

Review Article

The effect of propofol on mental health in Saudi Arabia

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Received: 15 April 2025

Revised: 29 April 2025

Accepted: 30 April 2025

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ABSTRACT

Propofol is a widely used intravenous anesthetic agent with a rapid onset and short duration of action. While extensively utilized for sedation and anesthesia, recent research has raised concerns regarding its impact on mental health, particularly addiction potential, hormonal effects, and neuropsychiatric implications in individuals with underlying neurological conditions. This review aims to examine the neurobiological, hormonal, and psychiatric effects of propofol with a focus on addiction mechanisms, its role in neurodevelopmental and neurodegenerative syndromes, and its modulation of stress- and mood-related hormones, especially within the healthcare landscape of Saudi Arabia. A comprehensive literature review was conducted, drawing from experimental studies, clinical trials, and pharmacological analyses that explored propofol's interaction with dopamine pathways, hormone regulation, and its implications in syndromes such as Down syndrome, fragile X syndrome (FXS), and Tourette syndrome (TS). Propofol's interaction with the mesolimbic dopamine system and dopamine transporter (DAT) contributes to its addictive properties. It alters hormonal responses by modulating GABAergic pathways, reducing stress hormone levels such as cortisol and epinephrine. In patients with specific syndromes, propofol demonstrates differential effects on cognition, recovery, and neurological activity, requiring tailored clinical considerations. While propofol remains a cornerstone of modern anesthesia, its psychoactive and addictive potential, especially among healthcare professionals, necessitates stricter regulation and education. Its impact on stress modulation and mental health highlights its dual therapeutic promise and risk, warranting further clinical research and policy development, particularly in Saudi Arabia, where regulatory oversight remains limited.

Keywords: Propofol, Anesthesia, Addiction, Down syndrome

INTRODUCTION

One often used intravenous anesthetic, propofol, is distinguished by its quick onset and short half-life. Clinical research has focused a lot of attention on its effects on mental and cognitive states, especially when it comes to issues like the possibility of addiction, hormone interactions, and its consequences for certain neurological disorders including Parkinson's disease and Down

syndrome. This field of study has become increasingly important in Saudi Arabia's clinical and scientific environment.

Many studies have focused on the risk of addiction associated with propofol represents a considerable concern, especially in individuals who might misuse the drug to experience its euphoric effects. Recent research highlights that propofol is capable of producing

sensations of euphoria comparable to those elicited by other addictive substances, thereby amplifying worries regarding its potential for non-medical use and dependence. Evidence suggests that the neurobiological foundations of propofol addiction are closely tied to the mesocorticolimbic pathway, a central component of the brain's reward system.¹

Due to its benefits and the growing need for painless diagnosis and treatment, propofol is being used more and more. Propofol, however, has the potential to be abused and is prone to addiction, according to mounting clinical and experimental data. Our review focuses on elucidating the involvement of the mesolimbic, noradrenergic, and nitergic systems in propofol addiction in order to better understand the underlying mechanism of this addiction. We have concentrated on how the mesolimbic system's gamma-aminobutyric acid, glucocorticoid, N-methyl-D-aspartic acid, adenosine A2A, and corticotropin-releasing factor receptors contribute to the development and maintenance of propofol addiction. Additionally, we have tried to elucidate the connection between the ventral tegmental area-nucleus accumbens (NAc) circuit, the extracellular signal-regulated kinase signaling pathway, and the dopaminergic pathway in mesolimbic system.²

Moreover the use of propofol can influence hormonal levels, especially those linked to stress and anxiety. By interacting with GABA receptors, it alters neurotransmitter balance, which in turn may affect hormonal regulation and mental well-being. Despite the fact that the precise neurological mechanisms underlying its association with feelings of happiness and euphoria are yet unknown. Lasker's well-known propofol is frequently utilized for general anesthesia. Propofol alleviates anhedonia by directly attaching to the DAT without affecting the serotonin transporter (SERT), according to this study. The binding configuration of propofol is simulated by molecular docking, and additional research confirms its function in raising dopamine levels in the NAc. These findings highlight propofol's potential therapeutic benefits for anhedonia and point to the necessity of more clinical research.³

In addition, individuals diagnosed with Parkinson's disease, propofol has been observed to exert significant effects on neuronal activity within subthalamic nucleus, a region critically implicated in motor control and higher-order cognitive processes. Empirical evidence suggests that propofol administration can diminish neuronal spiking activity, outcome that poses potential challenges to accuracy of microelectrode recordings (MER) during deep brain stimulation (DBS) procedures. Furthermore, emerging research highlights concerns regarding post operative cognitive outcomes associated with propofol use with some studies reporting detrimental effects on memory retention and overall cognitive performance.⁴

On the other hand, little is known about how propofol affects people with Down syndrome. However, given the

patients' specific neurodevelopmental and physiological traits, it is important to carefully assess how this anesthetic drug can interact with their particular hormone regulation and cognitive profiles. In contrast to general patients, those with Down syndrome may have abnormal drug metabolism and pharmacological sensitivity patterns, which could lead to different anesthetic needs and different cognitive or behavioral consequences after administration. Additionally, this study investigated risk factors linked to poor recovery and low peripheral oxygen saturation (SpO₂) in dental patients with impairments following intravenous sedation. Demographic and sedative characteristics were assessed in a retrospective examination of 1213 individuals. Significant odds ratios for SpO₂ <90% were found by multivariate logistic analyses in relation to age, gender, nitrous oxide use, midazolam and propofol doses, and certain impairments. Significantly, individuals with Down syndrome experienced the greatest impact (odds ratio, 3.003-7.978; $p < 0.001$). boys with Down syndrome who received large doses of propofol and younger boys who took longer to recover were shown to be at higher risk.⁵

REVIEW LITERATURE

For comfortable, efficient medical interventions, anesthesia is vital in alleviating pain and anxiety. Intravenous general anesthesia is a popular choice among various anesthetic techniques because it offers a rapid onset, controlled sedation depth, and minimal residual effects. Propofol, a short-acting intravenous anesthetic, enhances inhibitory neurotransmission and reduces neuronal excitability by allosterically modulating and agonising GABAA receptors. Clinically, it offers rapid induction, smooth recovery, and a favorable pharmacokinetic profile that minimizes respiratory irritation. Despite its effectiveness, propofol has side effects such as injection site pain, respiratory and cardiovascular depression, nausea, vomiting, and hypotension after rapid administration. Rarely, propofol infusion syndrome (PRIS) may cause serious metabolic problems and organ failure. These concerns necessitate a comprehensive understanding of its pharmacological effects beyond anesthesia, particularly in the context of mental health. The concerns raised necessitate fully understanding its pharmacological effects beyond anesthesia, especially regarding mental health.⁶

Functional imaging (PET and fMRI) reveals propofol significantly reduces glucose metabolism and cerebral blood flow in healthy brains, particularly the thalamus, more so during unconsciousness. With light anesthesia, there's reduced connection between the thalamus and cortex, but increased connection within the pons of the brainstem. While deeply anesthetized, cortical sensory interaction is preserved despite thalamocortical network suppression, leading to widespread metabolic and vascular depression.⁷ Besides, the selective reduction of neurons by propofol causes unconsciousness and long-term brain functional changes.⁸

Patients with mental illness require special consideration. Analysis of anesthesia in oral and maxillofacial surgery patients demonstrated that, although initially insignificant, mental illness correlated with increased propofol dosage after controlling for gender, BMI, and drug use, due to propofol's GABA-inhibitory effects.⁹

