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THOUGHT LEADERS INVITED REVIEW

MDMA in Psychiatry: From PTSD to emerging indications, safety, and future directions

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MDMA, 3,4-methylenedioxymethamphetamine ("ecstasy," "molly"), is a distinctive entactogen that reverses the serotonin (5-HT) transporter to increase synaptic 5-HT, while also engaging catecholaminergic and oxytocinergic pathways. In clinical trials, MDMA-assisted psychotherapy has yielded substantial improvements in treatment-resistant posttraumatic stress disorder (PTSD), although regulatory approval has been delayed over concerns about functional unblinding and protocol rigor. Early randomized, placebo-controlled studies also suggest benefits in autism spectrum disorder, eating disorders with comorbid PTSD, and anxiety related to life-threatening illness. Large epidemiological and naturalistic studies associate MDMA use with lower rates of depression, reduced suicidal ideation, and improved posttrauma coping, though causal inference is limited. MDMA-associated hyponatremia appears primarily linked to oxytocin-mediated antidiuresis (elevated plasma oxytocin without a copeptin rise), with arginine vasopressin potentially contributing under hyperthermia or polydipsia. In rodents, MDMA pretreatment enhances stress resilience and preserves adaptive neuroplasticity via a vagus-dependent gut–brain axis. This review traces MDMA's history; synthesizes evidence on acute risks (hyperthermia, hyponatremia, sympathomimetic overstimulation, and transient cognitive effects); and evaluates long-term outcomes and putative resilience mechanisms. Future work should standardize dosing and psychotherapeutic protocols, incorporate biomarkers to guide patient selection, and conduct adequately powered trials across emerging indications, alongside long-term safety monitoring and multidisciplinary collaboration.

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Introduction

MDMA (3,4-methylenedioxymethamphetamine), commonly known as ecstasy or molly, is a derivative of psychostimulant methamphetamine first synthesized by Merck chemist Anton Köllisch in 1912 as an "anorectic" under the names "Methylsafrylamin" and "Safrylmethylamin" (Figures 1 and 2) (1, 2). It is widely classified as an entactogen, reflecting its potent empathogenic effects in humans. Although Merck never developed it beyond a chemical precursor, Alexander Shulgin rediscovered its unique psychoactive effects in the 1970s (Figure 2). In the late 1970s and early 1980s, several psychotherapists began using MDMA to augment talk therapy (3). Early open-label pilot studies—most notably by Greer and Tolbert—reported pronounced and lasting improvements in mood, social functioning, and insight following a single MDMA-assisted session (3, 4).

By the mid-1980s, rising recreational use and concerns about neurotoxicity and dependence led to MDMA's classification as a Schedule I substance in 1985, effectively halting clinical research (Figure 2). Interest reemerged in the early 2000s when pilot trials demonstrated that MDMA-assisted psychotherapy could benefit treatment-resistant posttraumatic stress disorder (PTSD), prompting the Food and Drug Administration (FDA) to grant Breakthrough Therapy designation in August 2017 (Figure 2). Since then, controlled trials have investigated optimal dosing, safety profiles, and mechanisms of action, positioning MDMA as a potential paradigm shift in psychiatric treatment (5, 6).

Unlike classical stimulants, MDMA enhances monoaminergic transmission—particularly serotonin (5-HT) release—and stimulates oxytocin secretion, producing empathogenic effects such as increased sociability, emotional openness, and reduced fear responses (7–9). These interoceptive effects distinguish MDMA from both psychostimulants and classical hallucinogens. Today's research sits at the intersection of neuroscience, psychopharmacology, and psychotherapy, with ongoing studies clarifying long-term safety, refining therapeutic protocols, and exploring applications beyond PTSD—including autism spectrum disorder (ASD), eating disorders (EDs), depression, social anxiety, and substance use disorders (10).

This review traces MDMA's journey—from its chemical origins and early clinical promise through prohibition and resurgence—to summarize current evidence, highlight unresolved questions, and outline future directions for harnessing its therapeutic potential.

Pharmacology of MDMA

Serotonin and catecholamine systems

MDMA's primary action is to reverse the serotonin transporter (SERT), causing a massive efflux of 5-HT into the synaptic cleft that underlies its acute mood elevation, anxiolysis, and prosocial (empathogenic) effects (11–13). In rodents, genetic or pharmacological blockade of SERT or 5-HT_{1B} receptors in the nucleus accumbens (NAc) abolishes MDMA-induced social affiliation, whereas its rewarding (reinforcing) effects depend on dopaminergic signaling (14, 15). The new study shows that MDMA's strong 5-HT release in the NAc actively restrains its own dopamine (DA)-mediated reinforcement, helping explain why MDMA has lower abuse liability than methamphetamine despite similar DA-releasing capacity (16). In mice, NAc DA release scaled with conditioned place preference (CPP); knocking out SERT (or locally blocking SERT with escitalopram) or antagonizing 5-HT_{2C} receptors each boosted DA release and shifted CPP leftward, indicating that 5-HT tone in the NAc suppresses reinforcement. By contrast, blocking 5-HT_{1B} receptors—which mediate MDMA's prosocial effects—did not enhance reinforcement, suggesting distinct circuits for prosocial versus abuse-linked actions. Using this assay platform, (*R*)-MDMA is predicted to retain prosocial effects with low abuse potential.

