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A Review of the Safety of Selective Serotonin Reuptake Inhibitors for Long Duration Spaceflight

Charles H. Dukes
KBR
Houston, TX

Bashir B. El-khoury
University of Texas Medical Branch
Galveston, TX

Kristi L. Ray
University of Texas Medical Branch
Galveston, TX

John F. Reichard
NASA Johnson Space Center
Houston, TX

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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 (ICE) environment that lies outside the boundaries of low-earth orbit. Currently, selective serotonin reuptake inhibitors (SSRIs) are considered the gold standard treatment for many mental health diagnoses including anxiety and depression; however, SSRIs are also associated with several undesired side effects. The utility of non-pharmacologic therapies for the management of behavioral health conditions has not yet been fully explored.

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 non-pharmacologic treatments for anxiety and depression were reviewed. Over 100 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. Many non-pharmacologic therapies have been utilized with success for the management of behavioral health conditions in the terrestrial environment that 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 pharmacologic therapy may pose. The need to mitigate these risks by exploring alternative non-pharmacologic therapies has never been more relevant.

Keywords: Selective serotonin reuptake inhibitors; spaceflight; behavioral health; stressors

Introduction

As humankind continues to venture further into the depths of space, planning is already underway for long- duration exploration missions that will test the bounds of human performance. With this in mind, the aerospace medicine community has been fast at work developing preventative strategies and risk mitigation plans to optimize this performance and 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.[4] 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.[19] 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)[69]. Currently, SSRIs are considered the gold standard treatment for many mental health diagnoses including anxiety and depression.[30] 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 non-pharmaceutical therapeutic strategies that might be considered to prepare, prevent, and mitigate mental health stressors from long duration space travel. Additionally, this paper will review the evidence gleaned from the literature studying mental health in isolated and confined environments (ICE). 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 countermeasures. Moving forward, increased emphasis will be placed on mental health prevention and mitigation strategies including the use of pharmaceuticals and other non-pharmacologic alternatives as new cases of serious mental health problems arise on long duration missions.

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 post-mortem. Investigators found that 5-HT levels were 19% lower in the hind-brains of patients who had diagnoses of depression or "probably depressed" when compared to control subjects[55]. 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[69]. 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[26]. 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[26]. 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, 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,

post-traumatic stress disorder, and social anxiety disorder[13]. 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 utilization of SSRIs for use in the spaceflight environment, we must first review the history of psychiatric disease in aviation and spaceflight analog environments and their 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 (SI) 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 non-depression related condition for which a SSRI is used. The 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 months with no side effects that would affect aviation operations. Diagnoses of psychosis and suicidal and/or homicidal ideation are not considered for waiver. In addition, treatments including electroconvulsive therapy, treatments with concurrent multiple SSRIs, or a multi agent drug protocol are also considered not appropriate for issuance of a waiver.

Although never used, SSRIs are part of the onboard US 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 utilized; however, due to communication delays, other platforms such as virtual reality and a behavioral health dashboard are being 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.

The risks from SSRIs in long-duration space flight 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 fifty depressed patients followed for eight weeks, there was a significant ($p < 0.0001$) decline in Mini-Mental State Examination scores consistent with a decline in function during the first two months of treatment[54]. In a six-month study of patients with depression or anxiety, twenty percent of the patients reported cognitive symptoms including fatigue, inattentiveness, decrease concentration, apathy, and memory difficulties[46]. In contrast to the above two studies, in a meta-analysis of 33 studies, no significant neurocognitive effects were observed in healthy individuals[48]. 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 the 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[29]. As of the time of this paper, the Federal Aviation Administration, the USA certification authority, allows the use of four specific SSRIs, monitoring aviators using recurrent cognitive testing, with an instrument specifically designed to assess aviator neurocognitive functions[64].

These assessments are used to determine if the airman should be issued a medical certificate and to develop a database to assess aeromedically-significant consequences of long-term SSRI usage. The major shortcomings of all studies are the limited duration of follow-up, weeks or months, while clinically usage is months to years.

There are obvious consequences of crew members experiencing common psychiatric illnesses with known neurocognitive effects during a long-term space flight. Some available research raises the possibility of negative neurocognitive consequences from SSRIs while other 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 usages.

Anxiety and Depression 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 analogues 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[15,16,27].

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[43]. 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[73]. Additionally, Palinkas et al. determined that

the incidence of mood disorders, adjustments 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 South Pole between 1994 and 1997[44]. 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[70]. 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.