Since propofol is favored for sedating patients with neurological disorders, its effects on those with syndromes necessitate careful observation during administration. While rare, PRIS, serious and potentially fatal side effect, is linked to the use of high and prolonged doses of propofol. Prolonged anesthesia, rapid infusion rates, and critical illness are all risk factors for developing this syndrome. Therefore, patients on long-term propofol, like those in intensive care, require close dose monitoring.¹⁰ Despite the challenges of hyperuricemia, neurocognitive issues, and self-harm in Lesch-Nyhan

syndrome, propofol offers a surgical anesthetic option, although delayed awakening might occur.¹¹ Propofol effectively manages alcohol withdrawal syndrome (AWS), a serious condition marked by delirium and autonomic instability, providing potent sedation, seizure suppression, and symptom reduction while minimizing benzodiazepine complications. Moreover, hypotension and respiratory depression, among other side effects, necessitate careful monitoring and dose adjustments of propofol in this syndrome's treatment.¹² Despite propofol's sedative properties and potential mood-boosting effects, repeated injections stimulate neural pathways governing short-term mood. Interestingly, the first propofol injection's mood effects didn't vary with the dose, suggesting that initial exposure improves mood regardless of dose. However, while initially mood-enhancing, propofol's effects can decrease with repeated doses (Figure 1 and 2).¹³

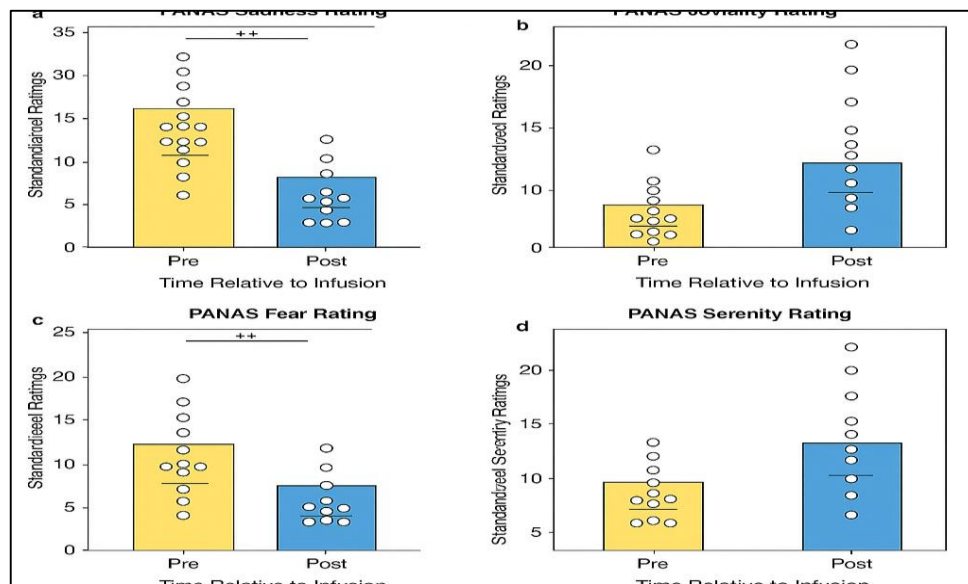


Figure 1 (a-d): Mood improvements with first propofol infusion.

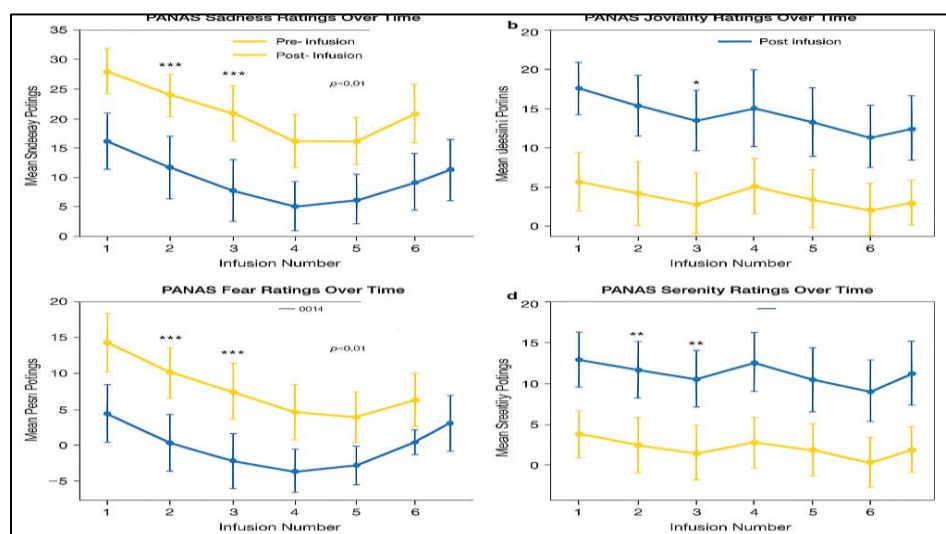


Figure 2 (a-d): Decay of mood improvement over treatment course.

While propofol shows promise in anesthesia, hypnosis, and positive mood enhancement, its capacity to increase dopamine secretion makes addiction and misuse a serious concern. This is increasingly concerning healthcare professionals, particularly anesthesiologists and specialists.²

The knowledge of propofol's pharmacological properties, fast onset of effects, short duration, and easy accessibility without supervision have led to its connection to up to 33% of unexpected deaths and by self-recognition in rehabilitation programs.¹⁴ The danger of propofol is underscored by studies revealing over 25% of its uses are undocumented.¹⁵ Cases of propofol addiction frequently occur early in the careers of anesthesia workers, a group identified as particularly high-risk.¹⁴

ADDICTION

Drugs are chemicals that work in changing the way the body works for a particular purpose. However, some other drugs can be with extensive and repetitive use it leads to addiction, Which is considered a comprehensive issue that leads to a lot of associated problems and death. What may lead to drug misuse are several factors in which they include rival pressure, mental instability, or curiosity which are motivations to proceed with drug intake. That perfectly includes the healthcare providers who are more exposed to the drugs than anyone else.

In specialized terms, sedate enslavement is characterized as an inveterate, backsliding malady coming about from the supported impacts of drugs on the brain. Through distance, improved characterization of the cerebral circuits is included, and the long-term alterations of the brain are initiated by addictive drug organizations.¹⁶ The progressive disruption caused by addictive drugs affects brain circuits responsible for reward, motivation, emotions, decision-making, and cognitive function.¹⁷

Where there is an increased demand for propofol due to its benefits, the growing need for painless diagnosis and treatment is driving its use. Nevertheless, a growing body of experimental and clinical data has demonstrated that propofol is prone to addiction and abuse as a result of its basic mechanism, In which it acts quickly (less than a minute) and lasts only 5 to 10 minutes, it becomes more and more abused.² Propofol is utilized in operating rooms and intensive care units (ICUs) and has not generally been designated as a prohibited substance. It is preferred by persons who abuse propofol because it requires only a tiny dose for pleasure, is easily accessible, acts quickly, and has no long-term negative consequences.¹⁸ Addiction to propofol is created and maintained by the interaction of many transmitters, receptors, signaling pathways, and brain circuits.²

Because it might result in impairment as previously mentioned, substance misuse is similar to a major problem for doctors in the field of clinical practices.¹⁹