Both systemic MDMA and direct optogenetic stimulation of NAc 5-HT inputs rescue social and empathy-like deficits in multiple ASD models, highlighting NAc 5-HT as a core mediator of its empathogenic profile

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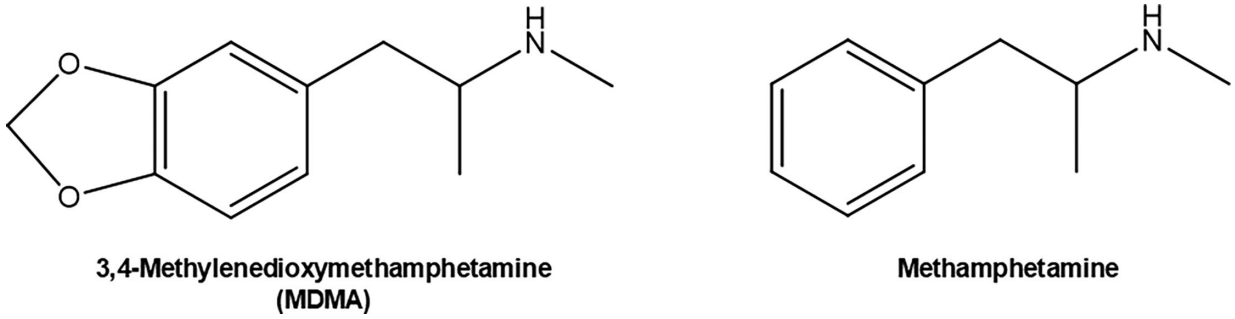

Figure 1. Chemical structures of MDMA and methamphetamine. Structures of 3,4-methylenedioxy-*N*-methylamphetamine (MDMA) and *N*-methylamphetamine (methamphetamine), illustrating their shared phenethylamine core and highlighting MDMA's unique 3,4-methylenedioxy bridge.

(17, 18). Using dynamic [^{11}C]DASB positron emission tomography (PET), Ionescu et al. (19) revealed clear changes in molecular connectivity after a single dose of MDMA in rats, establishing a direct link between SERT occupancy and alterations in the functional brain network.

In human volunteers, pretreatment with selective serotonin reuptake inhibitors such as citalopram markedly blunts MDMA's subjective "entactogenic" and cardiovascular effects (20–22), and the 5-HT$_{2A}$ receptor antagonist ketanserin selectively reduces its perceptual changes and emotional excitation (22). Together, these findings confirm that 5-HT release is both necessary and largely sufficient for MDMA's psychoactive effects.

Beyond 5-HT, MDMA acts as a releaser and reuptake inhibitor of norepinephrine—and to a lesser extent DA—fueling its sympathomimetic, stimulant, and reinforcing properties (23, 24). It also binds multiple receptors (5-HT$_{1A}$/$_{1B}$/$_{2A}$, M$_1$ muscarinic, H$_1$ histamine, α/β-adrenergic, and DA receptors), enriching its subjective and physiological profile. Microdialysis studies in mice demonstrate that MDMA elevates striatal DA via both DAT (DA transporter) and SERT, since increases are abolished only in DAT/SERT double knockouts (25).

Finally, MDMA provokes robust neuroendocrine responses: chronic users show 100%–200% higher basal cortisol (26), while acute "dancefloor" exposures can spike cortisol up to 800% (27). Transient prolactin surges and inappropriate vasopressin release also occur, occasionally precipitating hyponatremia (Figure 3) (28–32).

Oxytocin system and hypothalamic–pituitary–adrenal axis

Oxytocin is a hypothalamic peptide hormone and neuromodulator that promotes social bonding, trust, and prosocial behaviors by acting on limbic and reward circuits. It also modulates stress and anxiety responses, dampening the hypothalamic–pituitary–adrenal (HPA) axis and exerting anti-inflammatory effects (33–36). MDMA powerfully engages the oxytocin system, a key mediator of social bonding, trust, and empathy. In humans, a single oral dose produces rapid plasma oxytocin rises at 90–120 min that correlate more strongly with sociability and closeness than with blood MDMA levels (37–40). Genetic variation in the *OXTR* gene (rs53576) further modulates the prosocial effects of MDMA in humans (41).

Enantiomer-specific studies reveal that (*S*)-MDMA (125 mg) elicits greater stimulant-like subjective effects, cardiovascular activation, and elevations in prolactin, cortisol, and oxytocin than (*R*)-MDMA or the racemate, underscoring distinct pharmacological profiles (42). Neurophysin I, a stable surrogate for oxytocin, rises 20-fold after MDMA in healthy controls but not in patients with hypothalamic–pituitary dysfunction, validating its use as a biomarker and linking oxytocin surges to euphoria, trust, and fear reduction (43).

Additionally, a single 100 mg dose of MDMA in healthy control subjects stimulated the HPA axis, producing significant increases in plasma adrenocorticotropic hormone levels from baseline to 120 min (44). This was accompanied by a significant rise in cortisol levels. In contrast, MDMA did not alter levels of thyroid-stimulating hormone, luteinizing hormone, prolactin, growth hormone, free thyroxine, testosterone, or estradiol. These findings suggest that MDMA strongly activates the HPA axis in humans.

In rodents, MDMA activates oxytocin neurons in the paraventricular and supraoptic nuclei of the hypothalamus via 5-HT$_{1A}$ receptor stimulation—effects that, along with associated social behaviors, are blocked by the 5-HT$_{1A}$ antagonist WAY-100635 (45, 46). Drug-discrimination studies further show that the oxytocin analog carbetocin partially substitutes for MDMA's subjective cue, whereas the oxytocin antagonist atosiban disrupts MDMA-appropriate responding, underscoring oxytocin receptor activation as a key interoceptive component of its prosocial effects (47).

In a PTSD model, Avgana et al. (48) demonstrated that microinjecting MDMA into the medial prefrontal cortex (mPFC) of male rats enhanced fear extinction and reversed both the shock-induced increase in

