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EXPANDING KETAMINE APPLICATION FOR TREATMENT OF ACUTE SUICIDALITY IN LONG-DURATION SPACEFLIGHT (100 characters/spaces)

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ABSTRACT

Introduction. The transition to exploration missions places a heightened risk on behavioral health in spaceflight. Although serious psychiatric emergencies during spaceflight have been rare, longer duration missions increase the possibility of emergence in latent mental health disorders due to genetic predisposition, increased autonomy, isolation, helplessness, loss of family member, or catastrophic events. Complicated grief and bereavement have the highest rate of suicidal ideation. Recently, ketamine has been used as an emergent intervention for acute suicidality, promoting its stability, ease of administration, favorable safety profile, and outcomes for reduction of suicidal intent. The goal of this study was to review current literature and collate the understanding of ketamine as a safe, effective pharmacological adjunct for acute suicidality in spaceflight.

Methods. This literature review was conducted to collate data on ketamine use for acute suicidality and inform on stability, limitations and utilization of ketamine within extreme environments.

Results. 122 publications were reviewed for relevance including 23 randomized-control trials for ketamine use in behavioral emergencies.

Discussion. Ketamine is a diverse pharmaceutical with multiple advantageous indications, including acute suicidality, pain, and sedation. Terrestrial use of ketamine suggests a rapidly efficacious medication for reduction in acute suicidality. As behavioral stressors expand related to extended missions, contingencies for behavioral emergencies become increasingly important. Although this review is not intended to re-develop current International Space Station (ISS) protocols, it is the first to discuss the benefits of ketamine in spaceflight as a potential safe, effective multifaceted tool for future exploration missions and treatment for acute suicidal ideation.

Keywords
Ketamine, Suicidality, Spaceflight

INTRODUCTION

As the paradigm of space exploration shifts from low earth orbit (LEO) to earth independent medical operations (EIMO), more attention has been placed on the cumulative behavioral effects on crew.[1,2] Long-duration missions increase crew exposure to isolation, confinement, autonomy, monotonous work environments, separation from family support, and delay in communication which may exacerbate crews' feelings of isolation.[3] Although serious psychiatric emergencies during spaceflight have been rare, as missions place astronauts on longer assignments farther from Earth, the possibility of complicated life events – such as loss of a child or family member, catastrophic geopolitical news, or interpersonal turmoil, for example – may lead to the development of adverse cognitive and behavioral decrement.[3,4] Terrestrially, complicated grief and bereavement was shown to be associated with the highest rate of suicidal ideation.[5] Therefore, the summation of behavioral risk factors in EIMO missions highlights the importance of developing mitigation strategies and planning for the possibility of an acute psychiatric intervention during a mission.

Direct pharmacologic treatment for acute suicidality in the isolated, confined environment of spaceflight is not well defined. To date, pharmaceutical interventions for psychiatric emergencies during missions have been limited to selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), anxiolytics such as benzodiazepines, and atypical antipsychotics such as aripiprazole and ziprasidone.[6] **Table 1** lists the current behavioral formulary for contingency on the International Space Station (ISS).[6] Although long considered standard of care for depression, the prolonged neuroplasticity response in SSRI and SNRI can take weeks to months for a desired outcome, an operationally limiting timeline in spaceflight.[7] In addition, SSRI and the atypical antipsychotics can result in significant side effects, such as akathisias – or restlessness, inability to relax, nervousness – with the prevalence between 15% and 45%.[8] Although a paucity of data still exists between the relationship of akathisias and increased suicidal ideations, early evidence suggests a pressing need for further investigation into this relationship.[9] Further understanding in the regulation of emotions and the concept of brain functional connectivity have led to innovative advances in pharmacotherapy while attempting to limit side effects.

In recent years, ketamine is increasingly being used terrestrially as an emergent intervention for acute suicidality and depression, favoring its onset of action, stability, ease of administration, minimal side effects at desired doses, and favorable outcomes for reduction of suicidal intent.[10–12] At the time of this review, ketamine is currently on the ISS formulary as an anesthetic and for acute agitation.[6] The appeal of ketamine, in particular for spaceflight, is the multifaceted indications of use – including pain, sedation, agitation, anxiety and depression.[13] Effectively, for long-duration missions, ketamine can offer a broad pharmacologic tool while optimizing storage and mass in medical kits. This review article aims to provide an overview of the current literature for ketamine use in psychiatric emergencies and discuss the feasibility of use in exploration missions.

Table 1. ISS Formulary for Behavioral and Psychiatric Emergencies[6]

Medication Class		Medication	Route
Behavioral Emergencies			
	Antidepressants	Sertraline	PO
		Venlafaxine	PO
	Anxiolytics	Diazepam	IV / IM
		Lorazepam	PO
	Antipsychotics	Aripiprazole	PO
		Ziprasidone	IM
Acute Agitation			
		Ketamine	IM
PO, oral; IV, intravenous; IM, intramuscular			

Behavioral Emergencies in Spaceflight and Extreme Isolation Environments

Extensive reviews have been established on the anecdotal and empirical increased risk for behavioral and cognitive decrement during long-duration spaceflight operations.[1,2,14] This review focuses on the pharmacologic treatments for psychiatric emergencies as they pertain to the breadth of medications flight surgeons and crew may use during a mission. It is still important to highlight conceptually the unique constellation of stressors faced in space exploration. Currently, the extent of behavioral challenges extrapolated from LEO and analog missions of longer duration may affect crew psychosocial adaptation, a recognized cause in decremental decrease in performance with maladaptation.[2] In fact, the extent of cognitive impairment due to isolation under extreme environmental stressors has been shown to be akin to cognitive decline caused by hypoglycemia or alcohol intoxication.[15]