Recent research indicates that physicians are thought to be in danger of developing drug dependence at some time throughout their employment as a dangerous approach to cope with painful emotional situations, or it could be used purely for fun.²⁰ In particular, anaesthesiologists and certified registered nurse anesthetists have an easy approach to the wide variety of potent addictive drugs, basing a large number of medical professionals who abuse drugs especially propofol indeed even with acknowledging its pharmacodynamics, future investigations ought to center on deciding the centrality of this critical issue.^{14,21}

Two examples of propofol abuse were described by Wilfer et al. In the first, a major car accident necessitated treatment at a rehabilitation facility after an anaesthesiologist started using propofol after having trouble getting higher amounts of fentanyl. The second concerned a nurse who, following an ankle injury, started taking fentanyl and morphine before switching to propofol because it was readily available. Suspicions were raised by her physical injuries, yet she promptly began taking propofol following therapy, and then she voluntarily sought treatment. In all situations, people were unable to quit using propofol in spite of the devastation it caused to their personal and professional lives, and simple access to the drug was a significant contributing factor to addiction.¹⁴

And so some researchers contend that propofol should be placed on the list of restricted medications and that doctors should take caution when prescribing it.²²

Based on the recent ones, clinical and experimental data disclosed that addiction to propofol carries a significant death rate, peculiarly because of its limited therapeutic window and risk of overdose causing respiratory depression and repressing sympathetic activity, initiating bradycardia then cardiac arrest leading to death.^{1,23,24} More concerning is that there is no antitoxin for propofol and management depends on its metabolism in the liver and the clearance of the body's propofol throughout the kidney.²⁵ Unlike Opioids which are also contemplated as addictive drugs, Naloxone is an antidote making it more manageable in resuscitation on the counter of Propofol. Many occurrences of unexplained sudden deaths in a link have been established between medical professionals and unsupervised propofol self-administration precipitating a mortality rate of up to 33% among them.¹⁴ Treatment for propofol addiction has not become specific yet, where it made it questionable that, Is it possible to heal addiction? Not always, but addiction can be effectively treated, just like other chronic illnesses. And who receive treatment are able to reclaim control of their life and reverse the profoundly disruptive effects that substance abuse has on their brains and behaviours.²⁶

but there are several therapy treatments have been used to treat drug addiction which includes some of the following methods like in East Asian nations, acupuncture is widely

used as a conventional therapeutic approach. By inserting metallic needles into particular acupuncture sites on the skin and muscles, acupuncture generates therapeutic effects.²⁷ Various types of pharmaceuticals may be beneficial at different phases of therapy to assist a patient in stopping drug abuse, staying in treatment, and avoiding relapse. And so behaviour Associated treatments aid people in substance use disorder treatment by altering their mindsets and behaviours related to drug use and increasing their lifelong skills regarding dealing with stressful situations and environmental cues that may trigger intense cravings for drugs and set off another cycle of compulsive use. Behavioural therapy may additionally boost the efficacy of drugs and help people stay in treatment longer.²⁶

As for the legal and ethical implications, according to assessments of sedation practices in PICUs, a large majority of paediatric intensivists persist to utilise propofol, either alone or in combination with other drugs, as their preferred sedative agent to bring comfort and safety to mechanically ventilated kids.²⁸ Given its continued use, Propofol usage has led to discussions over its classification as a restricted substance. The ethical execution of a safety trial demands a careful assessment of two major factors: its acceptance of the study's risk-benefit regulate and the appropriateness of plans for obtaining participants' informed permission, In order to reduce diversion, countries such as the United States and Germany have enacted tougher controls for propofol storage and prescription. It will stop many unintentional fatalities, but it won't lower the overall prevalence of substance usage among medical workers.^{28,29}

Implementing strict pharmacy monitoring and regulating access to propofol is essential to mitigate its abuse among healthcare providers. Radiofrequency ablation of controlled drugs is a viable option. To halt the escalation of propofol abuse, a comprehensive strategy among healthcare providers is essential, encompassing early detection and intervention, rigorous treatment, education, and rehabilitation.³⁰ To that end in Saudi Arabia, there is little regulation regarding propofol usage, raising worries about its availability in hospital settings.

SYNDROMES

In addition to its well-known anesthetic effects, propofol has a major impact on patients with a number of neurological and mental disorders. These impacts can affect cognitive and physiological responses in people with Down syndrome and FXS, as well as alter neuronal activity in neurodegenerative diseases like Parkinson's disease.

Propofol has also been investigated in relation to severe mental illnesses such delirious mania, neuropsychiatric symptoms associated with encephalitis, and DBS operations. The literature on propofol's interactions with

neurological and psychiatric diseases is examined in this section.³¹

Involuntary motor and vocal tics are hallmarks of TS, a neuropsychiatric condition that manifests in childhood. One significant feature of TS is its correlation with neurobehavioral conditions including obsessive-compulsive behavior and attention deficit hyperactivity disorder. The clinical presentation and, consequently, quality of life are significantly impacted by the existence and severity of these comorbidities.

The prognosis for most TS patients is good, and most or all of their tics go away during puberty. However, a tiny proportion of people experience worsening symptoms that necessitate medical attention. Cognitive behavioral therapy and/or pharmaceutical therapies are used as therapeutic options for this group. In certain situations, DBS may be a viable choice if the response to both is insufficient. According to a recent meta-analysis, the Yale global tic severity scale improved by 53% after DBS treatment. Different centers use quite different anesthetic techniques during DBS treatments. MER and clinical testing to maximize target localization have historically been facilitated by local anesthetic. However, during DBS surgery, patients could feel pain, anxiety, or other types of discomfort. In addition to these stressors, TS sufferers may experience severe motor tics, which are frequently made worse by stress and worry. These render surgery risky and raise the possibility of perioperative complications, such as tachycardia or a cerebral hemorrhage brought on by extreme hypertension. As a result, sedation is frequently required or desired. The use of sedatives during DBS surgery raises concerns due to possible consequences on MER quality. Several studies have shown that anesthetic drugs decrease neuronal firing in patients with Parkinson's disease and dystonia. The effect on MER appears to be both drug and dose dependent but also varies depending on the underlying disease.

Therefore, data from DBS patients with Parkinson's disease and dystonia cannot be extrapolated to TS patients. To date, no studies have addressed the effect of anesthetic agents on MER quality in patients with TS. For this aim, we report our experience with different anesthetic drugs on MER quality during DBS implantation in the internal globus pallidus (GPi) in 6 patients with TS.³²

TS with DBS with propofol

DBS is used to treat neurological diseases such as Parkinson's disease and TS, which is characterized by involuntary vocal and physical tics. Although sedation is often required for DBS treatments, MER may be affected by anesthetics like propofol. Effects of propofol on DBS accuracy. Propofol can alter DBS recordings in TS patients by inhibiting neuronal firing rates.

