

Selective Serotonin Reuptake Inhibitors and Other Treatment Modalities for Deep Space Missions

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- INTRODUCTION:** As humankind ventures further into the depths of space, planning is already underway for long-duration exploration missions that will test the bounds of human performance. Deep space travel will include added risk related to stressors from the isolated, confined, and extreme environment that lies outside the boundaries of low Earth orbit. Currently, selective serotonin reuptake inhibitors (SSRIs) are considered the standard of care for many mental health diagnoses, including anxiety and depression; however, SSRIs are also associated with several undesired side effects. The utility of nonpharmacological therapies for the management of behavioral health conditions has not yet been fully explored.
- METHODS:** A comprehensive literature search was performed using PubMed. Relevant articles pertaining to the psychological impacts of isolated, confined, and extreme environments, use of SSRIs in spaceflight, side effects associated with SSRIs, and nonpharmacological treatments for anxiety and depression were reviewed. Over 70 studies were reviewed in total.
- RESULTS:** Reduced bone mineral density, impaired hemostatic function, significant individual variability resulting from gene polymorphisms, and drug-drug interactions are well described adverse effects of SSRIs that may complicate their operational use in the deep space environment. Four alternative therapies for the treatment of anxiety and depression may show promise for long duration missions.
- DISCUSSION:** Although SSRIs have long been considered standard of care treatment for many behavioral health conditions, we cannot trivialize the risk that prolonged pharmacological therapy may pose. The need to mitigate these risks by exploring alternative therapies has never been more relevant.
- KEYWORDS:** selective serotonin reuptake inhibitors, spaceflight, behavioral health, stressors.

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As humankind continues to venture further into the depths of space, planning is already underway for long-duration exploration missions lasting several years that will test the bounds of human performance. With this in mind, the aerospace medicine community has been hard at work developing preventative strategies and risk mitigation plans to optimize this performance and to anticipate the hazards that will affect human health and performance. One important hazard that will invariably affect the deep space traveler are the added stressors that will result from the isolated, confined, and extreme (ICE) environment that lies outside of the comfort of low Earth orbit. In addition to this stress and isolation, the space traveler must inherently be more autonomous with significantly less ground-level support for assistance given the anticipated delays that will likely hinder communication with mission control.³ As we anticipate the human factors and psychological stressors that threaten the safety of our astronauts and their incumbent risks

to mission accomplishment, mental health prevention and mitigation strategies have become exceedingly important and are a necessity for any long-duration exploration mission.¹⁷

Arguably, one of the most important medical breakthroughs of the 20th century in the field of psychiatry and mental health was the discovery of the class of medications known as selective serotonin reuptake inhibitors (SSRIs).⁵⁴ Currently, SSRIs are considered the gold standard treatment for many mental health

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diagnoses, including anxiety and depression.²⁷ Despite their known therapeutic benefits, however, SSRIs are also associated with undesired side effects. This paper will explore the history of SSRIs, their positive and negative effects, and several other novel and underexplored pharmaceutical and nonpharmaceutical therapeutic strategies that might be considered to prepare, prevent, and mitigate mental health stressors from long-duration space travel. While not synonymous, in this paper, the terms adverse effects and side effects are used interchangeably. We chose not to include psychotherapies due to the pragmatic constraints of delivering them when the communications gap is measured in minutes. Additionally, this paper will review the evidence gleaned from the literature studying mental health in ICEs. These environments serve as an analog for deep space missions as astronauts will need to be more autonomous and adaptable to changing conditions. Indeed, many of the factors indicating which individuals will successfully maintain high performance levels in isolated and confined environments remain under exploration. To date, NASA has relied heavily on astronaut selection as one of its strongest behavioral health countermeasures. Long-duration missions pose several unique challenges that will require careful selection and consideration of which candidates might be most suitable for settings involving communication delays and extreme isolation. Individuals who might be genetically predisposed and vulnerable to developing a mental health problem are of particular concern. The likelihood of the emergence of a psychiatric illness on a long-duration mission becomes greater with increased time and distance from Earth. Careful consideration, forethought, and discussion of appropriate pharmaceutical agents to treat mental illness occurring in deep space, such as SSRIs and non-pharmacological agents, need to be debated and discussed early on in mission development and planning.