The current state of knowledge on the risk of psychiatric emergencies takes experience from prior space shuttle and ISS missions, analog environments, and data collected from analogous extreme environments – such as Antarctica and military field operations. The National Aeronautics and Space Administration (NASA) defines behavioral conditions as “any decrement in mood, cognition, morale, or interpersonal interaction that adversely affects operational readiness or performance.”[1] Alternatively, NASA distinguishes psychiatric disorders as those that meet the DSM-V clinical criteria for diagnosis.[1] The primary strategy for mitigation NASA employs is through an extensive astronaut selection process aimed to identify prior traits or history that may impose a danger to mission success and crew health. Yet, genetic predisposition to mental illness and an average late onset of depressive symptoms in adults (reported by Tozzi *et al*. at 41, standard deviation 13.7 years) still makes the development of behavioral symptoms plausible.[16] According to Cooper *et al*, despite an extensive selection and training by the Department of Defense, Special Forces (3.2%, n=537) and Ranger Qualified (5.3%, n=303) personnel still report development of mental disorders over a decade prospective cohort from 2001 to 2014, albeit a lower rate than general personnel with less mental health screening (16.8%, n=4552).[17]

Well-documented reports of increased stress on longer missions have yet to manifest into clinically significant mental disorders in ISS or shuttle astronauts.[1,14] However, history indicates signs and symptoms concerning for maladaptive behavior. During shuttle missions between 1981 and 1989, behavioral symptoms occurred at a rate of approximately one per 2.87 person-years, with predominance of anxiety and annoyance.[4] Among seven astronauts flying on Mir, two reported depressive symptoms, or an incidence of 0.77 incident-per-year.[1] During Skylab, high workloads and stress on the nearly 90-day mission led to irritability and adjustment complications, culminating in resentment to ground control and a daylong work stoppage.[18] Two Soyuz missions, TM-2 and T-14, were terminated early due to fatigue, adverse crew dynamics, depressive symptoms, and psychosomatic

complaints.[1,19] One NASA astronaut from the ISS (2000-2014) reported complicated bereavement related to a family member's unexpected death with grief likely heightened by isolation, leading to at least a week of operational adjustments to workload.[1] One well-documented case of adjustment disorder and depressive symptoms in a shuttle payload specialist led the entire crew and ground personnel to employ coping strategies due to dangerous behavior and off-hand comments regarding off-nominal hatch opening and suggestions as to not returning.[1,20] In fact, this payload specialist was documented stating "not going back" to Earth and fixated on hatch opening logistics to crewmembers.[1,20]

Comparable operations involving isolation and extremes – such as Antarctica – undergo a rigorous mental health screening for crewmembers and represent the closest analogous terrestrial model.[21] Reported incidence rates of depressive symptoms that meet DSM-V criteria were as high as 5.2% of crew at two Antarctic stations during austral winter, South Pole and McMurdo.[22] According to Otto *et al*, the rate from 1994 to 2005 for mental illness was 4.5% in three Australian bases, and 6.4% at the US McMurdo Station.[23] The reported incidence rate of depression that required pharmacological involvement was reported for nearly 1-in-50 participants at the South Pole.[23] Investigators postulated that chronic stress on the hippocampus during prolonged exposure to these environments may be contributing.[21] Subclinical levels of mood and adjustment disorders are commonly reported in these isolated environments as well.[21,24] Winter-over syndrome – the constellation of subclinical symptoms associated with cognitive decrement, negative affect, insomnia, and anhedonia – is a phenomenon experienced most prominently after the midway point in expeditions to extreme environments, often referred to as the 'third-quarter effect'.[25] Alternatively, submariners with missions greater than 90-days in confined, isolated environments with high degree of stress showed clinically significant incidence of psychiatric disorders from 0.44-2.8 per person-years, defined by medical evacuation or loss to mission productivity.[26] Similar findings were found in a Russian Mars 520-day simulated terrestrial mission, resulting in one crew developing depression symptoms and half of the six member crew experiencing cognitive confusion-bewilderment.[27] Although these unique terrestrial scenarios can provide a general indication of behavioral concerns in isolated environments, space exploration past LEO may present unique mental health challenges yet to be seen with current analog models.

Current Pharmacologic Interventions for Agitation, Depression, and Acute Suicidality in Spaceflight

Treatment with a pharmaceutical agent has yet to be emergently required during a NASA mission for acute agitation, depression, or acute suicidality.[28] In fact, data from shuttle-era missions indicates that the primary behavioral health intervention utilized was sleep medications in the nonbenzodiazepine imidazopyridine and pyrazolopyrimidine classes.[1,28] If emotional support and careful observation are unsuccessful in de-escalation for a behavioral emergency, the ISS formulary stocks antidepressants, anxiolytics and antipsychotics for contingency purposes as in **Table 1.**[6] In extreme cases of agitation requiring emergent psychotropic use for crew or mission safety, intramuscular routes of administration are reserved for diazepam and ziprasidone.[6] Intramuscular ketamine is also available for agitation, although nominally is reserved for procedural sedation – such as during advanced airway placement.[6]

METHODS

A comprehensive literature review of published research was performed for relevancy to behavioral health risk in space exploration, ketamine for acute suicidality and depression, and ketamine stability in austere environments. Databases searched included PubMed, Department of Defense Technical Information Center, and the NASA Archives and Technical Reports Server. Search terms included – but not limited to – “ketamine”, “acute suicidality”, “behavioral emergency”, “isolation”, “ketamine safety”, “shelf-life”, “intranasal”, “intramuscular”, “intravenous”, “radiation”, “pharmacokinetics”, and “pharmacodynamics”. Interviews concerning the formulary for the ISS were conducted with NASA flight surgeons when applicable. Textbooks in print were searched utilizing the University of Texas Medical Branch online medical library. In total, 122 references were reviewed, including 23 randomized control trials involving ketamine. Exclusions criteria were as follows: inability to access full text, no English translation, pediatric populations (age $\leq$17 years old), and editorials.