Despite these findings, pre-deployment screening is unlikely to fully mitigate the risk of clinically significant mental health issues during long duration space travel. The "third quarter phenomenon" has been well described in the literature and is characterized by a decline in performance during operations in the ICE environments[68]. It has also been associated with crewmember attitudes of initial anxiety, mid-mission depression, and late mission euphoria[52]. Similarly, in military populations, isolation and feelings of powerlessness were associated with increased stress and complaints of anxiety and depressed mood[8]. However, studies of spaceflight and spaceflight analog missions have demonstrated a lack of significant evidence of a "third quarter phenomenon" experienced by subjects within these environments[31].

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. found that although overall self-reported negative emotions have been found to be low in spaceflight, long duration space simulation analogs, and polar environments, broad-based assessments may not detect symptoms of anxiety and depression whereas more novel measures of emotion may be better suited[1]. These negative emotions can potentially have significant operational impacts on human performance making improved diagnostic testing a clinical necessity. The impact of these negative emotions can have medical implications as well. In a simulated mountain climb, climbers that showed greater sensitivity to environmental changes, including altitude sickness, also had higher levels of anxiety[39]. 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 (HI-SEAS) Mars analog facility, and the Human Exploration and Research Analog (HERA) at NASA's Johnson Space Center[3,9,12,38,62]. Several studies conducted within these analog environments have shown that exposed subjects may be at increased risk for development of depression, stress, and anxiety. 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[42].

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 non-pharmacologic treatments for anxiety and depression were reviewed. Specifically, articles that referenced the hematologic side effects of SSRIs, effects of SSRIs on bone mineral density, and pharmacologic effects of SSRIs were reviewed. Over 70 studies were reviewed in total.

Results:

Hematologic Effects of Spaceflight and SSRIs

The hematologic adaptation (astronaut anemia) to spaceflight has been recognized for several decades as an important clinical entity that has gained an increasing amount of recognition as a potential serious concern for orbital spaceflight. During the Gemini program, this was originally felt to be related to oxidative injury to the red blood cells due to the hypobaric hyperoxic environment[63]. However, even in sea level orbital environments, observed changes in red blood cells remained. The underlying mechanism involves a decrease in RBC mass which occurs secondary to the decrease in plasma volume that follows exposure to the microgravity environment in order to maintain normal hemoconcentration[2]. Trudel et al. found that in a group of fourteen astronauts on the ISS, exposure to spaceflight was associated with persistently increased levels of products of hemoglobin degradation, alveolar air carbon monoxide levels, and serum iron levels compared to baseline preflight levels indicating persistent erythrocytosis. Surprisingly, even one year post-landing, these erythrocytic effects persisted[65]. This is

hypothesized to be caused by a suppression of erythropoiesis, likely related to weightlessness resulting in increased marrow adipose tissue accumulation due to lack of bone stimulation in space.

Additional hematologic effects of spaceflight in astronauts including potential thrombotic risks as a result of microgravity remain unclear. In astronauts taking combined oral contraceptives, there may be an increased risk of developing venous thrombosis and possible embolism in the space environment. In a recent study, longitudinal health data of female astronauts were examined for pre and post flight hematological and biochemical blood markers to determine any potential trends for increased risk of venous thromboembolism (VTE). The study showed no evidence suggesting elevated VTE risk in female astronauts associated with spaceflight, regardless of contraceptive use[28]. Despite these findings, however, there was a documented venous thrombosis that occurred in a female astronaut during a long duration mission.[6] As a result, routine screening protocols for VTE have been implemented aboard the ISS for surveillance and risk assessment.

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. Although SSRIs are not likely to exacerbate the risks of thrombosis associated with long duration spaceflight, the operational impacts to impaired hemostatic function is no less consequential. 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[67]. Meta-analysis revealed an association between SSRI use and increased risk of severe bleeding (OR: 1.41, 1.27-1.57). Severe bleeding was defined as the need for prompt intervention of a healthcare professional or re-operation after surgery. The estimated increase in risk of bleeding was on average 36% in this meta analysis[33]. 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 non-steroidal anti-inflammatory drugs (NSAIDs), subjects had a significant increase in upper gastrointestinal bleeding compared to both SSRI alone and control groups.[5] This has broad operational implications for long duration exploration class missions given the relative ubiquitous use of NSAIDs for analgesia during spaceflight activities.