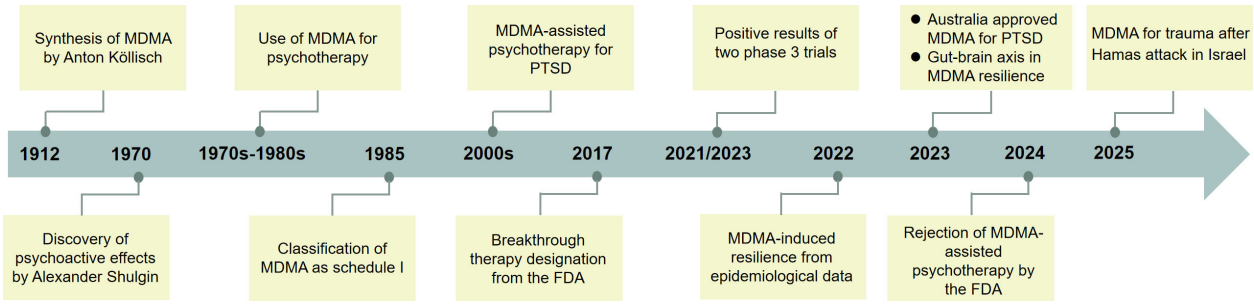

Figure 2. Timeline of MDMA's development and clinical research milestones. A chronological overview of pivotal events: (1) First synthesis of MDMA in 1912. (2) Rediscovery and early psychotherapeutic applications in the 1970s-1980s. (3) Drug Enforcement Administration (DEA) classifies MDMA as a Schedule I substance in 1985. (4) Launch of Phase I safety trials for MDMA-assisted psychotherapy in the early 2000s. (5) FDA grants Breakthrough Therapy Designation in 2017. (6) Publication of positive phase III trial results in 2021 and 2023. (7) FDA issues a non-approval decision for MDMA-assisted psychotherapy. (8) Emerging evidence of MDMA-induced resilience in humans and rodent studies from 2022. (9) Australia's Therapeutic Goods Administration approved MDMA for PTSD under Schedule 8, and key findings of gut–brain axis in MDMA resilience in 2023. (10) Ongoing controlled trials in PTSD, ASD, and EDs. Each milestone is annotated with the year and a brief descriptor of its impact on MDMA's therapeutic trajectory.

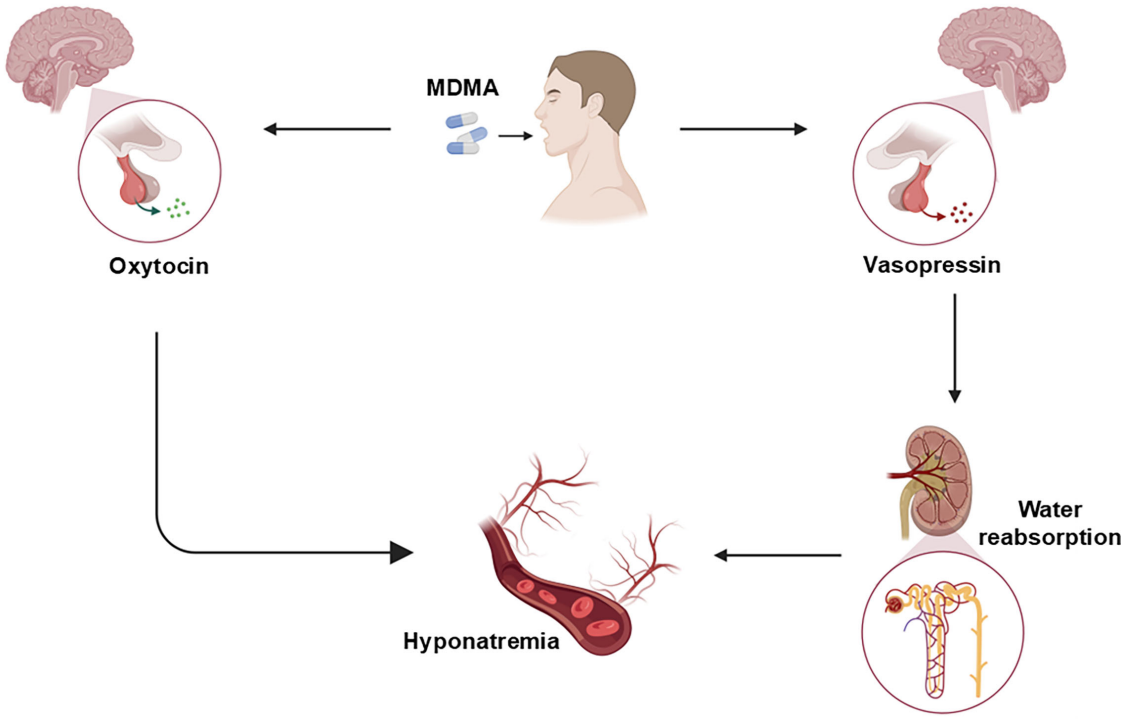

Figure 3. Mechanisms of MDMA-induced dilutional hyponatremia. MDMA acutely increases synaptic serotonin, promoting antidiuresis through two pathways. Primary evidence indicates an oxytocin-mediated effect: plasma oxytocin rises ~4- to 5-fold without a concomitant increase in copeptin (a vasopressin precursor fragment), consistent with enhanced free-water reabsorption. In parallel, nonosmotic vasopressin (ADH) release may contribute under heat stress, hyperthermia, or excessive water intake. Both pathways increase aquaporin-2 insertion in renal collecting ducts, reducing free-water clearance. When combined with high fluid intake, plasma becomes diluted and serum sodium falls, producing hyponatremia. Controlled trials show an average ~3 mEq/L sodium reduction and ~31% hyponatremia incidence with unrestricted fluids; fluid restriction mitigates risk. This illustration was created using BioRender.com.

freezing and deficits in social behavior. Shock exposure disrupted oxytocin receptor gene expression and triggered neuroinflammation in the mPFC and basolateral amygdala; MDMA treatment normalized these alterations. Importantly, the oxytocin receptor antagonist L-368,899 abolished MDMA's beneficial effects on extinction and freezing. Together, these findings suggest that MDMA's therapeutic actions in this PTSD model depend on modulating oxytocin receptor expression and neuroinflammatory processes, with oxytocinergic signaling mediating its impact on extinction and anxiety.

Vagus nerve plays a role in the communication between the brain and peripheral organs including gastrointestinal tracts (49–52). Finally, subdiaphragmatic vagotomy in rats drastically reduces both baseline and MDMA-induced oxytocin release and c-Fos activation in hypothalamic nuclei, demonstrating the vagus nerve's critical role in gut–brain mediation of MDMA's oxytocinergic effects (53).

Other systems

MDMA also modulates glutamatergic neurotransmission. It triggers a rapid extracellular glutamate surge in the dentate gyrus via 5-HT_{2A} receptor activation, causing parvalbumin interneuron loss that is prevented by *N*-methyl-D-aspartate receptor (NMDAR) antagonists (MK-801) or selective 5-HT_{2A} blockade (MDL100907) (54). Both NMDAR and AMPAR (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor) contribute to MDMA's modulation of social defeat stress in mice (55).

