Ketamine for Depression, but at What Cost? A Review of Ketamine's Neurotoxic Effects From Preclinical and Human Studies

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This review examines ketamine's neurotoxic potential across preclinical and clinical studies. The authors synthesized data from preclinical models, then integrated findings from human clinical trials of esketamine and observational studies in recreational users. Animal studies have found that repeated or high-dose subanesthetic ketamine administration results in consistent excitotoxic neuronal damage and lasting cognitive deficits, especially in perinatal animals. Infrequently administered relatively low and moderate subanesthetic doses (<1 mg/kg approximate human intravenous equivalent) do not yield overt histopathology in rat and nonhuman primate models. In humans, observational studies in frequent high-dose (>1 g/day) ketamine users show memory and executive function impairments. In contrast, a large clinical trial found that intranasal esketamine at doses up to 84 mg, administered weekly or every other week for several years, is associated with maintained or slightly improved cognitive function in adults with major depression. Lower cognitive function (attention, processing speed) showed some potential worsening among elderly patients; the clinical significance of this is unknown. Direct comparisons of esketamine and off-label racemic ketamine at higher doses have not been done. These studies underscore the potential for neurotoxic effects when ketamine is used at doses or frequencies beyond those utilized in clinical trials, highlighting a critical need for robust longitudinal research. Clinicians are advised to exercise caution, particularly when prescribing ketamine off-label at doses significantly higher than those used in clinical trials. When deviating from this in clinical practice, strong consideration should be given to conducting repeated cognitive assessments. Funding agencies should incentivize preclinical researchers to conduct studies that further elucidate the threshold of ketamine's neurotoxicity.

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Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist approved by the U.S. Food and Drug Administration (FDA) in 1970 as an anesthetic agent. Since then, numerous studies have documented rapid-acting antidepressant properties at subanesthetic levels (1). The S-enantiomer of ketamine (esketamine) received approval for treatment-resistant depression in 2019 as a nasal spray. Esketamine is subject to strict safety controls on dispensing, administration, and monitoring under a mandated safety program (Risk Evaluation and Mitigation Strategy [REMS]) (2). While racemic ketamine has not been approved for any psychiatric indication, many clinicians prescribe it off-label for a variety of psychiatric conditions, including treatment-resistant depression. Ketamine is not subject to a REMS, a fact that reflects a loophole in the regulation of medicine rather than implying that ketamine is safer than esketamine. Because ketamine is not subject to a drug safety program, clinicians have wide flexibility with respect to dosing and frequency without an equivalent mechanism to monitor and report adverse events. Thus, although esketamine treatment regimens are highly standardized, which affords patients, clinicians, and regulators a high degree of confidence regarding safety, racemic ketamine is often prescribed at higher doses and frequencies despite an absence of safety evidence (3). This raises significant concerns about potential long-term risks, as there is substantial evidence that high doses or chronic administration of ketamine can be neurotoxic in preclinical models (4–6). To mitigate the risk of irreversible neurotoxicity, the FDA's policy regarding the use of ketamine in adult psychiatric clinical trials has been to limit exposure to 60 mg/dose and eight total lifetime doses (7). Yet, the widespread clinical off-label use of ketamine by providers consistently exceeds this threshold. Considering the potential risks involved with some of the

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ketamine prescribing patterns that are emerging for off-label treatment of various psychiatric conditions, we review the literature on ketamine neurotoxicity in preclinical models and humans and outline the current landscape of evidence and the urgent need for robust studies in the near future.

MECHANISMS OF KETAMINE

While ketamine may generate antidepressant responses through a variety of mechanisms, its effects on the NMDA receptors are thought to be prominent (8). By blocking NMDA receptors on GABAergic interneurons, ketamine is thought to lead to disinhibition of presynaptic glutamatergic neurons and a surge in intrasynaptic glutamate in regions such as the prefrontal cortex (PFC) (8). The increased presence of glutamate results in activation of postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (8), which eventually results in the formation and strengthening of synaptic connections (thought to be mediated by mTORC1) (8, 9). Additionally, ketamine's direct inhibition of NMDA receptors on excitatory neurons is thought to modulate synaptic transmission and plasticity, which are believed to contribute to its rapid antidepressant effects (10), while others hypothesize that these effects can be independent of NMDA receptors, occurring instead through AMPA receptor activation (11) or opioid system activity (12).

