A Psychiatric Formulary for Deep Space

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1. Introduction

- The purpose of this project is to propose a psychiatric formulary suitable for long-duration spaceflight.
- Behavioral experience from both Antarctic and orbital space facilities provides insight into potential psychiatric issues on deep space missions.
- Data indicate the necessity and importance of a diverse on-site formulary.
- A robust formulary will allow treatment of a wide range of psychiatric conditions, contributing to crew safety, health and performance.

2. Antarctic psychiatric experience

- Isolation, confinement, cold temperatures, limited daylight exposure, and dependence on technology for survival make Antarctic facilities a useful analog for spaceflight.
- Differences vs. long-duration spaceflight: One year assignments, environmental hazards, crew size and characteristics.
- Psychiatric symptoms severe enough to meet DSM disorder criteria have been a significant concern at Antarctic facilities.
- Incidence of DSM-IV psychiatric disorders was 5.2% in a group of >300 wintering-over crewmembers, at two U.S. Antarctic facilities **(Table1**). Diagnoses included mood disorders (30.2%, n=13), 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).
- Data regarding psychotropic use by U.S. Antarctic crewmembers are not readily available. FOIA requests are pending.
- Psychotropic medications currently carried on-site at U.S. and British Antarctic facilities are listed in **Table 2**.

Diagnosis	DSM-IV Code	Number of cases	Rate per 100 debriefed	Weighted Rate per 100
Mood disorders		13	4·2	1·7
Major depressive disorder, single episode	296.2	6	1·9	0·8
Major depressive disorder, recurrent	296.3	2	0·6	0·3
Dysthymic disorder	300.4	1	0·3	0·1
Depressive disorder not otherwise specified	311.0	4	1·3	0·5
Personality disorders		5	1·6	0·5
Schizoid personality disorder	301.2	2	0·6	0·3
Dependent personality disorder	301.6	2	0·6	0·3
Personality disorder not otherwise specified	301.9	1	0·3	0·1
Substance-related disorders		4	1	1
Alcohol dependence	303.9	2	0.6	0.3
Cannabis abuse	304.3	1	0·3	0·1
Alcohol abuse	305.0	1	0·3	0·1
Sleep disorders		9	2·9	1·1
Circadian rhythm sleep disorder	307.45	9	2·9	1·1
Adjustment disorders		12	3·8	1·6
Adjustment disorder with depressed mood	309.0	6	1·9	0·8
Adjustment disorder with anxiety	309.24	2	0·6	0·3
Adjustment disorder with mixed emotion or conduct	309.4	2	0·6	0·3
Adjustment disorder unspecified	309.9	2	0·6	0·3
Total DSM-IV disorders		39	12·5	5·2

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

***Table:* Unadjusted and weighted[a] prevalence (per 100 people debriefed) of DSM-IV disorders in people on the United States Antarctic Program at end of an austral winter**

TABLE 1: Unadjusted and weighted prevalence (per 100 people debriefed) of DSM-IV disorders in U.S. Antarctic Program after an austral winter. *Palinkas LA et al. Lancet. 2008 Jan 12;371(9607):153-63.* Reproduced with the permission of the author.

Psychotropic drugs listed in Antarctica
Antidepressants
Amitriptyline
Bupropion
Citalopram
Fluoxetine
Mood stabilizers
Carbamazepine
Antipsychotics
Chlorpromazine
Haloperidol
Olanzapine
Quetiapine
Risperidone
Anxiolytics and anticholinergics
Buspirone
Diazepam
Diphenhydramine
Lorazepam
Midazolam
Procyclidine
Sleep agents
Eszopiclone

TABLE 2: Psychotropic drugs at U.S. and British Antarctic facilities. National Science Foundation, FOIA request, Case #17-98F; Hicks A, British Antarctic Survey Medical Unit, personal communication.

3. Spaceflight psychiatric experience

- Behavioral issues have affected orbital missions since the 1970s, in both the American and Soviet/Russian space programs.
- Psychiatric disorders have been documented in astronaut applicants.
- Nine of 117 (7.7%) astronaut applicants (1959-1987) met DSM-III disorder criteria, including anxiety disorder, adjustment disorder, uncomplicated bereavement, compulsive personality disorder, narcissistic personality disorder, and schizotypal personality disorder.[1]
- From a larger pool of 1,414 astronaut applicants (1978-2004), 35 of 373 (9%) medical disqualifications were due to psychiatric symptoms.[2]

4. Spaceflight psychiatric experience

- Documented incidence rates of on-orbit psychiatric symptoms **(Table 3)** vary and may be affected by a reluctance to report symptoms.