In summary, MDMA's multifaceted pharmacology—spanning monoamines, neuroendocrine hormones, the oxytocin system, and glutamatergic circuits—underpins its distinctive therapeutic profile and highlights diverse targets for probing its clinical benefits and potential risks.

Adverse events of MDMA

Hyperthermia and hyponatremia are the most significant acute adverse effects of MDMA use. MDMA can cause dangerous elevations in body temperature and dilute blood sodium—even when taken alone—and these risks are amplified by vigorous activity and excessive fluid intake (Table 1) (24, 56–59). Sympathomimetic overstimulation produces tachycardia, hypertension, sweating, jaw clenching (bruxism), nausea, and blurred vision (Figure 4). In severe cases, this overstimulation can progress to serotonin syndrome, rhabdomyolysis, acute liver injury, multiorgan failure, or sudden death (Figure 4). Headache, difficulty concentrating, insomnia, and fatigue frequently occur in the hours to days following MDMA ingestion (Table 1) (60, 61).

Acute hyponatremia is a potentially serious complication after even a single dose of MDMA. Across four placebo-controlled crossover trials (100–125 mg), MDMA lowered plasma sodium by ~3 mEq/L; with unrestricted fluids, ~31% developed hyponatremia. Concurrently, plasma oxytocin rose ~4- to 5-fold without an accompanying increase in copeptin (a vasopressin precursor fragment), implicating oxytocin-mediated antidiuresis as the principal mechanism. Arginine vasopressin (ADH) cannot be excluded under heat stress, hyperthermia, or excessive water intake, where nonosmotic ADH release may occur. Importantly, fluid restriction mitigated this risk (Figure 3) (62).

A recent study by Rana et al. (63) demonstrated that bile acids and the gut microbiota contribute to MDMA-induced hyperthermia. A single injection of MDMA (20 mg/kg) altered serum levels of primary unconjugated bile acids (cholic acid and chenodeoxycholic acid) and the secondary bile acid deoxycholic acid in control rats. Five days of microbiome depletion—via vancomycin, bacitracin, and neomycin in the drinking water—abolished these bile acids and converted MDMA's hyperthermic effect into a hypothermic response. These findings suggest that gut microbiota-derived bile acids are key mediators of MDMA-induced hyperthermia (Figure 4) (63).

Heavy, prolonged recreational MDMA use has been linked to persistent sleep disturbances, depressed mood, anxiety, impulsivity, and hostility. Cognitive deficits—particularly in episodic memory, working memory,

Table 1. Adverse events in humans after acute and chronic treatment of MDMA (3,4-methylenedioxymethamphetamine)

Acute adverse events of MDMA[a]	Symptoms
Cardiovascular effects	Tachycardia, hypertension, and, less frequently, arrhythmias or chest pain
Thermoregulatory disturbances	Hyperthermia or, paradoxically, hyponatremia due to inappropriate vasopressin release and excessive water intake
Neuropsychiatric and somatic symptoms	Anxiety, agitation, confusion, jaw clenching (bruxism), nausea, headache, sweating, and, in rare cases, serotonin syndrome
Adverse events with chronic MDMA use	**Symptoms**
Cognitive and mood disturbances	Persistent memory impairments, deficits in attention and executive function, as well as increased risk of depression and anxiety during withdrawal
Neurotoxicity indicators	Evidence of long-term serotonergic axon damage and reduced serotonin transporter density on neuroimaging
Other health issues	Sleep disorders, dental problems (from bruxism), potential liver strain, and the development of substance-use disorder patterns

[a]3,4-methylenedioxymethamphetamine.

and attention—may last 6 months or longer after cessation (Table 1) (59, 64).

Neurotoxicity in the brain of MDMA users

Human neuroimaging and cognitive findings

PET studies in abstinent MDMA users consistently show reduced SERT availability throughout cortical and subcortical regions, alongside compensatory upregulation of postsynaptic 5-HT_{2A} receptors (65–68). These parallel presynaptic and postsynaptic changes suggest serotonergic terminal damage may underlie the mood, cognitive, and impulse-control disturbances observed in chronic users. Structural magnetic resonance imaging (MRI) further reveals hippocampal volume losses and cortical thinning (notably in orbitofrontal and parietal areas), while diffusion- and functional-MRI studies document white-matter microstructural alterations and aberrant activation during memory and attention tasks (69, 70). Neuropsychological testing corroborates these imaging findings, showing deficits in verbal/visual memory, sustained attention, and executive function that often correlate with individual SERT reductions (71). However, variability in polydrug exposure and abstinence duration underscores the need for longitudinal, controlled studies to distinguish lasting neurotoxicity from reversible neuroadaptations.

