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Research Article

A Translational Framework for KETARx: Scientific Basis, Regulatory Context, and Clinical Integration

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Abstract

Ketamine is a mechanistically complex agent with clinical effects that span anesthesia, analgesia, and neuropsychiatric modulation. Although long associated with N-methyl-D-aspartate (NMDA) receptor antagonism, contemporary translational research emphasizes a broader pharmacologic profile that includes state-dependent circuit effects and metabolite-linked signaling. The recent approval of KETARx, a ketamine hydrochloride injection entering the U.S. market through the contemporary generic approval pathway, provides an opportunity to reassess ketamine within a framework that integrates modern pharmacokinetic and pharmacodynamic modeling, biomarker science, and updated regulatory standards.

This review synthesizes mechanistic, pharmacologic, and regulatory evidence to construct a translational framework for KETARx in perioperative and chronic pain medicine. Advances in PK-PD modeling distinguish the contributions of parent ketamine and downstream metabolites, supporting infusion-forward strategies that preserve anti-hyperalgesic benefit while limiting psychotomimetic effects. Emerging biomarker and neuroimaging studies indicate that ketamine acts through network-level modulation rather than single-target receptor occupancy, although no clinically actionable predictors have been validated. Clinical evidence supports opioid-sparing effects in perioperative care and selective benefit in sensitization-linked pain trajectories, while longer-horizon safety considerations center on urological and hepatobiliary risks during repeated exposure. Special populations, including pediatric, geriatric, hepatically impaired, and peripartum patients, require protocol adaptation due to differences in metabolism, vulnerability, and tolerability. Overall, KETARx does not alter ketamine's fundamental biology; however, it reinforces the need for precision in practice through PK-PD grounded dosing, phenotype-aligned outcome selection, and safety surveillance scaled to cumulative exposure.

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Introduction

Ketamine remains one of the most mechanistically complex small molecules in perioperative and pain medicine, with clinically useful effects spanning anesthesia, analgesia, and neuropsychiatric symptom modulation. Although ketamine is historically anchored to NMDA receptor antagonism, contemporary translational work increasingly frames its clinical phenotype as an emergent property of multi-receptor pharmacology combined with state-dependent circuit effects and metabolite contributions (Antos et al., 2024; Wellington et al., 2025). For analgesia specifically, ketamine's value is often conceptualized as anti-hyperalgesic rather than purely analgesic. By attenuating NMDA-dependent amplification of nociceptive signaling,

ketamine can reduce central sensitization, blunt opioid-induced hyperalgesia, and decrease wind-up phenomena that otherwise sustain postoperative pain trajectories and promote transition to chronic postsurgical pain (Abouarab et al., 2024). This mechanistic framing matters because many failures in perioperative analgesic development reflect a mismatch between drug target and the biology of sensitization, where downstream synaptic plasticity and network gain, rather than peripheral nociceptor input alone, dominate symptom persistence.

KETARx is a ketamine hydrochloride injection product that recently entered the United States market via the generic approval framework, creating an opportunity to re-examine ketamine's translational profile using current PK-PD modeling, biomarker science, and higher-order outcomes such as recovery trajectories and longer-horizon safety monitoring (U.S. Food and Drug Administration, 2025a; PharmaTher Holdings Ltd., 2025). Importantly, while ketamine's clinical footprint is broad, the present manuscript is deliberately scoped to translational and scientific considerations, emphasizing mechanism, dosing biology, predictors and biomarkers, perioperative and chronic pain outcomes, safety with maintenance or repeated exposure, and special population considerations relevant to procedural medicine.

To avoid conflating KETARx's FDA-approved labeling with broader off-label ketamine practices, it is important to specify the approved indication. Ketamine hydrochloride injection is FDA-approved as a general anesthetic: as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation, for induction of anesthesia prior to the administration of other general anesthetic agents, and as a supplement to other anesthetic agents (U.S. Food and Drug Administration, 2022). Subanesthetic ketamine regimens used for chronic pain syndromes or psychiatric indications (including depression) remain off-label for racemic ketamine injection products and require context-specific clinical governance, monitoring, and risk mitigation (National Institute on Drug Abuse, 2024).

