

Etomidate-Induced Cortical Inhibition: Prefrontal–Amygdala and Its Implications for Emotion and Behavior

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ABSTRACT: Etomidate is a widely used anesthetic that produces hypnosis through positive allosteric modulation of γ -aminobutyric acid type A (GABA_A) receptors, enhancing inhibitory neurotransmission and suppressing cortical activity. Growing evidence suggests that etomidate's effects extend beyond sedation, involving disruption of cortical-limbic regulatory circuits. Inhibition within the prefrontal cortex (PFC) may impair top-down modulation of the amygdala, a pathway critical for emotional and behavioral regulation. This narrative literature review synthesizes mechanistic and clinical evidence on how etomidate-induced cortical inhibition affects prefrontal–amygdala circuitry and its implications for cognition, emotion, and behavior. Peer-reviewed experimental and clinical studies examining GABA_A receptor modulation, cortical inhibition, and prefrontal–amygdala connectivity following etomidate exposure were reviewed. The literature indicates that etomidate enhances both synaptic and extrasynaptic GABA_A receptor activity, producing a sustained inhibitory tone that suppresses PFC function and weakens executive control over limbic processing. Excessive inhibition may disrupt prefrontal–amygdala balance, potentially contributing to emotional dysregulation and maladaptive behavioral responses in a dose, duration, and context-dependent manner. This review highlights the importance of considering etomidate circuit-level effects on prefrontal–amygdala interactions when evaluating its broader neuropsychological and neurobehavioral consequences.

KEYWORDS: Medical & Neuroscience, Etomidate & GABAergic Modulation, Amygdala and Prefrontal-limbic Connectivity, Cortical Inhibition.

■ Introduction

Etomidate is a general anesthetic with hypnotic effects mediated through GABA_A receptor activity. It exerts distinct effects on both synaptic and extrasynaptic GABA_A receptors, enhancing inhibitory neurotransmission. Although the precise structural details of its binding site remain limited, growing evidence suggests that etomidate interacts with the interface between the receptor's α and β subunits within the transmembrane domain.¹ This interaction amplifies GABA_A receptor function, resulting in sustained suppression of neuronal excitability and a marked reduction in cortical activity.

Within the mammalian neocortex, billions of neurons form dense networks interconnected through chemical synapses. These networks are organized into functional processing units known as microcircuits and support large-scale parallel information processing.² Each microcircuit consists of tightly coupled excitatory and inhibitory neurons that determine how information is transmitted across cortical regions. Because the prefrontal cortex (PFC) depends on a finely regulated balance of excitation and inhibition to regulate downstream limbic structures, understanding how etomidate enhances GABA_A-mediated inhibition is essential for explaining its effects on cognition, emotion, and behavior.

Functional specialization within the PFC further underscores its central role in higher-order regulation. Distinct prefrontal subregions contribute differentially in cognitive control, emotional appraisal, and behavioral inhibition. The dorsolateral PFC is primarily associated with executive functions such as

working memory and cognitive reappraisal, whereas the ventromedial PFC contributes to emotional valuation and the inhibition of fear-related responses. Through these functions, the PFC exerts top-down modulatory influence over subcortical limbic structures, most notably the amygdala. Disruption of prefrontal–amygdala connectivity is implicated in affective and behavioral disturbances, including anxiety and mood disorders.^{3–6}

The amygdala plays a central role in detecting emotionally salient stimuli and generating affective responses, particularly those related to fear, threat, and stress.⁴ Effective emotional and behavioral regulation depends on intact prefrontal–amygdala communication, whereby PFC activity constrains or modulates amygdala reactivity in a context-dependent manner. Disruption of this regulatory circuitry has been linked to maladaptive emotional responses and behavioral dysregulation.

Given etomidate's potent enhancement of GABA_A-mediated inhibition, its effects on PFC microcircuits are likely to have downstream consequences for prefrontal–amygdala interactions. By increasing inhibitory tone within the PFC, etomidate may alter the balance between cortical control and limbic reactivity, thereby influencing emotional processing and behavioral output.⁷ These effects suggest that the clinical and non-clinical use of etomidate and its neuropsychological impacts extend beyond generalized hypnosis and may involve selective modulation of regulatory brain networks.⁸ This review synthesizes evidence from both clinical administration and emerging non-medical misuse of etomidate to examine how

etomidate-induced cortical inhibition modulates prefrontal–amygdala circuitry and influences cognitive, emotional, and behavioral regulation.