RESULTS

Canonical approach to depression and suicidal ideation

Over the past half-century, the prevailing theory of depression management was via the monoamine hypothesis, stating that neurotransmitters like serotonin, norepinephrine, and dopamine deficiencies were responsible for depressive symptoms in psychiatric conditions such as Major Depressive Disorder (MDD).[29] This theory spearheaded the development of antidepressant medications specific for modulation of these neurotransmitter levels in the brain – colloquially referred to as a persons' 'chemical imbalance'.[29] The current first line treatment of choice are SSRIs, which enhance levels of serotonin in the synapse and improve depressive symptoms.[7] A major limitation in this class of medications is the prolonged efficacy, often taking 4- to 6-weeks for response.[7] Even then, approximately one third of patients do not respond to treatments and fall under Treatment Resistant Depression (TRD), often requiring multiple antidepressants (at least two or more) with mixed results.[29] Increasingly, favorable evidence in TRD treatment towards axonal synaptic neuroplasticity aimed at the glutamatergic system and modulation of the NMDA receptor signaling cascade led to the initial studies for ketamine use in depression.[30] In February 2019 after four phase 3 clinical trials, the US Food and Drug Administration (FDA) approved intranasal esketamine through the Fast Track and Breakthrough Therapy designations for TRD **(Figure 1)**.[31]

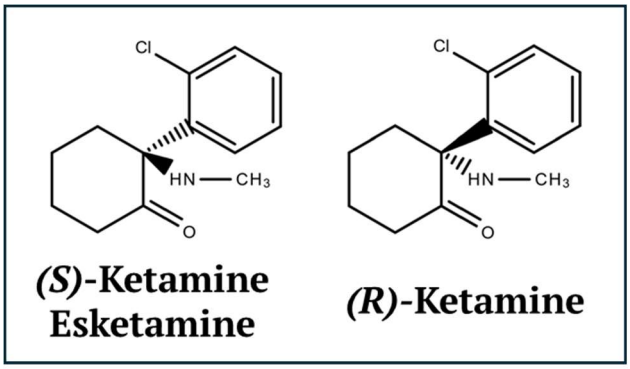

Figure 1. Stereoisomers of ketamine, including the *(S)*-ketamine, or esketamine, formulation FDA approved for TDA.

Neuroplasticity in Depression

Neuroplasticity underlies the ability of neurons to adapt to stressors through structural, molecular, and functional changes.[32] Altered neuronal connectivity and atrophy in key limbic and cortical regions contribute to many symptoms of depression, including cognitive decrement, loss of emotional control, increased anxiety, and reduced motivation or reward.[33] The density of dendritic spines, or protrusions located throughout neurons, have shown a direct link to neuronal connectivity through both physical substrate availability and postsynaptic signaling.[33] Under standard, non-stressed states, spine synapse connections proliferate and provide control over mood, emotion, and cognition.[33] During chronic stress, loss of synaptic spines and connectivity was appreciated – anecdotally paralleling the difficulty in coping with stress during periods of depression.[33,34] Chronic use of SSRIs have shown to mediate neuroplasticity changes, yet is a slow process.[7,33] As ketamine evolved as an antidepressant, Li *et al*. showed that ketamine rapidly attenuated the stress-induced retraction of apical dendrites and synaptic spines in the medial prefrontal cortex and hippocampus and improved synaptic connectivity **(Figure 2A)**.[34]