Data Source	Psychiatric Findings	Incid. per person-yr
Shuttle program, 1981-98	Anxiety, irritability sympt.	2.87
NASA astronauts on Mir, 1995-98	Depressive sympt.	0.77
LSAH data, Shuttle program	Anxiety sympt.	0.832
LSAH data, Shuttle program	Depressive sympt.	0.139
IMM risk estimates	DSM-defined anxiety disord.	0.0071 F, 0.0019 M
IMM risk estimates	DSM-defined depressive disord.	0.0036 F, 0.0029 M
IMM risk estimates	Emergency (depression/anxiety)	0.000087 to 0.000324
Stuster risk est. for Mars mission (6% incid. in transit, 2% surface)	Serious psychiatric sympt. (equiv. to hospitalization)	0.626 short stay (661 d) 0.534 long stay (905 d)
Stuster risk est. for Mars mission (6% incid. in transit, 2% surface)	Serious psychiatric sympt. (equiv. to hospitalization)	0.652 short stay (661 d) 0.893 long stay (905 d)

TABLE 3: Actual and estimated incidence rates of psychiatric symptoms during orbital spaceflight. Data is derived from documented experience and statistical extrapolation.[3]

- From 89 Space Shuttle missions (1981-1998), 34 behavioral symptoms (most commonly anxiety and irritability) were reported among 208 crewmembers, an incidence of 2.87 per person-year.
- Two of seven (29%) NASA astronauts who flew on Mir (1995-1998) reported depressive symptoms, an incidence of 0.77 per person-year.
- Of 41 ISS expeditions (2000-2014), only one behavioral event (death of an astronaut's parent) could have potentially affected the mission.
- NASA behavioral data has been collected in the Lifetime Surveillance of Astronaut Health (LSAH) and Integrated Medical Model (IMM) databases.
- LSAH Shuttle data from physician notes, comprising 28 person-years, revealed 24 reports of anxiety symptoms (incidence 0.832 per person-year) and four reports of depression (incidence 0.139).
- IMM behavioral data record symptoms severe enough to meet DSM criteria for depressive and anxiety disorders. To date, no NASA astronaut has met criteria for a DSM psychiatric disorder.
- The IMM also uses general population incidences to estimate psychiatric disorder risk . Anxiety disorder risk is 0.0071 per person-year for female astronauts and 0.0019 for males. Depressive disorder risk is 0.0036 for females and 0.0029 for males. Risk estimates of a psychiatric emergency with severe mission impact range from 0.000087 to 0.000324.

5. Use of psychotropic drugs on-orbit

- During the Shuttle and ISS programs, most psychotropic drug use was related to sleep disturbances. This might be underestimated due to a reluctance to report.
- Sleep aids may impair functioning of crew if emergently awakened from sleep. Zolpidem is associated with sleep-walking and sleep-driving. Long-term use of benzodiazepine and other hypnotics is associated with dependency and neuropsychiatric symptoms.
- Among 64 Shuttle astronauts over 80 missions (2001-2011), 78% used a sleep agent. Sleep agents were used on 500 (52%) of 963 nights, with two doses taken on 87 (17%) of those nights. Sleep aids were used on 60% of nights prior to an EVA. On four Shuttle missions, all crewmembers used sleep aids on the same night 6% of the time. Agents used were zolpidem (73%), zolpidem controlled release (12%), and zaleplon (11%). Total sleep time was not significantly affected by sleep agents, and sleep efficiency increased by just 1.3%.[4]
- Sleep aids were used by 71% of 24 ISS crewmembers, during 20 missions averaging 159 days. Most sleep agents (83%) were taken on ordinary nights, while 10% were taken prior to a schedule shift and 3% prior to an EVA. Agents used were zolpidem, zaleplon, or both. Wake promoting agents were used on 12 occasions by 5 ISS crew, 4 of these with a schedule shift and 2 with an EVA.[5]
- NASA research into effects of sleep agents on astronauts is ongoing.