■ Methodology

Studies relevant to etomidate-induced cortical inhibition and its effects on prefrontal–amygdala circuitry and emotional regulation were included in this literature review. Literature searches were conducted using PubMed and Google Scholar between January 2025 and December 2025.

Search terms included combinations of “etomidate”, “GABA_A receptor”, “cortical inhibition”, “synaptic inhibition”, “extrasynaptic GABA receptors”, “prefrontal cortex”, “amygdala”, “prefrontal–amygdala connectivity”, and “emotional regulation”. Boolean operators (AND/OR) were used to refine searches and capture mechanistic, preclinical, and clinical studies relevant to the aims of the review. Studies were selected based on relevance to the review topic, regardless of publication year.

Inclusion criteria:

Studies were included if they were peer-reviewed, available in full text, and provided mechanistic, experimental, or observational data on etomidate, GABA_A receptor modulation, or cortical inhibition. Articles were also required to examine the prefrontal cortex, amygdala, or their connectivity, and to report findings relevant to emotional or behavioral regulation. Only studies published in English were considered.

Exclusion criteria:

Studies were excluded if they were not peer-reviewed, not available in full text, or focused solely on peripheral or non-cortical effects of etomidate, such as adrenal suppression. Articles that did not examine GABA_A receptor modulation, cortical inhibition, or brain-based mechanisms relevant to emotional regulation were also excluded. Preprints, conference abstracts, and studies unrelated to the prefrontal cortex, amygdala, or associated neural circuitry were omitted.

■ Results and Discussion

This review aims to underscore the significance of etomidate circuit-level effects on prefrontal–amygdala interactions when assessing the neurological impacts on humans. By understanding these mechanisms, etomidate-related issues are urgent and relevant, highlighting why it deserves immediate attention and informed action in light of emerging reports of non-medical etomidate exposure. This highlights the need for further experimental research on its long-term cognitive, emotional, and behavioral consequences.

Etomidate Modulation of GABA_A Receptors:

Etomidate exerts its primary neuropharmacological effects through potentiation of γ -aminobutyric acid type A (GABA_A) receptors, resulting in enhanced inhibitory neurotransmission across cortical and subcortical networks, as shown in Figure 1. Experimental studies using GABAergic inhibitory models

support this mechanism. Muscimol, a direct GABA_A receptor agonist, administered at concentrations ranging from 0.1 μ M to 100 μ M, increases GABA_A-mediated chloride ion influx, leading to neuronal hyperpolarization, reduced neuronal excitability, and widespread suppression of neural activity by using an *in vitro* neurons model to examine chloride flux across isolated brain membranes following muscimol exposure, functionally similar to etomidate.⁹ These findings support the mechanistic role of enhanced GABAergic chloride conductance in mediating neuronal inhibition, although the experimental membrane preparation may not fully replicate physiological or clinical etomidate exposure.

Similarly, an *in vivo* electrophysiological study using intact feline models demonstrated that propofol and etomidate, used without reported doses or concentrations, significantly reduced neuronal firing activity across cortical, thalamic, and reticular regions during intravenous anesthetic exposure, accompanied by electroencephalography (EEG) changes consistent with anesthetic-induced unconsciousness.¹⁰ These findings support the concept that widespread GABAergic inhibition disrupts higher-order neural integration and cortical information processing. However, the relatively deep anesthetic exposure used in the study may exceed typical clinical or recreational etomidate exposure.

At the cellular level, etomidate enhances both synaptic and extrasynaptic GABA_A receptor activity, producing sustained inhibitory tone beyond normal phasic GABA signaling. At higher concentrations, etomidate can directly activate GABA_A receptor-associated chloride channels even in the absence of endogenous GABA, as shown in Figure 1, resulting in profound neuronal hyperpolarization and severe suppression of cortical, thalamic, and limbic activities.^{9,10} These findings provide a mechanistic basis for the downstream effects of etomidate on higher-order neural regulation.

