A Psychiatric Formulary for Long-Duration Spaceflight

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INTRODUCTION: Behavioral health is essential for the safety, well-being, and performance of crewmembers in both human spaceflight and Antarctic exploration. Over the past five decades, psychiatric issues have been documented in orbital spaceflight. In Antarctica, literature suggests up to 5% of wintering crewmembers could meet criteria for a psychiatric illness, including mood disorders, stressor-related disorders, sleep-wake disorders, and substance-related disorders. Experience from these settings indicates that psychiatric disorders on deep space missions must be anticipated. An important part of planning for the psychological health of crewmembers is the onboard provision of psychotropic drugs. These medications have been available on orbital missions. A greater variety and supply of these drugs exist at Antarctic facilities. The size and diversity of a deep space psychiatric formulary will be greater than that provided on orbital missions. Drugs to be provisioned include anxiolytics, antidepressants, mood stabilizers, antipsychotics, and hypnotics. Each drug category should include different medications, providing diverse pharmacokinetic, pharmacodynamic, and side effect profiles. The formulary itself should be rigorously controlled, given the abuse potential of some medications. In-flight treatment strategies could include psychological monitoring of well-being and early intervention for significant symptoms. Psychiatric emergencies would be treated aggressively with behavioral and pharmacological interventions to de-escalate potentially hazardous situations. On long-duration space missions, a robust psychiatric formulary could provide crewmembers autonomy and flexibility in treating a range of behavioral issues from depression to acute psychosis. This will contribute to the safety, health, and performance of crewmembers, and to mission success.

KEYWORDS: psychiatry, psychology, behavioral, drugs, medications, disorders, recommendations, pharmaceuticals.

Friedman E, Bui B. *A psychiatric formulary for long-duration spaceflight*. Aerosp Med Hum Perform. 2017; 88(11):1024–1033.

Psychiatric health is a central part of planning human missions on the frontiers of exploration. Over the past 60 yr, behavioral experience from Antarctica and near-Earth space has provided a foundation for anticipating psychiatric issues on future missions into deep space. That experience indicates the need for a robust onboard psychiatric formulary, which will allow crewmembers autonomy and flexibility in treating psychiatric conditions ranging from depression to acute psychosis and delirium. This will significantly contribute to the safety, health, and performance of crewmembers, and to mission success in deep space.

Behavioral Experience in Antarctica

The frontier of human exploration for over a century, Antarctic behavioral experience is a useful analog for spaceflight. Isolation, confinement, cold temperatures, limited daylight exposure, and dependence on technology for survival make Antarctic facilities a laboratory for psychiatric health, one which has produced over 50 yr of formal behavioral studies.

Studies have revealed common psychological symptoms among people living and working in Antarctica. Among these are somatic symptoms (fatigue, headaches, gastrointestinal complaints), sleep disruption (loss of slow-wave and REM sleep), impaired cognition (memory, vigilance, attention, reasoning, mild fugue state, i.e., "Antarctic stare"), negative affect (depressed mood, anxiety, anger, irritability), and interpersonal stressors.[35] This pattern of symptoms has been referred to as "winter over syndrome," noted as a subclinical syndrome, akin to subclinical depression.[23] The frequency of symptoms is underscored by a survey conducted of personnel at McMurdo

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This manuscript was received for review in April 2017. It was accepted for publication in August 2017.

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DOI: https://doi.org/10.3357/AMHP.4901.2017

Station in Antarctica during the 1989 winter season, in which 64.1% of people reported difficulty with sleep, 62.1% reported feeling depressed, 51.5% reported difficulties with concentration or memory, and 47.6% reported feeling more irritable than usual.[33]

Symptoms severe enough to meet criteria for psychiatric disorders, while lower in incidence than the U.S. general population, are of significant concern in Antarctica, where medical evacuation is not possible for part of the year. In the 1960s, Gunderson et al. found that 3% of U.S. Navy personnel stationed at Antarctic facilities developed psychiatric disorders, three times the rate elsewhere, underscoring the importance of psychological screening.[18] Studies on the Australian National Antarctic Research Expeditions by Lugg et al. in the 1970s show a 1–5% incidence of psychiatric disorders, as a percentage of total morbidity, in crewmembers who had undergone prior medical and psychological screening.[26] In the 1990s, Palinkas et al. assessed incidence of psychiatric disorders in over 300 civilian and military crewmembers at two Antarctic research stations over a 3-yr period.[34] All crewmembers had undergone medical and psychological screening prior to stationing in Antarctica. After weighting for low participation in civilian personnel, psychiatric debriefings conducted at the end of the Antarctic winter revealed that 5.2% of crewmembers endorsed symptoms that met criteria for at least one Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) defined disorder. As listed in **Table I**, mood disorders comprised 30.2% ($N = 13$) of all diagnoses, followed by adjustment disorders (27.9%, $N = 12$), sleep-related disorders (20.9%, $N = 9$), personality disorders (11.6%, $N = 5$), and substance-related disorders (9.3%, $N = 4$). Depressive symptoms were significantly associated with several variables, including military occupation and female gender.[34] Data related to medication use were not included in the study.