FXS in relation to propofol

A genetic condition known as FXS is linked to autism-like symptoms, hyperactivity, anxiety, and intellectual disability. It is caused by a mutation in the FMR1 gene, which modifies neurotransmission and impairs synaptic plasticity.³³

The function of propofol in FXS

Endocannabinoid system regulation

Research indicates that propofol may influence the endocannabinoid system by blocking fatty acid amide hydrolase (FAAH), which raises anandamide levels, a neurotransmitter linked to stress reduction and cognitive flexibility. This could account for propofol's possible therapeutic benefit in lowering anxiety and hyperactivity in patients with FXS.³⁴

Effect on learning and memory

Propofol has been demonstrated to enhance cognitive function in animal models by altering neurotransmitter activity; however, the long-term consequences on neurodevelopmental trajectories are yet unknown, and more clinical research is required.⁵

Both Down syndrome and propofol

Trisomy 21 causes Down syndrome, a neurodevelopmental condition marked by intellectual impairment, abnormal metabolic processes, and unique physiological reactions to anesthesia. Because of differences in drug metabolism and neuronal sensitivity, propofol's effects on patients with Down syndrome are different from those in the general population.³⁵

TS with propofol

Usually involuntary, TS is characterized by vocal and physical tics. The disorder is linked to anomalies in the dopaminergic and basal ganglia systems, which impair motor function control and cause disinhibition.

Impact on tics

It's unclear how propofol affects tics in people with TS. But there are a few broad observations.³²

Modulation of dopamine

Primarily, propofol functions as a GABA agonist, meaning it increases GABA's inhibitory activity in the brain. Since tics are frequently linked to increased neuronal excitability and inadequate inhibition, it is conceivable that propofol could temporarily suppress or ameliorate tics in TS patients, even if the exact mechanism by which propofol may alter tics is unknown.

Exaggerated response to sedation

Although this is more frequently seen with other sedatives, especially those that have dopaminergic interactions, some people with TS may exhibit increased sensitivity to sedatives.

Propofol may not have as much of an impact on dopamine transmission as other sedatives because its main mechanism of action is on the GABA-A receptor, but it may still have an impact on the frequency or intensity of tics during the perioperative phase.³²

HORMONES

Hormones are chemicals that arrange distinctive capacities in your body by carrying messages through your blood to your organs, skin, muscles and other tissues. They impact numerous viewpoints of our body's working, counting digestion system, development, sexual wellbeing, and regenerative framework working. Nearly all of hormones influence your disposition, feelings, and mental wellbeing in one way or another. In our audit we'll examine the relationship between the medicate propofol and its impact on body hormones. Surgical patients' hormone levels may be affected by general anesthesia like propofol. Propofol may lower hormone levels during surgery and it has inhibitory effects on the change in hormone levels after surgery.³⁶

While levels of copeptin, norepinephrine, and adrenaline decreased, renin, angiotensin, and aldosterone plasma levels increased. It appears that propofol inhibits the release of catecholamines and copeptin, which are markers of arginine vasopressin.³⁷

Propofol decreased cortisol levels in postoperative blood and follicular fluid. Higher PGE2 levels in follicular fluid with propofol are thought to be related to the regulation of prostaglandin E2 fertilization with propofol and the protective action of sperm against phagocytosis in the ovaries (Figure 3).³⁸

An elevated risk for anxiety is linked to the activation of corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus (PVN). Propofol may be used as a treatment for mood disorders because of its capacity to provide euphoric feelings and offer long-lasting relaxation. We assessed how propofol affected pain-related anxiety-like behaviors using models of acute and chronic pain.

The anxiolytic effects of propofol remain for at least three days following therapy, and it quickly reduces anxiety-like behaviors linked to both acute and chronic pain.³⁹ Controlling the release of stress hormones is a constant effect of propofol. It had a low level of epinephrine.^{40,41} Propofol raises PTH levels in healthy people regardless of how it affects the levels of ionized calcium or total magnesium (Figure 3).⁴²

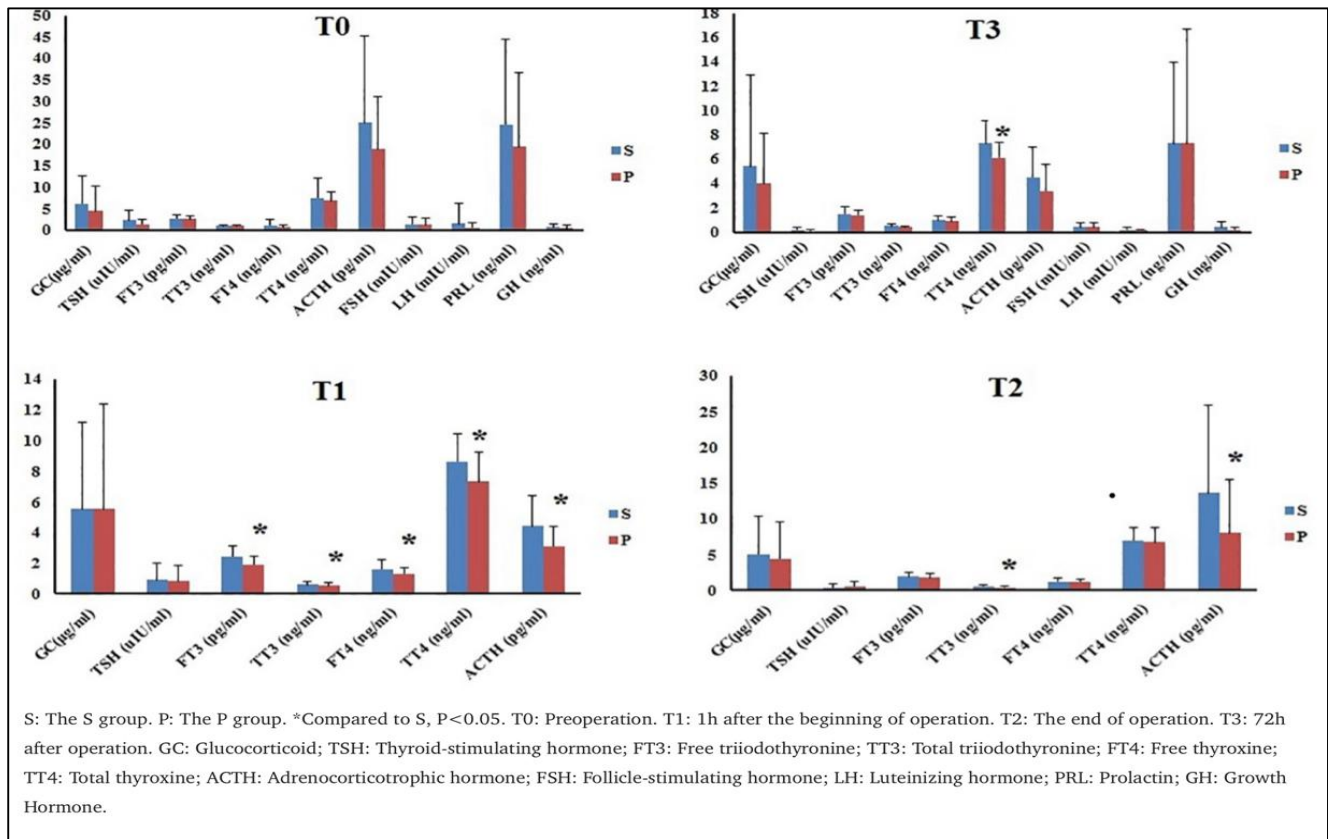


Figure 3: Perioperative hormones levels of two groups.

The red chart represents the propofol.