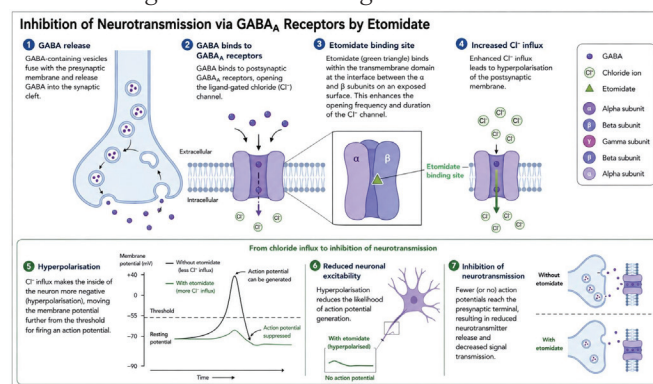


Figure 1: Etomidate enhances GABA_A receptor-mediated inhibition. (1) GABA is released from the presynaptic neuron. (2) GABA binds to postsynaptic GABA_A receptors, opening ligand-gated chloride (Cl⁻) channels. (3) Etomidate (green triangle) binds at the interface between the α and β subunits within the transmembrane domain, enhancing channel opening. (4) This increases Cl⁻ influx. (5) The resulting Cl⁻ influx hyperpolarises the postsynaptic membrane. (6) Hyperpolarisation reduces neuronal excitability and the likelihood of action potential generation. (7) Consequently, less neurotransmitter is released, leading to inhibition of neurotransmission. Created by the author, Joshua Goh, under the guidance of his mentor, Xing Yan Choo.

Etomidate Effects on Prefrontal Cortex:

The prefrontal cortex (PFC) plays a central role in emotional regulation by exerting top-down control over subcortical structures, most notably the amygdala. This regulatory function supports cognitive reappraisal, impulse control, and adaptive decision-making, depending on a finely tuned balance of excitation and inhibition within prefrontal microcircuits.¹¹⁻¹³ Etomidate-induced enhancement of GABA_A-mediated inhibition has the potential to disrupt this balance by suppressing neuronal firing and weakening functional connectivity within prefrontal networks.

Distinct PFC subregions contribute differentially to emotional regulation. The dorsolateral PFC supports executive control and cognitive reappraisal, whereas ventromedial and ventrolateral regions are involved in emotional valuation and inhibition of fear-related responses.¹³ Suppression of activity across these regions may weaken executive oversight of emotional processing, increasing vulnerability to maladaptive emotional responses, impaired decision-making, and reduced behavioral inhibition.

Neurophysiological evidence suggests that etomidate can impair synaptic plasticity and reduce frontal network coherence, both of which are essential for dynamic prefrontal regulation.^{14,15} In addition to these direct cortical effects, etomidate may indirectly compromise PFC function through suppression of cortisol production. Even a single dose has been shown to reduce cortisol levels for up to 24 hours,¹⁶ potentially impairing stress adaptation and further weakening prefrontal-mediated inhibition of limbic activity.

Overall, etomidate-induced suppression of prefrontal microcircuits may compromise executive control and emotional regulation under conditions requiring adaptive cognitive or stress-related responses. Limbic dysfunction can not only manifest as emotional and behavioral change, but also affect an individual with various psychological conditions.

Prefrontal-Amygdala Interactions under Etomidate:

The prefrontal-amygdala circuit represents a core neural substrate for emotional regulation and behavioral control. Within this circuitry, the PFC implements cognitive strategies that modulate emotional responses, while the amygdala processes emotional salience, fear, and affective memory.¹⁷ The PFC, connected to the limbic system, regulates emotional responses by exerting inhibitory control over the system, a network of subcortical structures, through inhibitory modulation of limbic structures, particularly the amygdala.¹⁸ Effective emotional regulation depends on intact bidirectional communication between these regions, allowing contextual information processed by the PFC to constrain amygdala reactivity.¹⁹

Etomidate-induced cortical inhibition may disrupt this regulatory balance by preferentially suppressing prefrontal activity relative to limbic responsiveness. Excessive inhibition within the PFC can weaken top-down control, allowing amygdala-driven emotional and behavioral responses to dominate, as shown in Figure 2.