With psychiatric symptoms and disorders documented among personnel, it is important that Antarctic facilities carry psychoactive medications. A diverse psychiatric formulary allows on-site treatment of psychiatric symptoms and disorders, including depression, anxiety, psychosis, substance intoxication, and withdrawal. A recent list of psychotropic medications provided by the Center for Polar Medical Operations being carried on formulary at McMurdo Station, Amundsen Scott Station, and Palmer Station for the U.S. Antarctic Program includes multiple psychotropics, including two selective serotonin reuptake inhibitor (SSRI) antidepressants (citalopram and fluoxetine), one norepinephrine dopamine reuptake inhibitor antidepressant (bupropion), one tricyclic antidepressant (amitriptyline), one anxiolytic (buspirone), three atypical antipsychotics (olanzapine, quetiapine, and risperidone), and one conventional antipsychotic (haloperidol).[32] A similar list provided by the British Antarctic Survey includes one SSRI antidepressant (fluoxetine), one tricyclic antidepressant (amitriptyline), three benzodiazepine anxiolytics (diazepam, lorazepam, midazolam), two anticonvulsant/mood stabilizers (carbamazepine, gabapentin), one anticholinergic agent (procyclidine), one nonbenzodiazepine hypnotic (eszopiclone), and one conventional antipsychotic (chlorpromazine) [Hicks A, British Antarctic Survey Medical Unit. Personal communication; February 10, 2017]. Both Antarctic psychiatric formulary lists are contained in **Table II**. When choosing components of a psychiatric formulary for long-duration space missions, these on-site psychotropics at Antarctic facilities are useful to consider.

Despite the advantages to using Antarctica as a behavioral analog for spaceflight, there are significant differences

Table I. Unadjusted and Weighted Prevalence (per 100 People Debriefed) of DSM-IV Disorders in the U.S. Antarctic Program After an Austral Winter.[35]

DSM-IV DIAGNOSIS	NUMBER OF CASES	RATE PER 100 DEBRIEFED	WEIGHTED RATE PER 100
Mood disorders	13	4.2	1.7
Major depressive disorder, single episode	6	1.9	0.8
Major depressive disorder, recurrent	2	0.6	0.3
Dysthymic disorder	1	0.3	0.1
Depressive disorder not otherwise specified	4	1.3	0.5
Personality disorders	5	1.6	0.5
Schizoid personality disorder	2	0.6	0.3
Dependent personality disorder	2	0.6	0.3
Personality disorder not otherwise specified	1	0.3	0.1
Substance-related disorders	4	1	1
Alcohol dependence	2	0.6	0.3
Cannabis abuse	1	0.3	0.1
Alcohol abuse	1	0.3	0.1
Sleep disorders	9	2.9	1.1
Circadian rhythm sleep disorder	9	2.9	1.1
Adjustment disorders	12	3.8	1.6
Adjustment disorder with depr. mood	6	1.9	0.8
Adjustment disorder with anxiety	2	0.6	0.3
Adjustment disorder with mixed emotion	2	0.6	0.3
Adjustment disorder unspecified	2	0.6	0.3
Total DSM-IV disorders	39	12.5	5.2

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Adjusted for differences between military or civilian status, age, and sex of participants in debriefing and all expedition members.

Table II. Psychotropic Drugs at U.S. and British Antarctic Facilities.[32]

PSYCHOTROPIC DRUGS LISTED IN ANTARCTICA*
Antipsychotics
Chlorpromazine
Haloperidol
Olanzapine
Quetiapine
Risperidone
Antidepressants
Amitriptyline
Bupropion
Citalopram
Fluoxetine
Anxiolytics and anticholinergics
Buspirone
Diazepam
Diphenhydramine
Lorazepam
Midazolam
Procyclidine
Mood stabilizers
Carbamazepine
Sleep agents
Eszopiclone

* Hicks A, British Antarctic Survey Medical Unit. Personal communication; February 10, 2017.

that might not be generalizable to a long-duration mission. These include limitation of Antarctic assignments to 1 yr, as well as differing environmental hazards, crew size, and crew characteristics. One way of addressing these differences has been the conduct of deep space mission simulations on Earth.

Behavioral Experience on the Mars 500 Project

One such terrestrial space mission analog is a recent simulation of a 520-d mission to Mars, conducted by the Russian Academy of Sciences. Replicating the isolated and confined environment (ICE) conditions of long-duration spaceflight with an internationally diverse crew of six men, the mission included regular documentation of behavioral parameters. Using such psychological measures as the Beck Depression Inventory and the Profile of Mood States–Short Form, it was found that one crewmember (16%) reported depressive symptoms and three (50%) endorsed signs of confusion-bewilderment.[6] Most crewmembers experienced some disturbance of sleep quality and sleep-wake cycle, and vigilance deficits. One (16%) experienced a sleep onset insomnia that worsened during the simulation.[5] Upon review, behavioral data from the full 520-d simulation indicated that only two crewmembers (33%) had reported no behavioral disturbances. Information regarding medication use was voluntarily submitted by crewmembers, but was unavailable for review by unaffiliated investigators [Basner M, Unit for Experimental Psychiatry, University of Pennsylvania Perelman School of Medicine. Personal communication, March 27, 2017]. Both the Antarctic and simulated space mission analogs, each with their own strengths and limitations, have played important roles in analyzing and planning countermeasures for behavioral issues documented over the past six decades of human spaceflight.

Behavioral Experience and Risk Estimates in Spaceflight

In assessing the role of psychiatric issues in spaceflight, it is important to note the psychological screening of astronaut applicants by space agencies. Screening is intended to identify and disqualify applicants with current or prior psychiatric disorders, traits, behaviors, or relevant psychiatric family history, features with the potential to endanger crew safety and mission success. Screening consists of detail structured psychiatric interviews (based upon the DSM or ICD classification systems), as well as clinical psychological testing with standardized instruments.