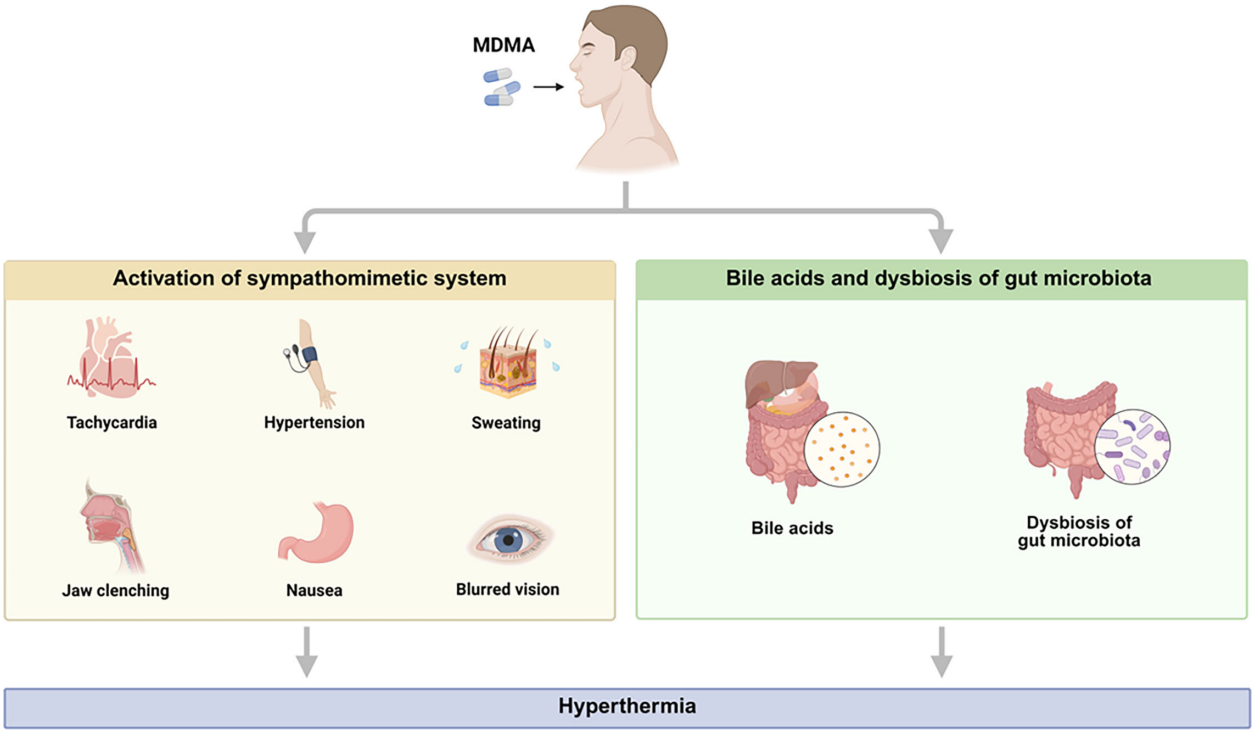

Figure 4. Sympathetic activation and thermoregulatory dysregulation in MDMA-induced hyperthermia. MDMA acutely elevates central monoamines (serotonin, norepinephrine, and dopamine), producing sympathetic hyperactivation that increases heart rate and blood pressure, induces peripheral vasoconstriction, and amplifies muscle activity (e.g., jaw clenching and tremor), thereby raising metabolic heat production. Concurrent thermoregulatory impairment—including reduced sweating and cutaneous heat loss—combined with environmental/behavioral stressors (crowded, warm venues; prolonged exertion) limits heat dissipation and precipitates hyperthermia. Emerging evidence also links MDMA to gut microbiota dysbiosis and altered bile acid profiles, which may further influence thermogenesis and heat clearance. This illustration was created using BioRender.com.

Preclinical rodent studies

In rodent models, high-dose MDMA triggers an acute phase of massive 5-HT depletion and tryptophan-hydroxylase inactivation, followed by a delayed, sustained reduction in tissue 5-HT levels, SERT binding, and synthetic-enzyme activity lasting months (11, 72–76). Histology reveals swollen, fragmented ("dystrophic") serotonin axons—especially from the dorsal raphe—consistent with distal axotomy without cell-body loss (77). MDMA-induced hyperthermia exacerbates oxidative stress and free-radical formation, and interventions that lower core temperature or scavenge radicals attenuate these serotonergic injuries (78).

Nonhuman primate studies

Squirrel monkeys and macaques display a similar but more protracted neurotoxic profile: forebrain 5-HT depletions and SERT losses persist for years, and histopathology shows argyrophilic axonal degeneration and microglial activation within serotonergic projection areas—while dopaminergic and other monoaminergic systems remain relatively intact (79–82).

Together, human imaging and behavioral data, rodent models, and primate studies converge to demonstrate that MDMA selectively injures serotonergic nerve terminals via mechanisms amplified by hyperthermia and oxidative stress. These findings have critical implications for balancing MDMA's therapeutic promise against its potential for long-term neurotoxicity.

MDMA-assisted psychotherapy

Posttraumatic stress disorder

Renewed interest in MDMA-assisted psychotherapy began in 1986 when Rick Doblin founded the Multidisciplinary Association for Psychedelic Studies (MAPS) to explore its therapeutic potential. Early Phase I safety trials around 2000 paved the way for Phase II work: the first randomized, controlled trial in 2010 treated 20 patients with treatment-refractory PTSD, reporting an 80% remission rate that persisted at 3 years (83, 84). A subsequent double-blind Phase II trial in military veterans showed that MDMA doses of 75 mg and 125 mg yielded significantly greater reductions in PTSD symptom severity than a low-dose (30 mg) comparator (85).

In August 2017, the FDA granted Breakthrough Therapy designation to MDMA-assisted psychotherapy, accelerating its clinical development (Figure 2). MAPS Public Benefit Corporation (now Lykos Therapeutics) completed two pivotal Phase III trials (86, 87) in December 2023 and submitted a New Drug Application; however, in August 2024 the FDA requested an additional Phase III study, citing concerns over trial conduct and data integrity (88, 89). Table 2 summarizes the frequencies of treatment-emergent adverse events (TEAEs) from two clinical trials (88, 89). Most participants experienced at least one TEAE during the studies. No serious TEAEs were reported. The most frequently reported TEAEs were muscle tightness, nausea, decreased appetite, and hyperhidrosis.

Australia's Therapeutic Goods Administration reclassified MDMA and psilocybin to Schedule 8, effective July 1, 2023, permitting trained psychiatrists to prescribe them alongside psychotherapy under ethics-committee oversight (Figure 2) (90–92). Critics argue this move is premature given the lack of standardized treatment protocols and limited high-quality evidence on real-world safety and efficacy. Recent systematic reviews report symptom, response, and remission benefits for PTSD, but rate the certainty of efficacy as low to very low due to bias, small samples, and short follow-up; safety conclusions remain constrained by inconsistent adverse event reporting (93). Future work must rigorously assess study bias, therapy protocols, dosing regimens, and long-term outcomes to inform clinical adoption.

