

## Ketamine a Useful Multi-faceted Medication: New Perspectives are Evolving from Current Research and Clinical Studies

**Duraiyah Thangathurai\*, Maggy Riad, Ashraf Sedra, Sarah Vitug, Yaroslava Longhitano, Andre Atoian and Maged Mikhail**

*Department of Anesthesiology, University of Southern California, USA*

**\*Corresponding Author:** Duraiyah Thangathurai, Department of Anesthesiology, University of Southern California, USA.

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### Abstract

Ketamine is a unique pharmacological agent that has been in use for many decades. Its pharmacodynamics allow it to be useful in applications that expand beyond the traditional anesthetic purposes. In this review article we will explore the clinical applications of ketamine for anesthesia and analgesia, for neurological and psychiatric conditions, for palliative care and chronic pain conditions, addiction medicine, prehospital settings, the emergency settings and the ICU.

**Keywords:** *NMDA Blocker; Brain Derived Neurotrophic Factor; AMPA Receptors; Neuroplasticity; Cytokines*

Ketamine was introduced in 1960's as an anesthetic drug of limited use, now its use has expanded to many diverse clinical situations as a multi-purpose medication. During the 1960s and 1970s, scientific knowledge pertaining to the central nervous system's (CNS) physiology and pathology, as well as mechanisms of anesthetic drugs, pharmacokinetics and pharmacodynamics, was limited. During this time, commonly used anesthetic agents were barbiturates, ethers and halogenated hydrocarbons, and opiates. Phencyclidine, anesthesia product known as PCP, trade name Sernyl (CI-395) was initially made in 1956, by Maddox chemist from Park Davis. Pharmacologists Dr. Chen and Dr. Domino conducted early studies on animals in 1958. Initial human studies were carried out by anesthesiologist, Dr. Griefenstein, who observed stable hemodynamics and respiratory function, but also severe and prolonged excitatory effects that lasted up to several days. In the 1960s, PCP was frequently abused as a psychedelic drug and was eventually banned against clinical human use due to its side effect profile and addiction potential [1,2].

Ketamine, a phencyclidine derivative (CI-581), was considered a safer anesthetic alternative with minimal excitatory side effects. Ketamine was synthesized in 1962 by American Chemist, Dr. Calvin Lee Stevens from Parke-Davis laboratories. Physicians and scientists including Dr. Domino and anesthesiologist Dr. Corrsen led many of the first human studies demonstrating the safety profile and therapeutic benefits of Ketamine as an anesthetic agent in the United States [3]. The FDA approved ketamine for clinical use in the 1970s and eventually was most notably utilized in treating battlefield settings, especially during the Vietnam War. European nations like France, Germany and Britain also were quick to utilize ketamine in field situations, however, their use of ketamine was still limited in hospital settings.

Many new anesthetic drugs were introduced in the 1970s which slowly began to overshadow ketamine. Such medications were intravenous propanidid, etomidate, althesin, midazolam, fentanyl, ultra-short acting barbiturate medications including sodium thiopental and

methohexitone, and inhalational agents such as halothane (Fluothane), trichloroethylene, cyclopropane, enflurane and isoflurane. Most of the above medications work via inhibitory GABA receptors. Ketamine's mechanism was not fully understood then, but was believed to have blocking actions on the primarily excitatory NMDA receptors of the glutamate neuronal system.

Several years following the introduction of ketamine, its use was frowned upon by the anesthesia community due to the negative publicity as a recreational street drug known as, "Special K," "Horse Tranquilizer," or "K-hole". It was miscategorized along with other popular drugs such as LSD, mescaline, marijuana, cocaine, psilocybin, peyote, amphetamines, ecstasy, PCP, heroin and other narcotics, barbiturates such as seconal and other sedatives such as methaqualone (Quaaludes), GHB (Rohypnol), Benzodiazepines (valium) and similar drugs. The beneficial effects of ketamine and its diverse uses were not fully understood nor appreciated by the medical community in the developed world. In contrast, many third world countries continued to embrace ketamine for its wide clinical utility, especially in the setting of emergent surgeries.

In the 1980s and onwards, technology and research pertaining to the CNS had become more advanced, with the invention of various imaging modalities such as computed tomography (CT), positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), functional MRI, electroencephalography (EEG), and magnetoencephalography (MEG) diffusion tensor imaging, etc. Such innovation contributed tremendously to the neuroscience and medical field at large, as functional and anatomical areas of the brain became easily identifiable. These new research methods expanded our understanding of brain function, neurophysiology, microanatomy, synaptic transmission and connectivity of various parts of the CNS. Researchers are able to identify the role of neurotransmitters, receptor proteins, mRNA, CREB, neuropharmacology, etc. which have paved the way for significant developments in neuroplasticity, synaptogenesis, neuroprotection, neurotoxicity, neuronal recovery and neuro-pharmacological agents including ketamine and other NMDA blockers.