Despite thorough screening procedures, behavioral issues have affected orbital space missions since the 1970s. This has been documented by both the American and Soviet/Russian space programs. During the Skylab 4 mission in 1973, the crew was sometimes characterized as irritable and hostile toward ground control. During that 84-d mission, the crew ceased cooperating with ground control at one point and conducted a daylong work stoppage.[19] In 1976, the Soyuz-21 mission to the Salyut-5 space station was terminated early after 49 d in orbit due to crew complaints of an overwhelming acrid odor. Subsequent Salyut-5 crews did not notice an odor, suggesting that this might have been an instance of a shared delusion.[13] In 1982, cosmonaut Valentin Lebedev recorded struggles with self-seclusion, depressed mood, and friction with his crewmate during a 211-d mission on the Salyut-7 space station.[25] A 2011 anecdotal report from the Russian Pravda news service apparently indicates hallucinations were reported in 1984 by the crew of the 62-d Soyuz T-10 mission to Salyut-7. These symptoms have been theorized as possibly being caused by toxins in the station's atmosphere.[46] In 1985, the planned 6-mo Soyuz T-14 mission to Salyut-7 was ended emergently after 65 d in orbit due to a cosmonaut complaining of fatigue and genitourinary symptoms that were thought to have had a psychosomatic component.[10] The mission was later assessed by Russian psychologists as having been terminated due to "mood and performance issues."[9] In 1987, the 174-d Soyuz TM-2 mission, which launched the Mir space station, was apparently terminated early—perhaps due to psychological issues along the crew.

Published studies have formally analyzed documented and estimated incidence rates of on-orbit psychiatric symptoms, which are summarized in **Table III**. During 89 Space Shuttle missions (1981–1998), 34 behavioral symptoms were reported among 208 crewmembers. From a total of over 4400 person-days in space, these findings accounted for an incidence rate of 0.11 per 14 d, extrapolated to 2.87 per person-year. Most common among reported symptoms were anxiety and irritability.[8] Two of the seven (29%) NASA astronauts who flew on Mir (1995–1998) reported depressive symptoms, an incidence of 0.77 per person-year.[27] From the 45 NASA astronauts who flew on 41 expeditions to the International Space Station (ISS) (2000–2014), only one behavioral event (the unexpected death of an astronaut's parent) was noted to be severe enough to potentially affect the mission.[7]

Behavioral data and incidence rates have also been recorded in the NASA Lifetime Surveillance of Astronaut Health (LSAH)

Table III. Actual and Estimated Incidence Rates of Psychiatric Symptoms During Spaceflight.

DATA SOURCE	PSYCHIATRIC FINDINGS	INCIDENCE PER PERSON-YEAR
Shuttle program, 1981–1998[8]	Anxiety, irritability symptoms	2.87
NASA astronauts on Mir, 1995–1998[27]	Depressive symptoms	0.77
LSAH data, Shuttle program[31]	Anxiety symptoms	0.832
LSAH data, Shuttle program[31]	Depressive symptoms	0.139
IMM risk estimates[29]	DSM-defined anxiety disorder	0.0071 F, 0.0019 M
IMM risk estimates[29]	DSM-defined depressive disorder	0.0036 F, 0.0029 M
IMM risk estimates[29]	Emergency (depression/anxiety)	0.000087 to 0.000324
Stuster risk estimates for Mars mission[44]	Serious psychiatric symptoms	0.626 short stay (661 d); 0.534 long stay (905 d)
Stuster risk estimates for Mars mission[44]	Serious psychiatric symptoms	0.652 short stay (661 d); 0.893 long stay (905 d)

Data is derived from documented spaceflight experience and statistical extrapolation.[8,27,29,31,44]

and Integrated Medical Model (IMM) databases. LSAH data derived from Flight Surgeon or Crew Surgeon notes during Space Shuttle missions, comprising over 28 person-years of spaceflight, documented 24 occurrences of anxiety symptoms, an incidence rate of 0.832 cases per person-year. The same data set showed four astronauts as endorsing depressive symptoms, an incidence of 0.139 per person-year.[31] It has been speculated that behavioral incidence rates may be underestimated due to astronaut reluctance to report symptoms for fear of negatively affecting their flight status.[3]

It is important to distinguish behavioral symptoms (as noted above) and behavioral illness that comprises a disorder. IMM behavioral spaceflight data, consisting of depression and anxiety findings that meet DSM criteria for psychiatric diagnoses, show that no active NASA astronaut has, to date, been diagnosed with a DSM-defined disorder. The IMM also estimates risk of depressive and anxiety psychiatric disorders in astronauts based on observed incidence rates in the U.S. general population. IMM incidence rates for anxiety disorders is 0.0071 per person-year for female astronauts and 0.0019 for male astronauts. For depressive disorders, incidence rates are 0.0036 per person-year for women and 0.0029 per person-year for men. These IMM incidence rates have also been extrapolated over the approximately 120 person-year history of NASA spaceflight, suggesting an 85.2% probability that a case meeting DSM criteria for an anxiety disorder has occurred sometime in the historical pool of female astronauts, with that probability being 22.8% for male astronauts. For a depressive disorder, this corresponds to a 43.2% chance for the female astronaut pool and 34.8% for male astronauts.[29]

IMM risk estimates for in-flight psychiatric emergencies due to anxiety or depressive symptoms leading to crewmember incapacitation and severe mission impact range from 0.000087 to 0.000324 cases per person-year. As the duration of the mission increases, the risk of such an event is assumed to increase.[29] There have been criticisms that the IMM behavioral risk estimates are overstated, due to potential behavioral differences between the U.S. general population and the astronaut corps, who are psychologically screened prior to admission.