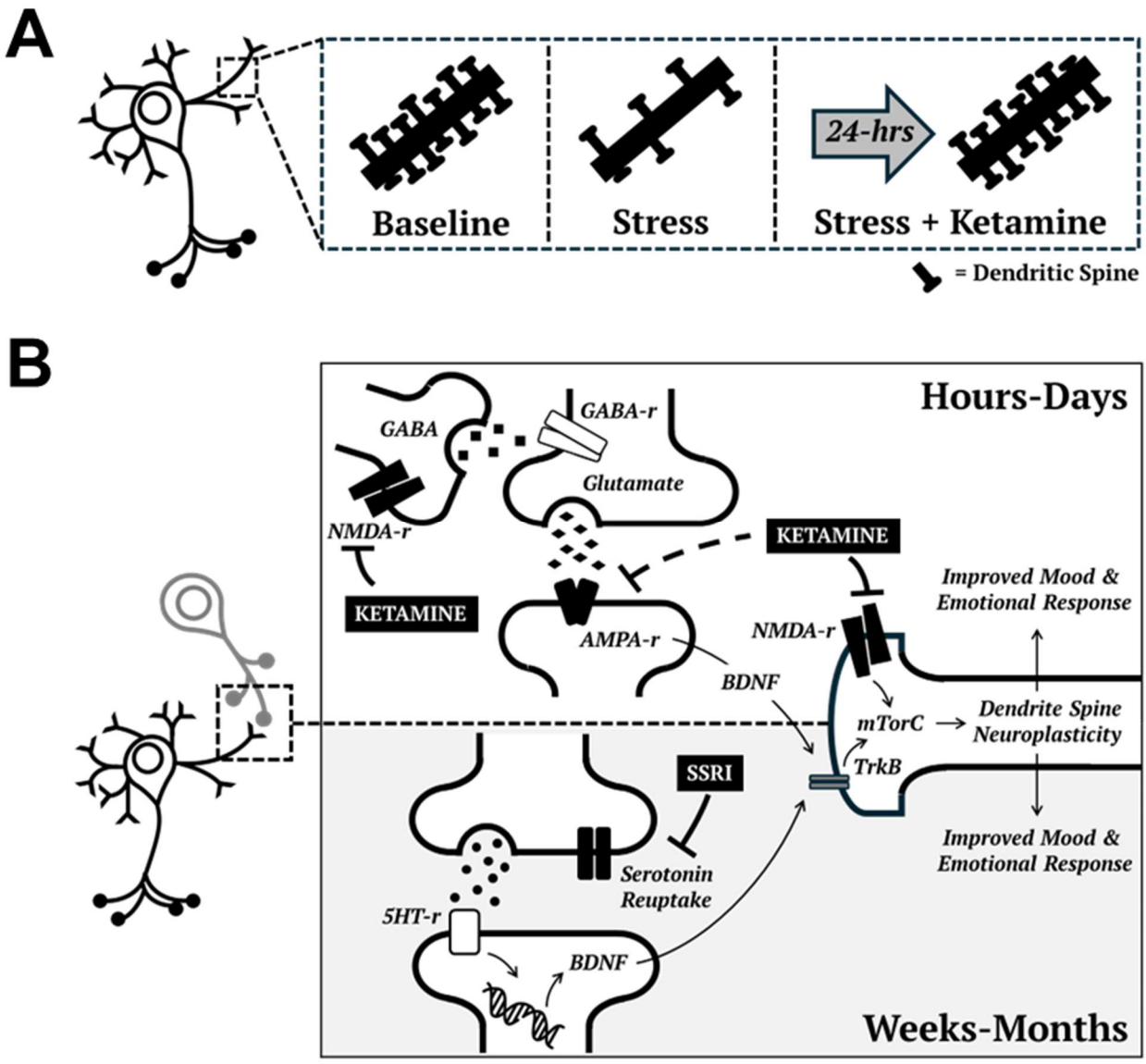

Figure 2. Ketamine provides rapid neuroplasticity in depression and acute suicidality. (A) Ketamine blunts the stress-induced loss of neuronal dendritic spines within 24-hours seen in depression.[34] (B) The top section demonstrates ketamine neuroplasticity occurring within hours-to-days.[32] Multiple mechanisms have been suggested for its antidepressive action including: disinhibition of glutamate neurotransmission via GABAergic signaling by noncompetive inhibition of presynaptic NMDA receptors, modulation of BDNF signaling through direct inhibition of AMPA receptors by ketamine metabolite norketamine, postsynaptic NMDA receptor inhibition mediating downstream mTorC1 signaling cascade.[35–37] Stress is shown to decrease BDNF in the hippocampus and prefrontal cortex, resulting in spine density modulation through its receptor TrkB and mTORC1 signaling cascade.[33] Contrary, the bottom section demonstrates SSRI neuroplasticity occurring after weeks-to-months by postsynaptic serotonin receptor-mediated BDNF signaling through inhibit of serotonin reuptake.[7,29]

Ketamine – the Swiss army knife psychoplastogen

Ketamine is considered a psychoplastogen, or a small molecule medication rapidly involved in neuroplasticity for the benefit of neuron growth, structural enhancement, and synaptic connectivity.[37] The first clinical trials for ketamine date back to 1967 as a human short-acting anesthetic.[38] Since then, ketamine has evolved over decades as a versatile medication in the fields of pain management, sedation and behavioral health – such as TRD.[39,40] Ketamine has a high lipid solubility and does not bind to proteins during distribution, therefore can rapidly cross the blood-brain barrier, which attributes to its fast onset of action within minutes.[36] The racemic enantiomer contains equimolar stereoisomers, *(R)*-ketamine and *(S)*-ketamine **(Figure 1)**. Isolated *(S)*-ketamine, or esketamine, has a nearly four-fold greater affinity for the N-methyl-D-aspartate (NMDA) receptor than its *(R)*-enantiomer and is associated with fewer psychotropic side effects.[35,36,38] Ketamine is an arylcycloalkylamine that primarily acts as an NMDA receptor noncompetitive antagonist that blocks glutamate and increases excitatory transition in the brain, although multiple additional mechanisms have been identified.[36,38,41] Esketamine, for example, was shown to inhibit dopamine transporters and increase brain dopamine activity.[35,42,43] The nociceptive pain effects of ketamine appear to be mediated partially by the potentiation of opiate receptors, and in part, have been postulated as a mechanism in depression for reduction in 'mental pain'.[12,44]

In general, the effects seen by acute administration of ketamine for depression manifest within hours, contrasting with SSRI efficacy, which can take several weeks to months. The rapid onset of ketamine neuroplasticity is key to understanding its favorable use in emergent depressive symptoms and acute suicidality.[10,39,45] **Figure 2B** highlights various downstream targets of ketamine. Extensive research in depression and chronic stress show downregulation of brain-derived neurotropic factor (BDNF), resulting in signal attenuation in mammalian target of rapamycin (mTOR) C1 pathway.[35,46] The mTORC1 pathway contributes to dendritic spine density and function in multiple brain regions, including the medial prefrontal cortex.[46] Glutamate release is modulated from disinhibition of GABAergic interneurons via presynaptic NMDA receptors.[43] Increased glutamate-mediated neurotransmission binds postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), leading to activity dependent release of BDNF, propagation of mTORC1 signaling, and synthesis of dendritic spine proteins.[33,46] Woelfer *et al.* characterized how ketamine-induced increase in BDNF was associated with synaptic plasticity in the prefrontal cortex.[41] A similar mechanism has been described for SSRI-mediated downstream modulation of mTORC1 signaling and synaptic plasticity, albeit much slower.[7]