Since the pioneering work of Domino and his colleagues, many research studies describing the beneficial properties of ketamine as an anesthetic, sedative, and analgesic effects have surfaced. The studies revealed that ketamine maintains stability of vital functions including hemodynamics, preservation of airway reflexes, and maintenance of respiratory drive. These findings impressed the scientific community as it is well known that the majority of anesthesia complications are primarily cardiopulmonary in nature. The World Health Organization (WHO) placed ketamine in the essential medicine list in 1985 because of its safety profile [4] broad clinical utility.

Currently, ketamine is considered one of the most commonly used anesthetic drugs in the world [5] because of its straightforward administration, safety profile and accessibility, especially in under-resourced areas where medical equipment and anesthesia-trained personnel is limited. "The medical benefits of ketamine far outweigh potential harm from recreational use," said Marie-Paule Kieny [6] Assistant-Director General for Health Systems and Innovation at WHO. Kieny states, "controlling ketamine internationally could limit access to essential and emergency surgery, which would constitute a public health crisis in countries where no affordable alternatives exist".

### Mechanisms of ketamine action

The human brain has 80 - 100 billion neurons and over one hundred trillion synaptic connections. Current research shows that the human neuronal network is predominantly glutamate neurotransmission (60 - 75%), followed by GABA (20 - 25%). The three types of receptors of the glutamate system are NMDA, AMPA, and kainate receptors. Other neuronal networks include acetylcholine, monoamines (dopamine), norepinephrine, serotonin, endorphins, enkephalins and several other neurotransmitters comprising < 10% of the neuronal system. Other cells of the CNS are glial cells (i.e. microglia, astrocytes, oligodendrocytes) which support, protect, insulate and provide nutrition to the neurons. Glial cells outnumber neurons approximately 4:1 and do not conduct electrical impulses.

In the past, anesthesia was thought to be mainly contingent on lipid solubility, and now other mechanisms involving neurotransmitters, receptors, ionic channels/receptors and G protein-mediated effects have been demonstrated. The predominant mechanism of most

of the anesthetic drugs act via the GABA neuronal system, by enhancing inhibitory activity, whereas ketamine acts by blocking NMDA inotropic receptors of the glutamate neuronal system, which is mainly excitatory. Ketamine is a mixture of equal parts of (R)-Ketamine and (S)-Ketamine. (S)-Ketamine has three to four times greater binding capacity for NMDA receptors than R-Ketamine. (S) Ketamine has greater potency and associated with higher incidence of psychotomimetic effects. The diverse therapeutic actions of ketamine is thought to be via interaction with a variety of protein channels and mediated by metabolites including norketamine, dehydroketamine and a series of hydroxyketamines and hydroxynorketamines.

Agonistic effects of ketamine via AMPA, serotonergic, cholinergic, GABAergic, dopaminergic and opioid receptors such as mu and delta [7]. Ketamine blocks  $Ca^{++}$  channels (L-type voltage dependent) resulting in relaxation of smooth muscles and subsequent bronchodilation. Thus, offering particular therapeutic benefit for and prevention of bronchospasm in asthmatic illness. Ketamine's antagonistic effects are achieved through rapamycin-induced mTOR receptors, HCN1 (hyperpolarization-activated cyclic nucleotide-gated channel) [8]. Ketamine also blocks voltage gated  $Na^{+}$  channels, when combined with local anesthetics can enhance its overall effects [9] - proven to be useful in the perioperative settings for pain management. Furthermore, inhibitory effects on BK channels, also known as Kca1.1 or potassium-activated Ca channel, results in suppression of spinal hyperalgesia and thus reducing neuropathic pain [10].

Ketamine has a high therapeutic index with minimal undesirable side effects. Many of the therapeutic effects are observed even in low doses or a single dose. Ketamine was found to have multiple clinical applications including anesthesia for human use and for veterinary use. Most notably, ketamine has long been used as an analgesic in acute and chronic pain states. As an anesthetic, ketamine is a good consideration especially during electroconvulsive therapy when patients cannot tolerate other agents. More recently, ketamine has expanded its utility to encompass psychiatric care. Many disorders including major depressive disorders, severe anxiety states, PTSD, OCD, suicidal ideations, psychoses and substance use disorders have seen improvement with ketamine. As stated, ketamine is useful in patients with severe respiratory failure or with asthmatic exacerbations by helping avoid intubation when standard therapies have failed.