The neurophysiological pathways and biochemical basis of disease in behavioral health remain a subject of intense debate and scrutiny in psychiatry and research to better understand these pathways is ongoing. The link of 5-hydroxytryptamine (5-HT, serotonin) to depression and mental health became better understood in the 1960s following the quantification of 5-HT levels in patients postmortem. Investigators found that 5-HT levels were 19% lower in the hindbrains of patients who had diagnoses of depression or “probably depressed” when compared to control subjects.⁴⁸ In the years surrounding this study, researchers set out to create a drug that solely inhibited the reuptake of serotonin. In 1971, this objective was completed by Drs. Hans Corrodi and Arvid Carlsson with the introduction of zimelidine. Shortly thereafter, fluoxetine was developed and was released for clinical use in 1988.⁵⁴ Since then, several other SSRIs have been introduced and their use has been a breakthrough for the field of psychiatry.

Mechanistically, selective serotonin reuptake inhibitors have 20–1500 times more affinity for the serotonin receptor over the norepinephrine receptor.²⁴ The drugs bind minimally to postsynaptic receptors (e.g., adrenergic, dopaminergic receptors), including the postsynaptic serotonin receptor. However, SSRIs do not induce the serotonin release and induce increased

activity at the postsynaptic receptor almost exclusively via inhibiting the reuptake of serotonin in the synaptic cleft.²⁴ As a class of medications, SSRIs have numerous side effects, most of which are seen with long-term therapy. Side effects include hypotension, nausea, bone loss, bleeding dysfunction, QT prolongation, and sexual dysfunction, among others.

The Food and Drug Administration (FDA) has approved the use of SSRIs in the treatment of major depressive disorder, generalized anxiety disorder, bulimia nervosa, bipolar depression, obsessive-compulsive disorder, panic disorder, premenstrual dysphoric disorder, treatment-resistant depression, posttraumatic stress disorder, and social anxiety disorder.¹² In addition, there are additional off-label uses for SSRIs that are outside the scope of this paper. Although SSRIs do possess adverse effects as noted, many are not as salient to the spaceflight environment with respect to exploration class mission planning and are, therefore, not covered in detail within this paper. However, in order to understand the potential usage of SSRIs in the spaceflight environment, we must first review the history of psychiatric disease in aviation and spaceflight analog environments and SSRIs’ current use in these environments.

Current Use of SSRIs in Aviation and Spaceflight

Although many psychiatric diseases were previously disqualifying for flight, the aviation medicine community has eased several restrictions to allow those with prior mental health diagnoses an opportunity to participate in aviation activities. Currently an individual may be considered for a Federal Aviation Administration (FAA) Authorization of a Special Issuance of a Medical Certificate if the applicant has one of the following diagnoses: major depressive disorder (mild or moderate, either single or recurrent episode), dysthymic disorder, adjustment disorder with depressed mood, or any nondepression-related condition for which an SSRI is used. The Federal Aviation Administration (FAA)-approved SSRIs are fluoxetine, escitalopram, sertraline, and citalopram. In order to qualify with the FAA, the applicant must be clinically stable for at least 6 mo with no side effects that would affect aviation operations.

Although never used, SSRIs are part of the onboard U.S. formulary that is currently deployed to the International Space Station (ISS) for contingency use. The current psychotropic medications on the ISS are sertraline and venlafaxine (antidepressant medications), diazepam and lorazepam (anxiolytic medications), and aripiprazole and ziprasidone (antipsychotic medications). Currently, the astronauts assigned to the ISS participate in private medical conferences with flight surgeons and private psychological conferences with psychology/psychiatry behavioral health providers biweekly to address any medical or behavioral health concerns during their missions. For long-duration missions, private psychological conferences will continue to be used; however, due to communication delays, other platforms such as virtual reality and a behavioral health dashboard are currently being investigated.

With regards to commercial space programs, it remains uncertain what protocols will be used for medical and psychiatric screening and evaluation while on orbit. Although it is likely

that there may be a certain degree of continuity with current medical operations, added flexibility regarding medical diagnoses and medication use is anticipated given the fact that most spaceflight participants are likely to be paying participants.