SSRIs and Bone Density

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. [18]. 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[41]. Subsequent studies have also used high resolution peripheral quantitative computed tomography (HR-pQCT) to study bone morphology and architecture by obtaining volumetric bone mineral density levels[14]. 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.

Leblanc et al. found that crewmembers on the Mir station flying multi-month missions lost BMD at average monthly rate of 0.3% from total skeleton compared to preflight values using magnetic resonance imaging (MRI) and DXA (97% of loss came from pelvis and legs)[34]. The etiology of bone loss in microgravity is likely due to an increased rate of bone resorption in the setting of an unchanged to slightly decreased level of bone formation[56]. Urinary hydroxyproline and urinary levels of collagen cross-links, markers of bone resorption, were noted to be >33% and >100% respectively over preflight values in some studies[58]. Gabel et al. used HR-pQCT to determine effects of microgravity on bone architecture of 17 astronauts before and after spaceflight. In this study, all astronauts were supplied Vitamin D3 800 IU

daily and exercise was conducted in-flight nearly daily consisting of treadmill, cycle ergometer, and ARED (advanced resistive exercise device). The investigators found that tibia volumetric bone mineral density (vBMD) declined by 0.9% per month of spaceflight without changes noted at radius consistent with prior studies. Additionally, the investigators noted that higher circulating biomarkers of bone resorption and formation preflight predicted higher bone losses in subjects[20].

To maintain calcium homeostasis and prevent bone resorption, calcium losses must not exceed intake. However, studies in microgravity have shown astronauts to be consistently in negative calcium balance. Smith et al. studied three male astronauts before, during and after long duration spaceflight and found that subjects lost ~250 mg bone calcium/day and regained bone calcium at a slower rate of ~100 mg/day[60]. Alterations in vitamin D metabolism also occur in the microgravity environment. Pre-vitamin D3 is formed in skin by the action of UV light on 7-dehydrocholesterol, and without adequate oral intake and sunlight exposure, vitamin D deficiency will ensue. The decreased body stores of 25-OH vitamin D noted in 84-day Skylab mission, 115-day Mir mission, and longer ISS missions led to increased oral supplementation in subsequent missions.

Additionally, compared to the Earth's atmosphere (~0.03%), carbon dioxide levels on the ISS are significantly increased due to the active scrubbing processes employed (~0.7-1.0%). The carbonates and phosphates found in bone serve to neutralize this acid load. Acidosis is a well-established cause of increased bone resorption. A study by Drummer et al. demonstrated that subjects who were exposed to 0.7% and 1.2% ambient CO2 levels were noted to have increased levels of bone turnover products[17]. High sodium diet is also a well described cause of increased calciuresis. Given that calcium reabsorption in the proximal tubule is coupled with sodium reabsorption, a higher concentration of filtered sodium may, in fact, predispose individuals to hypercalciuria. That being said, data suggests that sodium intake was likely high on Space Shuttle trips (>4 gm/day)[71]. High sodium diet may also predispose to kidney stones and potentiate further urinary calcium losses. High protein diets may also increase the acid load causing increased need for skeletal buffering, and as a result, bone loss. A review by Smith et al. noted residents on ISS had salt intakes exceeding >5 gm/day on average with individual

intakes up to 12 gm/day[59]. Another study by Heer et al. noted varied sodium intakes in D-2 and EuroMIR missions ranging from 45 to 462 mEq/day[57]. Efforts have been made in recent years to reduce the salt content of food consumed by astronauts while still preserving its shelf life and storage capabilities.

Having previously summarized the 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[40]. In this rodent study, a dual mechanism of action was demonstrated where in short term use (3 weeks), treatment with fluoxetine (Flx) resulted in a local anti-resorptive response which increased bone mass; however, with prolonged use of Flx (6 week 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 weeks or 6 weeks 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 three weeks had lower osteoclast surface whereas bone formation rate and osteoblast surface were not affected. In contrast, mice treated with Flx for six weeks had no effects on osteoclast surfaces whereas 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 co-administration of low dose propranolol. Calarge et al. studied the skeletal effects of SSRI use on older adolescents by performing a two-year prospective study that examined bone density using whole body DXA and lumbar spine DXA at study entry and every 8 months and calculating vBMD at non-dominant radius using pQCT at study entry and every 4 months of participants aged 15-20 years old[11]. After adjusting for potential confounders such as depression severity, the researchers found that SSRI use was associated with increasing lumbar spine (LS) aBMD and bone formation in female participants, but decreasing LS aBMD in male participants. Haney et al. examined the link between SSRI use and reduced BMD in a review published in *Bone* in 2009[24]. 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 non-users. An increase in fracture risk in SSRI users have 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. conclude 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[75]. 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 pattern that suggests accelerated bone loss, making the need for further larger controlled studies to examine these effects[50].