Many recent studies reveal that the anesthesia effect of ketamine results from the disruption of connectivity between brain networks spanning many brain regions. Ketamine and other anesthesia agents are proven to, propofol, and sevoflurane induces disruption of frontal-to-parietal ("top down") connectivity distribution, but does not disrupt auditory and visual networks [11,12]. Muthukumraswamy [13] found subanesthetic doses of ketamine to be related to sustained disruptions of NMDA and AMPA mediated frontal-parietal connectivity, which may potentially explain the "blissful" side effects.

Ketamine can be administered via multiple routes, including intravenous, intramuscular, subcutaneous, transdermal, and intranasal, rectal, intrathecal and epidural. Ketamine use has expanded to many clinical settings, such as intensive care units, emergency rooms, perioperative management, and chronic pain centers. Due to its ease of administration and accessibility, ketamine has found its way in more nontraditional clinical settings, such as field situations involving military exercises, police use, and mass casualty management in acute disasters.

### Uses of ketamine: Anesthesia and acute analgesic

Ketamine has wide range of clinical applications. It is used as an anesthetic, analgesic, amnesic, and a sedative. It is used as a preoperative drug to minimize the requirement of post-operative analgesics, which acts by preventing central sensitization of nociceptors. Ketamine can be used as an induction agent alone, or in combination with other anesthesia drugs including inhalational agents, benzodiazepine (midazolam) or narcotics (fentanyl). Ketamine has minimal depressive effects on hemodynamics, respiration, and airway reflexes. Ketamine offers hemodynamic stability, therefore it is useful in high risk patients and shock states, as well as low cardiac output states from tamponade, aortic/mitral stenosis or severe congenital cardiac conditions. More so, ketamine is used commonly in blunt/penetrating chest trauma leading to aortic rupture, cardiac contusion, hemothorax, or flail chest. Overall, ketamine is widely used in polytrauma patients with severe injuries due to its hemodynamic stabilizing properties, easy administration and high therapeutic index.

Other benefits to ketamine is neuro protection, especially during complex operative procedures or those requiring cardiac bypass. Ketamine is known to decrease cytokine levels such as TNF (Tumor Necrosis Factor) levels, interleukin-6, NF kappa B and other pro-inflammatory cytokines. This effect is helpful to minimize central and peripheral inflammation. Centrally, glial cell activation causes neuro-inflammation and ketamine is contributed to blunting this inflammatory state. Thus, ketamine prevents inflammatory processes and decreases the incidence of post-operative cognitive dysfunction (POCD).

POCD (Post-Operative Cognitive Dysfunction) is common in elderly following lengthy complicated surgical procedures, especially in patients following cardiac surgery. Incidence hypoxemia, hypotension, increased level of cytokines related bypass, altered blood brain barrier states, results in inflammatory states. Ketamine is known to inhibit activation of microglial cells, and glutamate neuronal system and prevent the release of pro-inflammatory cytokines thereby protects the brain from inflammatory damage. Ketamine can be used in high risk patients in emergency rooms as operative room settings and in ICU settings. Ketamine used safely during head injury, neurosurgery and cerebral endovascular surgical procedures involving carotid, and aortic arch procedures.

Ketamine is used for anesthesia during surgical procedures that compromise cerebral blood flow.

Brain is vulnerable for ischemic damage during surgical procedures during which cerebral circulation is compromised. Circulatory arrest is often required for procedures such aortic arch repair procedures. In addition to hypothermia, several medications are used including ketamine. Other situations such as complicated carotid surgery, intracranial vascular procedures, for aneurysms, subarachnoid head injury, cerebral edema, post cardiac arrest situations to prevent further damage ketamine can be used.

Research reveals ketamine treatment results positive neuroplastic changes by increasing the levels of Brain derived neurotrophic factor (BDNF). Excessive glutamate activity, causes  $Ca^{++}$  influx intracellularly resulting in neuronal damage, often occurs in head injury, status epilepticus, cerebral hypoxemia resulting from pulmonary causes of hypoxemia and cerebral edema, cerebral spasms extreme hypo-perfusion states, or conditions resulting elevated intracranial pressure.