Mental Health Symptoms in Austere and Remote Environments

In order to fully appreciate the importance of preventative health and contingency planning for psychiatric disease, it is worthwhile to review the published data with regards to the development of psychiatric disease in austere and remote environments, as they are often considered the best terrestrial analogs for deep space exploration. One important trait that is felt to be advantageous for deep space missions is adaptability. Many studies aimed at better understanding the effects of ICE environments on mental health have been conducted in Earth-based space exploration analogs with varying crew numbers and time lengths. Several of these studies have concluded that emotional stability (or instability) was an important factor affecting adaptability in extreme environments.^{14,15,25}

An important operational environment analog that has been well-studied in the literature is the Arctic/Antarctic. One study by Palinkas *et al.* conducted in personnel overwintered in Antarctica noted significant seasonal variation in depressive symptoms felt to be likely linked with social isolation and the absence of sunlight.³⁷ The investigators also found that marital status and summer depression were significant independent predictors of winter depression. Another study conducted by Wright *et al.* found that Arctic workers with low supervisor ratings were higher in psychopathology indicators and were concluded to have poor adaptability to their environment.⁵⁷ Additionally, Palinkas *et al.* determined the incidence of mood disorders, adjustment disorders, and sleep disorders to be as high as 4.2%, 3.8%, and 2.9%, respectively, at the end of austral winter in those working at McMurdo and the South Pole between 1994 and 1997.³⁸ In a specific review looking at submariners, it was found that those with depression, anxiety, and interpersonal problems had higher rates of disqualifications from duty. Failure to adapt was listed as a conclusion from these findings.⁵⁵ These studies corroborate the importance of routine screening for pre-existing mental health disorders and emphasize the importance of adaptability in subjects being deployed to ICE environments.

When examining previous and current analog missions, there has been some qualitative data to suggest the presence of negative emotions in subjects after an analog exposure. A review by Alfano *et al.*¹ found that overall self-reported negative emotions have been found to be low in spaceflight, long-duration space simulation analogs, and polar environments. Their group found that broad-based assessments may not detect symptoms of anxiety and depression and choosing more novel measures of emotion may be better suited.¹ These negative emotions can potentially have significant operational impacts on human performance. Additional analog studies that have demonstrated a correlation between mental health indicators and the remote environment include the Mars500 study,

winter-over studies in Antarctica, the Hawai'i Space Exploration Analog and Simulation Mars analog facility, and the Human Exploration and Research Analog at NASA's Johnson Space Center.^{10,33,50} Several studies conducted within these analog environments have shown that exposed subjects may be at increased risk for development of depression, stress, and anxiety.^{2,6} Invariably, our prior experience in analog environments suggests that any decrements in the psychological health of our crewmembers during long-duration spaceflight may pose a real threat to the success of future missions, despite the selection of crews without a history of psychological health problems.³⁶

METHODS

A comprehensive literature search was performed using PubMed and relevant articles pertaining to the psychological impacts of ICE environments, use of SSRIs in spaceflight, side effects associated with SSRIs, and nonpharmacological treatments for anxiety and depression were reviewed. Specifically, articles that referenced the hematologic side effects of SSRIs, effects of SSRIs on bone mineral density (BMD), neurocognitive effects of SSRIs, and pharmacological effects of SSRIs were reviewed. Common search terms used included "bone loss in spaceflight," "hematologic effects of SSRIs," "neurocognitive effects of SSRIs," "hematologic effects of spaceflight," "effects of spaceflight on bone density," "stress and anxiety in spaceflight analog," and "non-pharmacologic treatment of anxiety and depression." Over 70 studies were reviewed in total.

RESULTS

Hematologic Effects of Spaceflight and SSRIs

Although selective-serotonin reuptake inhibitors have been considered safer than previous classes of psychotropic medications and have often boasted a more favorable side effect profile, many SSRIs have been found to alter hemostatic functions and, in particular, impair hemostasis. Numerous mechanisms have been thought to contribute to this effect, including nitric oxide inhibition, blockade of platelet calcium mobilization, and reduction of platelet factors leading to decreased expression of platelet activation.⁵³ Meta-analysis revealed an association between SSRI use and increased risk of severe bleeding (odds ratio: 1.41, 1.27–1.57). Severe bleeding was defined as the need for prompt intervention of a healthcare professional or reoperation after surgery. The estimated increase in risk of bleeding was on average 36% in this meta-analysis.²⁹ Given the possible increased risk of bleeding and altered hemostatic function related to SSRI use, the prolonged use of these medications is not inconsequential, especially with the increased operational demands of exploration class missions and the higher probabilities of traumatic or accidental injury with the longer durations of spaceflight that would invariably result. In fact, a recent meta-analysis by Anglin *et al.* found that when SSRIs are used in combination