Behavioral risk estimates have also been applied to long-duration mission scenarios. As described in a 2016 report by the NASA Human Research Program, Stuster used Antarctic behavioral data to extrapolate psychiatric symptom incident rates for planned Mars missions.[44] Two six-crewmember mission scenarios were considered, one lasting 661 d with a short stay on the Martian surface, and the other 905 d in duration with a longer surface stay. A 6% per person-year incidence rate of serious psychiatric problems was used during interplanetary transit and 2% during surface operations. The lower incidence rate on the Martian surface assumes mitigation of risk from less confinement and the salutary emotional impact of exploring a new world. The risk of serious psychiatric symptoms, equivalent to those necessitating psychiatric hospitalization on Earth, was calculated at 0.626 for the short surface stay Mars mission, and 0.534 for the longer surface stay option. It was also noted that with a constant incidence rate of 6% throughout the mission, the longer surface stay mission would confer a greater risk (0.893) than the short stay option (0.652).

Psychopharmaceutical Use On-Orbit

In light of the behavioral issues documented in astronaut screening, on-orbit, and corresponding risk estimates of psychiatric symptoms and disorders, it is important to examine actual astronaut usage of psychiatric medications during space missions. Data collected during the Space Shuttle and ISS programs reveal that most on-orbit psychotropic use has been related to pervasive sleep deficiency. From astronaut debriefings in 79 Space Shuttle missions (1981–1996), it was found that 44.7% of all medications (comprising the largest number of drug doses given for any single indication) were taken for sleep disturbances. The sleep medications used most frequently were the benzodiazepine hypnotics temazepam (67%), triazolam (10%), flurazepam (7.5%), and the nonbenzodiazepine hypnotic zolpidem (10%).[36]

From an observational study investigating sleep and hypnotic use in 85 astronauts on the Space Shuttle and ISS missions (2001–2011), 78% of Shuttle crewmembers reported taking a sleep agent in flight.[4] Sleep aids were used on 500 (52%) of 963 in-flight nights, with two doses taken on 17% (87) of those 500 nights. Sleep agent use was reported on 60% of nights prior to an extravehicular activity (EVA). On four Shuttle missions in which all crewmembers participated in the study, all crewmembers reported taking sleep aids on the same night 6% of the time. On analysis, total sleep time was not significantly affected by sleep aid use and sleep efficiency was increased by just 1.3%. Of the 21 ISS crewmembers who participated in this study, 75% reported use of sleep agents. Sleep aids were reported on 11% (96) of 852 ISS sleep logs, with 19% of those reporting use of two doses. Notably, over a third ($N = 8$) of participating ISS crewmembers declined to provide information about sleep aid use at some point during their mission.

ISS psychotropic use was also documented in a study examining overall medication use by 24 crewmembers (2002–2012) during 20 missions averaging 159 d.[49] Sleep agents comprised the largest number of dosages used for any one indication. Sleep aid use was reported by 71% of crewmembers, with 10% of hypnotic use prior to a schedule shift and 3% taken prior to an EVA. Most sleep medications (83%) were taken on ordinary nights. The most commonly used sleep agents were zolpidem, zaleplon, or both. Wake-promoting agents (the ISS stocks caffeine and modafinil) were used on 12 occasions by 5 crewmembers, 4 of these being associated with a schedule shift and 2 with an EVA. From these Shuttle and ISS data, 2.568 sleep aid uses per crewmember were calculated for the ISS and 1.767 uses per crewmember for Shuttle missions.

These drug usage studies bring special attention to widespread incidence of astronaut sleep disturbance and its potential hazards. Not only is sleep restriction itself associated with neurobehavioral performance deficits, but chronic use of sleep-promoting agents also carries its own risks. Sleep aids can impair functioning of crewmembers, although zolpidem and zaleplon have been carefully studied and approved for flight crew who require sleep medication. The use of these agents, while an important resource for managing sleep deficiency, must be carefully regulated. On the ISS, significant nonpharmacological measures have been taken to improve crewmembers' duration and quality of sleep, including diurnal wavelength-adjusted LED lighting and scheduling adjustments for sleep time.

When reviewing the occurrence of psychiatric symptoms and psychotropic usage in spaceflight and in terrestrial analogs, it is interesting to examine the psychoactive medications currently carried aboard the ISS. As listed in **Table IV**, the ISS medical kit includes one SSRI antidepressant (sertraline), one serotonin and norepinephrine reuptake inhibitor antidepressant (venlafaxine extended-release), two atypical antipsychotics (aripiprazole and ziprasidone), two benzodiazepines (diazepam and lorazepam), three sleep agents (melatonin, zaleplon, and zolpidem), two wake-promoting agents (caffeine and modafinil), and one antihistamine/anticholinergic agent (diphenhydramine) [Beven G, Space Medicine Operations Division, NASA Johnson Space Center, Houston, TX. Personal communication; January 6, 2017].[15] This array of medications provides coverage for psychiatric issues on-orbit, a situation in which a return to Earth during a psychiatric emergency is an option. For future long-duration missions, in which an immediate return to Earth is not possible, a more extensive psychiatric formulary (similar to that carried at Antarctic facilities) will be required to treat a range of both acute and chronic psychiatric issues.

Table IV. Psychotropic Medications Held on the ISS.[15]

PSYCHOTROPIC DRUGS HELD ON ISS*
Antidepressants
Sertraline
Venlafaxine
Antipsychotics
Aripiprazole
Ziprasidone
Anxiolytics & anticholinergics
Diazepam
Diphenhydramine
Lorazepam
Sleep agents
Melatonin
Zaleplon
Zolpidem
Wake agents
Caffeine
Modafinil

* Beven G, Space Medicine Operations Division, NASA Johnson Space Center, Houston, TX. Personal communication; January 6, 2017.