When the FDA ultimately rejected the application, it highlighted pervasive functional unblinding—90% of active-drug and 75% of placebo participants correctly guessed their assignment—and inadequately defined psychotherapeutic protocols. Serious safety and data-integrity issues (including under-reported adverse events, compromised informed consent, mishandled sexual-misconduct allegations, and missing abuse-liability data) further undermined the submission (94). In draft guidance, the FDA recommended more rigorous blinding strategies (e.g., low-dose comparators) and clearer metrics for evaluating therapy's contribution to outcomes. Despite this setback, MDMA-assisted psychotherapy remains one of the most promising treatments for refractory PTSD; the field must now establish consensus on acceptable unblinding thresholds, standardized therapy protocols, and integrated trial designs that combine drug and psychotherapeutic elements (94).

Table 2. Adverse events in clinical trials of MDMA (3,4-methylenedioxymethamphetamine) for PTSD (posttraumatic stress disorder) (Mitchell et al. 2021 and 2023)

Adverse event	MDMA[a] (n = 46)	Placebo (n = 44)
Muscle tightness	29 (63.0%)	5 (11.4%)
Decreased appetite	24 (52.2%)	5 (11.4%)
Nausea	14 (30.4%)	5 (11.4%)
Hyperhidrosis	9 (19.6%)	1 (2.3%)
Feeling cold	9 (19.6%)	3 (6.8%)
Restlessness	7 (15.2%)	0
Mydriasis	7 (15.2%)	0
Adverse event	**MDMA (n = 53)**	**Placebo (n = 51)**
Muscle tightness	31 (58.5%)	13 (25.5%)
Nausea	24 (45.3%)	11 (21.6%)
Nausea	19 (35.8%)	5 (9.8%)
Hyperhidrosis	18 (34.0%)	3 (5.9%)
Feeling hot	14 (26.4%)	6 (11.8%)
Feeling cold	11 (20.8%)	3 (5.9%)
Paresthesia	10 (18.9%)	1 (2.0%)
Chest discomfort	9 (17.0%)	2 (3.9%)
Dry mouth	9 (17%)	4 (7.8%)
Chills	8 (15.1%)	1 (2.0%)
Feeling jittery	8 (15.1%)	0
Restlessness	8 (15.1%)	2 (3.9%)
Vision blurred	8 (15.1%)	0

[a] PTSD: posttraumatic stress disorder

NOTE: The most common treatment-emergent adverse events with incidence >15%. From the data of Mitchell et al. (86, 87).

In a double-blind, placebo-controlled crossover trial in 16 adults with subthreshold PTSD symptoms, participants were first stratified by baseline nonconscious threat-evoked functional magnetic resonance imaging (fMRI) responses into high ($NTNA^+$) and low ($NTNA^-$) amygdala reactivity groups (95). After 120 mg MDMA versus placebo, only the $NTNA^+$ subgroup showed acute normalization of negative-affect circuitry—marked by significant reductions in amygdala and subgenual anterior cingulate cortex (sgACC) activity, enhanced sgACC–amygdala connectivity, and greater likability of threat expressions. These findings demonstrate that pre-treatment neural profiling can predict MDMA's capacity to modulate threat processing, suggesting neuroimaging biomarkers may guide personalized MDMA-assisted therapies (95).

Autism spectrum disorder

Individuals with ASD often struggle with nonverbal communication—eye contact, facial expressions, and gestures—and pragmatic language, which impairs reciprocal social interaction (96). MDMA's entactogenic profile—emotional openness, reduced social fear, and enhanced empathy—suggests therapeutic potential in ASD (97–100). In a randomized, double-blind, placebo-controlled trial, adults with ASD who received MDMA-assisted psychotherapy showed significant reductions in social anxiety compared with placebo, as measured by the Liebowitz Social Anxiety Scale (primary endpoint) (101). Since MDMA drives oxytocin release, which may ameliorate social deficits in ASD, larger studies are needed to confirm its safety and efficacy in this population.

Eating disorders

Individuals with EDs often experience social withdrawal, heightened social anxiety, and impaired social cognition—such as difficulty interpreting others' emotions and intentions—which can erode their support networks (102, 103). MDMA-assisted psychotherapy offers reduced fear, self-criticism, and increased compassion, trust, and sociability (104), making

it a promising intervention for patients with ED, especially those with comorbid PTSD. In a randomized, placebo-controlled trial of patients with severe PTSD and comorbid eating pathology, MDMA-assisted therapy significantly reduced ED symptoms (105). The primary endpoint was CAPS-5, with ED measures as secondary endpoints. While encouraging, these findings require confirmation in larger, well-powered trials to establish efficacy and safety in ED populations.

Life-threatening illness

Depression, anxiety, and existential distress are common in patients with life-threatening illnesses and can undermine quality of life and treatment adherence (106). Early clinical work indicates that MDMA-assisted psychotherapy may relieve this psychological burden (107–110). In a Phase II Australian trial, up to 32 individuals with stage III–IV cancer were randomized to receive MDMA-augmented therapy versus placebo, with primary endpoints of anxiety, depression, and quality of life. In a double-blind cohort of 18 patients, those in the MDMA group (two 8-h sessions at 125 mg) experienced a mean 23.5-point reduction in State-Trait Anxiety Inventory scores 1-month posttreatment—compared to an 8.8-point reduction in the placebo group—with benefits sustained at 6 and 12 months following crossover sessions (111). Earlier pilot data in mixed cancer and neurological disease cohorts also demonstrated significant improvements in anxiety, depression, and sleep quality. These promising results underscore the need for larger, controlled trials to establish MDMA's efficacy and safety in relieving distress associated with life-threatening illnesses.

MDMA as a resilience enhancer

Epidemiological evidence

In a 2008–2019 sample of 484,732 U.S. adults, lifetime MDMA/ecstasy use was linked to lower odds of past-year suicidal thinking and planning, while psilocybin use was associated with reduced risk of past-month psychological distress and suicidal thoughts; by contrast, LSD use showed a modest increase in suicidal thinking (112). Similarly, analysis of 213,437 adults found that lifetime MDMA/ecstasy and psilocybin users had significantly lower odds of lifetime and past-year severe major depressive episodes, whereas other substances conferred no protection (113). In a nationally representative cohort of 241,675 adults (2015–2020), MDMA (ecstasy/molly) use corresponded with reduced rates of serious psychological distress, depression, and suicidal ideation (114). Together, these observational data suggest that MDMA and psilocybin use correlates with lower depression and suicidality, underscoring the need for controlled trials to establish causality.