with nonsteroidal anti-inflammatory drugs, subjects had a significant increase in upper gastrointestinal bleeding compared to both SSRI alone and control groups.⁴ This has broad operational implications for long duration exploration class missions given the relative ubiquitous use of nonsteroidal anti-inflammatory drugs for analgesia during spaceflight activities.

Bone Density Effects of Spaceflight and SSRIs

Bone demineralization and reduced bone density are well established consequences of microgravity exposure and have consistently been observed in astronauts throughout the history of human spaceflight following mission completion. Although primarily a result of the loss of mechanical loading secondary to microgravity, other important factors have been implicated, including dietary factors such as high sodium and animal protein intake, increased ambient levels of carbon dioxide, and reduced 1, 25-Vitamin D conversion related to reduced sun exposure.¹⁶ Since 1998, NASA has medically required the use of dual X-ray absorptiometry (DXA) to screen and quantify areal bone density in astronauts given the risk of microgravity exposure to bone health and it has been extensively used to quantify bone losses from spaceflight in experimental studies.³⁵ Subsequent studies have also used high resolution peripheral quantitative computed tomography to study bone morphology and architecture by obtaining volumetric bone mineral density levels.¹³ Due to the morbid nature of the procedure, there is a paucity of data on bone loss in spaceflight that have used bone histomorphology for evaluation.

While there are many factors that may contribute to the bone loss associated with spaceflight and their implications, one important and underrecognized adverse effect of SSRI use is the inhibitory effect on normal bone remodeling. Ortuno *et al.* showed that the extent of SSRI use likely mediates its effect on bone mass.³⁴ In this rodent study, a dual mechanism of action was demonstrated where in short term use (3 wk), treatment with fluoxetine (Flx) resulted in a local antiresorptive response which increased bone mass; however, with prolonged use of Flx (6-wk use), a net loss of bone occurs which is mediated by a centrally triggered increase in sympathetic activity. Researchers studied wild-type female mice treated with either 3 wk or 6 wk of Flx to achieve levels comparable to therapeutic plasma levels in humans and observed its effect on long bones and vertebrae. They found that the mice treated with Flx for 3 wk had lower osteoclast surface, whereas bone formation rate and osteoblast surface were not affected. In contrast, mice treated with Flx for 6 wk had no effects on osteoclast surfaces; however, the osteoblast surface and bone formation rate were significantly lower. The second effect is associated with decreased serotonin signaling in the hypothalamus and increased sympathetic nervous system activity, which is mitigated by coadministration of low dose propranolol. Calarge *et al.* studied the skeletal effects of SSRI use on older adolescents by performing a 2-yr prospective study that examined bone density using whole body DXA and

lumbar spine DXA at study entry and every 8 mo and calculating volumetric bone mineral density at the nondominant radius using peripheral quantitative computed tomography at study entry and every 4 mo of participants ages 15–20 yr old.⁹ After adjusting for potential confounders such as depression severity, the researchers found that SSRI use was associated with increasing lumbar spine areal bone mineral density and bone formation in female participants, but decreasing lumbar spine areal bone mineral density in male participants. Haney *et al.* examined the link between SSRI use and reduced bone mineral density (BMD) in a review published in *Bone* in 2009.²¹ Several cross-sectional studies have suggested a link between lower BMD and SSRI use in both men and women. Longitudinal studies have also shown that SSRI users have a 1.6-fold greater decline in BMD compared to nonusers. An increase in fracture risk in SSRI users has also been noted in case-control studies done in large administrative datasets. However, mixed results have been noted when studying reduced BMD in association with increasing dose and duration of SSRI. Additionally, many studies have found that depression is an independent risk factor for decreased BMD, making it difficult to disentangle the causal relationship between SSRI and reduced BMD. Despite this, Haney *et al.* concluded that, based on the mounting evidence suggesting a causal relationship between reduced BMD and SSRI use, SSRIs should be listed among medications that contribute to the development of osteoporosis. Zhou *et al.* performed the first meta-analysis to study the relationship between SSRI use on BMD in 2018.⁵⁹ The researchers selected 11 studies that examined the effect of SSRI use on bone density and found that the use of SSRIs was significantly associated with lower BMD values of the lumbar spine, but not of the total hip or femoral neck. Additionally, SSRI use was associated with greater BMD loss in older people. Rawson *et al.* studied the effects of venlafaxine treatment in older adults with depression and found that levels of bone turnover products change in a pattern that suggests accelerated bone loss.⁴⁴ Although venlafaxine is a serotonin-norepinephrine reuptake inhibitor and not an SSRI, these findings suggest that further examination of its use in deep space missions is warranted given its inclusion in the ISS formulary.