While brief, limited surges in glutamate may reverse synaptic dysconnectivity, prolonged exposure to elevated extracellular glutamate can lead to excitotoxicity and apoptosis in key regions including the PFC, hippocampus, and retrosplenial cortex. Excess extracellular glutamate may overstimulate NMDA receptors and induce excitotoxicity through apoptosis. Moreover, chronic exposure to ketamine can cause NMDA receptors to become hypersensitive to the presence of typical levels of glutamate, exacerbating excitotoxic apoptosis over time (13).

NEUROTOXICITY IN PRECLINICAL MODELS

Approximate Dose Equivalence

In comparing ketamine's effects across species, it is important to note the high degree of variability between species in the dose required to achieve anesthetic or analgesic effects. Comparison is further complicated by the differences in the common routes of administration between species. For instance, rodent studies primarily make use of intraperitoneal (IP) or subcutaneous (SC) injections, whereas in humans, intravenous infusion (IV), intramuscular (IM) injection, or intranasal administration (for esketamine) comprise most clinical administrations. Additionally, anesthetic dosing varies across species, with rodents typically requiring 60–100 mg/kg IP, nonhuman primates requiring 2 mg/kg IV followed by 0.5 mg/kg/hour infusion, and humans requiring 1–4.5 mg/kg IV or 6.5–13 mg/kg IM for anesthesia induction (14). To help facilitate comparison between studies, Table 1 provides approximate dose equivalences across the different species discussed in this review (see Table S1 in the online supplement for additional details on dose equivalence calculations).

TABLE 1. Ketamine dose equivalences across different species[a]

Species	Dose equivalence based on allometric scaling (mg/kg)	Approximate animal:human ratio
Human	0.5	1 (reference)
Mouse	12.34	24.7
Rat	6.16	12.3
Nonhuman primates	1.85	3.7

[a] Equivalence doses in rats, mice, and nonhuman primates were calculated against 0.5 mg/kg in a human based on allometric scaling (67) using the formula: approximate animal dose=(human dose[mg/kg])×(animal K_m)/(human K_m), where K_m is the "correction factor" related to body surface area and typical metabolic rate for each species. For each animal dataset, we also calculated an estimated range of dose equivalencies based on published plasma concentration data (see Table S1 in the online supplement for more detail).

Rodents

The neurotoxic effects of single, high-dose ketamine administration were first observed by Olney and colleagues (4). They reported that NMDA receptor antagonists, including racemic ketamine, could cause neuronal vacuolation in retrosplenial and cingulate cortices ("Olney lesions"). One hypothesis is that this vulnerability stems from efferent thalamic glutamate release converging with acetylcholine release from the nucleus basalis (15). Olney et al. reported that ketamine triggered measurable neuronal damage at or above approximately 40 mg/kg SC in rats. The vacuoles they observed set a precedent for understanding ketamine's neurotoxic profile. More recent studies corroborate these findings, showing dose- and exposure-dependent neurotoxic effects following six exposures of 20 mg/kg SC every 2 hours (16, 17), while fewer exposures (one or three doses) or lower doses (5 mg/kg or 10 mg/kg) did not elicit neurotoxic effects. Similarly, other studies investigating single doses up to 20 mg/kg IV or up to 60 mg/kg IP dosed four times over the course of 15 days did not produce similar levels of cell death, suggesting a dose- and frequency-dependent threshold for neurotoxicity (18, 19).

In infant and juvenile rodent models, where the developing brain is especially vulnerable, repeated subcutaneous or intraperitoneal administration of racemic ketamine in the range of 5–20 mg/kg has been associated with apoptotic cell death, caspase-3 activation, and increased neuronal degeneration in the cortex and hippocampus (16, 17, 20). Importantly, in these studies, neurotoxic effects were reported under high-frequency dosing conditions, such as six injections administered at 2-hour intervals or daily high-dose treatments over several days, whereas lower doses (5–10 mg/kg) or fewer injections (one to three) did not elicit significant neurotoxicity. While these paradigms were designed to probe maximal vulnerability during sensitive developmental windows, these studies underscore the need to investigate various dosing and exposure regimens, particularly given that there is evidence of neurotoxic deficits extending into adulthood following multiple exposures during adolescence (21).

In adult rats, higher subanesthetic single doses (50–60 mg/kg) can produce transient cortical vacuolation, neuronal degeneration, and learning and memory impairments.