6. Psychiatric drugs currently on the ISS

- Current psychiatric medications in the ISS medical kit are listed in **Table 4.**
- For deep space missions, on which a rapid return to Earth is not possible, a more extensive formulary will be required to treat a wide range of both acute and chronic psychiatric diagnoses.

TABLE 4 : Psychotropic drugs held on the ISS. FOIA request, Case #16-JSC-F-0014, http://www.governmentattic.org/19docs/NASA-ISSmedicalEmerg Manual_2016. pdf; Beven G, NASA Johnson Space Center, personal communication.

Psychotropic drugs listed on ISS
Antidepressants
Sertraline
Venlafaxine
Antipsychotics
Aripiprazole
Ziprasidone
Anxiolytics and anticholinergics
Diazepam
Diphenhydramine
Lorazepam
Sleep agents
Melatonin
Zaleplon
Zolpidem
Wake agents
Caffeine
Modafinil

7. Drugs and the space environment

- Astronaut reporting has documented some variation in drug efficacy on orbital missions.
- Microgravity and the space environment may alter the pharmacokinetics, pharmacodynamics, and shelf-life of pharmaceuticals.
- Oral bioavailability of medications may be altered by changes in gastric drug dissolution, gastric emptying, and gut microflora.
- Cephalad fluid shifts and volume of distribution changes may alter hepatic first-pass metabolism of some agents, including antidepressants.
- Studies have demonstrated an apparent advantage in bioavailability to the intramuscular administration of some drugs.
- Stability of pharmaceuticals stored on-orbit may be affected by the space environment, raising a potential role for radioprotection and cryopreservation of medications. **(Figure 1)**
- Although additional research is needed, these factors may be considered when choosing pharmaceuticals for long-duration space missions.

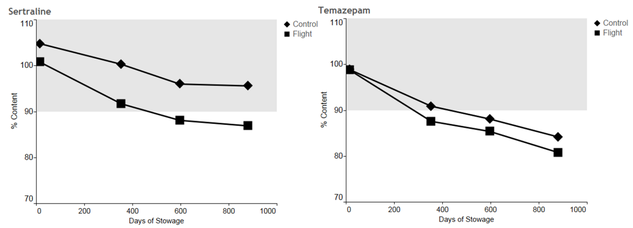


FIGURE 1: Degradation of active pharmaceutical content (API) in sertraline and temazepam samples stowed on the ISS (squares) or on Earth (diamonds). Shaded area represents USP range for label claim. From a single sample of each drug. Unpublished data, mentioned in Du B et al. *Evaluation of physical and chemical changes in pharmaceuticals flown on space missions*. AAPS J. 2011 Jun;13(2):299-308. Data available at NASA Life Sciences Data Archive, Dataset SMO_Stability_Pharm_3050746468.xls, https://lsda.jsc.nasa.gov/scripts/experiment /exper.aspx?exp_index=1791

8. Psychiatric disorders in deep space

- Data from spaceflight and terrestrial analogs help to assemble a listing of DSM-5 psychiatric disorders and emergencies to be anticipated on long-duration missions **(Table 5)**

TABLE 5: DSM-5 disorders and psychiatric emergencies to be anticipated on deep space missions.

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

9. A deep space psychiatric formulary

- Guidelines by Santy remain relevant for a psychiatric formulary capable of treating a range of conditions.[6]
- Formulary will include antidepressants, mood stabilizers, antipsychotics, anxiolytics, anticholinergics, and sleep/wake agents.
- Multiple examples of each drug class will provide diverse pharmacokinetic, pharmacodynamic, and side effect profiles.
- Formulary access will be controlled, given abuse potential of some medications. A proposed formulary is listed in **Table 6**.