With our visions set toward the lunar and Martian surfaces, the importance of strategies to mitigate and counter bone losses in spaceflight participants has become exceedingly important. While data regarding fracture risk in the microgravity environment have not been clearly elucidated given our limited operational experience, low incidence, and lack of generalizability of validated fracture risk assessment tools, there remains concern that clinically meaningful bone loss may occur in any exploration-class mission.³⁰ The long-term use of SSRIs potentially adds to and confounds this risk by introducing a pharmacological means of accelerating bone loss and should prompt further study into alternative methods for the treatment of anxiety, depression, and other mental health disorders where SSRIs may be historically indicated.

Neurocognitive Concerns for Long-Duration Spaceflight and SSRIs

The risks from SSRIs in long-duration spaceflight are not clear. A concern is whether use of SSRIs, separate from the underlying disease, will lead to neurocognitive impairment. Information available is limited. Most studies of SSRIs are in individuals with illness. We are unaware of studies of long-term use in healthy controls. In a study of 50 depressed patients followed for 8 wk, there was a significant ($P < 0.0001$) decline in Mini-Mental State Examination scores consistent with a decline in function during the first 2 mo of treatment.⁴⁷ In a 6-mo study of patients with depression or anxiety, 20% of the patients reported cognitive symptoms including fatigue, inattentiveness, decreased concentration, apathy, and memory difficulties.⁴⁰ In contrast to the above two studies, in a meta-analysis of 33 studies, no significant neurocognitive effects were observed in healthy individuals.⁴² In patients with depression, modest positive effects were observed, including executive function, divided attention, processing speed, recent memory, sustained attention, and divided attention.

Aeromedical regulators are concerned about aviators with untreated psychiatric disorders as well as the effects of an SSRI. In 2004, an Aerospace Medical Association report urged certification authorities to develop protocols to manage adverse effects from SSRIs and to consider their safe use in aviators without negative side effects.²⁶ Historically, the Federal Aviation Administration required neuropsychological testing of individuals taking SSRIs prior to granting a special issuance, out of concern the medications themselves may impact the aviator's performance. For many years, they also required routine retesting of aviators still taking SSRIs. With over a decade of experience, they found repeat neuropsychological testing did not yield useful information in the majority of aviators, so within the past year they ceased requiring routine neuropsychological retesting. They only require cognitive retesting if there are unique individual circumstances. As of the time of this paper, the Federal Aviation Administration, the United States' certification authority, allows the use of four specific SSRIs, monitoring aviators using cognitive testing, with an instrument specifically designed to assess aviator neurocognitive functions.⁵¹

There are obvious consequences of crewmembers experiencing common psychiatric illnesses with known neurocognitive effects during a long-term spaceflight. Some available research raises the possibility of negative neurocognitive

consequences from SSRIs while others do not. Operational medical decision making will need to balance crew selection while considering the known deleterious effects of illnesses such as depression and anxiety, and the possible effects of long-term SSRI usage.

Pharmacological Concerns for Spaceflight and SSRIs

Seven SSRIs are currently marketed in the United States: fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone, escitalopram, and citalopram. The last two, escitalopram and citalopram, are therapeutically the same drug because escitalopram is the (S)-enantiomer of racemic citalopram, and the therapeutic effects of citalopram are mediated by the escitalopram. Although all SSRIs have broadly similar antidepressant effects pharmacologically, they have important pharmacokinetic distinctions.