Ketamine is useful in the following situations for its neuroprotective effects such as open heart surgical procedure, while on cardiopulmonary bypass or, intended circulatory arrest situations performed for aortic arch replacement procedures. After unexpected cardiac arrest and during hypotensive situations in the operating rooms, recovery rooms, ICU, and emergency rooms. Ketamine is useful as induction agent for pediatric patients with right to left shunt such as Falots tetralogy and Eisenmeger syndrome. It can be used via intramuscular route when IV access is limited in pediatric population.

### Ketamine in emergency medicine

Ketamine is used to provide anesthesia and analgesia for many procedures that are generally short in duration and because of the airway protective effects and stable hemodynamics. Emergency medical services are also using for ketamine in settings prior to hospital arrival for sedation of violent and agitated patients [14] and excited delirium syndrome [15]. As mentioned above, ketamine is also useful for conscious sedation in pediatric emergency care [16] as well as the management of acute pain, agitation and delirium.

Ketamine is also increasingly useful for conscious sedation in emergency rooms when IV access may be difficult. Ketamine in the emergency department is growing in popularity due to cardiorespiratory stability and analgesic effects, especially in pediatric trauma patients, as well as easy administration via IV or intramuscular, subcutaneous, intranasal, oral, and rectal access [16].

### Ketamine use in ICU settings

In the Intensive Care Unit, ketamine is useful in many ways for pain relief, sedation, and amnesia especially in patients on ventilator. Ketamine is known to have minimal respiratory depressant and hemodynamic adverse effects. Such properties facilitate early extuba-

tion, preventing ventilator dependence and related complications. Prolonged ventilation can result in pulmonary complications, such as atelectasis from retention of secretions, pneumothorax, pulmonary dysplasia, and aspiration risks. Hemodynamic disturbances such as hypotension, reduce venous return and promote embolic complications. Early extubation is instrumental for early mobilization, thus decreasing sedative and narcotic requirements and minimizing drug-related complications. Hyperalgesia, glial activation, and addiction are common issues in ICU settings that may arise if pain and sedation agents are not weaned appropriately. Thus, a multimodal approach to pain and sedation with ketamine serves to expedite ICU recovery and improve clinical outcomes.

Ketamine minimizes many ICU related abnormal psychological states such as depression, psychosis, PTSD, and extreme anxiety states. The incidence of PTSD is approximately 30%-60% in the ICU or other states of critical illness. Other psychological manifestations such as fear of dying, panic attacks, phobias, emotional numbness, demoralization, dehumanization, learned helplessness, and sleep deprivation are also prevalent in critical care settings. Endotracheal tubes, nasogastric tubes, urinary catheters, rectal tubes and various indwelling lines are common in ICU patients and can be extremely uncomfortable and at times, traumatizing. More so, patients suffer from sleep disturbances as the normal circadian sleep rhythm is disrupted by frequent lab draws, routine imaging, constant alarming from nearby monitors and bright flickering lights, thus it is not uncommon for patients to associate hopelessness and hostility with ICUs.

For some patients, initial bouts of depression and anxiety are induced by critical illness. The loss of autonomy or ability to engage in activities of daily living contributes largely to a patient's depressed affect and emotional instability. Feelings of extreme loneliness, suffering, dehumanization and demoralization are common emotional states of critically ill patients. ICU providers and nursing staff may not be aware of such emotional upheaval that patients endure. This phenomenon known as "psychic numbing" or "psychophysical numbing" [17,18] may inadvertently compromise a provider's delivery of patient care.

### **Ketamine use in field situation (Prehospital settings)**

Ketamine is used in prehospital environment to provide sedation or anesthesia. It is useful as analgesic patients with acute traumatic pain with multiple injuries [19]. Ketamine is used for procedures such as manipulation, entrapment, and splinting of unstable fractures without any significant drop in blood pressures or respiratory issues. Prehospital administration can be performed by non-anesthesia care experts working as immediate care practitioners [20]. Ketamine can be used with morphine safely, for uncontrolled acute pain [21]. Fisher, *et al.* published a case series of using ketamine for combat wounds [22]. Ketamine was first used in the 75<sup>th</sup> Ranger Regiment in 2005, fell out of favor as the medical providers had limited experience. In 2009 they were given more training and protocols were in place regarding the use of ketamine for procedures such as amputations, long-bone fractures, and application of tourniquet. Ketamine appeared to be a safe, and effective battlefield analgesic. Moy also found ketamine as an effective agent for military use, as a battlefield analgesic and sedative in combat casualties and outline. Paramedics were given training evaluated regarding safety and efficacy prehospital use of sub-dissociative dose of ketamine.