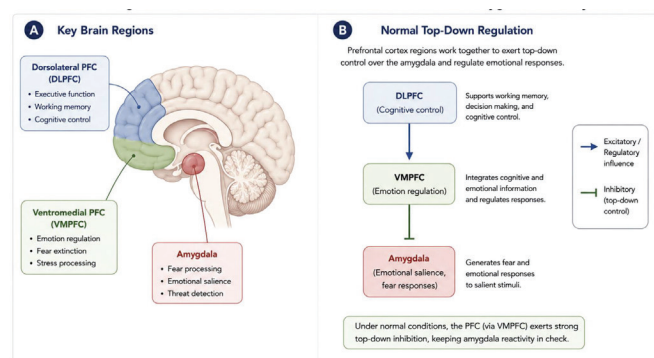


Figure 2: (A) Key brain regions involved in prefrontal-amygdala circuitry. The dorsolateral prefrontal cortex (DLPFC) supports cognitive control and executive functions, while the ventromedial prefrontal cortex (VMPFC) regulates emotions and stress responses. The amygdala mediates fear and emotional salience. (B) Under normal conditions, the DLPFC supports cognitive control through engagement of the VMPFC, which modulates and suppresses amygdala activity. This top-down regulation prevents excessive emotional reactivity and maintains adaptive behavioral responses. Created by the author, Joshua Goh, under the guidance of his mentor, Xing Yan Choo.

Consistent with this mechanism, experimental studies in animal models have shown that prolonged or excessive etomidate exposure disrupts neurotransmitter signaling, compromises neural integrity, and induces behavioral alterations, including heightened aggression, psychiatric-like manifestations, and neurotoxicity, with evidence of irreversible nervous system damage and increased mortality in severe cases.²⁰ Importantly, the effects of etomidate on prefrontal-amygdala connectivity appear to be highly dose-, duration-, and context-dependent. Acute exposure in infant mice did not result in long-term behavioral or motor impairments and was associated with recovery-related hippocampal changes.²¹ Clinical studies similarly suggest that carefully titrated etomidate use may preserve cognitive function, with reduced postoperative cognitive dysfunction observed in elderly patients receiving etomidate alone or in combination with propofol.²²

Etomidate may also indirectly disrupt prefrontal-amygdala regulation through cortisol suppression, as reduced cortisol weakens medial PFC inhibition of the amygdala and impairs stress regulation.²³ As a result, disruption of prefrontal-amygdala balance represents a plausible circuit-level mechanism by which excessive or prolonged etomidate exposure may contribute to emotional dysregulation and maladaptive behavioral outcomes. In addition, etomidate is also frequently associated with extrapyramidal-like motor manifestations, particularly myoclonus. Although these movements may resemble extrapyramidal symptoms clinically, current evidence suggests they arise from transient cortical disinhibition and altered glutamatergic activity rather than classical basal ganglia dopaminergic dysfunction.²⁴⁻²⁶ Etomidate induces myoclonus through rapid cortical inhibition preceding subcortical suppression, resulting in disinhibition of motor pathways.²⁷ As a GABAergic anesthetic, etomidate also suppresses arousal networks and can induce loss of consciousness through enhanced inhibitory neurotransmission.²⁵ Acute inhalation of etomidate-laced e-cigarettes, an emerging concern, leads to CNS depression and adrenal insufficiency by inhibiting adrenal cortical

enzymes, resulting in unresponsiveness and loss of consciousness.²⁶

Implications for Emotional and Behavioral Regulation:

Collectively, these findings indicate that etomidate influences emotional and behavioral regulation through converging effects on GABAergic inhibition, PFC function, cortical–limbic connectivity, and neuroendocrine modulation. By enhancing inhibitory signaling, etomidate suppresses PFC activity and weakens top-down regulatory control over the amygdala. This shift in cortical–limbic balance increases vulnerability to emotional dysregulation, heightened stress reactivity, and impaired emotional reappraisal, particularly in emotionally salient or stressful contexts.

From a behavioral perspective, disruption of PFC-mediated executive control may result in increased impulsivity, maladaptive decision-making, and difficulty regulating goal-directed behavior. Experimental models demonstrating aggression, behavioral disturbances, and neurotoxicity following chronic and high-dose etomidate exposure support the link between impaired cortical regulation and adverse behavioral outcomes.