All SSRIs undergo significant hepatic metabolism as a step in their elimination from the body. Consequently, factors that affect their metabolism can have significant effects on drug exposure. The two greatest pharmacokinetic concerns are drug-drug interactions and gene polymorphisms of the liver cytochrome P450 (CYP) xenobiotic-metabolizing enzymes. CYP enzymes are responsible for metabolism of a large proportion of drug substances. Two isoenzymes in particular, CYP2D6 and CYP3A4, are responsible for metabolism of more than half of all orally effective drugs, including SSRIs.³⁹ In addition, some SSRIs undergo significant metabolism by isoenzymes CYP2C9 and CYP2C19 (**Table I**).

A common cause of drug-drug interactions is when one drug interferes with the metabolism of another. In the case of SSRIs, drugs that interfere with CYP2D6 can inhibit the metabolism of paroxetine, fluoxetine, and fluvoxamine. Similarly, interference with CYP2C19 can significantly increase exposure to citalopram, escitalopram, and sertraline. SSRIs may also affect the metabolism of other drugs. As shown in Table I, fluoxetine and paroxetine are inhibitors of CYP2D6, which can affect a broad array of drugs. Fluvoxamine, together with its metabolites, inhibits several important CYPs, making it especially prone to increasing exposure to other liver-metabolized drugs. Notably, citalopram, escitalopram, and sertraline are thought to have minimal effects on cytochrome P450 enzymes, which gives these SSRIs an advantage in the context of clinical polypharmacy. Gene polymorphisms are common contributors to variability in individual response to drug treatment and susceptibility to adverse effects. Many CYP genes are highly

Table I. Summary of Key Pharmacokinetic Characteristics of SSRIs.^{23,43,49}

SSRI	$t_{1/2}$	APPARENT Vd (L · kg ⁻¹)	LINEAR KINETICS	METABOLIZING ENZYMES	INHIBITED CYP
Citalopram	36 h	14–16	Yes	CYP2C19 , CYP3A4, CYP2D6	Minimal
Escitalopram	27–33 h	15	–	CYP2C19 , CYP2D6 , CYP3A4	Minimal
Fluoxetine	1 to 4 d	20–45	No	CYP2D6 , CYP2C9 , CYP2C19 CYP3A4	2D6
Fluvoxamine	15 h	5	No	CYP2D6 , CYP1A2	1A2, 2D6, (2C19)
Paroxetine	20 h	3–12	No	CYP2D6, catechol-O-methyltransferase,	2D6
Sertraline	26 h	20	Yes	CYP2C19 , CYP2D6, CYP3A4	Minimal

SSRI: selective serotonin reuptake inhibitor; $t_{1/2}$: half-life; Vd: apparent volume of distribution; CYP: cytochrome P450 enzymes.

Bolded CYPs indicate primary metabolism pathway; CYP enzymes in parentheses indicate indirect effects of metabolites.

polymorphic¹⁸ and allele frequency can vary substantially among racial and ethnic groups.⁴¹ For this reason, gene polymorphisms are an important clinical consideration as NASA strives to increase ethnic and racial diversity of the astronaut corps and the role of polymorphism should be seriously considered when selecting SSRIs for Earth-independent medical care. For example, CYP2D6 has a very large number of haplotypes that produce highly variable functional activity classified into four levels of activity ranging from poor to ultra-rapid metabolizers. The complete loss of CYP2D6 enzyme activity is rare in Asian populations, with a frequency of around 10% of the Caucasian, Hispanic, and African populations.^{8,43} Conversely, ultra-rapid metabolizer phenotypes are reported to be less than 5% of Caucasians and African Americans, but up to 30% of Ethiopians and Saudi Arabians.⁴³

Multiple studies have demonstrated that CYP2D6 ultrarapid metabolizers have low or undetectable paroxetine plasma concentrations, contributing to therapeutic failure of paroxetine and potentially fluvoxamine. For such individuals, it is reasonable to select an alternative SSRI that is not extensively metabolized by CYP2D6. Conversely, poor metabolizers have significantly greater exposures to paroxetine and fluvoxamine.^{11,22} Consequently, the product label contains caution for the use of these SSRIs in patients with reduced CYP2D6 activity.