### **Chronic pain conditions**

Ketamine has analgesic, sedative, amnesic, anesthetic, anti-inflammatory effects, and antidepressant effects. Ketamine uses for chronic pain has become popular in the last two decades because of its safety profile, and diverse and rapid therapeutic effects as analgesic, amnesic, anxiolytic, anti-depressant, and anti-inflammatory effects [23]. In 2020 re-emphasized the diverse therapeutic effects mechanisms are mediated by multiple targets in addition to NMDA, and AMPA receptors. Those sites are dopaminergic, serotonergic, cholinergic, voltage gated  $NA^+$  channels, and L type calcium channels [24]. Ketamine and its active metabolites are also contributing to the therapeutic effects. Ketamine can be used with other drugs such as gabapentin, NSAID's anti-depressant drugs, magnesium, lidocaine, and other behavioral therapies such as CBT (cognitive behavioral therapy, MET (motivational enhancement therapy). Consensus guidelines on the use of intravenous ketamine infusion for chronic pain developed and approved by American Society of Regional Anesthesia and Pain Medicine,

American Academy of Pain Medicine, and American Society of Anesthesiology [25].

Ketamine is useful in many chronic pain conditions such as migraine, cluster headache, chronic headache and neuralgias, complex regional pain syndromes (CRPS), neuropathic pain, Phantom limb pain, back pain, fibromyalgia [26] and severe pain associated to sickle cell crisis. Intranasal ketamine is effective for migraine patients in reducing the severity of aura and pain. Pribish reviewed the nonanesthetic uses of ketamine [27].

### Palliative care settings

Ketamine is used in palliative care situations to relieve pain, depression [28] and fear of dying. Extreme anxiety states, phobias, learned helplessness, panic attacks, suicidal ideations, psychosis, post-operative cognitive dysfunction (POCD) and addiction to narcotics and benzodiazepines are common in many palliative care patients. It is well known that chronic narcotic use is associated with hyperalgesia and tolerance. Studies have shown that ketamine/midazolam (KM) or ketamine/fentanyl (KF) combinations are associated with decreased incidence of such psychological manifestations as well as preventing gastrointestinal complications.

High doses of narcotics often has many gastrointestinal complications such as ileus and narcotic bowel syndrome (NBS), which is increasingly worsening abdominal pain in the setting of escalating opioid requirements. Common symptoms of such gastrointestinal complications are abdominal pain/distension and nausea. Furthermore, dry mouth is very common in older patients, and ketamine is commonly used adjunct as it promotes secretions and relieves dry mouth discomfort [29,30].

### Ketamine use in psychiatric settings

Major depressive disorder (MDD) is a common malady, and when severely debilitating can lead to serious health consequences. Current treatment is focused on increasing the levels monoamines such as serotonin, norepinephrine, and dopamine in the limbic system. Initially, monoamine oxidase inhibitors (MAOI) and tricyclic drugs were used. The lag period for the drugs to reach therapeutic effect was too long and many patients were unable to tolerate the side effects. For these reasons, SSRI and SNRI were more desirable treatment choices as many patients experienced fewer relapses and milder residual symptoms.

Ketamine was found to be effective in depressed patients (MDD), in low or single dose without any few side effects. It is useful in resistant depression, both unipolar, bipolar states, and suicidal ideation. For instance, intranasal ketamine spray has shown to be useful for rapid relief of depression and suicidality [31]. The rapid antidepressant effects of ketamine also provide more insight to current and future research on molecular, cellular and synaptic network levels. Some studies show active metabolites of ketamine maybe associated with the synaptic plasticity and glutaminergic balance.

According to the neurotropic hypothesis, the hippocampus plays key role in depression, where brain derived neurotrophic factor (BDNF) can be found. BDNF levels are important in maintaining neuroplasticity and synaptogenesis. Low BDNF levels are associated with depressive illnesses and ketamine increases BDNF in the brain which provides relief to resistant depression. Recent studies found an association between ketamine and an increase in the synaptic growth of neurons of the medial prefrontal cortex, as well as an overall increase in the plasma levels of BDNF [32] in depressed patients. Other studies utilizing MRI showed that ketamine normalizes the structural alterations inferior frontal gyrus in patients with major depression and PTSD.

Ketamine is thought to also act via AMPA receptors as agonist [33]. There are many recent studies evaluating electrophysiological [34] and neurobiological biomarkers of ketamine in treating resistant depression. Diffusion magnetic resonance imaging (DMRI) shows antidepressant effects through ketamine-induced changes in the white matter [35]. Another study showed that a prolonged infusion of ketamine at 15 mg/kg/h modulates limbic connectivity and induces sustained remission of resistant depression [36]. Overall, ketamine

facilitates global brain connectivity leading to improvements in patients suffering from major depression.

