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ADVERSE EFFECTS OF ESKETAMINE IN TREATMENT RESISTANT DEPRESSION: A COMPREHENSIVE LITERATURE REVIEW (2020-2025)

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ABSTRACT

Background: Esketamine nasal spray represents the first FDA approved treatment with a novel mechanism of action for treatment resistant depression (TRD) in decades. While its efficacy has been well established, a thorough understanding of the adverse effect profile remains essential for informed clinical decision making and optimal patient safety. We therefore undertook this systematic review to characterize the safety profile of esketamine in treatment resistant depression.
Aim: This review examines esketamine's adverse effect profile, focusing on common effects, cardiovascular safety, urological considerations, cognitive outcomes, abuse liability, special populations, and serious adverse events.
Materials and Methods: We performed a comprehensive literature search across multiple databases including PubMed, Cochrane Library, Web of Science, Embase, Google Scholar, and MEDLINE for studies published 2020-2025.
Results: Common adverse effects like dissociation and sedation resolved within two hours. Blood pressure elevations normalized within 1.5 hours without intervention. Pre approval concerns were not confirmed: no bladder cystitis occurred despite years of exposure, cognitive function remained stable or improved, and misuse was rare (less than 0.01%). Serious adverse events were infrequent (less than 0.2% of sessions), occurring mainly during initial treatments. Mortality rates matched background rates in treatment resistant depression. Elderly patients showed similar tolerability but needed closer cardiovascular monitoring.
Conclusion: Under proper clinical supervision, esketamine shows an acceptable safety profile. Most adverse effects are temporary and mild to moderate. Long term studies extending up to 6.5 years found no evidence of organ damage, cognitive decline, or meaningful abuse problems. For patients who have failed multiple treatments, esketamine provides an important alternative with manageable safety concerns.

KEYWORDS

Esketamine, Adverse Effects, Treatment Resistant Depression, Safety, Dissociation, Cardiovascular Effects

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Introduction

Major depressive disorder (MDD) currently affects approximately 280 million individuals worldwide.[1] Despite the availability of numerous treatment options, up to one third of patients develop treatment resistant depression, defined as depression in adults who have failed to respond adequately to at least two different antidepressants (administered at appropriate doses for sufficient duration) during the current moderate to severe depressive episode.[2,18] This therapeutic resistance carries significant clinical implications, including elevated suicide risk, persistent functional impairment, and substantial healthcare costs.[3,13] Esketamine offers a fundamentally different mechanism of action. As the S-enantiomer of racemic ketamine, esketamine works through N-methyl-D-aspartate (NMDA) receptor antagonism, thereby modulating glutamatergic neurotransmission rather than the traditional monoaminergic pathways.[18] Notably, the S-enantiomer demonstrates approximately three to fourfold greater affinity for NMDA receptors compared to its R-enantiomer counterpart.[18] The FDA approval timeline includes March 2019 for adjunctive use with oral antidepressants in TRD, July 2020 for depressive symptoms accompanied by acute suicidal ideation or behavior, and most recently January 2025 for monotherapy in TRD.[4] Several factors underscore the importance of comprehensive safety evaluation. First, ketamine possesses known psychoactive and dissociative properties that may appeal to recreational users.[5] Second, NMDA antagonism raises potential cardiovascular concerns.[6,14] Third, illegal ketamine literature documents severe urological complications, including ketamine induced cystitis.[7,8] Fourth, high dose non-medical use data suggest possible cognitive effects with repeated administration.[9] Finally, understanding real world tolerability beyond the controlled trial environment remains paramount.[15]

Materials and Methods

We conducted a comprehensive review focusing on adverse effects associated with esketamine in treatment resistant depression. Our systematic analysis drew upon literature published between 2018 and 2025, with primary focus on esketamine safety data from 2020-2025, supplemented by pivotal registration trials from 2018-2019 and foundational studies on ketamine pharmacology and adverse effects. Multiple databases were searched: PubMed, Cochrane Library, Web of Science, Embase, Google Scholar, and MEDLINE. Search terms included: esketamine, adverse effects, treatment resistant depression, safety, dissociation, and cardiovascular effects.