With our visions set towards the lunar and Martian surfaces, the importance of mitigation 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 (i.e. FRAX), there remains concern that clinical meaningful bone loss may occur in any exploration-class mission[35]. The long-term use of SSRIs potentially adds to and confounds this risk by introducing a pharmacologic 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.

Pharmacologic Considerations of SSRIs

Seven selective serotonin reuptake inhibitors (SSRIs) are currently marketed in the US: 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 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[45]. In addition, some SSRIs undergo significant metabolism by isoenzymes CYP2C9, 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 also common contributors to individual response to drug efficacy and susceptibility to adverse effects. Many CYP genes are highly polymorphic[21]. CYP2D6, for example, has a

very large number of haplotypes that produce widely variable functional activity, which are classified into four phenotypes ranging from poor metabolizer to ultra-rapid metabolizers. Ethnicity plays an important role in CYP2D6 activity[47]. The frequency of CYP2D6 polymorphisms are rare in Asian populations, while around 10% of the Caucasian, Hispanic, and African populations have a complete loss of activity[49]. Conversely, the ultra-rapid metabolizer phenotype is reported to be less than 5% of Caucasians and African Americans, but up to 30% of Ethiopians and Saudi Arabians[49]. CYP2C19, like CYP2D6, is also highly polymorphic with a distribution of functional activity that varies according to ethnicity. For example, a non-functional allele is present in approximately 15% in 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. 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 awareness 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 US FDA has already warned of the risks of QT changes and serotonin syndrome in individual 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.

Table I. Summary of key pharmacokinetic characteristics of SSRIs[25,49,61]							
SSRI		$t_{½}$	Apparent Vd (L/kg)	Linear kinetics	Metabolizing enzymes	Inhibited CYPs	Source
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 CYPCYP3A	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	
Abbreviations: t½, Half-life; Vd, apparent volume of distribution; CYP, cytochrome P450 oxidoreductase; Bolded CYPS indicate primary metabolism pathway; CYP enzymes in parentheses indicate indirect effects of metabolites.							

Non-Pharmacologic Adjuvant Therapies

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 non-pharmacologic 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[23]. Furthermore, three large multisite, sham-controlled randomized controlled trials (RCTs) 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[23]. Given that many of TMS protocols require sessions >30 minutes 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[7]. Blumberger et al. conducted a randomized, multicenter non-inferiority study to compare the efficacy, safety, and tolerability of iTBS compared to standard 10 Hz rTMS and found iTBS to be non-inferior in patients with treatment-resistant depression.

Cranial electrotherapy stimulation (CES), or Alpha-Stim, is another alternative therapy for depression and anxiety that has been well studied over the years which utilizes small microcurrents which stimulate neurotransmitter activity in the brain to induce relaxation[10]. Morriss et al. studied the cost effectiveness and efficacy of Alpha stim cranial electrotherapy stimulation in patients with moderate to severe generalized anxiety disorder (GAD) 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 three months later and is cost effective[37]. Kirsch and Nichols published a review on the use of cranial electrotherapy stimulation (CES) and concluded that CES is an effective therapy that can be used as a first-line or adjuvant treatment for anxiety, depression and insomnia that may have a role given its cost-effectiveness and non-invasiveness compared to other neurostimulation techniques with a side effect profile that is mild and self-limited[32].

Transcranial ultrasound has also been examined as a noninvasive 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 MDD as a single or supplemental antidepressant therapy[66,74]. Indeed, Reznik et al. explored this hypothesis by conducting a double-blind pilot study of transcranial ultrasound (TUS) as a five-day intervention and found that active delivery of TUS decreases worry after five sessions in patients with depression compared to placebo[51].

Other pharmacologic 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. Rosenblat 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[53]. 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 ketamine were efficacious in the rapid treatment of unipolar and bipolar depression[36]. 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 hours.[72] However, significant concern continues to exist regarding the tolerability of ketamine for routine use as 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[22]. 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.