### Ketamine for Situational Stress Related Conditions

Many stress related and diverse spectrum disorders occur in the hospital settings. These conditions are precipitated by several factors including the unfamiliar environment, loss of autonomy, sleep deprivation, stress related anxiety disorders, post-traumatic stress disorders, phobias, panic attacks, fear of impending death, demoralization, and dehumanization. Patient with a history alcohol, tobacco, opioid and other drugs dependence, may present withdrawal symptoms. Panic disorders have higher incidence suicidal ideation. Many studies have shown that Ketamine has been useful to prevent and treat the symptoms of stress induced disorders [37].

### Ketamine prevents suicidal ideations

Suicidal ideation is a devastating symptom of MDD, where its manifestation can be associated with mental disorder or as an acute response to an adverse event. Risk factors are traumatic life events, psychiatric disorders such as severe major depression, or merely late adolescence. Few medications are available such as lithium, and other medications such as clozapine require several weeks or months to take effect, which may not address suicidal ideation in a safe and timely manner.

There is a high incidence of suicide among adolescents and the elderly. Of note, suicidal ideation is common in ICU settings. As stated, many ICU patients suffer from depression, suicidal ideations, dehumanization, demoralization, and pain. Currently, ketamine is used in patients with acute suicidal ideation and can be used in conjunction with SNRI, CBT, ECT and other therapeutic modalities. In recent studies, a variety of psychological benefits of ketamine were observed with just one or two doses [38,39]. Certain studies show that ketamine given two weeks prior to a stressor, blunts behavioral and neurochemical effects of the stressor, leading to improved psychological states. Thus, evidence shows that ketamine continues to play a role in the reduction of the harmful physiological response to stress, leading to improved clinical outcomes in the setting of psychiatric illness.

Incidence of suicide is increasing all over the world. Suicidal ideation is an emergency, and a challenge to the medical system. There is no rapid treatment currently available to prevent it. Ketamine has been identified as a fast acting drug useful for treating suicidal ideation, even with a single dose [40]. Suicidal thoughts have behavioral, or environmental, or genetic components. Precipitating factors are psychological pain, hopelessness, burdensomeness and belongingness [41]. Ketamine acts rapidly compared to any known anti-depressants drugs. Ketamine acts rapidly compared to other therapeutic approaches. Ketamine can be combined with other methods such as cognitive behavioral therapy (CBT), dialectical behavioral therapy (DBT), motivational enhancement therapy (MEA), antidepressants, ECT and other forms of therapeutic modalities. Ketamine can be given via several routes or iv, im, sc and other methods. Ketamine is also available as nasal spray. Esketamine is more potent, rapid, the effect lasts and approved by FDA.

### Ketamine and eating disorder

Eating disorders are related abnormal eating habits originated from deep mental illness. The common eating disorders are anorexia nervosa, bulimia nervosa, rumination syndrome, and avoidant/restrictive food intake disorder. These disorders do not respond adequately to current psychiatric medications. Anxiety disorders, depression and substance abuse are common among people with eating disorders. Ketamine maybe useful to reset the balance of the neuronal disturbances. Ketamine can be used in conjunction with other forms of therapies such as cognitive behavior therapy (CBT) and other forms of counseling methods [42].

### Ketamine treatment for substance use and alcohol use disorders

Substance abuse disorders including alcohol, narcotic, benzodiazepines and many illicit drugs are escalating resulting in global health burden. In United States, opioid epidemic resulting in 25% of global overdose deaths, an 88% increase in opioid overdose deaths each year from 2013 - 2016. Ketamine seems to be a beneficial drug resulting in improvement, motivation to quit, minimize cravings. The are

several studies carried out with ketamine, which show improvement in cocaine use disorders, heroin addicts and alcoholics, the beneficial effects of benzodiazepines v ketamine on alcohol withdrawal states.

In our own institution we have favorable results with use midazolam ketamine combinations in patients with narcotic dependence and history of seizures. Ketamine is used for withdrawal states to minimize the undesired effects. Ketamine is useful in addicts with history of suicidal ideations. Ketamine is found to be useful as a multimodal analgesia with regional techniques, or dexmedetomidine, IV lidocaine in opioid tolerant patients, or recovering opioid addicts. At Norris cancer hospital, after major cancer surgery we have been using ketamine combinations over 20 years [43]. Low dose ketamine can be used in conjunctions with other medications without any serious interactions.