Alternatively, other suggestive mechanisms for ketamine efficacy point to NMDA receptor-mediated regulation in major reward circuits including the ventral tegmental area in the midbrain and serotonin dorsal raphe nucleus.[35,47] Wong *et al.* suggested ketamine implications in mood regulation could be described by the functional connectivity of the subgenual anterior cingulate cortex via cognitive and emotional networks modulated at subtherapeutic doses.[48]

Clinical use of Ketamine for Acute Psychiatric Emergencies

Extensive randomized-controlled trials (RCT) have been published on the effectiveness of ketamine in areas of MDD, TRD, and suicidal ideation, as outlined in **Table 2**. Since March 2019, Intranasal (IN) esketamine is currently the only US FDA approved form of ketamine available for MDD and TRD with imminent risk of suicide, yet multiple off-label clinical protocols exist.[49] Four large, Phase-III trials spearheaded the FDA approval of IN esketamine for TRD – including TRANSFORM-2[50], TRANSFORM-3[51], SUSTAIN-1[52], and SUSTAIN-2.[53] The primary outcomes compared improvement in depressive symptoms measured by change in baseline Montgomery-Asberg Depression Rating Scale (MADRS).[54] In brief, esketamine significantly reduced depressive symptoms, in as little as 24-hours.[50,52,53] Intranasal ketamine significantly abated relapse in depressive symptoms after 16-weeks when compared to placebo standard of care.[52,54]

Recently, ketamine use in the emergency department for acute presentations of psychiatric emergencies has gained favor as well, due to its rapid outcome.[10,39,45] Studies have shown improvement in suicidal ideation as

soon as 4-hours post IN esketamine by MADRS-SI scores in emergency care.[45] Anecdotally, although not significant in this study, length of hospitalization was also reduced in the ketamine treatment group and rates of suicidal behavior remained low after 28-days.[45]

Research continues evolving to include intravenous (IV) administration of ketamine as well. Murrough *et al* corroborated esketamine findings, indicating the effect of IV ketamine as quickly as 40-180 minutes, with peak effect at 24-hours after a single dose.[55] Abbar *et al* demonstrated a full reduction in suicidal ideation at 72-hours (odds ratio 3.7, $p<0.001$).[12] In a systematic review by Siegel *et al*, totaling 480 participants in 8 RCTs for both IN (84 mg) and IV ketamine (0.5 mg/kg) for effect on depressive symptoms, indicated a reduction in depressive symptoms within the first 24-48 hours of administration in both IN and IV.[56] This is consistent with a more recent meta-analysis, indicating significant reduction in depressive symptoms and suicidal ideation up to 72-hours post IV infusion.[11] In another meta-analysis focused on a single ketamine infusion given at emergency presentation, Wilkinson *et al.* presented that 55% of patients were suicide free at 24-hours and 60% at one-week post-ketamine in both self-reported and clinician-reported metrics.[57] Compared to the benzodiazepine midazolam, rapid reduction of MADRS at 24-hours by IV ketamine was significantly more effective (odds ratio, 2.18; 95% CI, 1.21-4.11).[55]

Interestingly, when controlling for the anxiety and depression effects of ketamine, suicidal ideation showed significant reduction compared to control, indicating the antisuicidal reduction may not be exclusively driven by depression symptoms.[58] One recent hypothesis for ketamine's reduction in suicidal behavior, although admittingly supported by a paucity of evidence, suggests a transdiagnostic clinical risk reduction – such as repetitive negative thinking as one potential factor.[57,59]

335 **Table 2. Randomized Controlled Trials utilizing Ketamine for psychiatric emergencies based on**
336 **stereoisomer and route of administration.**
337

	Study	Dose	Indication	Outcome
Intravenous (IV) Racemic Mixture Enantiomers				
	Abbar *et al.*[12]	0.5 mg/kg	SI	Reduction at day-3 with ketamine (*n*=156)
	Domany *et al.*[10]	0.2 mg/kg	SI	Reduction at 2-hours after infusion in the Emergency Department (*n*=18)
	Fava *et al.*[60]	0.1-1 mg/kg	TRD	Compared to midazolam controls, >0.5 mg/kg ketamine was significant in reduction (*n*=99)
	Grunebaum *et al.*[61]	0.5 mg/kg	SI	Greater reduction in SI compared to midazolam (*n*=80)
	Albott *et al.*[62]	0.5 mg/kg	TRD	93% reported reduction at 20-days (*n*=80)
	Su *et al.*[63]	0.2-0.5 mg/kg	TRD	Dose-response reduction in HAM-D scores at 14-days (*n*=71)
	Grunebaum *et al.*[64]	0.5 mg/kg	SI	Greater improvement in mood disturbances and depression at 1-week (*n*=16)
	Ghasemi *et al.*[65]	0.5 mg/kg	TRD	Comparison to ECT at 24-hours, 72-hours, and 1-week, greater decrease HAM-D scores with ketamine (*n*=18)
	Murrough *et al.*[55]	0.5 mg/kg	TRD	Decrease MADRS score at 24- and 72-hours (*n*=73)
	Zarate *et al.*[66]	0.5 mg/kg	TRD	Decrease HAM-D score at 24-hours (*n*=18)
	Berman *et al.*[67]	0.5 mg/kg	TRD	Decrease HAM-D score at 72-hours (*n*=7)
Intravenous (IV) Esketamine				
	Singh *et al.*[68]	0.2-0.4 mg/kg	TRD	Reduction MADRS by 24-hours (*n*=30)
Intranasal (IN) Esketamine				
	Fu *et al.*[69]	84 mg	MDD	Depressive symptoms improved by 2-hours and no significance in SI on MADRS (*n*=226)
	Canuso *et al.*[70]	84 mg	MDD	Esketamine plus standard care improved depression symptoms at 4-hours and 25-days (*n*=456)
	Ionescu *et al.*[71]	56-84 mg	MDD	Improvement in depressive symptoms at 24-hours and 1-week with twice daily dosing (*n*=227)
	Fedgchin *et al.*[72]	56, 84 mg	TRD	Reduction in depression with esketamine plus antidepressant vs antidepressant alone (*n*=297)
	Popova *et al.*[73]	56, 84 mg	TRD	Reduction MADRS with esketamine plus antidepressant vs antidepressant alone (*n*=197)
	Daly *et al.*[74]	28, 56, 84 mg	TRD	Dose-response reduction by MADRS (*n*=67)
	Canuso *et al.*[75]	84 mg	MDD	Significant reduction in depressive symptoms at 11-days and SI on MADRS (*n*=68)
	Lapidus *et al.*[76]	50 mg	MDD	Reduction in depressive symptoms at 24-hours (*n*=18)