Dopamine and propofol

Dopamine is not only essential for the brain's reward system but also influences several behavioral and physiological processes. As the brain's "feel-good" chemical, dopamine is deeply involved in regulating mood, emotional responses. Its release during rewarding activities helps drive behaviors associated with seeking pleasure. In addition to its role in pleasure and motivation, dopamine is crucial for motor control and learning. Imbalances in dopamine levels, whether due to underproduction or overactivity, can lead to various disorders, including Parkinson's disease, where the loss of dopamine-producing neurons impairs movement, and conditions like schizophrenia, which are linked to dopamine dysregulation.⁴³

As a neurotransmitter, dopamine interacts primarily with dopamine receptors, which are part of the larger family of G protein-coupled receptors (GPCRs). These receptors mediate dopamine's effects by binding to specific target cells and initiating intracellular signaling. However, dopamine levels are tightly regulated by transporters, such as the DAT, which recycles dopamine after it is released into the synapse. This regulation ensures that dopamine's effects are not prolonged, contributing to the proper balance of neural activity.^{43,44}

Propofol, a widely used anesthetic, interacts with DAT, altering dopamine dynamics in the brain. By directly binding to DAT, propofol competes with dopamine for binding sites, thereby blocking the reuptake of dopamine.⁴⁴ As a result, dopamine accumulates in the synaptic cleft, leading to an increase in extracellular dopamine levels, particularly in brain regions like the NAc.⁴³ The NAc is a critical region for reward processing, and changes in dopamine levels in this area are thought to influence both reward and aversion responses.⁴² This modulation of dopamine in the NAc likely contributes to propofol's euphoric effects and its potential to induce feelings of pleasure.⁴⁶

Unlike other neuroactive substances, such as opioids, propofol's ability to enhance dopamine release might make it more potent in certain contexts. While opioids primarily interact with the brain's opioid receptors, propofol's direct influence on DATs results in a more targeted increase in dopamine signaling.⁴⁵ This mechanism can lead to the reinforcing effects that are characteristic of addictive substances. While some studies suggest propofol may have antidepressant properties, the addictive potential associated with its euphoric effects complicates its therapeutic use. The idea that propofol might be employed as a treatment for depression remains controversial, and further research is required to better

understand its long-term effects, safety, and potential benefits in managing mood disorders.⁴⁶

The complexity of dopamine signaling and the role of DAT in regulating dopamine levels highlight the importance of understanding how drugs like propofol interact with brain's reward system. As research continues to explore these interactions, it could lead to development of more targeted treatments for a range of neurological and psychiatric disorders, while also offering insights into mechanisms underlying addiction and mood regulation. However, given addictive potential of propofol, any clinical application for mood disorders must be approached with caution and further investigation.

Propofol inhibits dopamine transport by binding to DAT

To gain a deeper understanding of the molecular mechanisms underlying the inhibition of the DAT by propofol, we employed homology modeling and molecular docking to explore the interactions between dopamine and propofol. The findings revealed that propofol primarily interferes with dopamine on the transport channel of DAT, rather than directly competing with dopamine (Figure 4 E), in the figure below, the section E illustrates the binding sites of dopamine and propofol in the transport channel of DAT, the pocket occupied by propofol is indicated by a red arrow.⁴⁶ Molecular docking proves to be a powerful tool that analyzes both the ligand and the target to identify species

of drugs.⁴⁷ In this study, there is also homology modeling to generate structural models of membrane transporter proteins, such as the DAT.⁴⁸ Based on the predicted binding mode (Figure 4 F), in the figure below, section F illustrates the binding mode of propofol and dopamine. The hydrogen bonds are shown in the red dashed line and the pi-pi stacking is shown in the green dashed line, and the interactions between the protein and the bound molecule in solution, the immobilized receptor, and the binding molecules-we performed molecular dynamics (MD) simulations of dopamine and propofol with DAT. These simulations provided insights into the transport activity of DAT, and we quantified the uptake of a fluorescent marker to assess this activity.⁴⁶

Propofol enhance the dopamine activity

Propofol increases dopamine levels by reducing the availability of the DAT, suggesting that it may bind to DAT and elevate dopamine concentrations (Figures 5 A-C) in the figure below, the section A illustrates Treatment protocol for measuring changes of DAT availability using PET scanning and section C illustrates the quantification of SUV max in saline and propofol (50 and 100 mg/kg) groups (n=6 mice per group). PET, positron emission tomography tomography. At a dose of 100 mg/kg, propofol significantly boosts dopamine levels. A previous study also found that propofol activates dopamine neurons in the ventral tegmental area, further enhancing dopamine concentration by increasing its release.⁴⁵