### Ketamine use as an anti-epileptic

Epileptic seizures are not uncommon emergencies and can be caused by a large number of conditions. Excessive activity of excitatory glutamate neuronal pathways trigger initiation and continuation, of seizure activity, and neuronal degeneration and death. Ketamine is a nonselective antagonist of the glutamate receptor NMDA, and stop the seizure activity, increase neuronal growth and neuroplasticity. When patients show resistance to benzodiazepines, or other standard antiepileptic drugs, ketamine should be given early, to prevent or reduce neuronal damage. Ketamine has an obvious effect on RSE in adults and children and can be administered intravenously. A combination strategy including midazolam, other drugs valproic acid, phenobarbital, and ketamine may be more effective in the treatment of epileptic status. Ketamine is now underutilized by many physicians. More studies are studied to confirm the usefulness in refractory or status epilepticus [44]. It is often selected when 5-6 anti-epileptic medications have failed. Ketamine is also useful in refractory convulsions in children avoiding endotracheal intubation.

### Ketamine and gut functions

Gut brain axis (GBA) is a bidirectional link between brain (central nervous system) and gut microbiota (enteric nervous system) of the body [45]. It involves direct and indirect pathways between cognitive and limbic system (emotional) of the brain and the gastrointestinal autonomous nervous system. Gut bacteria and the brain play an important role in the host physiology, homeostasis, development, and metabolism. Several studies show dysbiosis and inflammation of gut results in mental illness such as depression and anxiety states. Yang carried out with ketamine anti-depressant effect likely mediated by the immune modulation of gut bacteria [46]. Gut-brain psychology from the microbiota-Gut-Brain-Axis. According to gut brain psychology gut bacteria play an important function as gut brain network. Total number of gut microbiota are 10 times the total number of human cells, encoding genes are 200 times more than human genes.

Microbiome-the missing link of the gut-brain axis and focus on its role Gastrointestinal and mental health. The balance is disturbed in several circumstances and conditions, including major operative interventions and antibiotics. In experimental models, on rats researchers studied the effect of ketamine on microbiomes [47-48]. Ketamine effect of microbiomes on rat models found remarkable increase of probiotic bacteria are such as *Lactobacillus*, *Turicibacter*, *Sarcina*, and decrease in dysbiotic microorganism such as *Mucispirillum* and *Ruminococcus*. *Ruminococcus* is possibly associated with irritable bowel syndrome, *Mucispirillum* has been associated with inflammation. Narcotic bowel syndrome presents after surgical procedure, associated with opioid use. Abdominal from opioid use.it present with abdominal pain, distension, nausea vomiting constipation, and respiratory discomfort. Opioid use is associated with glial activation in the spinal cord from NMDA receptor stimulation resulting in hyperalgesia, and release of dynorphin and cholecystokinin resulting in bowel dysfunctions. Ketamine also has beneficial effects from preventing narcotic bowel syndrome, by preventing spinal hyperalgesic states resulting from opioid use.



### **New research: Prevent microglial hyperactivation and CNS inflammation**

Glial cells are found in the central nervous system including microglia, astrocytes, oligodendrocytes, and their progenitors NG2-glia. Microglia, are resident macrophage-like immune cells in the brain and spinal cord play an immunological role, including phagocytosis of invading microorganisms and removal dead or damaged cells. When microglia are hyperactivated in certain conditions such as major trauma, surgical procedures, shock, severe infections, septicemia, toxin, cerebral ischemia and drugs including narcotics resulting in hyper activation of microglial cells, leading to release of pro-inflammatory cytokines, chemokines, complements, reactive oxygen species (ROS) and reactive nitrogen species (RNS), prostaglandins (PGs) resulting in inflammation of central nervous system. Acute inflammation results in hyperalgesia causing pain. Ketamine prevents acute glial activation induced by narcotics such as fentanyl and remifentanyl. Chronic inflammation of the brain is implicated in CNS diseases such as Alzheimer's disease, multiple sclerosis, Parkinson disease, AIDS, dementia, and prion diseases.

Chronic glial activation may lead to damage to neurons through the release of pro-inflammatory cytokines, reactive oxygen radicals, proteinases and complement proteins. Other beneficial effects are prevented glial activation, preventing peripheral and central inflammation, minimizing cytokines production, suppression. Ketamine reset neuro-physiological and neuroplasticity balance from uncontrolled dysregulation of neuronal systems involving areas of prefrontal cortex, amygdala, nucleus accumbens, hippocampus, cingulate cortex, and insular cortex. Opioid glial activation is shown to be the mechanism of opioid hyperalgesia.