Additionally, non-pharmacologic treatment modalities for long duration missions could include various platforms such as virtual reality or the use of autonomous cognitive behavioral therapy modules to promote a sense of connectedness to earth and provide flexibility for psychological support when communication is delayed or abraded.

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 pharmacologic therapy with SSRIs may pose to spaceflight participants given the well-documented adverse effects that may be encountered. As humankind ventures beyond low earth orbit and towards 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 pharmacologic and non-pharmacologic therapies on anxiety and depression will be necessary to treat these conditions without exposing our spaceflight participant 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 gold standard 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 physiologic challenges that await. The time to explore other alternative pharmacologic and non-pharmacologic therapies is now.

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References

1. Alfano CA, Bower JL, Cowie J, Lau S, Simpson RJ. Long-duration space exploration and emotional health: Recommendations for conceptualizing and evaluating risk. Acta Astronautica. 2018; 142:289–99

2. Alfrey CP, Udden MM, Leach-Huntoon C, Driscoll T, Pickett MH. Control of red blood cell mass in spaceflight. Journal of Applied Physiology. 1996; 81(1):98–104

3. Anderson AP, Fellows AM, Binsted KA, Hegel MT, Buckey JC. Autonomous, Computer-Based Behavioral Health Countermeasure Evaluation at HI-SEAS Mars Analog. Aerospace Medicine and Human Performance. 2016; 87(11):912–20

4. Anglin KM, Kring JP. Lessons from a Space Analog on Adaptation for Long-Duration Exploration Missions. Aerospace Medicine and Human Performance. 2016; 87(4):406–10

5. Anglin R, Yuan Y, Moayyedi P, Tse F, Armstrong D, Leontiadis GI. Risk of Upper Gastrointestinal Bleeding With Selective Serotonin Reuptake Inhibitors With or Without Concurrent NonSteroidal Anti-Inflammatory Use: A Systematic Review and Meta-Analysis. American Journal of Gastroenterology. 2014; 109(6):811–9

6. Auñón-Chancellor SM, Pattarini JM, Moll S, Sargsyan A. Venous Thrombosis during Spaceflight. N Engl J Med. 2020; 382(1):89–90

7. Bakker N, Shahab S, Giacobbe P, Blumberger DM, Daskalakis ZJ, Kennedy SH, et al. rTMS of the dorsomedial prefrontal cortex for major depression: safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. Brain Stimul. 2015; 8(2):208–15

8. Bartone PT, Adler AB, Vaitkus MA. Dimensions of Psychological Stress in Peacekeeping Operations. Military Medicine. 1998; 163(9):587–93

9. Basner M, Dinges DF, Mollicone DJ, Savelev I, Ecker AJ, Di Antonio A, et al. Psychological and Behavioral Changes during Confinement in a 520-Day Simulated Interplanetary Mission to Mars. PLoS ONE. 2014; 9(3):e93298

10. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet. 2018; 391(10131):1683–92

11. Calarge CA, Mills JA, Janz KF, Burns TL, Schlechte JA, Coryell WH, et al. The Effect of Depression, Generalized Anxiety, and Selective Serotonin Reuptake Inhibitors on Change in Bone Metabolism in Adolescents and Emerging Adults. J Bone Miner Res. 2017; 32(12):2367–74

12. Carrère S, Evans GW, Stokols D. Winter-Over Stress: Physiological and Psychological Adaptation to an Antarctic Isolated and Confined Environment. In: Harrison AA, Clearwater YA, McKay CP, eds. From Antarctica to Outer Space. New York, NY: Springer New York; 1991:229–37.

13. Chu A, Wadhwa R. Selective Serotonin Reuptake Inhibitors. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022

14. Collet Ph, Uebelhart D, Vico L, Moro L, Hartmann D, Roth M, et al. Effects of 1- and 6-month spaceflight on bone mass and biochemistry in two humans. Bone. 1997; 20(6):547–51

15. Colodro J, Garcés-de-Los-Fayos EJ, López-García JJ, Colodro-Conde L. Incremental Validity of Personality Measures in Predicting Underwater Performance and Adaptation. Span J Psychol. 2015; 18:E15

16. Deppe AH. Performance criteria in diver training. Percept Mot Skills. 1971; 32(3):718

17. Drummer C, Friedel V, Börger A, Störmer I, Wolter S, Zittermann A, et al. Effects of elevated carbon dioxide environment on calcium metabolism in humans. Aviat Space Environ Med. 1998; 69(3):291–8