Effects of the Space Environment on Pharmaceuticals

Prior to making definitive recommendations for a deep space psychiatric formulary, the potential effects of microgravity and the space environment on the pharmacokinetics, pharmacodynamics, and storage of pharmaceuticals must be considered. Astronaut reporting has documented some apparent alteration in drug efficacy on orbital missions.[36,48] In light of limited pharmacological experience with empirical microgravity-based research, efforts are currently being made to intensify this field of study, with a range of projects examining physiology and drug efficacy for long-duration missions. Oral bioavailability of drugs could be altered by microgravity-mediated factors, including changes in gastric emptying and gut microflora.[37,40] Cephalad fluid shifts and changes in the volume of distribution may alter organ perfusion, affecting hepatic first-pass metabolism of many drugs, including SSRI antidepressants.[17] Changes in gastric drug dissolution and gastrointestinal absorption, noted with ibuprofen in human studies with simulated microgravity (bed rest), could also change prescription recommendations for other medications.[20] Studies using simulated microgravity have also demonstrated an apparent advantage in bioavailability to intramuscular promethazine over oral administration. This might be further investigated in other agents, including psychoactive drugs.[16]

Researchers have begun to examine multiyear stability of pharmaceuticals stored on orbit. Du et al. measured the active pharmaceutical content (API) of 35 diverse drugs from identical medical kits stored for 28 mo on the ISS or on Earth.[12] Results were calculated from a single sample of each drug. It was observed that 9 drugs from the ISS and 17 from the ground met the U.S. Pharmacopeia acceptance criteria for API content. A higher percentage of medications from the ISS kits had lower API content than each respective ground control. The rate of degradation appeared to be faster in space than on the ground for some medications. Psychoactive medications examined in this study included sertraline and temazepam. In **Fig. 1**, unpublished data reveals that these two psychoactive medications exhibited slightly increased potency loss after storage on the ISS when compared with ground control samples. Notably, the percent API loss per 100 d measured for sertraline was 1.62 on the ISS vs. 1.12 on the ground, and the temazepam percent API loss measured 2.01 on the ISS vs. 1.67 on the ground.[30]

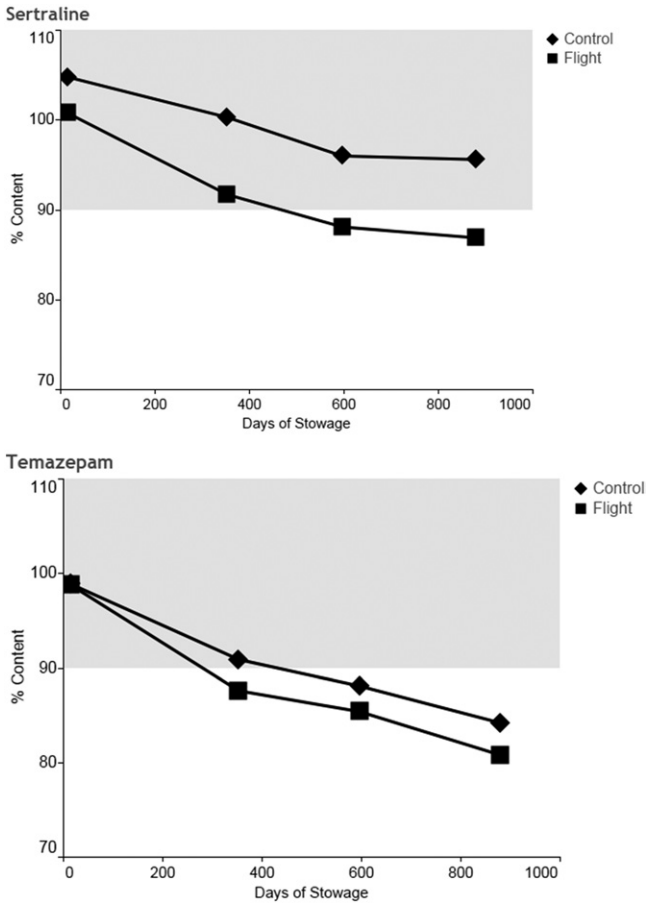

Fig. 1. Degradation of active pharmaceutical content (API) in sertraline and temazepam samples stowed on the International Space Station (squares) or on Earth (diamonds). Shaded area represents U.S. Pharmacopeia range for label claim. From a single sample of each drug.[12,30]

In another pharmaceutical stability study, Wotring examined the API content of nine medications from unused ISS supplies stored for 550 d on orbit.[48] Due to the opportunistic acquisition of the samples, only one timepoint was available, without controls. From the limited data available, it appeared that the ISS-stored drugs, including the psychotropics zolpidem and modafinil, exhibited degradation consistent with U.S. Pharmacopeia standards. Modafinil exhibited 100.6% of the label claim of 200 mg per tablet at 2 mo prior to its manufacturer expiration date. Zolpidem, analyzed at 9 mo beyond its expiration date, was also found to contain 100.6% of its label claim of 10 mg per tablet. According to the 2016 Pharmacology Risk Report by the NASA Human Research Program, there remains a need for research into pharmaceutical stability on long-duration missions, including potential roles for radioprotection and cryopreservation of drugs.[22]

In addition to space-based pharmacological effects, the impact of pharmacogenetics on drug efficacy is another important area to consider when planning a deep space psychiatric formulary. A recent study found that 24 (31%) of 78 drugs available on the ISS (in 2014) were significantly affected by polymorphic metabolizing enzymes.[43] Psychoactive drugs metabolized by the highly polymorphic cytochrome P450 enzyme (CYP450) 2D6 included aripiprazole, sertraline (also affected by CYP450 2C19), and venlafaxine. Additionally, CYP450 2C19 substrates included diazepam and zolpidem (although not included in the study, modafinil is also a CYP450 2C19 substrate). As there are significant interethnic differences in CYP450 2D6 and CYP450 2C19 drug metabolism, pharmacogenetic testing of astronauts could help determine both genotype-specific dosing changes and provision of medications on long-duration missions.[21]