CYP2C19, like CYP2D6, is also highly polymorphic, with a distribution of functional activity that varies according to ethnicity. For example, a nonfunctional allele is present in approximately 15% of Caucasians and Africans, and up to 30% of Asians. An ultra-rapid allele has a reported frequency of 16 to 21% among Caucasians and Africans but is rare among Asians. CYP2C19 ultrarapid metabolizers have significantly lower exposure to citalopram, escitalopram, and sertraline, and increased concentrations of these drugs have been observed in poor metabolizers, which may increase the risk of adverse drug reactions. Label dosing instructions for citalopram and sertraline (but not escitalopram) recommends reducing the starting dose by 50% in poor metabolizers or using an alternative SSRI not metabolized by CYP2C19 due to the risk of QT prolongation.²² Other CYP enzymes involved in SSRI metabolism may be rarely impacted by genetic polymorphisms (CYP3A4), or may have significant alterations in activity but play only a minor role in SSRI metabolism (i.e., CYP1A2, CYP2C9).

It is important for clinicians to be aware of the potential for drug-drug interactions and gene polymorphisms, particularly those that reduce SSRI metabolism. This knowledge enables clinicians to anticipate the need for adjusting a patient's dose or avoid particular products altogether. Since the U.S. FDA has already warned of the risks of QT changes and serotonin syndrome in individuals with reduced metabolism and package inserts contain warnings, particularly for poor metabolizers, the potential of drug-drug interactions and genetic polymorphisms should be anticipated prior to exploration missions.

Alternative Therapies to Consider

Many studies have been conducted to examine the efficacy of non-SSRI, alternative therapies for depression and anxiety. Transcranial magnetic stimulation (TMS) has been examined over the past several decades as a potential nonpharmacological therapy for depression. This therapy involves application of a strong, pulsed magnetic field to a region of the brain to induce local neuronal depolarization and generation of action potentials. Garnaat *et al.* noted that multiple meta-analyses found therapeutic benefit of low-frequency, high-frequency, and bilateral TMS for depression compared to sham.²⁰ Furthermore, three large multisite, sham-controlled randomized controlled trials confirmed these findings and found that TMS was effective as monotherapy for depression in treatment-resistant patients, setting the basis for FDA approval of the first TMS device for depression in 2008.²⁰ Given that many TMS protocols require sessions >30 min long, Bakker *et al.* conducted a study to examine the efficacy of shortened theta burst stimulation (iTBS) protocols and found comparable results to the longer TMS protocols.⁵ Blumberger *et al.* conducted a randomized, multicenter noninferiority study to compare the efficacy, safety, and tolerability of iTBS compared to standard 10-Hz rTMS and found iTBS to be noninferior in patients with treatment-resistant depression.⁷

Cranial electrotherapy stimulation (CES), or Alpha-Stim, is another alternative therapy for depression and anxiety that has been well studied over the years and uses small microcurrents which stimulate neurotransmitter activity in the brain to induce relaxation.⁷ Morriss *et al.* studied the cost effectiveness and efficacy of Alpha-Stim cranial electrotherapy stimulation in patients with moderate to severe generalized anxiety disorder and found that, in patients who did not respond to low intensity psychological treatment, Alpha-Stim CES may be effective after treatment and up to 3 mo later and is cost effective.³² Kirsch and Nichols published a review on the use of CES and concluded that it is an effective therapy with a side effect profile that is mild and self-limited that can be used as a first-line or adjuvant treatment for anxiety, depression, and insomnia and may have a role given its cost effectiveness and noninvasiveness compared to other neurostimulation techniques.²⁸

Transcranial ultrasound has also been examined as a non-invasive neuromodulation method that has many advantages over TMS such as being able to noninvasively target areas of the brain with precision, but a distinct advantage over TMS in that it can also target deeper areas of the brain. Animal studies by Zhang *et al.* have shown that low-intensity pulsed ultrasound can ameliorate depression-like behavior in rats and transcranial ultrasound has been hypothesized by Tsai to be an alternative treatment of major depressive disorder as a single or supplemental antidepressant therapy.^{52,58} Indeed, Reznik *et al.* explored this hypothesis by conducting a double-blind pilot study of transcranial ultrasound as a 5-d intervention and found that active delivery of transcranial ultrasound decreases worry after five sessions in patients with depression compared to placebo.⁴⁵

