;1:63–72.
68. Gray AL, Hyde TM, Deep-Soboslay A, Kleinman JE, Sodhi MS. Sex differences in glutamate receptor gene expression in major depression and suicide. *Mol Psychiatry* 2015;20:1139.
69. Lewis CP, Port JD, Blacker CJ, Sonmez AI, Seewoo BJ, Leffler JM, et al. Altered anterior cingulate glutamatergic metabolism in depressed adolescents with current suicidal ideation. *Transl Psychiatry* 2020;10:119.
70. Davis MT, Hillmer A, Holmes SE, Pietrzak RH, DellaGioia N, Nabulsi N, et al. In vivo evidence for dysregulation of mGluR5 as a biomarker of suicidal ideation. *Proc Natl Acad Sci U S A* 2019;116:11490–5.
71. Pandey GN, Dwivedi Y, Rizavi HS, Ren X, Pandey SC, Pesold C, et al. Higher expression of serotonin 5-HT(2A) receptors in the postmortem brains of teenage suicide victims. *Am J Psychiatry* 2002;159:419–29.
72. Anisman H, Du L, Palkovits M, Faludi G, Kovacs GG, Szontagh-Kishazi P, et al. Serotonin receptor subtype and p11 mRNA expression in stress-relevant brain regions of suicide and control subjects. *J Psychiatry Neurosci* 2008;33:131–41.
73. Underwood MD, Kassir SA, Bakalian MJ, Galfalvy H, Dwork AJ, Mann JJ, et al. Serotonin receptors and suicide, major depression, alcohol use disorder and reported early life adversity. *Transl Psychiatry* 2018;8:279.
74. Markopoulos A, Inserra A, De Gregorio D, Gobbi G. Evaluating the potential use of serotonergic psychedelics in autism spectrum disorder. *Front Pharmacol* 2021;12:749068.
75. Nardou R, Sawyer E, Song YJ, Wilkinson M, Padovan-Hernandez Y, de Deus JL, et al. Psychedelics reopen the social reward learning critical period. *Nature* 2023;618:790–8.
76. Rodriguez Arce JM, Winkelman MJ. Psychedelics, sociality, and human evolution. *Front Psychol* 2021;12:729425.
77. Mason NL, Mischler E, Uthaug MV, Kuypers KPC. Sub-acute effects of psilocybin on empathy, creative thinking, and subjective well-being. *J Psychoactive Drugs* 2019;51:123–34.
78. Simmons JQ 3rd, Leiken SJ, Lovaas OI, Schaeffer B, Perloff B. Modification of autistic behavior with LSD-25. *Am J Psychiatry* 1966;122:1201–11.
79. Bender L, Goldschmidt L, Sankar DV. Treatment of autistic schizophrenic children with LSD-25 and UML-491. *Recent Adv Biol Psychiatry* 1961;4:170–9.
80. Sigafoos J, Green VA, Edrisinha C, Lancioni GE. Flashback to the 1960s: LSD in the treatment of autism. *Dev Neurorehabil* 2007;10:75–81.
81. Freedman AM, Ebin EV, Wilson EA. Autistic schizophrenic children. An experiment in the use of d-lysergic acid diethylamide (LSD-25). *Arch Gen Psychiatry* 1962;6:203–13.
82. Campbell M. Pharmacotherapy in early infantile autism. *Biol Psychiatry* 1975;10:399–423.
83. Danforth AL, Struble CM, Yazar-Klosinski B, Grob CS. MDMA-assisted therapy: a new treatment model for social anxiety in autistic adults. *Prog Neuropsychopharmacol Biol Psychiatry* 2016;64:237–49.
84. Danforth AL, Grob CS, Struble C, Feduccia AA, Walker N, Jerome L, et al. Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: a randomized, double-blind, placebo-controlled pilot study. *Psychopharmacology (Berl)* 2018;235:3137–48.
85. Danforth AL. Embracing neurodiversity in psychedelic science: a mixed-methods inquiry into the MDMA experiences of autistic adults. *J Psychoactive Drugs* 2019;51:146–54.
86. Horton PC. The mystical experience as a suicide preventive. *Am J Psychiatry* 1973;130:294–6.
87. Schlegelmilch M, Plint AC, Barrowman N, Gray C, Bhatt M. Intravenous ketamine for emergency department treatment of suicidal ideation in a paediatric population: protocol for a double-blind, randomised, placebo-controlled, parallel-arm pilot trial (KSI study). *BMJ Open* 2024;14:e085681.
88. Shen Z, Gao D, Lv X, Wang H, Yue W. A meta-analysis of the effects of ketamine on suicidal ideation in depression patients. *Transl Psychiatry* 2024;14:248.
89. Wang YT, Wang XL, Lei L, Guo ZY, Kan FF, Hu D, et al. A systematic review and meta-analysis of the efficacy of ketamine and esketamine on suicidal ideation in treatment-resistant depression. *Eur J Clin Pharmacol* 2024;80:287–96.
90. Witt K, Potts J, Hubers A, Grunebaum MF, Murrough JW, Loo C, et al. Ketamine for suicidal ideation in adults with psychiatric disorders: a systematic review and meta-analysis of treatment trials. *Aust N Z J Psychiatry* 2020;54:29–45.
91. Chen MH, Su TP, Li CT, Lin WC, Wu HJ, Tsai SJ, et al. Effects of melancholic features on positive and negative suicidal ideation in patients with treatment-resistant depression and strong suicidal ideation receiving low-dose ketamine infusion. *Eur Arch Psychiatry Clin Neurosci* 2024;274:759–66.
92. Domany Y, Shelton RC, McCullumsmith CB. Ketamine for acute suicidal ideation. An emergency department intervention: a randomized, double-blind, placebo-controlled, proof-of-concept trial. *Depress Anxiety* 2020;37:224–33.
93. Evers AG, Murrough JW, Charney DS, Costi S. Ketamine as a prophylactic resilience-enhancing agent. *Front Psychiatry* 2022;13:833259.
94. Brachman RA, McGowan JC, Perusini JN, Lim SC, Pham TH, Faye C, et al. Ketamine as a prophylactic against stress-induced depressive-like behavior. *Biol Psychiatry* 2016;79:776–86.
95. Daws RE, Timmermann C, Giribaldi B, Sexton JD, Wall MB, Erritzoe D, et al. Increased global integration in the brain after psilocybin therapy for depression. *Nat Med* 2022;28:844–51.
96. Zeifman RJ, Singhal N, Breslow L, Weissman CR. On the relationship between classic psychedelics and suicidality: a systematic review. *ACS Pharmacol Transl Sci* 2021;4:436–51.
97. Zeifman RJ, Singhal N, Dos Santos RG, Sanches RF, de Lima Osorio F, Hallak JEC, et al. Rapid and sustained decreases in suicidality following a single dose of ayahuasca among individuals with recurrent major depressive disorder: results from an open-label trial. *Psychopharmacology (Berl)* 2021;238:453–9.