Results

Among the most commonly reported adverse effects, dissociation occurred in 41% of treatment sessions,[11] while sedation affected 35% of sessions.[11] Nausea appeared in 25 to 34% of patients,[12,13] dizziness in 32 to 34%,[12,13,14] and headache in 24 to 37%.[10,12,13] Importantly, these effects followed a highly predictable temporal pattern: onset within 5 to 15 minutes, peak intensity around 40 minutes post administration, and resolution within 1.5 to 2 hours, with 99.6% resolving completely on the same day.[11,16] Despite the notable frequency of these dissociative effects, which reached severe intensity in approximately 25% of cases,[10] actual treatment discontinuation due to dissociation remained remarkably low at less than 0.1%.[4] This suggests patients generally find these effects tolerable when balanced against therapeutic benefits. Furthermore, long term data demonstrate tolerance development, with mean scores on the Clinician Administered Dissociative States Scale (CADSS), a validated instrument measuring present state dissociative symptoms,[28] declining from 6.4 on day one to 1.0 at week 48,[14,17] indicating diminishing symptom intensity with repeated exposure.

Cardiovascular Safety Profile: Blood pressure increases constitute the primary cardiovascular concern, affecting 12.8% of patients.[6] However, these elevations typically peak around 40 minutes post dose before returning to baseline by 1.5 hours.[6] Most cases remain asymptomatic and self limiting, with only 2.2 to 2.4% requiring rescue medication. Throughout the entire clinical development program involving over 1,700 participants, investigators reported merely three serious cardiovascular events related to blood pressure elevation,[6] none resulting in permanent complications. Importantly, thorough QT studies found no clinically significant QTc prolongation at either therapeutic or supratherapeutic doses,[6] indicating no increased arrhythmia risk. Long term data from SUSTAIN-3 (extending to 6.5 years) showed that while 19.9% experienced hypertensive episodes, only 0.5% discontinued treatment for this reason. At least 95% of events resolved within the same day, with hypertensive emergency reported in just 0.1% (a single case).[10]

Cognitive Function Assessment: Contrary to concerns raised by recreational ketamine studies showing long term cognitive impairment with high dose chronic use,[9] therapeutic esketamine at approved doses produced no evidence of mental decline over periods extending to 6.5 years.[10,14,16,23,24,25] Comprehensive evaluations using validated instruments, including the Cogstate Computerized Test Battery and Hopkins Verbal Learning Test Revised, assessed multiple domains: processing speed, visual learning and recall, working memory, executive function, visuospatial memory, and episodic memory. Results consistently showed cognitive performance either remaining stable or improving from baseline across all domains.[14,23,26] This finding, replicated across multiple studies including SUSTAIN-2 (1 year)[14] and SUSTAIN-3 (6.5 years),[10] clearly distinguishes therapeutic esketamine use from recreational ketamine abuse.[24] The favorable cognitive profile likely reflects several factors: lower cumulative doses, intermittent rather than continuous dosing, supervised clinical administration in certified settings, and appropriate patient selection that excludes individuals with baseline cognitive impairment.

Urological Safety Findings: Despite significant concerns stemming from illegal ketamine literature documenting severe complications, including ketamine induced cystitis progressing to bladder contracture, hydronephrosis, and even renal failure in chronic high dose abusers,[7,8] therapeutic esketamine has demonstrated a remarkably favorable urological profile. Most critically, zero cases of interstitial or ulcerative cystitis emerged in clinical trials despite exposure extending to 6.5 years in SUSTAIN-3,[10] even though lower urinary tract symptoms appeared at low rates: dysuria (2.7%), pollakiuria (2.4%), urgency (1.3%), and hematuria (1.0%).[10] Prospective monitoring of urinary toxicity markers, including erythrocytes, hemoglobin, protein, and leukocytes, in 25 patients receiving esketamine revealed no significant changes,[17] suggesting therapeutic doses do not cause detectable early urothelial damage. The absence of severe bladder pathology with therapeutic use likely reflects multiple protective factors: substantially lower doses than non-medical use, intermittent dosing allowing metabolite clearance between administrations, intranasal route potentially

producing different metabolite exposure patterns, clinical monitoring enabling early symptom detection, and patient selection excluding those with pre-existing urological conditions.[15]

Hepatic and Renal Impairment: Clinicians may use esketamine cautiously in patients with mild to moderate hepatic impairment, though severe impairment (Child Pugh Class C) represents a contraindication due to limited safety data, potential for increased drug exposure, and elevated risk of adverse effects.[15] Renal impairment requires no dose adjustment based on pharmacokinetic studies, although monitoring remains advisable given potential urological effects.[15]