These effects may be further amplified by etomidate-induced suppression of cortisol, a hormone essential for stress adaptation and emotional stability.²⁸ Reduced neuroendocrine support of prefrontal–limbic circuitry may therefore exacerbate deficits in emotional and behavioral regulation. Importantly, the neurobehavioral effects of etomidate are highly context-dependent. Acute or carefully titrated exposure in clinical settings may preserve, or even facilitate, cognitive function and recovery. In contrast, chronic exposure or supratherapeutic dosing may compromise neural integrity and behavioral control.

Excessive etomidate exposure can produce exaggerated GABAergic inhibition, resulting in profound sedative effects and cumulative neuroendocrine disruption, particularly when used outside controlled clinical supervision.²⁹ Collectively, these observations highlight the importance of considering both neural circuit dynamics and neuroendocrine context when evaluating etomidate’s effects on emotional and behavioral regulation.

Research in some animals and humans demonstrates comparable prefrontal executive functions that regulate cognitive processes critical for behavioral inhibition, planning, decision-making, etc.³⁰ Experimental animal studies, summarized in Table 1, further indicate an increased risk of adverse neurological and behavioral outcomes in humans under such conditions, as summarized in Table 2. It is noted that the homology of prefrontal executive functions across animals and humans facilitates numerous translational studies using animal models of emotion and behavior regulation, as displayed in Table 1. For example, the emerging finding on the extinction of conditioned fear is elucidated, regardless of the challenge of researching the regulation of emotion in rodents.³¹

Table 1A: Animal evidence from behavioral and emotional domains relevant to amygdala-related GABAergic function. These animal studies exhibit key emotional domains, including fear regulation, stress, and behavioral issues such as aggression, unconsciousness, and developmental vulnerability, holistically demonstrating that GABAergic modulation strongly influences amygdala-related emotional and behavioral malfunctions.

Behavioral/Emotional Domain	References	Species/Model	Brain Region/System	GABAergic Mechanism	Key Behavioral/Emotional Findings	Translational Relevance
Fear, Anxiety, and Emotion Regulation	Quirk & Beer (2006) 17	Rat	Prefrontal–amygdala circuit	GABAergic inhibitory regulation of amygdala	Enhanced prefrontal inhibition reduces fear responses	Converges with human emotion regulation models
Anxiety	Allan & Harris (1986) 9	Rat brain membranes	Brain membranes	GABA antagonist effects on Cl ⁻ flux	Altered inhibition affects neural excitability linked to anxiety	Mechanistic support for anxiety modulation
Emotion	Kohl & Paulsen (2010) 2	Rodent	Cortical networks	GABA _A receptor modulation	Stabilization of neural network activity in emotional control	Supports connectivity findings in humans
Stress, Arousal, and Network Stability	Talavera <i>et al.</i> (2009) 7	Rodent	Thalamocortical system	Etomidate potentiation of GABA _A receptors	Reduced arousal and disrupted cortical integration	Exhibits stress-related neural dampening
Stress	Andrada <i>et al.</i> (2012) 11	Rat	Cortex, reticular formation	GABAergic anesthetic suppression	Decreased neuronal firing and responsiveness	Highlights Relevant to stress and affective blunting
Aggression and Affective Dysregulation	Li <i>et al.</i> (2025) 14	Zebrafish	Whole brain	Etomidate-induced GABAergic neurotoxicity	Increased aggression and behavioral dysregulation	Parallels emotional regulation in humans
Developmental Emotional Outcomes	Nyman <i>et al.</i> (2016) 21	Infant mice	Central nervous system	GABAergic anesthetic action and inhibitory CNS	No significant behavioral or emotional impairment	Elucidates developmental resilience
Dysregulation	Ding <i>et al.</i> (2024) 20	Mouse	Nervous system gut-brain axis	Chronic GABAergic disruption	Long-term neural and systemic dysregulation	Warns Prolonged exposure effects on the nervous system
Consciousness and Emotional Blunting	Talavera <i>et al.</i> (2009) 7	Rodent	Thalamocortical networks	GABA _A mediated suppression	Reduced conscious and emotional responsiveness	Relevant to anesthetic-induced injurious effects on consciousness
Emotion	Andrada <i>et al.</i> (2012) 11	Rat	Limbic–cortical networks	Global GABAergic depression	Emotional regulation under anesthesia	Explains reduced affect in humans

The findings presented in Table 1 are refined as follows: GABA_A receptor-mediated inhibition in PFC induced by low-to-moderate etomidate does not directly increase emotional reactivity, such as fear, anxiety, or impulsive responses. However, when excessive and prolonged etomidate is administered, limbic circuits become disinhibited. Decreased GABAergic inhibition makes Cl⁻ influx less, rendering neurons more excitable. As a result, increased anxiety-like behaviors, such as impulsiveness or aggression, are found.