Other pharmacological therapies have also been examined for the management of anxiety and depression. One such treatment that has garnered increased attention in the psychiatric community is ketamine. Although intravenous ketamine has a relatively well-established antidepressant effect, oral, intramuscular, and sublingual formulations have been recently studied given its ease of administration. Rosenblatt *et al.* conducted a systematic review of the use of oral ketamine as a treatment for depression and found that, although the onset of action was not as rapid as with intravenous ketamine, oral ketamine was effective as an antidepressant, with good overall tolerability.⁴⁶ Sublingual ketamine has also been used with good results for patients who have required intravenous ketamine for the management of depression. McGirr *et al.* conducted a meta-analysis and systematic review of the literature to determine the efficacy of ketamine in major depressive episodes and found that single administrations of ketamine were efficacious in the rapid treatment of unipolar and bipolar depression.³¹ In fact, a systematic review and meta-analysis conducted by Witt *et al.* also found that single-dose ketamine was beneficial in acute suicidality as it has been shown to have short-term benefits on suicidal thoughts for up to 72 h.⁵⁶ However, significant concern continues to exist regarding the tolerability of ketamine for routine use as a treatment for depression. Indeed, Galvez *et al.* performed a randomized, double-blind, placebo-controlled pilot study to examine the efficacy and tolerability of intranasal ketamine for treatment-resistant depression, but found that intranasal ketamine was not a useful treatment for depression given its variable absorption and poor tolerability in the study participants.¹⁹ Nonetheless, ketamine is currently being deployed to the ISS for its anesthetic effects; therefore, exploration of off-label use may be warranted. Further study of these alternative therapies is indicated to explore their utility in spaceflight and other remote environments given the potential side effects of SSRIs previously noted.

DISCUSSION

With the renewed interest in deep space travel, planning of exploration class missions, and the likelihood of increased prevalence of psychiatric illness and mental health disorders in spaceflight participants, we must be ready to address and mitigate the risk of acute mental health issues arising in our spacefaring population. Although SSRIs have long been considered standard of care treatment for depression and anxiety, we cannot trivialize the risk that pharmacological therapy with SSRIs may pose to spaceflight participants given the well-documented adverse effects that may be encountered in long-term use. As humankind ventures beyond low Earth orbit and toward long-duration exploration class missions, the prolonged exposure to the microgravity environment has highlighted the necessity to mitigate the risk to bone health and reduced bone density. Although never tested experimentally, there is reason to hypothesize that the combination of SSRI use and prolonged microgravity exposure may

potentially contribute to additive effects on bone mineral density and hasten the deleterious effects of each factor on bone health. While countermeasures such as resistive exercise have been the mainstay of prevention, the ability to mitigate the combined risk of these additive, negative effects on bone health may be limited during deep space exploration missions given mission requirements and volume restrictions of potential space vehicles limiting accommodations of countermeasures hardware. Additionally, prolonged exposure to SSRIs may inhibit normal hemostatic function and pose operational risks to the astronaut and mission given a potential increased likelihood of bleeding complications related to trauma and injury during exploration class missions.

From a human health and performance perspective, the need to address our treatment algorithms for anxiety and depression as we travel into deep space cannot be understated. As we begin to integrate the medical and psychological needs of an increasingly commercialized spaceflight enterprise, the need to test and develop alternative pharmacological and nonpharmacological therapies on anxiety and depression will be necessary to treat these conditions without exposing our spaceflight participants to the potential adverse effects of SSRI therapy.

The space medicine community must anticipate the challenges of the human system as we venture into deep space and develop risk mitigation strategies to the various health effects that the spaceflight participant will face. Although currently the standard of care for the treatment of anxiety and depression, SSRIs possess various side effects that the astute space medicine provider must consider when developing treatment plans for use in the microgravity environment, especially with prolonged use. Although the benefits of treatment with short-term and terrestrial use may outweigh the risks, our risk matrices may necessitate adjustment when exploring more prolonged use in the microgravity environment. With the rapid growth of the commercial spaceflight industry and imminent return to the Moon, we cannot be complacent with ensuring the human system is prepared for the physiological and psychological challenges that await. The time to explore other alternative pharmacological and nonpharmacological therapies is now.

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