18. Fettman MJ. Dietary instead of pharmacological management to counter the adverse effects of physiological adaptations to space flight. Pflügers Arch - Eur J Physiol. 2000; 441(S1):R15–20

19. Flynn CF. An operational approach to long-duration mission behavioral health and performance factors. Aviat Space Environ Med. 2005; 76(6 Suppl):B42-51

20. Gabel L, Liphardt A-M, Hulme PA, Heer M, Zwart SR, Sibonga JD, et al. Pre-flight exercise and bone metabolism predict unloading-induced bone loss due to spaceflight. Br J Sports Med. 2022; 56(4):196–203

21. Gaedigk A, Ingelman-Sundberg M, Miller NA, Leeder JS, Whirl-Carrillo M, Klein TE, et al. The Pharmacogene Variation (PharmVar) Consortium: Incorporation of the Human Cytochrome P450 (CYP) Allele Nomenclature Database. Clin Pharmacol Ther. 2018; 103(3):399–401

22. Gálvez V, Li A, Huggins C, Glue P, Martin D, Somogyi AA, et al. Repeated intranasal ketamine for treatment-resistant depression - the way to go? Results from a pilot randomised controlled trial. J Psychopharmacol. 2018; 32(4):397–407

23. Garnaat SL, Yuan S, Wang H, Philip NS, Carpenter LL. Updates on Transcranial Magnetic Stimulation Therapy for Major Depressive Disorder. Psychiatr Clin North Am. 2018; 41(3):419–31

24. Haney EM, Warden SJ, Bliziotes MM. Effects of selective serotonin reuptake inhibitors on bone health in adults: time for recommendations about screening, prevention and management? Bone. 2010; 46(1):13–7

25. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. Pharmacol Ther. 2000; 85(1):11–28

26. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: from monoamines to glutamate. Exp Clin Psychopharmacol. 2015; 23(1):1–21

27. Huang JL, Ryan AM, Zabel KL, Palmer A. Personality and adaptive performance at work: a meta-analytic investigation. J Appl Psychol. 2014; 99(1):162–79

28. Jain V, Ploutz-Snyder R, Young M, Charvat JM, Wotring VE. Potential Venous Thromboembolism Risk in Female Astronauts. Aerosp Med Hum Perform. 2020; 91(5):432–9

29. Jones DR, Ireland RR. Aeromedical regulation of aviators using selective serotonin reuptake inhibitors for depressive disorders. Aviat Space Environ Med. 2004; 75(5):461–70

30. Joshi A. Selective Serotonin Re-uptake Inhibitors: An overview. Psychiatr Danub. 2018; 30(Suppl 7):605–9

31. Kanas N, Gushin V, Yusupova A. Whither the Third Quarter Phenomenon? aerosp med hum perform. 2021; 92(8):689–91

32. Kirsch DL, Nichols F. Cranial electrotherapy stimulation for treatment of anxiety, depression, and insomnia. Psychiatr Clin North Am. 2013; 36(1):169–76

33. Laporte S, Chapelle C, Caillet P, Beyens M-N, Bellet F, Delavenne X, et al. Bleeding risk under selective serotonin reuptake inhibitor (SSRI) antidepressants: A meta-analysis of observational studies. Pharmacol Res. 2017; 118:19–32

34. LeBlanc A, Schneider V, Shackelford L, West S, Oganov V, Bakulin A, et al. Bone mineral and lean tissue loss after long duration space flight. J Musculoskelet Neuronal Interact. 2000; 1(2):157–60

35. Licata AA. Challenges of Estimating Fracture Risk with DXA: Changing Concepts About Bone Strength and Bone Density. Aerospace Medicine and Human Performance. 2015; 86(7):628–32

36. McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychol Med. 2015; 45(4):693–704

37. Morriss R, Xydopoulos G, Craven M, Price L, Fordham R. Clinical effectiveness and cost minimisation model of Alpha-Stim cranial electrotherapy stimulation in treatment seeking patients with moderate to severe generalised anxiety disorder. J Affect Disord. 2019; 253:426–37

38. Neigut J. Overview of the Human Exploration Research Analog (HERA). Prague: National Aeronautics and Space Administration; 2015