Methods

We performed a structured literature review to evaluate ketamine hydrochloride injection products, including KETARx, with emphasis on pharmacology, PK-PD modeling, predictors and biomarkers, perioperative and chronic pain outcomes, long-term safety with repeated exposure, and U.S. regulatory context. We searched PubMed, Embase, and ClinicalTrials.gov for publications from 2020 through 2025 using terms such as "ketamine," "ketamine hydrochloride," "KETARx," "norketamine," and "hydroxynorketamine." Reference lists of key reviews and primary studies were also screened to identify additional relevant sources.

We included mechanistic studies, human PK-PD analyses, biomarker and neuroimaging studies, randomized trials, observational studies, systematic reviews and meta-analyses, and publicly available regulatory documents. We excluded opinion pieces without primary data, conference abstracts lacking reproducible methods, and materials not supported by verifiable evidence. Findings were synthesized narratively to connect exposure, mechanism, clinical outcomes, and safety monitoring into a translational framework for KETARx integration in pain medicine.

Pharmacology and PK-PD

Ketamine is administered clinically as a racemic mixture of R- and S-enantiomers, each contributing to a composite pharmacodynamic signature that depends on dose, route, and neurophysiologic state at the time of exposure. At anesthetic concentrations, ketamine produces dissociative anesthesia characterized by preserved airway reflexes and sympathetic stimulation, whereas at subanesthetic concentrations, it can yield analgesia with variable psychotomimetic and cognitive effects. Mechanistically, NMDA receptor antagonism remains a central pillar, particularly for anti-hyperalgesic efficacy. However, ketamine's actions extend to a broader receptor and channel landscape that includes opioid receptors, sigma receptors, monoaminergic signaling, and ion channels whose state-dependence may shape both desired and undesired effects (Antos et al., 2024; Wellington et al., 2025). This breadth complicates simplistic dose-response assumptions and helps explain why similar dosing can produce divergent clinical phenotypes across settings such as opioid-tolerant surgical patients, neuropathic pain states, and affective disorders.

From a translational PK standpoint, ketamine is rapidly distributed due to high lipophilicity and a large volume of distribution, with hepatic metabolism producing multiple metabolites that can be pharmacologically relevant. Population PK modeling has advanced substantially, clarifying that the kinetics of parent drugs and metabolites differ meaningfully across regimens and may contribute differently to analgesia versus psychotomimetic effects (Kamp et al., 2020a; Kamp et al., 2020b). Across contemporary models, norketamine and downstream hydroxynorketamine species emerge as important exposure compartments rather than inert clearance products. These models support the practical observation that bolus-heavy regimens may accentuate peak-related adverse effects, whereas infusion-forward strategies can maintain effect-site exposure while reducing abrupt neuropsychological transitions. Translationally, this aligns

with a state-dependent gating concept in which baseline neural excitability and cognitive context shape how a given exposure translates into analgesic and experiential outcomes.

A significant development for perioperative translation is integrative PK-PD work linking antinociceptive outcomes and subjective psychedelic-type experiences within unified modeling frameworks. These approaches attempt to map effect-site concentrations to separable PD endpoints, treating analgesia and dissociation as related but partially dissociable manifestations with overlapping yet non-identical drivers (Olofsen et al., 2022). In practice, this supports rational protocol design that targets anti-hyperalgesia while limiting cognitive disruption by optimizing infusion rate, timing relative to incision, and co-analgesic context. It also motivates biomarker work aimed at identifying individuals whose dose-response curve is shifted toward neuropsychological sensitivity.