However, there appears to be a threshold below which significant histopathological changes are not consistently detected. Jordan et al. (19) observed no microscopic abnormalities in adult rat brains following single intravenous ketamine infusions of 12.5 mg/kg over 40 minutes, suggesting that at certain dose ranges and durations, overt histopathological changes may be minimal. Likewise, Morris et al. (18) reported no evident neuronal vacuolation or necrosis in adult rats given four doses of ketamine (up to 60 mg/kg IP) over 15 days. It is noteworthy that when ketamine does induce neuronal changes in adult rodents, they tend to be focal (e.g., in the retrosplenial cortex) and may not progress to widespread necrosis unless doses are further escalated (18, 22, 23).

A variety of chronic or long-term administration models indicate that racemic ketamine can elicit subtle neurotoxic outcomes over time. In a 6-month mouse study, Yeung et al. (6) found that chronic daily intravenous racemic ketamine at 30 mg/kg led to hyperphosphorylated tau in the prefrontal and entorhinal cortices; a fraction of these tau-positive cells showed significant evidence of apoptosis. Other long-term experiments consistently documented impaired cognition, elevated oxidative stress, glutamate toxicity, and morphological brain changes at daily doses of around 30 mg/kg IP or more (23–25). Studies utilizing daily doses at or greater than 25 mg/kg IP additionally highlight deficits in tasks of spatial learning and memory (26).

While esketamine is the pharmacologically more active isomer, with a greater binding affinity to NMDA receptors (27), there has been some question about whether it produces greater neurotoxic effects at equivalent racemic doses. One of the FDA-submitted esketamine studies in rats (TOX10768) noted minor inconsistent performance impairments on the Morris water maze in the absence of histological lesions among male rats dosed intranasally (22). This esketamine toxicity study spanned 26 weeks, with daily doses up to 45 mg/kg/day, which were found to produce dose-related ataxia, abnormal gait, and brief reductions in grip strength, effects that tended to wane with repeated exposure. However, single-dose studies of intranasal esketamine in adult rats demonstrated no discernible neuronal vacuolation or necrosis at this dose, an exposure equivalent to roughly 1.8 to 4.5 times the maximum recommended human dose (MRHD) of 84 mg/day (22). Even at intranasal doses approaching 270 mg/kg (around 18 to 23 times the MRHD), standard histopathological evaluations did not reveal overt necrosis, although some studies have found cortical loss of parvalbumin cells, white matter changes, and behavioral deficits with repeated subanesthetic dosing of esketamine (26, 28). This is compared to neuronal vacuolation when animals were given subcutaneous racemic ketamine at 60 mg/kg, while the no-observed-adverse-effect level for vacuolation was 15 mg/kg (22).

Thus, these data suggest that the S-enantiomer might be better tolerated than racemic ketamine at certain dose ranges, likely due to differences in metabolism and receptor pharmacodynamics (29). Having reviewed this evidence, the FDA has stated, "Though esketamine is derived from racemic ketamine, they are not the same drug. Animal studies have shown that racemic ketamine can cause lesions in the brains of rodents; the relevance of this finding to humans is unknown. Animal studies with esketamine do not show these brain lesions" (7). This thinking may underlie the differential approach to ketamine and esketamine from the FDA. It is important to note, however, that there were concerns that the mode of delivery in rodent studies (e.g., intranasal) did not achieve adequate serum esketamine levels to provide a reasonable safety margin to human exposure (22). Furthermore, given that there has been much more investigation of the neurotoxic effects of racemic ketamine than esketamine, it is quite possible that esketamine has similar potential for neurotoxicity that has not been as well characterized as racemic ketamine.

Nonhuman Primates

In nonhuman primates, ketamine's neurotoxic effects have been documented across diverse experimental designs and age groups, with some of the most striking findings emerging from developmental studies in infant or fetal monkeys, which are particularly sensitive to ketamine-induced neuronal damage. At anesthetic doses (i.e., prolonged exposure with 20 mg/kg IV followed by 3–24 hours of continuous infusion in the range of 20–50 mg/kg), Slikker et al. (30) exposed rhesus monkeys at gestational day 122 (equivalent to third trimester) or postnatal day 5 to racemic ketamine for up to 24 hours and observed significant increases in degeneration of cells in the frontal cortex. Shorter exposures of about 3 hours did not produce neurotoxicity, whereas 9–24 hours of continuous ketamine infusion led to robust neuronal degeneration (31). Interestingly, a single 24-hour ketamine infusion at an anesthetic dose (20 mg/kg IM followed by 20–50 mg/kg/hour IV) during the first postnatal week caused persistent cognitive and behavioral deficits lasting multiple years, demonstrating that prolonged high-dose ketamine in early life can have long-lasting or even permanent impacts on brain function (32). This phenomenon suggests that ketamine's neurotoxic cascade, particularly in immature brains and at anesthetic doses, requires either a certain cumulative exposure level or sufficient time to trigger excitotoxic and/or apoptotic processes.