Intranasal (IN) Racemic Mixture Enantiomers				
	Jones *et al.*[77]	50 mg	SI, MDD	(R,S)-Ketamine; Improvement in depressive symptoms and SI (*n*=33)
	Domany *et al.*[45]	40 mg	SI	Reduction SI at 4-hours by MADRS-SI in Emergency Department and shorter hospitalization stay (*n*=30)
Subcutaneous (SQ) Racemic Mixture Enantiomers				
	George *et al.*[78]	0.1-0.5 mg/kg	TRD, MDD	≥0.2 mg/kg greater effect compared to midazolam (*n*=15)

TRD, Treatment-Resistant Depression; MDD, Major Depressive Disorder; SI, Suicidal Ideation; MADRS, Montgomery-Asberg Depression Rating Scale; HAM-D, Hamilton Depression Rating Scale

Use of Ketamine in Austere Environments

Ketamine has been successfully deployed to forward combat hospitals and within field operations for decades, used primarily for analgesia and sedation.[79–81] In fact, the guidelines for the Department of Defense Tactical Combat Casualty Care (TCCC) currently recommends ketamine in its multimodal pain algorithm for prehospital and field casualty care.[81,82] In isolated-confined-extreme environments, ketamine offers a relatively wide therapeutic window and safety profile at low doses, preserving spontaneous respirations and requires limited expertise or resources for use.[83]

Civilian use of ketamine in austere environments is common as well. Surveys of alpine helicopter-based mountain rescue teams, ketamine was considered “irreplaceable” for acute patient management and ease of use in the pre-hospital setting.[84] Reports of extensive ketamine use by rural hospitals without anesthesiologists or specialist training – over 8000 patients in a 15-year span – have used ketamine as an anesthetic agent with minimal complications.[85] In a small case series (n=11), ketamine was successfully utilized as an anesthetic in a remote, isolated clinic at high altitude by an untrained primary care physician without the need for specialist equipment.[86]

Pharmacodynamics, Stability and Usability

The World Health Organization catalogues ketamine on its list of “essential medications”, a model formulary based on efficacy, safety, and clinical need worldwide.[87] Ketamine has been favored in prehospital, low-resource, extreme and combat environments for years – due in part to its stability in solution or powdered forms, but also due to its ease in administration.[79] Storage of the powder medication is at room temperatures and has a shelf-life of nearly 20-years.[88] Analysis by ultra-performance liquid chromatography of ketamine hydrochloride solution after 180-days stored at room temperature exposed to light indicated no degradation and within FDA standards for the active pharmaceutical ingredient (API).[89] In fact, multiple studies show stability in the field to extremes in temperatures.[90,91]

Various accepted routes of administration have been safely tested in humans including IV, IN, intramuscular (IM), oral (PO), sublingual, and rectal.[38,47] Esketamine, currently the only FDA approved form of ketamine for depression at the time of this review, is exclusive to the IN form.[31] The bioavailability for IV and IM continue to be highest at nearly 100%, with IN reduced by nearly half and highly variable (35-50%).[35] Galvez *et al*, performed an initial pilot study on the efficacy of IN ketamine for treatment-resistant depression, but identified limitations based on variable nasal mucosal absorption.[92] Oral is less bioavailable due to extensive first-pass metabolism, yet appears to have favorable outcomes in early clinical trials.[93] A systematic review by Short *et al.* indicated that IV ketamine was associated with greater psychotomimetic side-effects when compared with PO, IM and IN.[94]

Ketamine has a very large volume of distribution (3-5 L/kg) due to low protein binding and lipophilicity.[95] The half-life of esketamine is reported at 7-12 hours.[49] Hepatic biotransformation results in several metabolites via cytochrome P450, including its active metabolite norketamine.[47] Substrate ketamine is primarily metabolized by the enzymes CYP3A4 and CYP2B6.[95] Although consideration for drug-drug interactions must be considered for medications metabolized via P450 enzymes, there is a lack of warnings on specific human drug interactions or pharmacogenomics.[95] Diazepam, a CYP3A4 substrate for example, increased the half-life of ketamine and thus potentiated the sedative effects.[96] However, ketamine offers a high therapeutic index and thus, toxic levels achieved strictly due to metabolic changes in spaceflight are less likely.[95]

An extensive review by Blue *et al.* outlined the challenges in the stability of pharmaceuticals in the space environment.[97] In brief, exploring outside of LEO exposes greater risk to radioactive degradation of medications and thus, reduction in the API.[97] To date, limited data is available on ketamine stability post-flight in regards to drug degradation, radiosensitivity, and potency. Still, ketamine continues to be used in austere and extreme environments worldwide with little concern for instability or loss in efficacy.[81,98]