Predictors and Biomarkers

Despite ketamine's long clinical history, validated predictors of analgesic response and adverse effect susceptibility remain limited. Contemporary biomarker work is strongest in neuropsychiatric ketamine research; however, several concepts also translate to perioperative medicine, including baseline network state, neuroinflammatory tone, and inter-individual differences in metabolism and neural excitability. Systematic evidence syntheses indicate that blood-based biomarkers, including inflammatory markers and neurotrophic factors, show inconsistent associations with ketamine response, with no current biomarker reaching routine clinical utility (Medeiros et al., 2022). This negative result is still informative translationally because it implies that single-analyte approaches are unlikely to capture a multi-target, circuit-level intervention. The more plausible direction is composite modeling that integrates clinical phenotype, exposure metrics, and multivariate signals.

Brain-based biomarkers exhibit somewhat more precise, yet still non-definitive, patterns. A comprehensive systematic review of neuroimaging studies suggests partial convergence toward post-treatment electrophysiologic changes and connectivity shifts within prefrontal and striatal networks, while highlighting limitations including small sample sizes, methodological heterogeneity, and the lack of replicated signatures across independent cohorts (Medeiros et al., 2023). Parallel synthesis work emphasizes that candidate molecular and physiologic correlates often behave as state markers rather than stable predictors, further supporting models in which ketamine modulates system-level dynamics that depend on the baseline network configuration (Meshkat et al., 2023). For perioperative analgesia, an analogous hypothesis is that ketamine's anti-hyperalgesic efficacy depends on dampening sensitization-prone network states, which may be detectable through preoperative neurophysiologic features or early post-dose signatures that correlate with downstream pain trajectories.

Recent evidence synthesis has also advocated for "personalized ketamine" frameworks that distinguish between predictors of response and predictors of tolerability and safety, with implementation strategies that prioritize feasibility and actionability over mechanistic elegance (Medeiros et al., 2024). For KETARx and other ketamine injection products used in procedural contexts, the translational challenge is the pragmatic implementation of biomarkers: they must be rapid, inexpensive, and capable of changing management in real-time. Near-term candidates include PK-informed risk stratification using hepatic function proxies and interacting medication profiles, coupled with structured adverse effect surveillance rather than a binary responder test. The goal is to identify dose-sensitivity phenotypes and vulnerability to adverse events, enabling protocol adjustments that preserve analgesic benefits while minimizing cognitive liabilities.

Regulatory Developments and FDA Approval Pathway of KETARx

KETARx's entry into the United States market is best understood through the FDA's generic drug framework rather than as a de novo molecular innovation. The FDA Orange Book lists the ketamine hydrochloride product associated with PharmaTher as an approved drug product in 2025, reflecting formal entry into the approved product landscape and enabling lawful marketing consistent with an approved application and labeling requirements (U.S. Food and Drug Administration, 2025a). For sterile injectables such as ketamine hydrochloride, the translationally relevant regulatory burdens often center on chemistry, manufacturing, and controls, including sterility assurance, particulate control, stability, container-closure integrity, and manufacturing site compliance. These elements frequently determine approval timelines more than pharmacology, given the long-established active ingredient and well-characterized clinical effects.

Public corporate disclosures describe a complete response and resubmission pathway culminating in FDA approval in August 2025, consistent with typical generic review dynamics in which deficiencies are addressed through targeted remediation and data supplementation (PharmaTher Holdings Ltd., 2025). Translationally, the significance is not that ketamine's mechanism changes, but that a newly approved product is expected to meet contemporary manufacturing and regulatory standards

that affect supply reliability, labeling fidelity, and pharmacovigilance infrastructure in routine practice.

Post-approval regulatory oversight also includes promotional compliance. In 2025, the FDA issued correspondence regarding promotional material for ketamine hydrochloride injection associated with PharmaTher, underscoring that even established molecules can trigger regulatory scrutiny when communicated claims exceed approved labeling or evidentiary support (U.S. Food and Drug Administration, 2025b). While promotional enforcement is not a mechanistic topic, it is translationally relevant insofar as it delineates the boundary between evidence-based clinical use and claims that lack adequate substantiation, particularly in areas where ketamine is used off-label or where outcomes are difficult to standardize.