Later adolescent and young adult primate models also show vulnerability to chronic lower-dose exposures. Several research groups who administered racemic ketamine at subanesthetic doses of approximately 1–1.5 mg/kg/day (IV or IM) consistently reported structural and functional abnormalities in the PFC, hippocampus, and white matter tracts (6, 33–35). Specifically, daily intravenous ketamine at subanesthetic doses for 6 months in adolescent cynomolgus monkeys resulted in hyperphosphorylated tau in the PFC and entorhinal cortex, with a subset of these tau-positive cells also undergoing apoptosis (6, 36). Similarly, Li et al. (35) detected significant disruptions in white matter microstructure, specifically reduced fractional anisotropy in multiple fronto-thalamo-temporal pathways, after 13 weeks of daily intravenous ketamine (1 mg/kg) in adolescent monkeys.

Behaviorally, daily intravenous or intramuscular subanesthetic ketamine in adolescent or young adult nonhuman

primates often manifests as decreased motor activity, increased irritability or stereotypy, and cognitive impairments, both in memory tasks and in more complex assays of executive function (37, 38). Additionally, racemic ketamine given daily at gradually increasing doses (0.4–1.6 mg/kg/day IM, a subanesthetic range of doses) for 10 weeks induced significant addiction-like behaviors (i.e., irritability and aggression) alongside downregulation of dopaminergic markers in the PFC (33). Yu et al. (37) combined functional MRI analysis with behavioral assays in cynomolgus monkeys and found that 1 mg/kg/day IV for 6 months not only reduced locomotion but also produced aberrant neural activity patterns in dopaminergic pathways and decreased tyrosine hydroxylase expression in the PFC. These findings underscore that even moderate, subanesthetic doses, if given daily and for prolonged periods, can provoke marked neurochemical and behavioral alterations. To our knowledge, there have been no published reports examining the neurotoxic effects of esketamine in nonhuman primates.

Canine Models

In canine models, long-term esketamine administration generally elicited milder neurotoxic findings than those observed in rodents and nonhuman primates. In a 9-month intranasal study (TOX10701) conducted in adult beagle dogs, higher doses of esketamine (e.g., greater than approximately 4 mg/kg/day) produced clinical signs such as decreased activity, tremors, and occasional hemorrhagic vomiting, but there was no consistent evidence of marked neuropathological changes on postmortem examination (22). In a 3-month repeated intranasal toxicity study with a 1-month recovery phase (TOX10524), where beagle dogs received twice-daily esketamine at doses up to 72 mg/kg/day, routine histopathology revealed mild vacuolation and identified a no-observed-adverse-effect level of 72 mg/kg/day based on clinical signs and histopathology (22). A shorter, single-dose study in beagles (TOX13114) using racemic ketamine at approximately 0.3 mg/kg IV similarly showed primarily acute behavioral effects (ataxia, salivation, decubitus, and licking) without signs of neurodegeneration (22). This apparent species-specific resilience in dogs contrasts with more pronounced neurotoxic outcomes reported in rodents and nonhuman primates, emphasizing that ketamine's neurotoxic potential can vary substantially across different animal models.

Relevance and Implications for Humans

Taken together, studies in preclinical models have provided compelling evidence that ketamine can induce significant neurotoxic outcomes in the brain, although the degree of risk appears to be linked to dose, frequency, and developmental stage. Younger animals appear to be particularly susceptible to excitotoxic/apoptotic changes, whereas mature animals can tolerate moderate doses with less overt histopathology. However, repeated or prolonged administration, even at subanesthetic levels, can lead to learning delays, memory deficits, or biochemical/structural alterations. Importantly, these changes can manifest not only as acute neuronal loss but also as protracted behavioral and cognitive impairments, sometimes persisting years after the initial exposure.