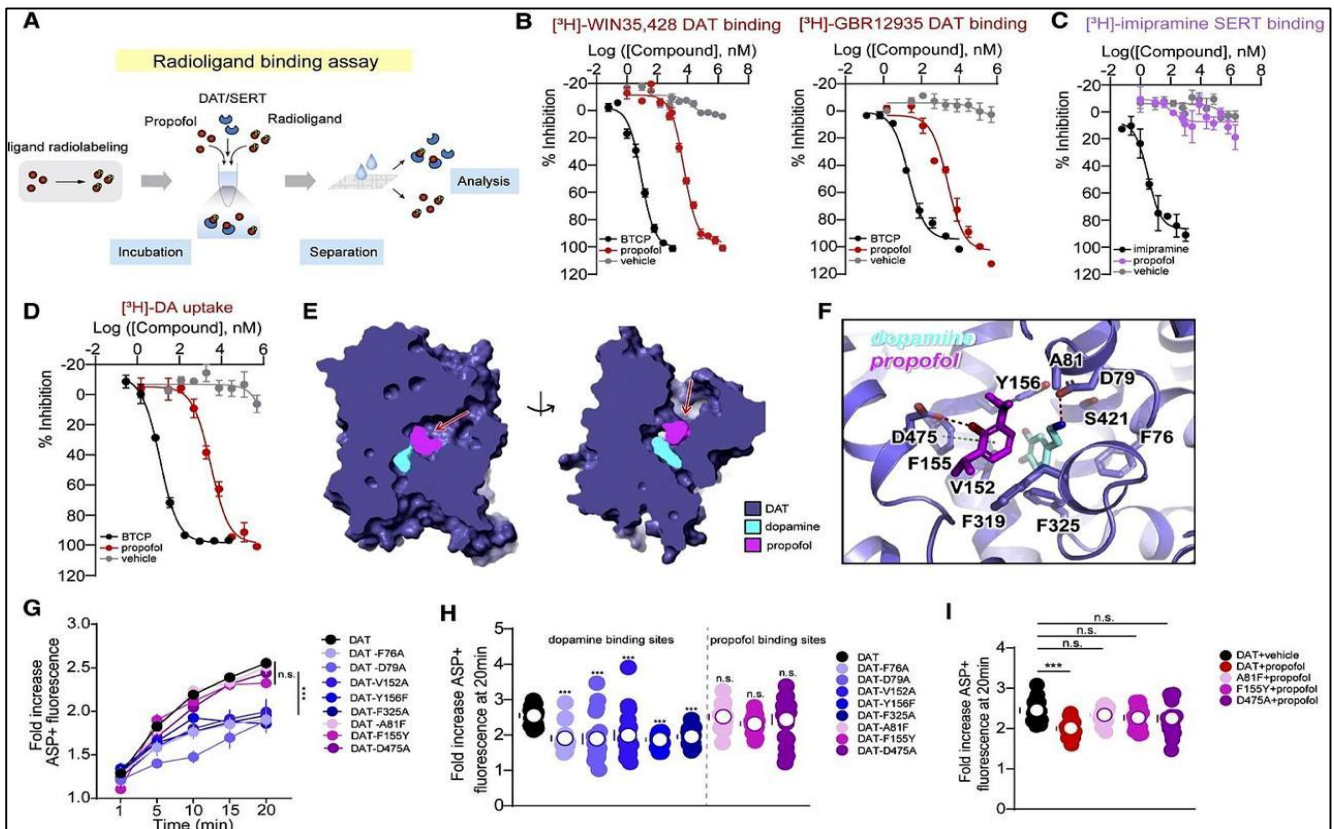
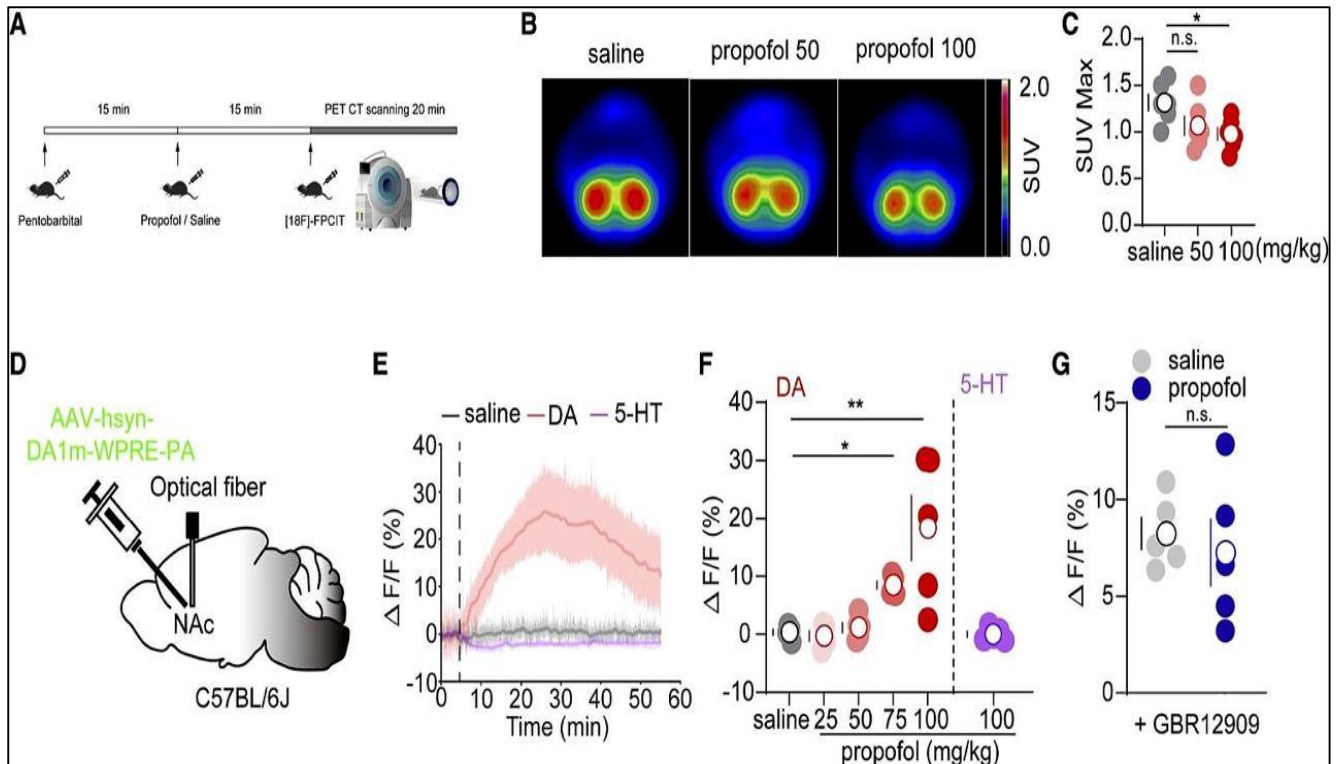


Figure 4 (A-I): Propofol inhibits dopamine transport by binding to DAT.



Figures 5 (A-G): Propofol enhances NAc dopamine levels *in vivo*.

Propofol and reproductive hormone

Reproductive hormones are sex hormones, such as androgens, estrogens, progestins and testosterone are naturally occurring compounds that tightly regulate endocrine systems in a variety of living organisms. used in the dairy industry to increase reproductive efficiency to increase the fertility in male and females. Propofol can affect sex hormones by impacting their balance. The effect of propofol on female sex hormones was not observed, it does not have a negative impact on female sex hormones, which encourages its use because it has no noticeable effect on female sex hormones specifically.^{49,50}

Propofol and anxiety-related hormone

Anxiety is a future-oriented emotional state characterized by the anticipation of potential negative events.⁵¹ It is often chronic, significantly impairing both quality of life and functioning. Anxiety disorders are frequently accompanied by physical symptoms such as palpitations and pain. The comorbidity of anxiety and pain leads to substantial clinical and social burdens. Propofol used as commonly anesthetic.³⁹ Anesthesia drugs like propofol activate endocrine and metabolic responses.⁴⁰ Propofol affects the hormonal system by changing the level of stress hormones of the patient.³⁹

Propofol may have regulatory effects on psychological disorders. In both models of acute and chronic pain ,When propofol induces a blood physiologic change to balance the hemodynamic level, it induces epinephrine,

norepinephrine, and cortisol, which are stress hormones to increase in the blood.³⁹

When the plus maze (EPM) and open field (OF) tests are elevated ,the propofol has been shown to reduce anxiety-like behaviors. Moreover, propofol works to lower stress-related hormones levels on the serum, including corticosterone, CRH, and norepinephrine. These findings provide a result that supports the hypothesis that propofol has potential treatment for pain-associated anxiety-like behaviors.³⁹

New studies suggested that propofol can alleviate perioperative anxiety that is caused by increasing secreting of a stress hormone in the blood, by inhibiting the hypothalamic-pituitary-adrenal (HPA) axis activation, thereby maintaining homeostasis. CRH is located in the hypothalamus, especially on the PVN. It regulates the HPA stress-response axis. The PVN neurons release CRH responses to stress. Models that are used are acute and chronic pain. The dose used is a single dose of propofol to alleviate anxiety-like behaviors and suppress the surge of stress-related hormones., because this local injection of propofol can reduce anxiety-like behaviors with complete Freund's adjuvant (CFA)-induced pain.³⁹

Patients who are injected by propofol anesthesia often feel euphoria and relief from postoperative anxiety. A single dose of propofol (100 mg/kg) also affects stress-induced anhedonia. It results in reduction in the levels of stress-related hormones, as shown in (Figure 6 J) in the figure below, the section J illustrates serum CORT

concentrations (left), serum CRH concentrations (middle), and serum NE concentrations (right) for control, CFA + saline, and CFA + propofol (100 mg kg⁻¹) groups at 4 h after drug injection (n=five mice per group). These findings also support the propofol can treatment of stress-related disorders.³⁹

How the propofol alleviates anxiety-like behaviors

In the first, the CRH is introduced to the pituitary gland and initiates a cascading response, leading to the release of a large amount of corticosterone (CORT), which suppresses homeostasis and leads to mental disease. Activation of PVN of CRH neurons is associated with an increased risk of anxiety. The PVN of CRH neurons can promote anxiety-like behaviors. Secondly PVN of CRH neurons induce hormonal response along the HPA axis to coordinate stress-related behaviors by pain of stress.