Diversion, Misuse, and Public Perception

Ketamine's legitimate clinical ecosystem extends beyond human anesthesia and pain medicine. The drug is widely used in veterinary practice as an injectable anesthetic and analgesic adjunct across species, which contributes to broad distribution channels and increases the importance of inventory control and diversion prevention (Merck Veterinary Manual, 2021; National Institute on Drug Abuse, 2024). In the United States, ketamine is a Schedule III controlled substance, reflecting accepted medical use alongside clinically meaningful abuse liability, and it has long been manufactured and trafficked for non-medical recreational use (Drug Enforcement Administration, 2020; National Institute on Drug Abuse, 2024). Non-medical use can become compulsive, with tolerance and dependence reported, and chronic high-dose exposure is associated with substantial morbidity, including cognitive effects and ketamine-associated urologic injury (Drug Enforcement Administration, 2020; Abdelrahman et al., 2025). Reports from law enforcement and public health agencies also identify ketamine among substances misused in drug-facilitated sexual assault, increasing the need for careful prescribing, patient counseling, and secure handling (Drug Enforcement Administration, 2022).

Public awareness regarding ketamine-associated harm increased sharply following the death of actor Matthew Perry on October 28, 2023. The Los Angeles County Department of Medical Examiner determined the cause of death to be the acute effects of ketamine, with the manner of death ruled accidental after Mr. Perry was found unresponsive in a pool at his residence (Los Angeles County Department of Medical Examiner, 2023). In subsequent federal proceedings, prosecutors reported that ketamine supplied through an illicit distribution network contributed to the fatal exposure, and multiple defendants have entered guilty pleas, including a September 2025 plea by Jasveen Sangha to charges that included distribution of ketamine resulting in death (U.S. Department of Justice, 2025; Reuters, 2025). For translational clinicians and regulators, these events underscore a core distinction that is easy to blur in public discourse: ketamine can be clinically useful when appropriately prescribed and monitored, yet it carries abuse liability that requires active mitigation across the supply chain, from procurement and storage to prescribing and follow-up (Drug Enforcement Administration, 2020).

Chronic and Perioperative Pain

In perioperative medicine, ketamine is commonly deployed as part of multimodal analgesia to reduce opioid exposure, improve early pain control, and attenuate sensitization. Recent evidence synthesis indicates that perioperative ketamine can reduce opioid consumption and improve acute pain endpoints. However, effect sizes vary, and many underlying systematic reviews are limited by heterogeneity in surgical populations, dosing strategies, and outcome definitions. An umbrella review focused on acute pain outcomes reported that perioperative intravenous ketamine reduced pain intensity in early post-dose windows and decreased postoperative opioid consumption across multiple included systematic reviews. However, it also emphasized that the methodological quality of many reviews was low according to AMSTAR-2 criteria (Viderman et al., 2024). These findings align with the mechanistic expectation that ketamine is most likely to deliver detectable benefit when the clinical phenotype includes central sensitization, opioid tolerance, or high-intensity nociceptive input.

Procedure-specific synthesis supports this pattern. A systematic review with meta-analysis focused on thoracotomy found that ketamine use was associated with lower acute pain levels and reduced morphine consumption in early postoperative days, consistent with ketamine's anti-hyperalgesic role in high-intensity surgical pain and with the broader concept that surgeries with inflammatory and neuropathic components may show a more robust signal (Zhaksylyk et al., 2024). Translationally, these data motivate the design of protocols that sustain effect-site exposure across the sensitization window, rather than relying on peak-heavy bolusing, which may increase psychotomimetic burden without proportionate analgesic gain.