39. Nicolas M, Thullier-Lestienne F, Bouquet C, Gardette B, Gortan C, Joulia F, et al. An anxiety, personality and altitude symptomatology study during a 31-day period of hypoxia in a hypobaric chamber (experiment 'Everest-Comex 1997'). J Environ Psychol. 1999; 19(4):407–14

40. Ortuño MJ, Robinson ST, Subramanyam P, Paone R, Huang Y-Y, Guo XE, et al. Serotonin-reuptake inhibitors act centrally to cause bone loss in mice by counteracting a local anti-resorptive effect. Nat Med. 2016; 22(10):1170–9

41. Orwoll ES, Adler RA, Amin S, Binkley N, Lewiecki EM, Petak SM, et al. Skeletal health in long-duration astronauts: Nature, assessment, and management recommendations from the NASA bone summit: SKELETAL HEALTH IN LONG-DURATION ASTRONAUTS. J Bone Miner Res. 2013; 28(6):1243–55

42. Palinkas LA, Browner D. Effects of Prolongea Isolation in Extreme Environments on Stress, Coping, and Depression1. J Appl Social Pyschol. 1995; 25(7):557–76

43. Palinkas LA, Cravalho M, Browner D. Seasonal variation of depressive symptoms in Antarctica. Acta Psychiatr Scand. 1995; 91(6):423–9

44. Palinkas LA, Glogower F, Dembert M, Hansen K, Smullen R. Incidence of psychiatric disorders after extended residence in Antarctica. International Journal of Circumpolar Health. 2004; 63(2):157–68

45. Parkinson A, Ogilvie BW, Buckley DB, Kazmi F, Czerwinski M, Parkinson O. Biotransformation of Xenobiotics. In: Casarett and Doull's Toxicology: The Basic Science of Poisons, 8e. New York, NY: McGraw-Hill Education; 2012

46. Popovic D, Vieta E, Fornaro M, Perugi G. Cognitive tolerability following successful long term treatment of major depression and anxiety disorders with SSRi antidepressants. J Affect Disord. 2015; 173:211–5

47. Porcelli S, Fabbri C, Spina E, Serretti A, De Ronchi D. Genetic polymorphisms of cytochrome P450 enzymes and antidepressant metabolism. Expert Opinion on Drug Metabolism & Toxicology. 2011; 7(9):1101–15

48. Prado CE, Watt S, Crowe SF. A meta-analysis of the effects of antidepressants on cognitive functioning in depressed and non-depressed samples. Neuropsychol Rev. 2018; 28(1):32–72

49. Probst-Schendzielorz K, Viviani R, Stingl JC. Effect of Cytochrome P450 polymorphism on the action and metabolism of selective serotonin reuptake inhibitors. Expert Opinion on Drug Metabolism & Toxicology. 2015; 11(8):1219–32

50. Rawson KS, Dixon D, Civitelli R, Peterson TR, Mulsant BH, Reynolds CF, et al. Bone Turnover with Venlafaxine Treatment in Older Adults with Depression. J Am Geriatr Soc. 2017; 65(9):2057–63

51. Reznik SJ, Sanguinetti JL, Tyler WJ, Daft C, Allen JJB. A double-blind pilot study of transcranial ultrasound (TUS) as a five-day intervention: TUS mitigates worry among depressed participants. Neurology, Psychiatry and Brain Research. 2020; 37:60–6

52. Rohrer JH. Human adjustment to Antarctic isolation. Washington DC: Georgetown Univ; 1960.

53. Rosenblat JD, Carvalho AF, Li M, Lee Y, Subramanieapillai M, McIntyre RS. Oral Ketamine for Depression: A Systematic Review. J Clin Psychiatry. 2019; 80(3):18r12475

54. Sayyah M, Eslami K, AlaiShehni S, Kouti L. Cognitive Function before and during Treatment with Selective Serotonin Reuptake Inhibitors in Patients with Depression or Obsessive-Compulsive Disorder. Psychiatry J. 2016; 2016:5480391

55. Shaw DM, Camps FE, Eccleston EG. 5-Hydroxytryptamine in the hind-brain of depressive suicides. Br J Psychiatry. 1967; 113(505):1407–11

56. Smith SM, Heer M. Calcium and bone metabolism during space flight. Nutrition. 2002; 18(10):849–52

57. Smith SM, Heer M, Shackelford LC, Sibonga JD, Spatz J, Pietrzyk RA, et al. Bone metabolism and renal stone risk during International Space Station missions. Bone. 2015; 81:712–20