Although animal studies cannot be extrapolated directly to clinical settings, the preclinical literature suggests that sufficiently high or chronic exposures to ketamine can produce adverse neurobehavioral and structural effects in the rodent and nonhuman primate brain. These results have been especially pronounced in juveniles, pointing to a developmental window of heightened vulnerability to NMDA receptor antagonism. At the same time, several studies have shown no microscopic signs of neurodegeneration at moderate doses of esketamine approximating or exceeding human-equivalent levels, suggesting that established esketamine regimens remain below the toxic threshold, although preclinical investigation of esketamine's neurotoxic potential remains comparatively sparse. However, due to the lack of studies utilizing higher or frequent dosing regimens common in off-label ketamine treatments (Figure 1), caution is warranted regarding possible subclinical or cumulative neurotoxic risks during long-term use.

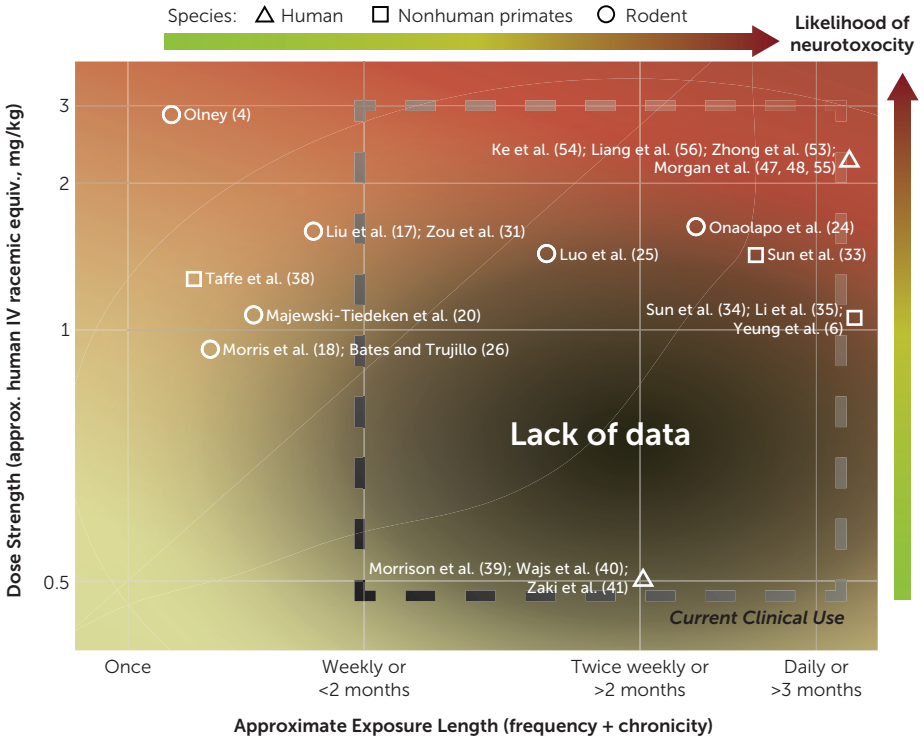
NEUROTOXICITY IN HUMANS

Clinical Trials

As is the case with preclinical studies, there is a dearth of research investigating ketamine's neurotoxic potential at the frequency and doses sometimes used off-label in community settings. In the absence of high-quality evidence surrounding the long-term safety of frequent ketamine use, inferences are often drawn from the long-term SUSTAIN trials of intranasal esketamine. SUSTAIN-1 was a randomized withdrawal study, where esketamine+antidepressant responders were randomized to continue esketamine+antidepressant treatment or initiate placebo+antidepressant. It showed a reliable, small to moderate positive effect of esketamine+antidepressant over placebo+antidepressant on tasks of attention, verbal memory, and visual and verbal learning after 16 weeks of treatment (39). SUSTAIN-2 was a long-term open-label follow-up study of maintenance treatment with weekly or every-other-week esketamine dosed at 28, 56, or 84 mg for up to 48 weeks following a 4-week induction phase (40). Overall cognitive performance across multiple domains remained stable from baseline through the end of maintenance treatment. SUSTAIN-3, an extension study of SUSTAIN-2 that followed 1,148 patients over a median of 38 months of follow-up, also found either improvement or no significant worsening in higher cognitive functioning. Notably, results for lower cognitive functioning (e.g., attention and processing speed) demonstrated potential worsening over time, which was more pronounced for participants over 65 years old. The significance of these changes is unknown, and it should be noted that there was no control group (41).