Naturalistic trauma study in israel

On the morning of October 7, 2023, around 3500 festivalgoers at Israel's Nova event—many of whom were under the influence of MDMA or LSD—were caught in a Hamas gun attack that killed hundreds. Researchers at the University of Haifa followed more than 650 trauma survivors, about two-thirds of whom had used recreational drugs. Primary outcomes included the PTSD Checklist for DSM-5 (PCL-5; cutoff $\geq$ 33) and the Kessler Psychological Distress Scale (K6; cutoff $\geq$ 13). Survivors who had used MDMA alone showed notably better psychological outcomes over the critical 5 months posttrauma—improved sleep quality, lower distress, stronger social bonding, and greater openness to support (115). The authors attribute these benefits to MDMA's enhancement of prosocial hormones like oxytocin and its promotion of neural plasticity, despite ongoing legal and ethical challenges.

Although these observational studies suggest that MDMA and classic psychedelics may foster resilience, causality cannot be established. Unmeasured factors—such as baseline personality traits, social support networks, or self-selection into surveys—could partially explain the associations. Longitudinal, prospective research is needed to disentangle drug effects from pre-existing individual differences and to elucidate the mechanisms underlying these epidemiological observations.

Gut–brain axis and oxytocin-mediated mechanisms

Approximately 90% of the body's 5-HT is synthesized by enterochromaffin cells in the gastrointestinal mucosa, where it regulates intestinal motility, secretion, and blood flow (116–118). Beyond local effects, gut-derived 5-HT signals to the enteric and central nervous systems—via neural pathways and the circulation—modulating appetite, mood, and overall gut–brain communication (52). Preclinical studies in rodents have demonstrated that MDMA can promote stress resilience across multiple paradigms. Pretreatment with MDMA did not produce systemic inflammation and depression-like behaviors in mice exposed to chronic social defeat stress (CSDS) (119) or chronic restraint stress (CRS) models (120). In the CSDS paradigm, repeated MDMA administration preserved sucrose preference, normalized splenomegaly, and prevented stress-induced shifts in gut microbiota composition—findings that link MDMA's prophylactic effects to modulation of the microbiota–brain axis. In a CRS model, daily MDMA pretreatment (10 mg/kg for 14 days) prevented the onset of anhedonia-like behavior and restored levels of synaptic proteins and BDNF in the prefrontal cortex—effects that were abolished by subdiaphragmatic vagotomy, implicating a critical role for the gut–brain axis via the vagus nerve in MDMA's resilience-enhancing actions (120).

Repeated intermittent MDMA administration (10 mg/kg, three times weekly for 6 weeks) significantly reduced demyelination in the corpus callosum of cuprizone-treated mice (121). Gut microbiota and nontargeted metabolomics analyses revealed notable differences in specific gut bacteria and plasma (β-D-allose and L-sorbose) or fecal metabolite (carnitine) levels between MDMA-treated and vehicle-treated cuprizone-exposed mice. Negative correlations were found between the levels of metabolites (β-D-allose, L-sorbose, and carnitine) and the relative abundance of *Romboutsia* and *Romboutsia timonensis*. These findings suggest that intermittent MDMA administration may alleviate brain demyelination of cuprizone-treated mice via the gut–brain axis (121). Moreover, repeated intermittent MDMA administration (10 mg/kg, three times weekly for 6 weeks) significantly reduced bone mineral density of ovariectomized female through a gut–microbiota–bone axis (122).

Additionally, repeated oral MDMA administration to male rats caused significant changes in the gut microbiota across these regions (small intestine, cecum, and colon), with distinct effects observed in each (123). Untargeted metabolomics analysis revealed that MDMA significantly altered levels of two metabolites-ferulic acid and methylmalonic acid-in the colon, without changes in the blood, small intestine, or cecum. Notably, methylmalonic acid levels in the colon positively correlated with *Lawsonibacter* and *Oscillibacter*. These findings suggest that repeated oral MDMA treatment can alter gut microbiota composition across intestinal regions, potentially contributing to its pharmacological effects (123).

In addition, MDMA triggers the release of oxytocin—a hormone that enhances social bonding, trust, and emotional openness—which likely contributes to its therapeutic benefits by reducing stress and facilitating trauma processing (28, 37). Oxytocin is synthesized in the hypothalamus, particularly in the paraventricular and supraoptic nuclei, and is released via the posterior pituitary to regulate social bonding, stress responses, and emotional behaviors. Recent research has revealed that the human intestinal epithelium produces oxytocin and that *Limosilactobacillus reuteri* promotes its secretion via secretin from enteroendocrine cells, thereby identifying oxytocin as an intestinal hormone and revealing a mechanism by which gut microbes enhance host health (124). Furthermore, another study demonstrated that the subdiaphragmatic vagus nerve is critical for MDMA's effects on the oxytocin system in rats, as subdiaphragmatic vagotomy significantly reduced both baseline and MDMA-induced increases in plasma and hypothalamic oxytocin levels (53). Collectively, these findings suggest that brain–body communication via the vagus nerve plays a key role in MDMA-induced resilience (Figure 5).

Conclusion and future perspectives

MDMA's unique pharmacology—marked by robust 5-HT and oxytocin release, engagement of the HPA axis, and modulation of glutamatergic circuits—underlies its rapid and potent psychological effects (125, 126). These actions converge on limbic and reward pathways to foster emotional openness, reduced fear, and enhanced social cognition. Preclinical and early-phase clinical data collectively demonstrate that MDMA can both acutely alleviate distress and, with repeated dosing, confer durable resilience to stressors via vagus nerve-mediated gut–brain axis.