Table 1B: Summary of animal studies examining neural mechanisms, levels of dysfunction, and reported neuronal damage or cell death associated with etomidate exposure. Findings range from minimal functional impairment under low-to-moderate exposure to neurotoxicity, neural disruption, and behavioral dysregulation following excessive or prolonged exposure, highlighting the dose- and duration-dependent nature of etomidate’s effects.

Behavioral/Emotional Domain	References	Exposure Level	Neural Mechanism	Level of Dysfunction	Neuronal Damage / Cell Death	Reported Key Findings
Fear, Anxiety, and Emotion Regulation	Quirk & Beer (2006) 17	Not reported	Enhanced prefrontal inhibitory regulation	Circuit-level	Not reported	Enhanced prefrontal inhibition reduced fear responses
Anxiety	Allan & Harris (1986) 9	Not reported	Altered inhibitory neural excitability	Synaptic/ Circuit-level	Neuronal damage	Altered inhibition affected neural excitability linked to anxiety

Emotion	Kohli & Paulsen (2010) 2	Not reported	Stabilization of neural network activity	Network-level	Not reported	Stabilization of neural network activity involved in emotional control
Developmental Emotional Outcomes	Nyman <i>et al.</i> (2016) 21	Unclearly reported (clinically induced unconsciousness level)	Minimal developmental neural disruption	Systems-level	No significant neuronal damage reported	No significant behavioral or emotional impairment observed
Behavioral/Emotional Dysregulation	Ding <i>et al.</i> (2024) 20	Excessive (chronic exposure)	Chronic neural disruption and hyperexcitability	Systems-level	Neuronal damage	Increased etomidate-induced myoclonus
Stress, Arousal, and Network Stability	Talavera <i>et al.</i> (2009) 7	Unclearly reported (clinically relevant anesthetic exposure)	Disrupted cortical integration and suppression	Network-level	Functional suppression reported; cell death not specified	Reduced arousal and disrupted cortical integration
Stress	Andrada <i>et al.</i> (2012) 11	Moderate / Excessive	Suppressed neuronal firing responsiveness	Circuit-level	Neuronal suppression reported; cell death not specified	Decreased neuronal firing and responsiveness
Aggression and Affective Dysregulation	Li <i>et al.</i> (2025) 14	Not reported	Neurotoxicity and apoptosis-associated dysregulation	Molecular/ Systems-level	Neuronal damage; neurotoxicity and apoptosis reported	Increased aggression and behavioral dysregulation
Dysregulation	Ding <i>et al.</i> (2024) 20	Excessive	Chronic systemic neural disruption	Systems-level	Chronic neural disruption reported	Long-term neural and systemic dysregulation
Consciousness and Emotional Blunting	Talavera <i>et al.</i> (2009) 7	Not reported	Functional cortical suppression	Network-level	Functional cortical suppression reported	Reduced consciousness and emotional responsiveness
Emotion	Andrada <i>et al.</i> (2012) 11	Unclearly reported (clinically relevant anesthetic exposure)	Global neural suppression under anesthesia	Systems-level	Global neural suppression reported	Emotional regulation suppression under anesthesia

However, human research conducted to verify etomidate's potential effects is constrained by underlying risks. Only a few studies have been conducted, leading to the limited findings, thereby providing inconclusive findings regarding emotional, cognitive, and behavioral effects, as reflected in Table 2.

Table 2: Statistically reported cognitive, emotional, and affective outcomes following etomidate administration in human subjects, with respective study models.