The SUSTAIN studies support the efficacy and safety of weekly and every-other-week esketamine treatment at doses up to 84 mg. Esketamine's higher NMDA

FIGURE 1. Estimated threshold of neurotoxicity by dose strength and frequency[a]



[a] Summary figure of major studies highlighted in this review, including humans, nonhuman primates, and rodents, with increasing likelihood of neurotoxicity shaded from green to red. Approximated current clinical use of ketamine and esketamine for treatment-resistant depression is highlighted within the dotted lines, with shading corresponding to clinical use prevalence. The dark shaded cloud denotes the significant lack of evidence on the neurotoxic effects of ketamine and esketamine at the corresponding dosage and exposure, which overlap significantly with current clinical regimens. Dose strength is estimated based on the relative human intravenous ketamine dose (see Table 1 for approximate dose equivalence across species).

receptor affinity compared to racemic ketamine and the differential bioavailability of ketamine's intranasal route—48%, compared with 100% for intravenous and 93% for intramuscular administration—complicate extrapolations of esketamine's apparent safety compared with racemic ketamine (Table 2). No clinical studies have investigated long-term safety with emerging patterns of off-label ketamine treatments that involve higher doses or more frequent administrations of ketamine.

The largest controlled clinical trial of ketamine was the ELEKT-D study, which compared ketamine and ECT in patients with treatment-resistant depression. Patients received either six intravenous ketamine infusions (0.5 mg/kg over 40 minutes) or nine right unilateral ECT sessions over 3 weeks. Neurocognitive outcomes for the ketamine group showed improvements or no change in all domains tested (42).

Notably, many of the preclinical studies examining ketamine's effects on cognition were conducted in adolescents. Human trials of adolescents utilizing ketamine or esketamine are limited. At least three short-term randomized studies of ketamine or esketamine in adolescents have been conducted (NCT03185819, NCT02579928, ChiCTR2000041232), although only one (43) reported neurocognitive outcomes. In that 4-week study, participants received either esketamine at doses of 28 mg, 56 mg, or 84 mg or midazolam; no consistent effects of esketamine were found on any of the cognitive domains assessed, including attention/processing speed, executive function, working memory, and visual and verbal learning and memory.

Observational Studies

Given the lack of more controlled long-term studies, observational studies in recreational ketamine users provide some insights into the long-term safety of higher and more frequent dosing compared to the dosing and frequency used in esketamine clinical trials. This body of research demonstrates an association between chronic, frequent, high-dose ketamine use and impairments in both short- and long-term memory, particularly episodic and semantic recall (44–46). Some studies have also found associations with impairments in executive function, attention, and verbal fluency (47, 48). Studies investigating the relationship between chronic, frequent ketamine use and neuroanatomical changes have generally also found patterns of structural or functional abnormalities in brain regions involved in memory and in executive functioning (49).

Notably, some cognitive deficits associated with prolonged ketamine use may be reversible. Studies comparing current frequent ketamine users and former frequent ketamine users found greater cognitive impairments among the current users in some domains (47, 48, 50). One prospective cohort study evaluated cognitive function in 18 frequent ketamine users after 3 days of abstinence and again 3–4 years later, during which time the average frequency of ketamine use decreased from roughly 6 days per month to roughly 2 days per month (51). On average, they observed a recovery of semantic memory function, which was correlated with reduction in ketamine use; impairments in episodic memory persisted despite reduced ketamine exposure. Similarly, Tang et al. (52) evaluated changes in memory and executive function in 114 frequent ketamine users admitted to a residential substance use disorder treatment program in Hong Kong at the start of treatment and after 12 weeks of abstinence in a controlled environment. They found that verbal and visual memory, planning,

TABLE 2. Bioavailability and equivalent dosing of ketamine in humans[a]

Dosing route	Bioavailability	Relative strength	0.5 mg/kg IV equivalent dose for 70 kg human
Intravenous	100%	1	35 mg
Intramuscular	93%	0.93	37.6 mg
Intranasal	50%	0.5	70 mg
Sublingual	30%	0.3	116.7 mg
Oral	20%	0.2	175 mg

[a] Bioavailability for intravenous, intramuscular, intranasal, and oral ketamine were derived from Mion and Villevieille (68), and bioavailability of sublingual ketamine was derived from Peltoniemi et al. (69). Dose equivalency for a 70 kg human was calculated using the formula: equivalent dose=(IV dose for 70 kg human)/(relative strength).

and attention were significantly improved at the 12-week follow-up. It is worth noting that most observational studies of frequent ketamine users relied on small samples and thus may have been underpowered to detect small but still clinically relevant differences.