A Psychiatric Formulary & Treatment Strategies for Long-Duration Spaceflight

In compiling a psychiatric formulary for long-duration spaceflight, it is useful to refer to guidelines originally published by Santy and, more recently, by Flynn regarding provision of psychotropic medications for space-based facilities.[14,41] Suggested categories of psychotropic drugs included anxiolytics, antidepressants, mood stabilizers, antipsychotics, and hypnotics. Recommendations were made for each drug class to be represented by multiple medications, in order to provide a range of pharmacokinetic, pharmacodynamic, and side effect profiles. It was mentioned that the formulary itself should be carefully maintained to safeguard the medications. In accordance with these principles, a candidate psychiatric formulary suitable for deep space missions is listed in **Table V**. Included for each proposed medication are psychiatric indications and common side effects.[42] Such a formulary would be equipped to treat a range of acute and chronic psychiatric scenarios, which we will further explore below.

During long-duration missions, psychiatric formulary use would take place within a comprehensive behavioral health program for crewmembers. In mission planning, scenarios with longer surface stays (i.e., on the Moon and Mars) could be favored to potentially mitigate the rigors of extended ICE habitation.[44] Preflight psychological testing and education could emphasize psychosocial skills, which could be periodically refreshed in flight via computer education. An open and supportive command environment would help address psychological issues among crewmembers as they emerge. Personal communication with family and friends via email and videos would be encouraged.[24] Duration and quality of sleep would be improved with diurnal wavelength-adjusted lighting, mitigation of noise, and sleep time scheduling.

Psychiatric treatment approaches would include periodic psychological assessment by a qualified crewmember and early treatment intervention for symptoms of psychiatric disorders. Treatment could incorporate both psychotherapy options (e.g., supportive therapy, cognitive behavioral therapy, interpersonal therapy) and psychotropic medications. Psychiatric emergencies would be treated aggressively with behavioral interventions and medication to de-escalate potentially hazardous situations. Physical restraints and a predesignated seclusion/close observation area would be available if needed.

When reviewing behavioral experience in spaceflight and its terrestrial analogs, certain psychiatric disorders and scenarios appear more relevant to long-duration missions. As listed in

Table V. Proposed Psychiatric Formulary Suitable for Long-Duration Space Missions.[38,42]

DRUG	PSYCHIATRIC INDICATIONS	COMMON SIDE EFFECTS
Antidepressants		
Bupropion	Major Depressive DO, Seasonal Affective DO	Dry mouth, constipation, nausea
Ketamine	Treatment-resistant depression (investigational)	Confusion, hallucinations
Mirtazapine	Major Depressive DO	Sedation, dry mouth, constipation
Paroxetine	Major Depressive DO, Panic DO, PTSD, General Anxiety DO, OCD	GU, GI, dry mouth, sedation, constipation
Venlafaxine	Major Depressive DO, General Anxiety DO, Panic DO	GI, GU, headache
Antipsychotics		
Aripiprazole	Acute agitation/mania, Bipolar DO, Schizophrenia, Depression adjunct	GI, dizziness, insomnia, activation, akathisia
Haloperidol	Acute psychosis/agitation, Bipolar DO, Schizophrenia	Sedation, dry mouth, akathisia, EPS
Olanzapine	Schizophrenia, Acute agitation/mania, Bipolar DO, Schizophrenia	Sedation, dry mouth, constipation, weight gain, diabetes
Ziprasidone	Acute agitation/psychosis/mania, Bipolar DO, Schizophrenia	Sedation, dizziness, dry mouth, nausea
Anxiolytics and Anticholinergics		
Benztropine	EPS, Acute dystonia	Confusion, dry mouth, nausea, constipation
Buspirone	Anxiety DOs, Acute anxiety	Dizziness, HA, sedation
Clonidine	Acute anxiety, PTSD, Substance withdrawal	Dry mouth, dizziness, sedation, constipation
Diazepam	Anxiety DOs, Acute anxiety, Substance WD	Sedation, fatigue, confusion, disinhibition
Diphenhydramine	EPS, Acute dystonia	Sedation, dry mouth, dizziness, nausea
Hydroxyzine	Acute anxiety, Sedation, Agitation, Substance WD	Sedation, dry mouth, tremor
Lorazepam	Anxiety DOs, Serotonin Syndrome, NMS, Akathisia, Substance WD	Sedation, fatigue, confusion, disinhibition
Prazosin	Nightmares associated with PTSD	Dizziness, headache, fatigue
Propranolol	Akathisia, Anxiety	Bradycardia, hypotension, dizziness, GU
Mood Stabilizers		
Divalproex	Acute mania, Mixed episodes, Bipolar DO	Sedation, nausea, hepatotoxicity, TCP, pancreatitis
Sleep agents		
Melatonin	Insomnia in Sleep-wake DOs	Sedation
Trazodone	Insomnia in Sleep-wake DOs, Depression, Anxiety	Sedation, dizziness, HA
Zolpidem	Insomnia in Sleep-wake DOs	Sedation, dizziness, ataxia, anxiety, amnesia
Wake-promoting agents		
Caffeine	Somnolence in Sleep-wake DOs	Anxiety, diarrhea, insomnia
Modafinil	Somnolence in Sleep-wake DOs	Anxiety, HA, insomnia

DO: disorder; PTSD: posttraumatic stress disorder; OCD: obsessive compulsive disorder; GU: genitourinary; GI: gastrointestinal; EPS: extrapyramidal symptoms; HA: headache; WD: withdrawal; NMS: neuroleptic malignant syndrome; TCP: thrombocytopenia.