Thirdly, entering propofol to PVN of CRH to inhibit it, thereby that can alleviate anxiety-like behaviors. Then can inhibit stress hormone such as epinephrine.³⁹

propofol also can effects are exerted primarily with its interaction with the GABAA receptor by activating GABAA in two ways directly or enhancing its response to the GABA molecule.⁵² The propofol targets the $\beta 3$ subunit of GABAA. Deregulation of GABAA $\beta 3$ subunits expression in PVN of CRH neurons decrease the anxiety-relieving effects of propofol (Figure 7 E-G) in the figure below, the section E illustrates time in the open arms during the EPM test for scramble + propofol and Gabrb3 + propofol groups in CFA mice at 4 h after treatment (n=seven mice per group) and section G illustrate total distance traveled during the OF test in scramble + propofol and Gabrb3 + propofol groups in CFA mice at 4 h after treatment (n=seven mice per group).³⁹

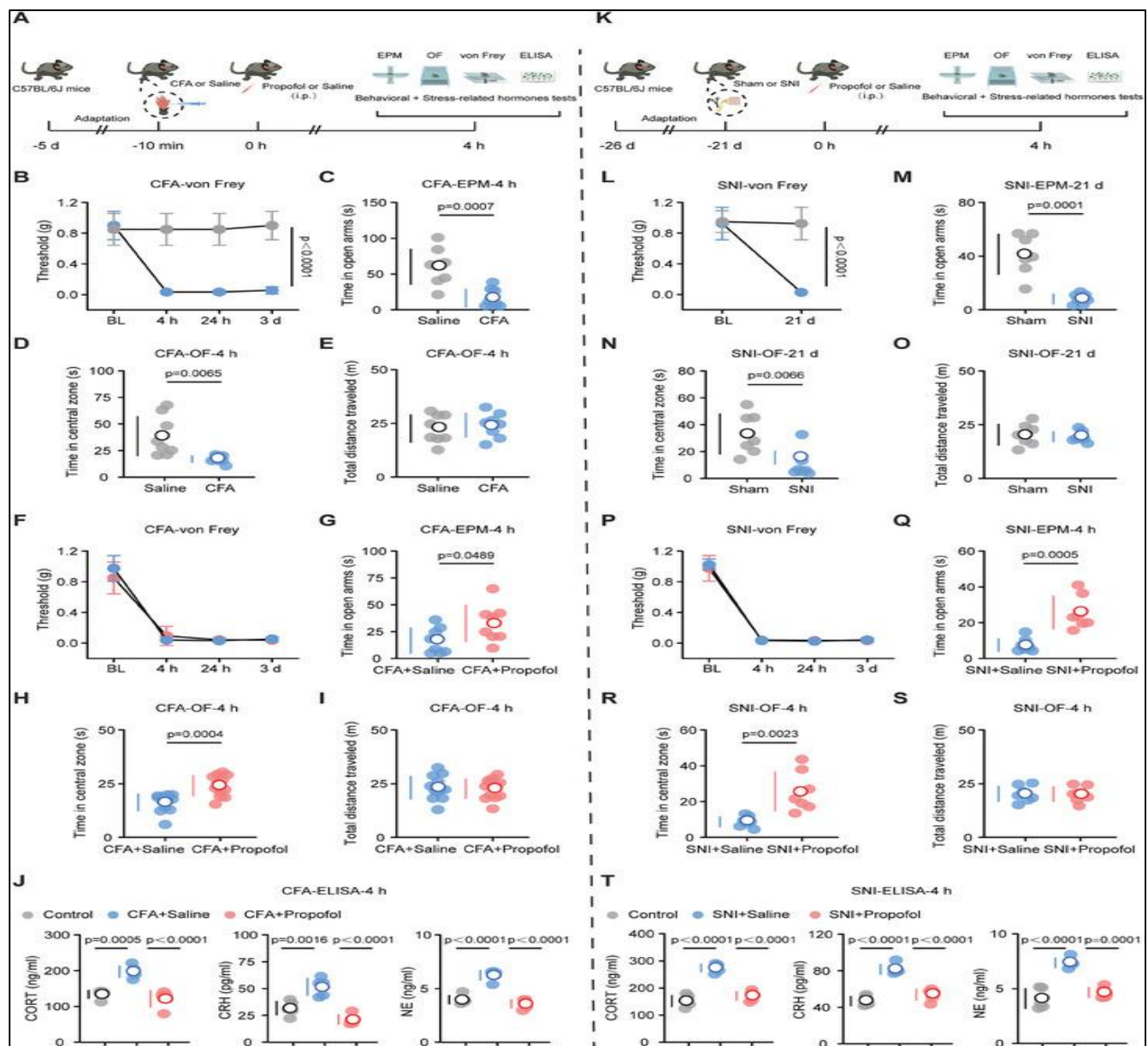


Figure 6 (A-T): Propofol alleviates anxiety-like behaviors and stress-related hormones surge associated with pain.