While many observational studies are not well suited to establish causality, the studies cited here included design features intended to make alternative causal explanations less plausible. Excluding polysubstance users from the sample (50, 53, 54) or including a control group comprised of polysubstance users who do not use ketamine (47, 48, 55, 56) makes it less plausible that the observed abnormalities could be attributable to the use of drugs other than ketamine. Similarly, Morgan et al. have conducted well-designed prospective observational studies and have included several relevant control groups (e.g., former ketamine users, polysubstance users who do not use ketamine) in retrospective studies (47, 48, 55). Beyond recreational use, some insights into the cognitive risks of prolonged ketamine use can be gleaned from the literature on its use in chronic pain. One study (57) showed that patients on long-term frequent ketamine treatment performed worse on neuropsychological tasks, particularly of executive functioning, compared to those who received it less frequently. Other studies of ketamine use in pain disorders have not systematically evaluated cognitive functioning after treatment (58, 59).

Limitations

Key gaps remain in our understanding of the neurocognitive safety of sustained ketamine administration. The dose, frequency, and duration of use reported by the typical participant in most observational studies of frequent ketamine users would seem to greatly exceed the typical maintenance dosing used in treatment of treatment-resistant depression, although the low reliability of data obtained through retrospective self-report means that it is not feasible to compare between dose exposures because the data on dose, purity, frequency, and route of administration reported in the observational studies are not available. The evidence presented here suggests a threshold of dosage and frequency above which ketamine exerts neurotoxic effects. Human studies examining the effects of ketamine on cognition at doses and frequencies used in community settings (up to 3 mg/kg) are not available (3).

There is also a notable scarcity of longitudinal studies tracking ketamine users over extended periods. Most studies are cross-sectional, providing only a snapshot of cognitive and neurobiological status at a single point in time. Studies that have tracked patients receiving ketamine over longer periods are missing key data, including on dose and cognitive functioning (60, 61). Additional longitudinal studies would fill a key evidence gap to identify potential delayed or progressive neurocognitive impairments resulting from chronic ketamine use. Addressing these gaps is crucial for developing evidence-based guidelines for the safe administration of ketamine. Standardized dosing measurements, reliable reporting methods, and comprehensive longitudinal studies are needed to enhance our understanding of ketamine's long-term impact on the brain.

DISCUSSION

The cumulative body of evidence from preclinical and clinical investigations highlights the therapeutic potential of ketamine and esketamine, particularly in treatment-resistant depression, while underscoring the need for proactive vigilance regarding possible neurotoxic effects. On the one hand, controlled clinical trials employing subanesthetic doses of esketamine have repeatedly demonstrated that careful dosing and monitored regimens can offer relief from depressive symptoms without substantial or persistent cognitive detriment. On the other hand, findings from both preclinical and human studies reveal a clear pattern: heightened or prolonged exposure to ketamine can, under certain circumstances, lead to structural and functional neuronal injury (Figure 1). This risk appears even greater in younger or developing brains.

Rodent and primate models have shown that high-frequency, high-dose ketamine administration can induce alterations in apoptosis as well as in learning and memory. Although the extent of neurotoxicity depends on a variety of factors, these studies collectively raise concerns about potential harm when ketamine is administered repeatedly at or above thresholds established largely in the anesthesia field. Future preclinical studies should focus on dosing protocols that more closely mimic clinical regimens to enhance the applicability of the results and further elucidate the neurotoxicity threshold.

Within the human literature, important gaps remain. Observational studies of individuals engaging in frequent, high-dose recreational use consistently document cognitive and neurobiological impairments, most notably in memory and executive functioning. Conversely, the clinical trial data, focused predominantly on esketamine, are generally reassuring but are limited to specific dosing regimens that may not represent many of the off-label patterns currently employed for ketamine. Moreover, while the available evidence supports the safety of esketamine with current dosing

parameters, preclinical investigations into potential neuroanatomical or behavioral indications of esketamine neurotoxicity have been relatively sparse compared to the wealth of clinical trial data, limiting our understanding of the risk of overexposure generally as well as relative to racemic ketamine.

These considerations call for rigorous, comprehensive investigations designed explicitly to assess neurotoxicity at the doses and frequencies relevant to current clinical practice. Future studies must be sufficiently powered and longitudinal in design, with standardized outcome measures that capture not only acute safety signals but also subtle or cumulative effects on cognition.