Drug	Relevant Psychiatric Indications	Selected Side Effects
Antidepressants		
Bupropion	Major Depr. DO, Seasonal Affective DO	Dry mouth, constipation, nausea
Mirtazapine	Major Depr. DO	Sedation, dry mouth, constipation
Paroxetine	Major Depr. DO, Panic DO, PTSD, Gen. Anxiety DO, OCD	GU, GI, dry mouth, sedation, constipation
Venlafaxine	Depression, Gen. Anxiety DO, Panic DO	GI, GU, headache
Mood Stabilizers		
Divalproex	Acute mania, mixed episodes, Bipolar DO	Sedation, nausea, hepatotox, TCP, pancrts
Antipsychotics		
Aripiprazole	Depr. adjunct, acute agit./mania, Bipolar DO, Schizo.	GI, dizzy, insomnia, activation, akathisia
Olanzapine	Schizophr., acute agit./mania, Bipolar DO, Schizo.	Sedat, dry mouth, constip, wt gain, diabetes
Haloperidol	Acute psychosis/agitation, Bipolar DO, Schizo.	Sedat, dry mouth, akathisia
Ziprasidone	Acute agit./psychosis/mania, Bipolar DO, Schizo.	Sedat, dizzy, dry mouth, nausea
Anxiolytics and anticholinergics		
Benztropine	EPS, acute dystonia	Confusion, dry mouth, nausea, constipation
Buspirone	Anxiety DOs, acute anxiety	Dizzy, HA, sedation
Clonidine	Acute anxiety, PTSD, substance withdrawal	Dry mouth, dizzy, sedation, constipation
Diazepam	Anxiety DOs, acute anxiety, substance withdrawal	Sedation, fatigue, confusion, disinhibition
Diphenhydramine	EPS, acute dystonia	Sedation, dry mouth, dizzy, nausea
Hydroxyzine	Acute anxiety, sedation, agitation, subst. withdrawal	Sedation, dry mouth, tremor
Lorazepam	Anxiety DOs, Serotonin Synd, NMS, akasthisia, subst. with	Sedation, fatigue, confusion, disinhibition
Prazosin	Nightmares associated with PTSD	Dizzy, headache, fatigue
Propranolol	Akasthisia, anxiety	Bradycardia, hypotension, dizzy, GU
Sleep agents		
Melatonin	Insomnia in sleep-wake disorders	Sedation
Trazodone	Insomnia in sleep-wake disorders, depression, anxiety	Sedation, dizzy, HA
Zolpidem	Insomnia in sleep-wake disorders	Sedation, dizzy, ataxia, anxiety, amnesia
Wake-promoting agents		
Caffeine	Somnolence in sleep-wake disorders	Anxiety, diarrhea, insomnia
Modafinil	Somnolence in sleep-wake disorders	Anxiety, HA, insomnia

TABLE 6: A proposed psychiatric formulary suitable for long-duration spaceflight.

10. Psychiatric strategies for deep space

- Pre-flight pharmacogenetic testing, for variation in polymorphic metabolizing enzymes such as CYP450, will determine genotype-specific dosing and provision of medications.
- Psychiatric approaches will stress frequent monitoring of psychological health and early treatment intervention for significant symptoms.
- Treatment will consist of a combination of psychotherapy (e.g., cognitive behavioral therapy, interpersonal therapy) and medications.
- Psychiatric emergencies will be treated aggressively with behavioral interventions and psychotropic medications to de-escalate potentially hazardous situations. Availability of physical restraints and a pre-designated seclusion/close observation area will be necessary.
- Proposed algorithms for treatment of circadian rhythm sleep-wake disorder and acute agitation are listed in **Figure 2** and **Figure 3**.
- Additional algorithms are available upon request.

FIGURE 2: Algorithm for treatment of Circadian Rhythm Sleep-Wake Disorder

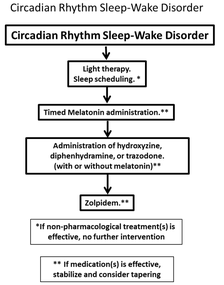
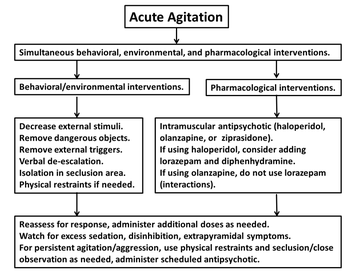


Figure 3: Algorithm for treatment of acute agitation.



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[1] Santy PA et al. Psychiatric diagnoses in a group of astronaut applicants. Aviat Space Environ Med. 1991 Oct;62(10):969-73.
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Disclosure Information: E. J. Friedman, AsMA 88th Annual Scientific Meeting
- I have no financial relationships to disclose.
- I will not discuss off-label use and/or investigational use in my presentation.