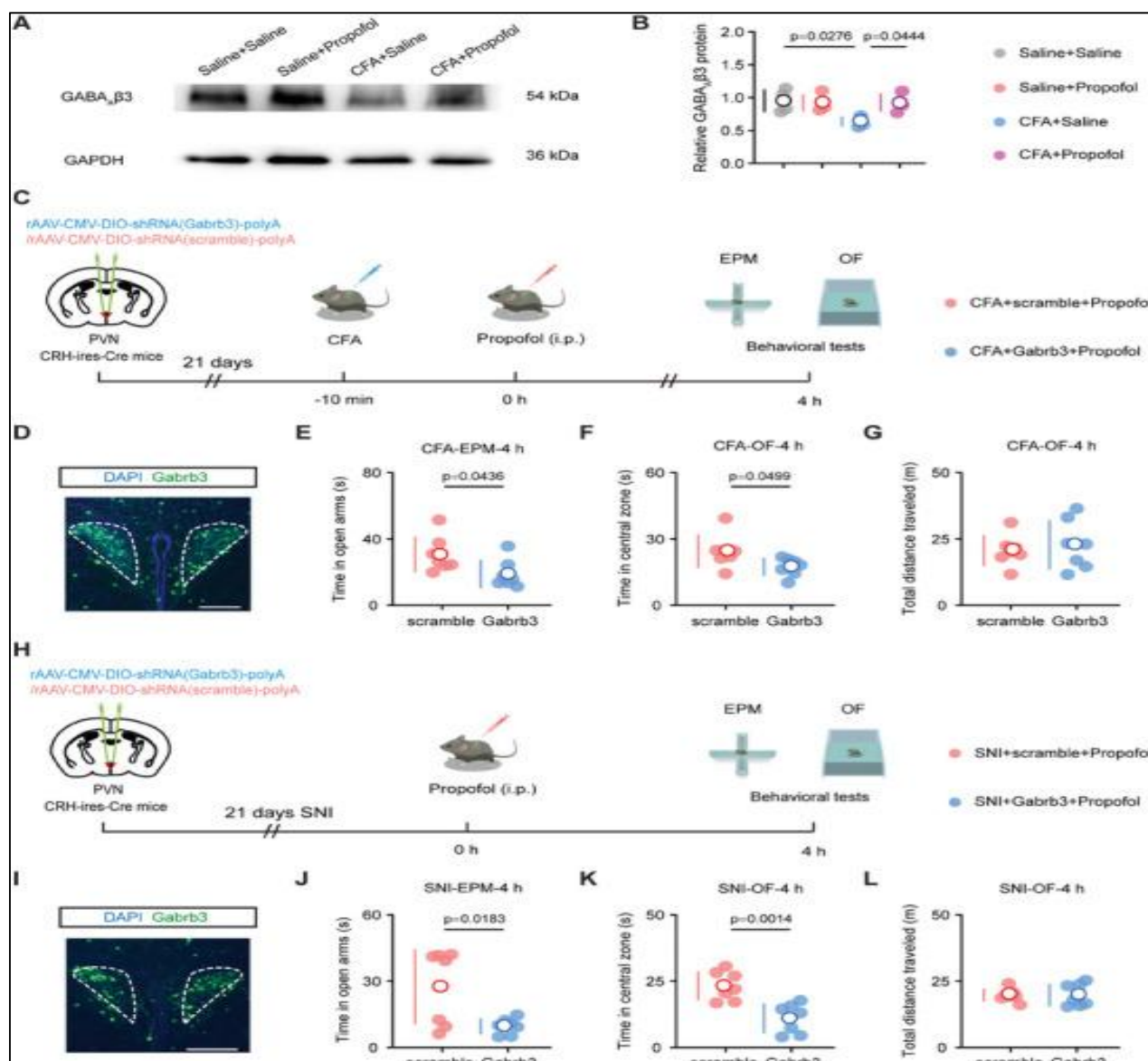


Figure 7 (A-L): Propofol effects on and dependence on GABA A β3 subunits in PVN CRH neurons.

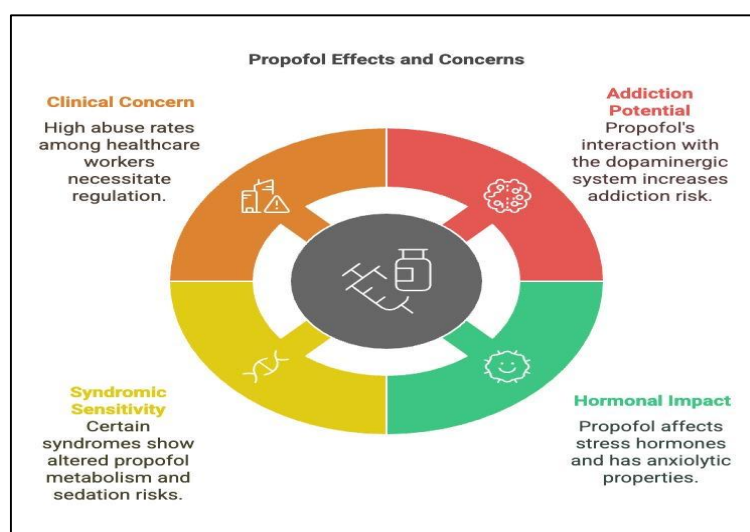


Figure 8: Hormonal changes pre-and post-propofol administration.

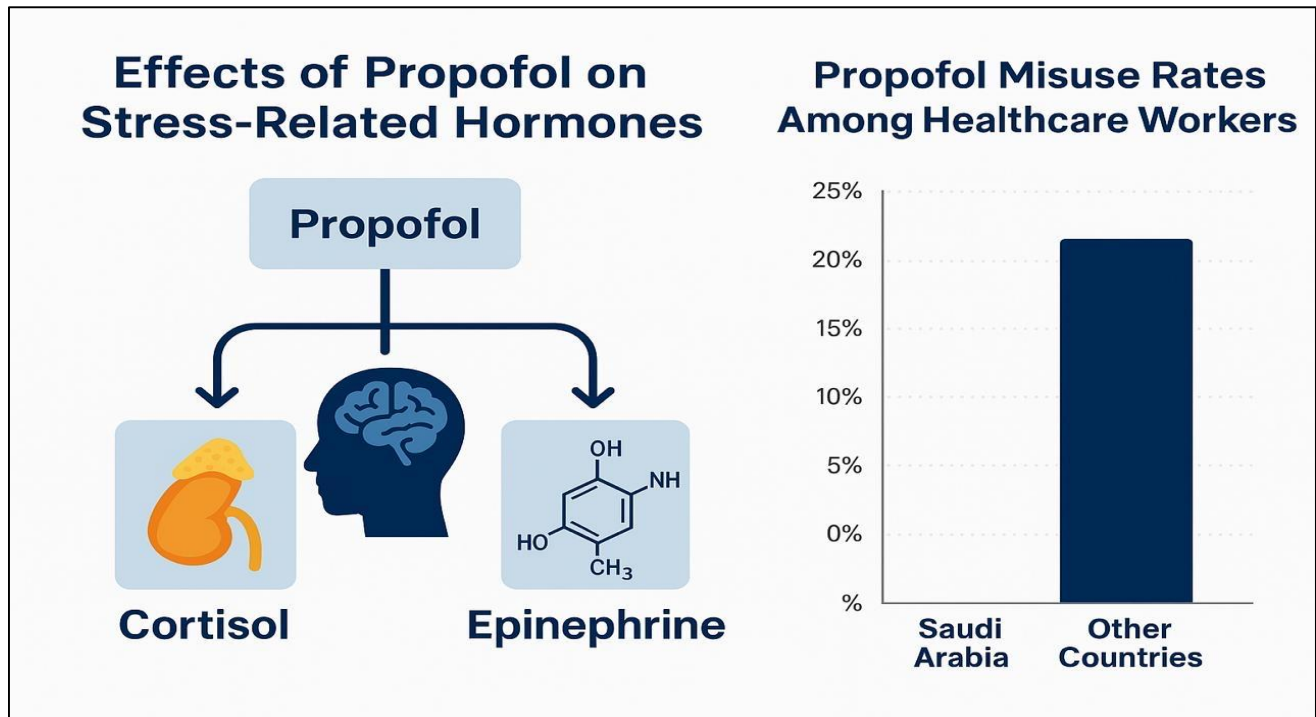


Figure 9: Propofol's neural impact in patients with Down syndrome (e.g., DBS interference).

CONCLUSION

This review underscores propofol's significant effects on neuroendocrine and neuropsychiatric systems, particularly in relation to addiction risk, hormonal modulation, and patient-specific vulnerabilities.

Propofol alters stress-related hormones such as cortisol and epinephrine. These hormonal reductions contribute to its anxiolytic effects, offering short-term emotional relief during procedures. However, suppression of stress responses may be harmful in critically ill or hormonally sensitive patients, highlighting need for personalized anesthetic planning.

The drug's interaction with the brain's dopaminergic reward system also raises concerns about psychological dependence. Its rapid onset, euphoric effects, and accessibility-especially among healthcare professionals-make it prone to misuse shows that global propofol misuse among medical personnel exceeds 20%, while local data in Saudi Arabia remain scarce. This indicates pressing need for national research, regulation, and education to curb potential abuse.

Additionally, patients with neurodevelopmental syndromes such as Down syndrome and FXS exhibit greater sensitivity to propofol, with increased risks of sedation-related complications. Clinical evidence supports tailored dosing and vigilant monitoring for these high-risk groups to reduce adverse outcomes and ensure safe use.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Albanna AK, Alnefaie ZM, Al Shammari AM, Al Sayedeash FH, Alalwei RH, Alturki AI, et al. The effect of propofol on mental health in Saudi Arabia. *Int J Community Med Public Health* 2025;12:2862-75.