Ketamine is also useful in other pro-inflammatory states involving other organs, especially as it protects the lungs from cytokine injury and progressing to ARDS. Ketamine attenuates postoperative cognitive dysfunction (POCD) after cardiac surgery [49]. Other respiratory conditions that ketamine has shown great utility in, is reactive airway disease such as asthma, status asthmatics, and COPD with bronchospastic components. Ketamine has also been showed to prevent cytokine induced pulmonary hypertension and protect against those with history of allergy or severe anaphylaxis complicated by hypotension.

### **Ketamine may minimize severity of POCD**

Postoperative cognitive dysfunction (POCD) is a major complication after surgery, more common in elderly patients, has significant social, clinical, and financial implications. The pathophysiology is multifactorial and current studies suggest that neuro-inflammation and oxidative stress as a major contributing factor, probably related to anesthesia and surgery [50,51]. POCD occurs in 25 - 50% of patients undergoing cardiac surgery. Ketamine is shown to attenuate post-operative cognitive dysfunction by reducing the inflammatory process [49].

### **Conditions associated with high level of cytokines: Useful of ketamine in COVID-19**

In general, COVID-19 is known to cause cytokine storming and multisystem inflammatory syndromes. Ketamine is known for blocking pro-inflammatory cytokines effects, protect the vital organs lungs, brain, kidney, heart and liver [52]. In light of today's crowded ICU's caring for severely ill COVID-19 patients who have succumbed to ventilator dependence, isolation and inevitable psychological unrest, ketamine has become a pivotal agent in alleviating ICU-related suffering, both physically and emotionally.

Cytokine storm or cytokine release syndrome are life threatening systemic inflammatory syndromes with elevated levels of cytokines and immune cell hyperactivation. Many septic conditions such as gram negative sepsis, shock states, immune complex mediated conditions are associated with massive increase pro inflammatory cytokines IL-1 IL-6, IL-18, IFN Gamma and TNF-alfa. C-reactive protein, ESR resulting inflammation, associated with thrombotic and embolic episodes resulting in multi-organs dysfunctions and ARDS. Several studies done to confirm the beneficial effects ketamine on lowering the levels pro-inflammatory cytokines such as IL-6, IL-1, and TNF  $\alpha$  [53]. Inflammatory cytokines levels are downregulated after repeated ketamine administration.

### Ketamine promotes neuroplasticity and neuro-protection

Neuronal inflammation following acute or chronic insult to the central nervous system may be amenable to pharmacologic intervention, although, to date, no such therapy exists. Ketamine use is emerging as a novel therapy for a number of clinical situations in recent years, such as chronic refractory pain conditions, depression, PTSD and drug-induced hyperalgesia, neuropathic conditions, cognitive function deterioration. There is enough evidence for ketamine as a neuroprotective agent in stroke, neuro-trauma, subarachnoid hemorrhage, and status epilepticus preventing excitotoxicity, and neuroinflammation [54].

There are several mechanisms of ketamine-induced neuroprotection summarized by Bell [54]. Ketamine attenuates excitotoxicity through reduction of extrasynaptic stimulation of neurotoxic NR<sub>2</sub>B-containing NMDA receptors, and presynaptic glutamate release through disruption of SNARE complex formation and glutamate vesicle fusion with the presynaptic membrane, which results in a reduction of calcium-mediated cell death processes, including the generation of neuronal nitric oxide. Ketamine also reduces proinflammatory cytokine release, including IL-8 and TNF- $\alpha$  from microglial cells. Ketamine may reduce microthrombosis in cerebral circulation by inhibiting of platelet aggregation and maintains cerebral blood flow. ketamine also upregulates the density of dendritic spines, leading to the sprouting of new synaptic branches and synaptoplasticity. Ketamine reduces the levels and minimize the effects proinflammatory mediators and free radicals.

### Limitations of the Study

Prolonged use in higher doses of ketamine maybe associated with pain which mimic cystitis, seen commonly in ketamine addicts. In patients with the history of psychosis, including schizophrenia ketamine may precipitate acute psychotic episodes.

### Conclusion

Many current studies show ketamine may be beneficial in schizophrenic patients. Ketamine is used to control exited hyperactive states, including methamphetamine induced psychosis. Earlier studies were concerned about elevation of intracranial pressure with ketamine, current studies show there is no elevation of ICP, and is neuro-protective.

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