Table VI, these include sleep-wake disorders (circadian rhythm sleep-wake disorder and insomnia disorder), depressive disorders (major depressive disorder with seasonal pattern and substance/medication-induced depressive disorder), trauma and stressor-related disorders (adjustment disorder, acute stress disorder, and posttraumatic stress disorder), anxiety disorders (panic disorder), and schizophrenia spectrum and other psychotic disorders (brief psychotic disorder and substance/medication-induced psychotic disorder). Psychiatric emergencies that have been noted in analog environments should be considered relevant to long-duration space missions, including delirium, agitation, substance intoxication and withdrawal, serotonin syndrome, and neuroleptic malignant syndrome.

Two of these scenarios, circadian rhythm sleep-wake disorder and agitation, will be chosen here for closer examination. Relevant DSM-5 disorder criteria, psychiatric treatment options, and treatment algorithms will be listed here for reference.[11,39,45]

Circadian rhythm sleep-wake disorder as defined by DSM-5 is a persistent/recurrent pattern of sleep disruptions, primarily due to an alteration of the circadian system or to a misalignment between the endogenous circadian rhythm and the sleep-wake schedule required by the physical environment or social/professional schedule. The sleep disruption leads to excessive sleepiness or insomnia, or both, and causes clinically significant distress or impairment in social, occupational, and other areas of functioning. Treatment consists of both nonpharmacological and pharmacological options.[1,28] Initial interventions include planned sleep schedules (adjusting work schedules) and timed light exposure (adjusting the timing, brightness, and/or wavelength of lighting). Medication-based treatments include timed melatonin administration and other sleep agents such as hydroxyzine, diphenhydramine, trazodone, and zolpidem. See **Fig. 2** for an algorithm concept for circadian rhythm, sleep-wake disturbance.

Agitation is a psychiatric emergency defined as a state of poorly organized and aimless psychomotor activity, stemming from physical or emotional unease. Signs and symptoms include motor restlessness, hyperactivity, irritability, increased mood lability, decreased sleep, and uncooperative or inappropriate behavior. Agitation may occur in different psychiatric settings, including delirium, psychosis, anxiety, depression, mania, substance intoxication and/or withdrawal, and

Table VI. DSM-5 Psychiatric Disorders and Psychiatric Emergencies to be Anticipated on Long-Duration Space Missions.[11]

DSM-5 PSYCHIATRIC DISORDERS IN DEEP SPACE
Anxiety disorders
Panic disorder
Depressive disorders
Major depressive disorder with seasonal pattern
Substance/medication-induced depressive disorder
Schizophrenia spectrum and other psychotic disorders
Brief psychotic disorder
Substance/medication- induced psychotic disorder
Sleep-wake disorders
Circadian rhythm sleep-wake disorder
Insomnia disorder
Trauma and stressor-related disorders
Adjustment disorder
Acute stress disorder
Posttraumatic stress disorder
Psychiatric emergencies in deep space
Agitation
Delirium
Neuroleptic malignant syndrome
Serotonin syndrome
Substance intoxication and withdrawal

medication side effects. Management of an agitated psychiatric patient consists of simultaneous behavioral, environmental, and pharmacological interventions.[2,47] Initial behavioral and environmental interventions include empathic interaction with the patient, removal of potentially dangerous objects, and relocating the patient to a seclusion/close observation area in order to decrease external stimuli. Initial pharmacological interventions include administration of an antipsychotic (haloperidol, olanzapine, or ziprasidone). If using haloperidol, consider adding a benzodiazepine anxiolytic (lorazepam or diazepam) and/or an anticholinergic agent (benztropine or diphenhydramine). Intramuscular administration is recommended for rapid de-escalation of dangerous situations. Treatment response should be periodically assessed and additional medication doses administered as needed, while watching for excess sedation, disinhibition, and extrapyramidal symptoms. For persistent agitation/aggressive behavior, physical restraints should be available and scheduled dosing of an atypical antipsychotic administered. See **Fig. 3** for an algorithm concept for agitation management. Relevant diagnostic criteria, treatment options, and algorithms for all psychiatric disorders and emergencies listed in Table VI are available upon request as appendices from the authors.

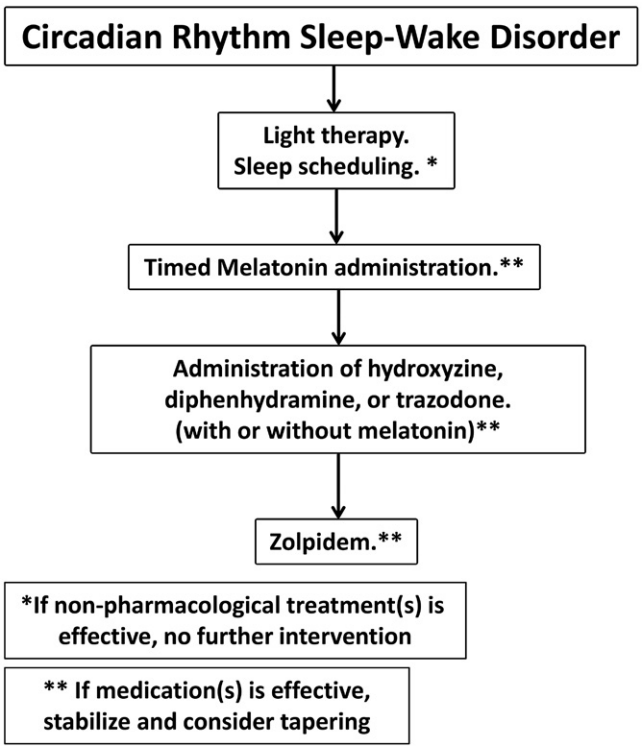

Fig. 2. Algorithm concept for circadian rhythm, sleep-wake disturbance.[1,28]

Summary and Conclusions

In recent years, there has been a surge of interest from both government and private sectors in expanding the human presence in space beyond low Earth orbit. The behavioral health of crewmembers during long-duration spaceflight, when a return to Earth is months or years away, has become an important focus of planning and research. A capable psychiatric formulary is one component of supporting psychological well-being on such lengthy missions.