58. Smith SM, Nillen JL, Leblanc A, Lipton A, Demers LM, Lane HW, et al. Collagen cross-link excretion during space flight and bed rest. J Clin Endocrinol Metab. 1998; 83(10):3584–91

59. Smith SM, Rice BL, Dlouhy H, Zwart SR. Assessment of Nutritional Intake During Space Flight and Space Flight Analogs. Procedia Food Science. 2013; 2:27–34

60. Smith SM, Wastney ME, Morukov BV, Larina IM, Nyquist LE, Abrams SA, et al. Calcium metabolism before, during, and after a 3-mo spaceflight: kinetic and biochemical changes. Am J Physiol. 1999; 277(1 Pt 2):R1-10

61. Solhaug V, Haslemo T, Kringen MK, Molden E, Dietrichs ES. Genotyping of patients treated with selective serotonin reuptake inhibitors. Tidsskriftet. 2022

62. Tafforin C. Time effects, cultural influences, and individual differences in crew behavior during the Mars-500 experiment. Aviat Space Environ Med. 2013; 84(10):1082–6

63. Tavassoli M. Anemia of spaceflight. Blood. 1982; 60(5):1059–67

64. Taylor JL, O'Hara R, Mumenthaler MS, Yesavage JA. Relationship of CogScreen-AE to flight simulator performance and pilot age. Aviat Space Environ Med. 2000; 71(4):373–80

65. Trudel G, Shahin N, Ramsay T, Laneuville O, Louati H. Hemolysis contributes to anemia during long-duration space flight. Nat Med. 2022; 28(1):59–62

66. Tsai S-J. Transcranial focused ultrasound as a possible treatment for major depression. Med Hypotheses. 2015; 84(4):381–3

67. Turner MS, May DB, Arthur RR, Xiong GL. Clinical impact of selective serotonin reuptake inhibitors therapy with bleeding risks. J Intern Med. 2007; 261(3):205–13

68. Van Wijk CH. Coping During Conventional Submarine Missions: Evidence of a Third Quarter Phenomenon? Journal of Human Performance in Extreme Environments. 2018; 14(1)

69. Vaswani M, Linda FK, Ramesh S. Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. Prog Neuropsychopharmacol Biol Psychiatry. 2003; 27(1):85–102

70. Weybrew BB, Noddin EM. Psychiatric aspects of adaptation to long submarine missions. Aviat Space Environ Med. 1979; 50(6):575–80

71. Whitson PA, Pietrzyk RA, Pak CYC. RENAL STONE RISK ASSESSMENT DURING SPACE SHUTTLE FLIGHTS. Journal of Urology. 1997; 158(6):2305–10

72. Witt K, Potts J, Hubers A, Grunebaum MF, Murrough JW, Loo C, et al. Ketamine for suicidal ideation in adults with psychiatric disorders: A systematic review and meta-analysis of treatment trials. Aust N Z J Psychiatry. 2020; 54(1):29–45

73. Wright MW, Chylinski J, Sisler GC, Quarrington B. Personality factors in the selection of civilians for isolated northern stations: A follow-up study. Canadian Psychologist / Psychologie canadienne. 1967; 8a(1):23–31

74. Zhang J, Zhou H, Yang J, Jia J, Niu L, Sun Z, et al. Low-intensity pulsed ultrasound ameliorates depression-like behaviors in a rat model of chronic unpredictable stress. CNS Neurosci Ther. 2021; 27(2):233–43

75. Zhou C, Fang L, Chen Y, Zhong J, Wang H, Xie P. Effect of selective serotonin reuptake inhibitors on bone mineral density: a systematic review and meta-analysis. Osteoporos Int. 2018; 29(6):1243–51

Table I: Summary of key pharmacokinetic characteristics of SSRIs

Table I. Summary of key pharmacokinetic characteristics of SSRIs[25,49,61]							
SSRI		$t_{½}$	Apparent Vd (L/kg)	Linear kinetics	Metabolizing enzymes	Inhibited CYPs	Source
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 CYPCYP3A	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	

Abbreviations: t½, Half-life; Vd, apparent volume of distribution; CYP, cytochrome P450 oxidoreductase;
Bolded CYPS indicate primary metabolism pathway; CYP enzymes in parentheses indicate indirect effects of metabolites.