Clinical evidence in treatment-resistant PTSD is the most mature, with Phase II and III trials showing high remission rates and durable benefits

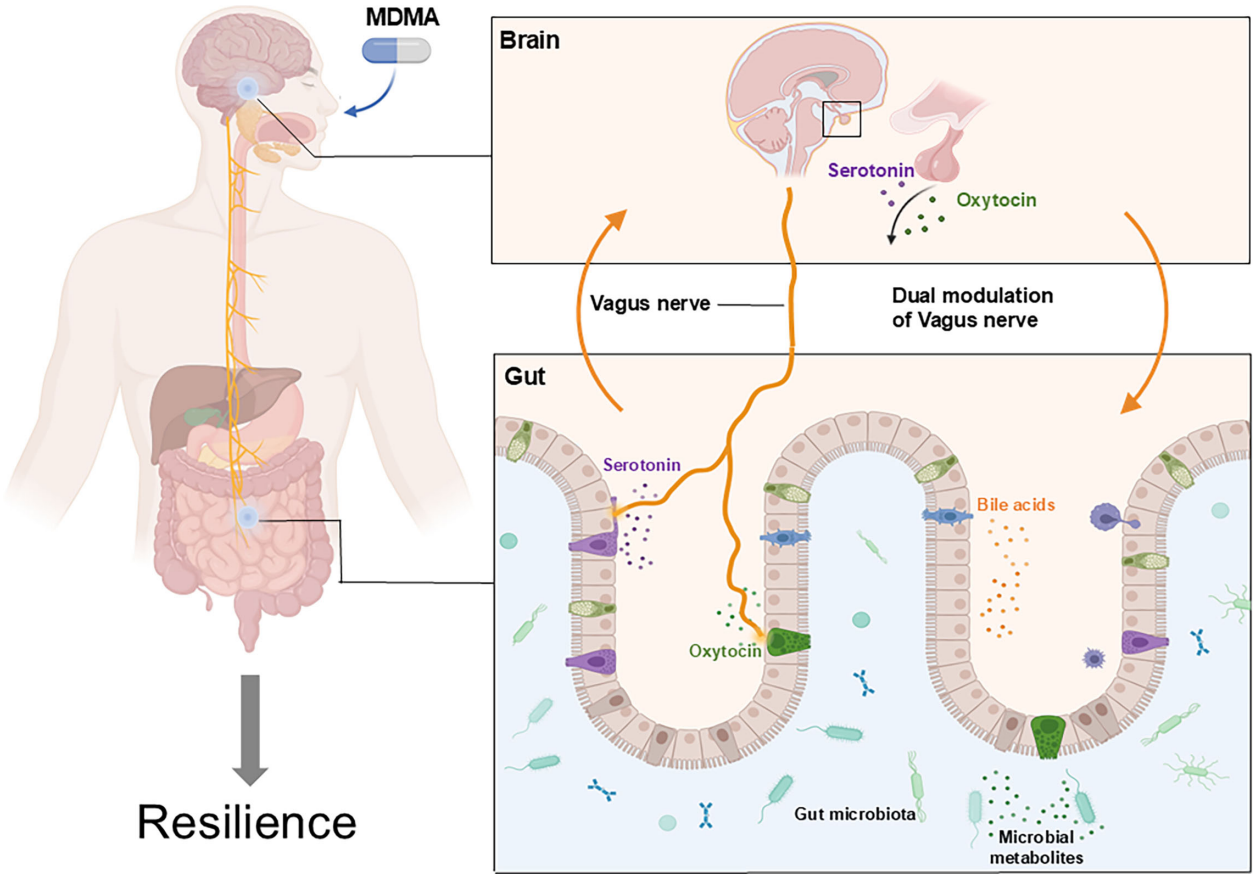

Figure 5. Vagus-dependent gut–brain signaling in MDMA-induced stress resilience. MDMA elevates central 5-HT and stimulates peripheral release of 5-HT from enterochromaffin cells, alongside oxytocin from enteroendocrine cells and the posterior pituitary. These gut-derived signals—together with bile acid changes—activate vagal afferents in the intestinal wall, relaying to brainstem nuclei. Downstream modulation of limbic and cortical circuits enhances neuroplasticity, stress resilience, and adaptive behaviors. This illustration was created using BioRender.com.

after MDMA-assisted psychotherapy. Emerging indications—including ASD, EDs, and existential distress in life-threatening illness—have shown promising initial signals of efficacy, particularly in improving social functioning and reducing anxiety. Observational studies further suggest that MDMA use may correlate with lower rates of depression and suicidality at the population level, pointing to broader resilience-enhancing properties.

Despite its therapeutic promise, MDMA carries clear risks. Acute adverse events such as hyperthermia, hyponatremia, sympathomimetic overstimulation, and potential progression to serotonin syndrome necessitate stringent monitoring and risk mitigation (e.g., fluid restriction and temperature control). Long-term neuroimaging and cognitive data indicate selective serotonergic terminal injury—amplified by hyperthermia and oxidative stress—underscoring the importance of dosing limits, controlled settings, and posttreatment follow-up to safeguard neurocognitive health.

Harmonizing dosing schedules, therapeutic modalities, and blinding approaches—such as using active low-dose comparators—will be essential to reduce bias and improve reproducibility in future trials. Incorporating biomarkers like threat-evoked fMRI, OXTR genotyping, and gut–brain axis profiles could enable patient stratification and more precise prediction of who will benefit from MDMA-assisted therapy. Well-powered, rigorous studies are required across ASD, EDs, resilience enhancement, and life-threatening illness populations, paired with mechanistic work on microbiota-mediated effects, vagal signaling, and receptor-specific actions. Longitudinal monitoring of cognition, neuroimaging changes, and adverse-event patterns will help define the long-term risk–benefit profile and guide clinical practice.

Achieving MDMA's full therapeutic promise will require close collaboration among neuroscientists, clinicians, psychotherapists, and regulators. By marrying mechanistic insights with high-quality clinical data and robust safety protocols, the field can responsibly transition MDMA-assisted treatments from research settings to approved therapies, offering new hope for patients with treatment-resistant psychiatric disorders.

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Author disclosures

The authors declare no conflict of interest related to this study.

Author contributions

MMZ, JJY, and KH conceived, drafted, and approved the final version of this work. The manuscript has been read and approved by all authors. All authors take full responsibility for all data, figures, and text and approve the content and submission of the study. No related work is under consideration elsewhere. All authors state that all figures and tables provide accurate presentations of the original data. These corresponding authors JJY and KH take full responsibility for the submission process.

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