A central translational question is whether perioperative ketamine meaningfully prevents chronic postsurgical pain. In this domain, NMDA antagonism is mechanistically attractive but clinically difficult to prove due to variability in surgery type, baseline risk, and outcome measurement. A meta-analysis evaluating perioperative ketamine for chronic postsurgical pain prevention reported low-certainty

evidence for reducing chronic postsurgical neuropathic pain at three months, while finding no apparent effect on broader chronic postsurgical pain outcomes and highlighting uncertainty around ideal dosing and duration (Abouarab et al., 2024). This pattern may indicate that ketamine's durable benefit is most plausible in neuropathic-featured trajectories, while broader endpoints dilute the signal by mixing mechanistically distinct phenotypes. For chronic pain, ketamine's translational rationale is strongest in neuropathic and centralized pain states where NMDA-dependent plasticity contributes to symptom persistence. Contemporary synthesis suggests that ketamine can provide short-term benefits in selected refractory neuropathic pain conditions; however, the durability of these benefits is variable and should be weighed against cumulative toxicity risks, functional outcomes, and realistic maintenance planning, rather than focusing solely on short-term analgesia (Odutola et al., 2023). Preclinical and translational analysis also support ketamine's preferential relevance to neuropathic mechanisms, with an animal model meta-analysis indicating reductions in pain-related behaviors across neuropathic paradigms, while reinforcing that a mechanistic signal does not guarantee durable clinical benefit without careful dosing design and outcome selection (van Velzen et al., 2021). For clinical integration, this encourages ketamine programs to establish explicit definitions of target phenotypes and to develop monitoring frameworks that are proportional to cumulative exposure.

Long-Term Safety and Maintenance Use

Long-term ketamine safety is best treated as a composite of organ-specific toxicity and exposure-dependent adverse effects that become more salient as cumulative exposure increases. Two domains are particularly relevant to maintenance or repeated exposure: urinary tract toxicity and hepatobiliary injury.

Ketamine-associated urinary symptoms are well-established in chronic recreational use. However, the translational question is whether medically supervised ketamine, typically delivered with lower cumulative exposures and different dosing patterns, produces meaningful urological risk. A systematic review focusing on ketamine treatment for psychiatric disorders reported urological symptoms ranging from 0% to 24.5% across studies, with symptoms generally mild to moderate when present and with important limitations including inconsistent ascertainment and sparse long-term follow-up (Kerr-Gaffney et al., 2025). The same review highlights a practical translational gap: urological endpoints are often not systematically captured, raising the possibility that low-grade toxicity may be under-detected. Case-level evidence reinforces that clinically significant uropathy can occur even in supervised therapeutic contexts. A case report of ketamine cystitis occurring during ketamine therapy for treatment-resistant depression supports the need for symptom surveillance and low thresholds for evaluation when dysuria, frequency, or hematuria develop (Chang et al., 2023). A broader review of ketamine-induced cystitis synthesizes mechanistic and clinical perspectives, supporting the interpretation that repeated exposure can lead to inflammatory uropathy, making structured screening relevant when considering repeated courses (Abdelrahman et al., 2025).

Hepatotoxicity is a second domain where cumulative exposure can become clinically important. Mechanistic and clinical synthesis suggest that ketamine-associated liver injury may present with cholestatic or mixed patterns and may relate to dose intensity and repeated exposure, supporting a conservative stance toward monitoring when multi-day infusions or frequent repeated sessions are used (Thakkar & Wu, 2024). Translationally, hepatotoxicity risk stratification should incorporate baseline liver disease, concurrent hepatotoxic medications, and dosing schedules that concentrate exposure into short time windows. For procedural medicine, the highest-yield implementation is not complex biomarker testing, but systematic baseline screening and pre-specified thresholds for pausing or discontinuing therapy when liver enzymes rise.

Cognitive and neuropsychiatric outcomes remain more complex to interpret because ketamine produces acute cognitive disruption in some contexts while being associated with stable or improved cognitive performance in others, often confounded by symptom relief and baseline disease state. Rather than assuming a uniform cognitive risk signature, a more defensible translational framing is phenotype dependence and dose dependence. In perioperative settings, delirium has historically been a concern, but recent evidence synthesis suggests that ketamine and esketamine may reduce postoperative delirium under specific conditions. A systematic review and meta-analysis reported an overall association between intraoperative ketamine or esketamine and a lower incidence of postoperative delirium, with subgroup signals suggesting benefits in cardiac surgery and among older adults, and with dose-response patterns favoring subanesthetic dosing (Chen et al., 2025). These findings are mechanistically plausible through opioid-sparing effects and neuroinflammatory modulation, but they remain sensitive to study quality and co-interventions. Translationally, the key point is that ketamine's cognitive risk profile should not be treated as monolithic, and perioperative protocols should prioritize dosing strategies that minimize abrupt dissociation while maintaining anti-hyperalgesic exposure.