Abuse Potential and Real World Misuse: While pre approval studies in non-medical polydrug users confirmed esketamine possesses inherent abuse potential comparable to intravenous racemic ketamine, with Drug Liking scores reaching similar levels,[18] actual abuse and misuse in real world practice remained remarkably low when administered within the Risk Evaluation and Mitigation Strategy (REMS) program framework, a mandatory FDA safety program requiring supervised administration in certified healthcare settings with post dose monitoring.[11] Analysis of approximately 58 months of post approval data encompassing 1,486,213 total treatment sessions identified only 210 instances of abuse or misuse, representing an extraordinarily low rate of less than 0.01%.[11] The FDA Adverse Event Reporting System database through 2023 recorded merely 12 substance abuse reports, 5 dependence cases, 10 withdrawal cases, 8 overdose cases, and 1 diversion case among 5,132 total esketamine related reports,[19] further confirming the rarity of problematic use. Long term trials including SUSTAIN-2 (up to 1 year)[14] and SUSTAIN-3 (up to 6.5 years)[10] showed no indication of esketamine abuse, no withdrawal symptoms up to 4 weeks after cessation, and no systematic tolerance requiring dose escalation.[22] Individual case reports have documented drug seeking behaviors in isolated patients, successfully managed through gradual dose reduction and adjunctive pharmacotherapy.[20] The REMS program effectiveness, mandating supervised administration in certified settings with mandatory 2 hour post dose monitoring and prohibiting home dispensing,[15] appears crucial in preventing translation of pharmacological abuse potential into actual clinical abuse.

Serious Adverse Events and Mortality: Clinical trials reported serious adverse events in approximately 5 to 6% of patients,[12,13] though real world data from REMS and US-GMS databases showed lower rates: less than 0.1% and 0.18% of treatment sessions respectively. The highest rate occurred during first sessions (0.3%), declining to below 0.1% during maintenance treatment.[11] Types of serious events included rare cardiovascular complications (hypertensive crisis, acute coronary syndrome),[6] severe neuropsychiatric reactions (severe dissociation, panic attacks, transient psychotic symptoms),[19] very rare respiratory depression (almost exclusively in patients with significant comorbidities or concurrent CNS depressant use),[21] rare anaphylaxis and severe allergic reactions,[15] and treatment emergent suicidality, particularly challenging to distinguish from disease related suicide risk in this high risk population. Completed suicide incidence in real world data reached 0.18 per 100 patient years,[11] notably lower than background rates in TRD populations (estimated at 2 to 5% lifetime risk). However, FDA labeling explicitly states that "effectiveness in preventing suicide or reducing suicidal ideation or behavior has not been demonstrated,"[15] despite approval for the suicidality indication.[27] In SUSTAIN-3, [9] deaths occurred among 1,148 participants over 6.5 years (3 COVID-19 related, 2 pneumonia, 1 completed suicide, 1 myocardial infarction, 1 multiple injuries, 1 unknown cause), representing an overall mortality rate of 0.6 per 100 patient years.[10] None were definitively attributed to esketamine, and this rate must be interpreted within the context of elevated baseline mortality risk in TRD populations compared to the general population.[10,11]

Age Related Considerations: Elderly patients (aged 65 years and older), comprising approximately 11.4% of trial participants,6 exhibited larger blood pressure increases (both systolic and diastolic) compared to younger patients, likely related to age associated arterial stiffness.[6] This necessitates more stringent blood pressure criteria for dosing (SBP <150 mmHg versus <140 mmHg for younger patients) and enhanced cardiovascular monitoring.[15] Despite these cardiovascular differences, elderly patients showed similar incidence and tolerability of dissociative symptoms compared to younger adults.[22] Cognitive assessments in SUSTAIN-3 generally demonstrated stable performance with no systematic decline attributable to esketamine in elderly participants, though individual variability was noted.[10]