Spaceflight poses multiple challenges to drug stability, not exclusive to ketamine. Du *et al* characterized medications from shuttle era, showing lower potency and percent API content in ground-matched controls.[99] Interestingly, dosage form seemed to show increased stability for solid formulations compared to liquid over a duration of 880 days in flight.[99] Sertraline, an SSRI currently in PO form on the ISS, showed slightly decreased potency when compared to ground-controls, although still contained the minimum US Pharmacopeia accepted API content after 550 days.[28]

Side Effect Profile of Ketamine

Hesitation on ketamine use likely stems from its use as a recreational drug since the early 1970's and unfortunately, most recently in the news as drugs of abuse amongst celebrities. At supratherapeutic levels reported as high as 10-fold the sedative dose, recreational ketamine can produce psychedelic effects, with users experiencing cataleptic-like dissociation from reality.[94,100] Although these doses far exceed the normal indication dose for treatment-refractory depression, as highlighted in **Figure 3**. Reports of "psychological pain-relief" have been evidenced at lower doses in clinical trials, possibly linked to ketamine's dissociative properties.[12] The most common side effects reported in clinical trials were disassociation, dizziness, nausea, sedation, vertigo, hypoesthesia, and "feelings of being drunk".[39,75,94] In the clinical trials submitted to the FDA, esketamine reported the following side effects: sedation (48-61%), loss of consciousness (0.3-0.4%), derealization or depersonalization (61-84%), and very rarely reported respiratory depression.[52,53,94] The dissociative effects of ketamine reach critical threshold at approximately 1-1.5 mg/kg IV, or 3-4 mg/kg IM.[35] However, doses as low as 0.1-0.4 mg/kg have reported psychoactive dissociative symptoms and thus, reflect the accepted sub-dissociative threshold for ketamine.[38] Cognitive performance and mental effort returned to baseline levels comparable to placebo after 2-hours of receiving a dose of esketamine.[51,94] Loo *et al.* demonstrated similar side effect profiles for equimolar doses of IV, IM, and subcutaneous routes of administration in depression.[101]

Ketamine has no absolute contraindications but should be used cautiously in at-risk populations such as untreated hypertension, known elevated intracranial pressure, untreated coronary artery disease, or hypersensitivity to esketamine.[49,102] Ketamine has shown to increase blood pressure and heart rate within minutes of administration, due to sympathomimetic action and inhibition of catecholamine reuptake.[38] Esketamine reported systolic blood pressure increases more than 40 mmHg at an incidence rate up to 17% within the first 90-minutes of administration.[49] In fact, esketamine treatment centers require patients to remain two-hours for monitoring after administration, in part due to these cardiovascular effects in at-risk individuals.[49,102] For professional astronauts, a population with strict pre-flight medical standards on blood pressure, ketamine deleterious effects on blood pressure are likely pathologically negligible.

Because of the risks for sedation and dissociation at higher doses, in addition to potential for abuse, esketamine distribution is currently restricted by the FDA, under a Risk Evaluation and Mitigation Strategy (REMS).[31,49,54] REMS programs focus on monitoring and reinforcing safe medication habits, while limiting severe adverse events associated with abuse.[103] Clearly, a notable concern when discussing ketamine use in future operational environments.