Considerations for Clinicians and Future Directions

The current clinical landscape of ketamine and esketamine for psychiatric disorders presents a paradox. Esketamine is approved by the FDA for treatment-resistant depression and is tightly regulated by a REMS. The REMS was imposed by the FDA in part because of the potential for neurotoxicity and serves to limit the dose and frequency of esketamine administration. On the other hand, ketamine is used off-label for psychiatric disease and, because of its nonapproved status, lacks formalized dosing guidelines, let alone a REMS program to mitigate risk. This means that the effective dose and frequency of ketamine used in practice can considerably exceed that of esketamine.

The absence of a mandated safety program for racemic ketamine leaves open the possibility of unmonitored escalations in dosage or frequency. Moreover, as many clinicians are understandably eager to harness ketamine's rapid antidepressant effects for patients whose conditions are often dire and intractable, the drive to optimize symptomatic relief can tempt clinicians to explore dosing schedules that have never been systematically evaluated for safety.

Some clinics have offered ketamine lozenges for oral administration so that patients can take the medication at home, an approach that makes daily dosing feasible. Notably, at-home administration of the FDA-approved esketamine is explicitly forbidden. Moreover, with the pandemic-related relaxing of regulations that traditionally required in-person assessments for prescription of controlled substances, the availability of oral and sublingual ketamine troches and, more recently, at-home subcutaneous injectable ketamine through telehealth providers further complicates the contemporary clinical landscape (62, 63). High, frequent, and at-home dosing increases risk of other potential adverse effects of ketamine, including misuse and severe cystitis (64, 65). Clinicians should be aware that the FDA generally limits intravenous ketamine exposure in research settings (including in clinical trials) to 60 mg per dose (0.75 mg/kg in an 80 kg individual) for adults to reduce the risk of neurotoxicity (7). Yet clinical practices often exceed these limits, reporting doses as high as 3 mg/kg (3, 66).

Given the potential neurotoxic risks, clinicians should exercise caution in prescribing racemic ketamine and recognize that neurotoxicity cannot be observed clinically. Cognitive changes, the most overt sign of neurotoxicity, are not easily detected in routine clinical assessments. For dosing regimens exceeding well-established doses and frequencies, such as the FDA's limits for research or the approximate dose equivalent of 84 mg of esketamine (maximum dose), incorporating neurocognitive testing (both comprehensive and brief) could help track cognitive changes and minimize long-term risks. Yet, high-quality neurocognitive testing is unlikely to be implemented broadly in clinical settings, and there is no regulatory mechanism to mandate this.

Additional evidence as to the safety threshold is urgently needed to provide more guidance for clinicians. Key funding agencies should incentivize preclinical researchers to more fully establish the neurotoxicity threshold, especially in nonhuman primate models. Other regulatory agencies (e.g., the Drug Enforcement Administration, state medical boards) should consider ways to mitigate the existing loophole in health care regulation that allows for ketamine dosing that varies greatly in frequency, dosing, and even at-home use.

In the meantime, professional and educational organizations (e.g., APA, the American Psychiatric Nurses Association) should expend efforts to educate clinicians and the public about the neurotoxic potential of ketamine and urge caution for providers who choose to provide this treatment off-label. Additionally, collecting long-term data from a large and well-characterized sample of patients who receive ketamine as a therapy for psychiatric illness through a registry would be immensely helpful for the field.

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Examination Questions for "Ketamine for Depression, but at What Cost? A Review of Ketamine's Neurotoxic Effects From Preclinical and Human Studies"

1. **What is the primary mechanism by which ketamine is thought to produce neurotoxic effects in the brain?**
   A. Inhibition of GABA receptors, leading to oxidative stress
   B. Upregulation of serotonin and dopamine receptors
   C. Excessive activation of AMPA receptors causing chronic glutamate suppression
   D. Prolonged extracellular glutamate elevation leading to excitotoxic apoptosis
2. **How does the FDA-approved esketamine differ from off-label racemic ketamine in its regulation and administration?**
   A. Esketamine lacks formalized dosing guidelines, while racemic ketamine is subject to a Risk Evaluation and Mitigation Strategy (REMS).
   B. Racemic ketamine is approved for treatment-resistant depression, while esketamine is used off-label.
   C. Esketamine is subject to a mandated safety program (REMS) that limits dose and frequency, whereas racemic ketamine is not.
   D. At-home administration is explicitly permitted for esketamine but forbidden for racemic ketamine.
3. **In non-human primates, what does prolonged anesthetic ketamine infusion (~24 hours) during early development lead to?**
   A. Long-lasting cognitive and behavioral deficits.
   B. A temporary increase in motor activity and irritability.
   C. No significant changes in brain function.
   D. Widespread neuronal necrosis that persists into adulthood.