Maintenance use is most relevant in contexts where repeated ketamine courses are provided (for example refractory depression or chronic pain), but even in perioperative medicine, repeated procedural exposures can occur in complex surgical patients. A systematic review of maintenance ketamine treatment for depression identified intravenous, intranasal, oral, and subcutaneous protocols, generally supporting the feasibility of sustaining antidepressant benefit in treatment resistant populations while emphasizing substantial heterogeneity in dosing schedules, follow up duration, and safety reporting (Smith-Apeldoorn et al., 2022). Translationally, these findings reinforce that maintenance planning should be treated as a distinct clinical program with explicit monitoring thresholds, predefined reassessment points, and organ specific surveillance rather than as a simple extension of acute dosing.

Special Populations

Ketamine's translational profile shifts across different special populations because the determinants of benefit and harm vary with physiology, comorbidity, and polypharmacy. In pediatrics, ketamine remains widely used for procedural sedation and analgesia, with intranasal routes offering practical advantages in time-sensitive settings. A systematic review and meta-analysis of intranasal ketamine for pediatric sedation concluded that intranasal ketamine is an effective treatment option. However, they highlighted heterogeneity in dosing strategies, outcome definitions, and comparators, reinforcing the need for protocol standardization and careful endpoint selection (Alkhalifah et al., 2024). Translationally, pediatric use emphasizes dose-shaping to minimize emergence phenomena and requires attention to developmental vulnerability when repeated exposure is considered.

In older adults, balancing analgesia, hemodynamic effects, and neurocognitive outcomes is a particularly nuanced task. Recent studies suggest that perioperative ketamine or esketamine may reduce postoperative delirium under certain conditions, with subanesthetic dosing appearing more favorable than higher dosing strategies (Chen et al., 2025). For geriatric perioperative care, the translational emphasis is individualized dosing that minimizes sympathetic surges, integrates multimodal opioid-sparing strategies, and embeds ketamine within delirium prevention bundles rather than treating it as a standalone neurocognitive intervention.

In hepatic impairment or in patients with baseline liver disease, ketamine's hepatic metabolism and the growing literature on ketamine-associated liver injury justify a lower threshold for liver function monitoring, mainly when ketamine is used in prolonged infusions or repeated sessions (Thakkar & Wu, 2024). While renal impairment does not directly alter ketamine hepatic metabolism, overall physiologic fragility and co-medication profiles may alter tolerability, supporting cautious titration and closer surveillance.

Pregnancy and lactation considerations are often driven by limited controlled data and by the need to distinguish a single procedural exposure from repeated therapeutic courses. In practice, ketamine decisions during pregnancy require individualized risk assessment that accounts for maternal hemodynamics, fetal considerations, and alternative options. When ketamine is considered in peripartum settings, the translational emphasis should remain on the lowest effective dosing, avoidance of repeated exposures without a clear indication, and integration of maternal-fetal monitoring standards appropriate to the procedural context.

Conclusion

KETARx's regulatory entry does not alter the underlying pharmacology of ketamine. However, it refocuses attention on contemporary evidence standards: PK-PD modeling that separates analgesic from dissociative effects, biomarker research that acknowledges circuit-level heterogeneity, and outcomes that extend beyond pain scores to longer-horizon safety. The translational picture that emerges is not of a single-mechanism analgesic, but of a multi-target, state-dependent intervention whose clinical value depends on protocol design, patient phenotype, and structured monitoring when exposure becomes repeated or maintenance-like. Across perioperative and chronic pain settings, the most defensible near-term strategy is precision-in-practice: dosing regimens grounded in modern PK-PD, outcome selection aligned with mechanistic intent, and safety surveillance scaled to cumulative exposure risk.

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