Domain	References	Study Model	Key Findings	Reported Statistics
Cognitive function	Zhi & Li (2023) 22; Absalom <i>et al.</i> (1999) 16	Older adults	Transient postoperative cognitive dysfunction	Incidence happens in 25–30% within 7 days post-anesthesia
Emotional state	Zhi & Li (2023) 22	Human through experiments	Increased anxiety and depressive symptoms following anesthesia	Significant increases vs. baseline ($p < 0.05$)
Emotional regulation	Veer <i>et al.</i> (2012) 23	Human through neuroimaging	Altered prefrontal–amygdala functional connectivity	Significant connectivity changes associated with cortisol levels ($p < 0.05$)
Affective processing	Banks <i>et al.</i> (2007) 12; Wager <i>et al.</i> (2008) 13	Humans through functional imaging	Disrupted prefrontal–limbic interactions relevant to emotion control	Significant network-level modulation vs. baseline

■ Limitation

First, for ethical reasons, direct investigation of etomidate's effects on cognition, emotional regulation, and behavior in humans is inherently limited. Deliberate exposure of participants to potentially harmful doses or prolonged use of etomidate is not permissible, restricting human studies largely to clinical, observational, or case-based evidence.

Second, data regarding non-medical and recreational etomidate use remain limited. Most available evidence originates from case reports, toxicology studies, and observational investigations, making it difficult to fully characterize patterns of misuse, long-term neurobehavioral effects, and associated risks. Furthermore, unlike clinical anesthetic use, in which etomidate is administered intravenously at standardized and well-characterized doses, the actual dose exposure associated with inhalational use remains poorly defined. Variability in product formulations, inhalation patterns, and frequency of use, along with the lack of standardized toxicological analyses, makes exposure estimation difficult. Similarly, epidemiological data regarding duration of use and peak-age distribution among users remain limited, restricting conclusions about dose-response relationships and long-term risk.

Third, the neurobehavioral risks associated with etomidate are likely to vary across patient populations. Vulnerable groups, including elderly individuals and patients with chronic medical conditions, may be at increased risk of adverse cognitive, emotional, or physiological effects, limiting the generalizability of findings derived from healthier populations.

Finally, severe neuropsychiatric outcomes such as mental disorders, self-harm behaviors, and fatal events have been reported in cases of extreme etomidate exposure. However, systematic research on etomidate toxicity remains limited due to the scarcity of controlled studies, inconsistent reporting of poisoning manifestations, and the lack of standardized assessment protocols. These gaps highlight the need for more structured toxicological and clinical investigations.

■ Recommendations and Future Directions

Recent reports indicate that etomidate has emerged as a misused psychoactive substance, drawing increasing attention due to its presence in certain illicit formulations, including products such as K-POD. This trend has heightened concern regarding non-medical exposure to etomidate and reinforced the urgency of further investigation to understand its neurobiological, emotional, and behavioral consequences. The potential for abuse-related outcomes, including irreversible neural damage and emotional or behavioral disturbances, underscores the need for targeted preventive and public health measures.

Future research should prioritize elucidating the mechanisms underlying etomidate-related morbidity and mortality, particularly in cases of suspected poisoning. While adrenocortical suppression and myoclonus are recognized contributors to adverse outcomes, additional mechanisms may be involved. Integrated neuroendocrine, neuroimaging, and clinical studies are needed to directly assess amygdala–prefrontal cortex dysfunction, cortisol suppression, and their roles in cognitive, emotional, and behavioral impairments associated with etomidate toxicity.

■ Conclusion

Longitudinal and translational studies examining repeated or chronic etomidate exposure are needed to more clearly char-

acterize its long-term neuropsychological effects, particularly in contexts extending beyond controlled clinical use. Disruption of emotional regulation and behavioral control may carry meaningful psychosocial consequences, including impaired interpersonal functioning and increased risk of maladaptive behaviors. A clearer understanding of these risks would support improved clinical risk stratification, inform regulatory and preventive strategies, and provide a foundation for targeted interventions aimed at minimizing potential harm associated with etomidate-containing substances. Greater awareness of the neural, behavioral, and neuroendocrine consequences of etomidate exposure is therefore essential to ensure its safe and responsible use.

■ Acknowledgments

The author would like to thank the mentors and educators who guided the development of this narrative literature review. Special appreciation is extended to those who offered feedback on the research structure, scientific writing, and interpretation of findings. The author is also grateful to the researchers whose published work formed the foundation of this review. Finally, sincere thanks are given to family and peers for their encouragement and support throughout the research and writing process.

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