When choosing the components of a deep-space psychiatric formulary, it is vital to understand the psychiatric symptoms and disorders that could occur on deep space missions. To do so, it is useful to review behavioral experience under ICE conditions from terrestrial analogs. Best represented by Antarctic facilities and Earthbound simulations, analogs indicate that psychiatric disorders do occur and are very disruptive to the mission. In examining spaceflight experience, behavioral symptoms have been anecdotally identified as negatively impacting orbital missions. NASA risk analysis of LSAH and IMM data indicate a measurable risk for psychiatric disorders and emergencies on long-duration exploration missions, with

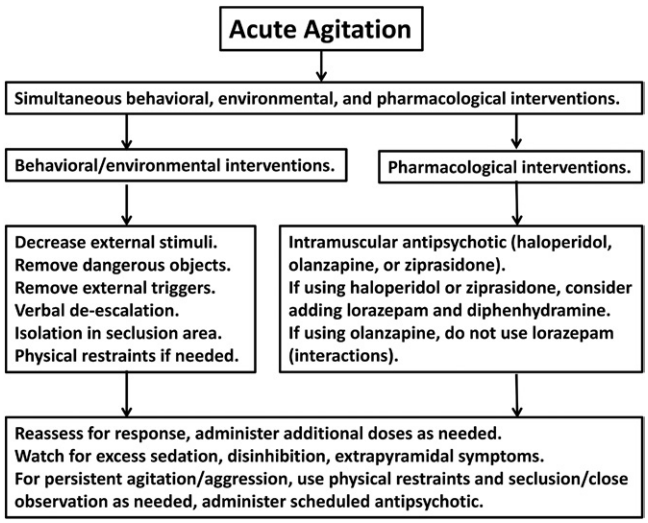

Fig. 3. Algorithm concept for agitation management.[2,47]

extrapolation that the risk will increase with prolonged duration under ICE conditions. Documented psychotropic drug use on orbit has been mostly related to sleep disturbances. The frequent use of sleep and wake-promoting agents by astronauts is under study, as chronic use of these medications carries some risk.

Although additional research is needed, it may also be important to consider potential effects of microgravity and the space environment on the efficacy and administration of pharmaceuticals. Changes in oral bioavailability, fluid shifts, and hepatic first-pass metabolism may alter how medications are administered on long-duration missions. There could be negative effects on the shelf life of pharmaceuticals, leading to novel forms of drug storage (i.e., cryopreservation and radiation shielding). Variability in drug metabolism indicates the utility of documenting genetic polymorphisms in astronauts for genotype-specific dosing and provision of medications.

Components of a long-duration space-based psychiatric formulary should correspond to previously published guidelines. As shown in Table V, a variety of anxiolytics, antidepressants, mood stabilizers, antipsychotics, hypnotics, and wake-promoting agents would provide differing pharmacokinetic, pharmacodynamic, and side effect profiles. The formulary would be controlled to prevent abuse of some medications.

Use of the formulary in treating psychiatric disorders and emergencies would take place within a larger behavioral health program for astronauts. Treatment approaches would include on-site psychological assessment and early treatment interventions, and could incorporate either psychotherapy or medications, or both. Psychiatric emergencies would be treated aggressively to de-escalate hazardous situations. Physical restraints and a seclusion/close observation area would be available if needed.

Based on historical analog data, certain psychiatric issues are relevant to consider for long-duration spaceflight missions, as listed in Table VI. Algorithm concepts in response to two scenarios (circadian rhythm sleep-wake disturbance and agitation management) are presented in Fig. 2 and Fig. 3. Each involves a unique sequence of behavioral and pharmacological treatment options, underscoring the importance of thorough contingency planning.

It is apparent that the expansion of humanity beyond low Earth orbit may commence within the next decade. In order to enable crewmembers to work and thrive on long-duration missions, a comprehensive program for their behavioral wellbeing must be used. On extended missions to such destinations as the Moon, near-Earth objects, and Mars, a large and diverse psychiatric formulary will make an important contribution to the psychological health and performance of crewmembers and to mission success.

ACKNOWLEDGMENTS

Thank you to the following people for their assistance in bringing this exciting project to fruition. Gary Beven, M.D., Space Medicine Operations Division, Johnson Space Center; Anne Hicks, M.B.B.S., British Antarctic Survey Medical Unit; and Lawrence Palinkas, Ph.D., Suzanne Dworak-Peck School of Social Work, University of Southern California, contributed professional advice. Richard Britten, Ph.D., Department of Radiation Oncology, Eastern Virginia Medical School; Paul Sayegh, M.D., Department of Psychiatry and Behavioral Sciences, Eastern Virginia Medical School; and David Spiegel, M.D., Department of Psychiatry and Behavioral Sciences, Eastern Virginia Medical School, provided essential support to this project. Gregg Friedman, M.S., M.B.A., provided technical assistance for several of the figures.

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