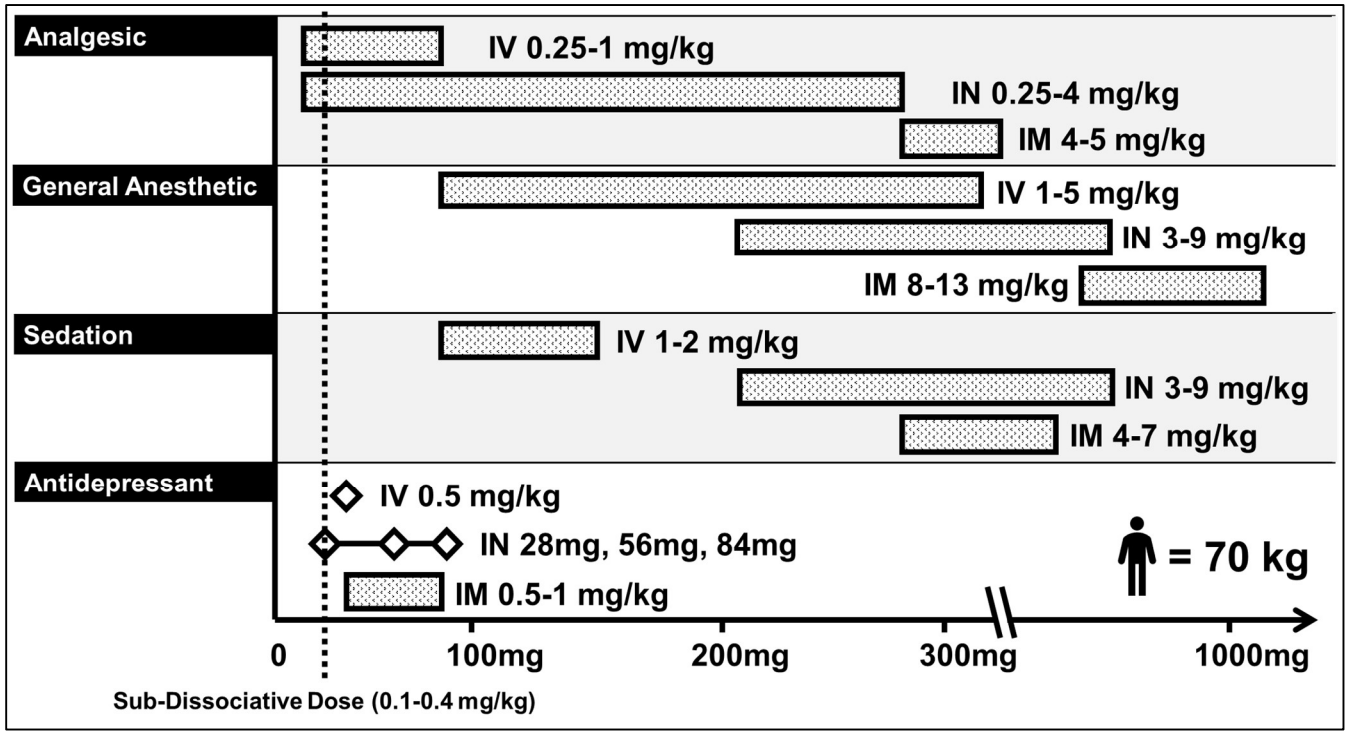

Figure 3. Multiple indications for ketamine and acceptable dose ranges for desired outcomes in a standard 70-kg person. Ketamine is indicated as an analgesic, anesthetic, sedative, and antidepressant.[38] Acceptable routes of administration include intravenous (IV), intranasal (IN), and intramuscular (IM). Due to the variable bioavailability with routes of administration, dosage of ketamine differs and often requires higher concentration for IN and IM routes. Doses indicated for depression reflect significantly lower concentrations compared to sedative or anesthetic indications. The sub-dissociative dose of ketamine is reported at 0.1-0.4 mg/kg, or the minimum dose with reported dissociation.[47,104,105]

DISCUSSION

This review demonstrates the first initial consideration of ketamine as a possible intervention for psychiatric emergencies and acute suicidality on exploration missions. The heightened risk of behavioral challenges anticipated with EIMO – and the limited toolbox currently available to treat possible in-flight psychiatric emergencies – highlights the importance of early discussion. To date, psychiatric formularies suitable for exploration missions did not include ketamine, primarily because the indications and evidence for ketamine has only recently been gaining traction as an effective and safe medication for MDD, TRD and SI.[28] Ketamine is currently a part of the ISS formulary, albeit reserved for anesthesia and sedation.[6] The aim of this review focused on the strengths and areas requiring additional investigation when considering ketamine for psychiatric emergencies in spaceflight.

Robust screening remains the foundation of crew behavioral health mitigation strategies, primarily focusing on identifying participants capable at adapting to the spaceflight environment.[1] Yet, the future exposes multifactorial challenges, including unique stressors on EIMO and incorporation of private-industry, commercial astronauts. Adverse cognitive and behavioral conditions may propagate development of mental disorders, requiring acute or chronic interventions during spaceflight.[1,18] Certainly, no documented cases of emergent behavioral disorders have occurred. Despite suicidal ideation frequently being associated with depressive symptoms, suicidal behavior is not exclusive to depression. Frequent stressful thoughts perceived uncontrollable, akin to challenges expected in deep space exploration, have been characterized as a transdiagnostic symptom linked to increased suicide risk.[59] Therefore, despite preflight screening in depressive symptoms, suicidal ideation may still be a required risk assessment. Thus, as mission profiles are rapidly evolving, consideration of the utility for current and future formularies remains necessary.

The terrestrial pharmacologic standard of care for depression and anxiety continues to be with SSRIs as first line therapy. El-Khoury *et al* recently published an extensive review on the benefits and challenges SSRI pose within the spaceflight environment – including difficulties in prolonged therapy for desired outcome and potential effects on bone mineral density.[7] In particular, the delayed neuroplasticity of SSRIs may limit their utility in an emergent operational scenerio.[7,33,106] The real strength in consideration of ketamine as an antidepressant, independent of its ease of dosing and administration, is the fast outcomes reported in emergent situations – a testament to ketamine's proliferative neuroplasticity.[39] When considering use for EIMO, it's notable that esketamine's approval by the FDA was in conjunction with standard of care for depression, such as with an SSRI.[49] Therefore, it is not without consideration that an emergent psychiatric indication could benefit from ketamine's expedited onset of neuroplasticity in tandem with an SSRI. In other words, rapid improvement in depressive or suicidal behaviors by ketamine could be utilized as a bridge to SSRI and intervene early in a person's vulnerable state.

Ketamine continues to be widely used in prehospital and field medicine, often with minimal training or resource requirements.[107] The ease of ketamine administration requires minimal training by healthcare providers, and thus, may be ideal for crew without formal professional medical training. Additionally, indications for ketamine our broad, spanning from use as an analgesic, anesthetic, sedative, and antidepressant.[38] Although the cost has improved over the past decade with the advent of commercial spaceflight, utilizing a medication with multiple indications can provide payload space and mass optimization, ultimately reducing overhead costs associated with medical kit design.

Intranasal esketamine is the only FDA-approved formulation at the moment for behavioral emergencies, and thus, off-label roles for IV or IM ketamine would need to be applied.[49,54] Certainly, ketamine's side effect profile continues to be a major hurdle in support of its use. The risk of inability to perform duties from dissociation in spaceflight is concerning. Yet, in the context of a true psychiatric emergency, flight controls for astronauts and critical mission operations will likely be restricted to the astronaut of behavioral concern. Nonetheless, dissociation has been reported to be transient and resolve by 90-120 minutes, yet, abatement in depression and suicidal thoughts continue well past this reported side effect.[47,108] Multiple studies have shown a single dose of

ketamine may be sufficient for reduction in depressive symptoms.[45,57,109] Anecdotally, repeat dosing of ketamine reported intrapersonal consistency in reduction of dissociation symptoms – in other words, the dissociative effects were blunted on repeat administration.[47]

Ketamine continues to be an intriguing pharmacologic treatment revolutionizing the psychiatric community. Variability in optimizing routes of administration and dosage continue to the focus of current research. Consideration for its utility in spaceflight is still controversial given its limitations outlined in this review. However, the potential for ketamine as a 'Swiss army knife' medication in spaceflight cannot be ignored and further investigations should be explored.

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795