Summary Table: Safety Profile

Domain	Finding	Clinical Significance
Common Adverse Events	41% dissociation, 35% sedation	Transient, resolve within 2 hours, rarely discontinue
Cardiovascular	12.8% BP elevation	Peak at 40 minutes, normalize by 1.5 hours, rarely need intervention
Cognitive	No impairment	Stable or improved up to 6.5 years
Urological	0 cystitis cases	Safe despite recreational ketamine concerns
Abuse	Less than 0.01% misuse	REMS effectively prevents diversion
Serious Adverse Events	Less than 0.2% sessions	Very rare, highest at first session
Mortality	0.6 per 100 patient years	Not higher than TRD background

Discussion

Our analysis covers six years of experience with esketamine in treatment resistant depression, with follow up extending to 6.5 years in SUSTAIN-3.[10] The data reveal an interesting pattern. Pre-approval concerns based on recreational ketamine use did not occur in therapeutic settings. The recreational literature describes devastating bladder complications, including cystitis and kidney damage.[7,8] Yet clinical trials found zero cystitis cases even after 6.5 years, with urinary monitoring showing no concerning changes.[10,17] Similarly, while recreational users show cognitive impairment,[9] therapeutic esketamine showed stable or improved cognitive function across multiple studies and timeframes, including in elderly patients.[10,14,16,22,23,24,25,26] The difference likely reflects lower doses, intermittent schedules, intranasal delivery, and appropriate patient selection.[15] Blood pressure elevations affected 12.8% of patients but followed a predictable pattern, peaking at 40 minutes and normalizing by 1.5 hours.[6] Only three serious cardiovascular events occurred among over 1,700 participants, with no lasting harm.[6] Long term data showed 95% of hypertensive episodes resolved same day, and only 0.5% stopped treatment for this reason.[10] Dissociation, though common at 41% of sessions,[11] proved tolerable. Episodes followed a consistent two hour time course with 99.6% resolving same day.[11,16] Discontinuation remained below 0.1% despite severe intensity in some cases,[4,10] and tolerance developed over time with CADSS scores dropping from 6.4 initially to 1.0 at week 48.[14,17] The abuse question required careful analysis. Pharmacological studies confirmed inherent abuse potential,[18] but real world data told a different story. Out of over 1.4 million treatment sessions, only 210 abuse instances occurred, representing less than 0.01%.[11] The FDA database showed similarly low rates of abuse, dependence, and diversion.[19] Long term trials found no dose escalation or withdrawal symptoms.[10,14,22] The REMS program, requiring supervised administration and two hour monitoring with no take home medication,[15] appears to effectively prevent the abuse that pharmacology would predict. Serious adverse events occurred infrequently and declined over time, from 0.3% during first sessions to below 0.1% during maintenance.[11] Types included rare cardiovascular and psychiatric reactions, very rare respiratory depression (mainly in patients with comorbidities), and treatment emergent suicidality, though distinguishing this from disease related risk proved challenging.[6,15,19,21] Suicide completion rates at 0.18 per 100 patient years[11] were lower than expected TRD background rates, though FDA labeling notes esketamine has not been shown to prevent suicide.[15,27] Mortality data from SUSTAIN-3 showed nine deaths among 1,148 participants over 6.5 years, representing 0.6 per 100 patient years, with none clearly attributable to esketamine.[10] This rate appears consistent with elevated mortality in TRD populations.[10,11] Several limitations affect interpretation. The literature search covered 2018-2025, with primary focus on safety data from 2020-2025. Most data come from selected trial populations, limiting generalizability to complex real world patients. No data extend beyond 6.5 years, and comparative data versus other TRD treatments remain limited. Despite these limitations, the pattern is clear. Pre-approval concerns were not confirmed, and six years of data support esketamine as a reasonable option for patients with treatment resistant depression who have exhausted standard treatments.

Conclusions

This safety analysis of esketamine in treatment resistant depression with follow up to 6.5 years reveals that the concerns preceding drug approval were not confirmed. Bladder cystitis observed with recreational ketamine use did not occur in therapeutic esketamine use, cognitive impairment did not emerge, and misuse remained exceptionally rare under appropriate medical supervision. Adverse effects proved predictable and manageable. Dissociation and transient blood pressure elevations resolve within hours. For patients with treatment resistant depression who have not responded to multiple standard treatment attempts and who are

characterized by elevated suicide risk and profound functional impairment, esketamine represents a valuable therapeutic alternative. Its distinct mechanism of action through the glutamatergic system and rapid therapeutic response within hours make esketamine a justified choice with an acceptable safety profile for patients without other treatment options.

Disclosures

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