1. Introduction

- The purpose of this project is to propose a psychiatric formulary suitable for astronauts.
- Behavioral experience from both Antarctic and orbital space-based missions 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 health, safety, and performance.

2. Antarctic psychiatric experience

- Isolation, confinement, cold temperatures, limited daylight exposure, and dependence on technology for survival make facilitating a large useful analog for spaceflight.
- Differences vs. long-duration spaceflight: One year assignments, environmental haustenostics.
- 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 (Table 1). Diagnosed include mood disorders (30.9%, n=11), adjustment disorders (27.9%, n=12), sleep-related disorders (20.9%, n=9), personality disorders (11.6%, n=5), and substance-related disorders (3.3%, n=4).
- Data regarding psychotropic use by U.S. Antarctic crewmembers are not readily available. FOA requests are pending.
- Psychotropic medications currently carried on-site at U.S. and British Antarctic facilities are listed in Table 6.

3. Spaceflight psychiatric experience

- Behavioral issues have affected orbital missions since the 1970s, in both the American and Soviet/Russian space programs (1996). Twelve out of DSM-III disorder categories, including anxiety disorder, adjustment disorder, uncomplicated bereavement, compulsive personality disorder, narcissistic personality disorder, and schizotypal personality disorder.
- From a larger pool of 2,448 astronaut applicants (1978-2004), 35 of 373 (9.4%) medical disqualifications were due to psychiatric symptoms.

4. Spaceflight psychiatric experience

- Documented incidence rates of on-orbit psychiatric symptoms (Table 3) long-duration spaceflight differ from on-ground reports.
- Current psychiatric medications in the ISS medical program are listed in Table 4.
- Data indicate that for general population incidences to estimate psychiatric disorders in U.S. Antarctic Program after an austral winter.

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 zolpidem and other benzodiazepines is associated with dependency and neuropsychiatric symptoms.
- Among 84 Shuttle astronauts over 82 missions (2001-2011), 78% used a sleep agent. Sleep agents were also 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 clonazepam (11%). Total sleep time was not significantly affected by sleep agents, and sleep efficiency increased by just 1.3%.
- 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. A
- NASA research into effects of sleep agents on astronauts is ongoing.

6. Psychotropic drugs currently on the ISS

- Current psychiatric medications in the ISS medical program 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 conditions.

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 some medications may be altered by changes in gastric drug dissolution, gastric emptying, and gut microbiota.
- Capillary 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 at the intramuscular administration of some drugs.
- Stability of pharmaceuticals stored on-orbit may be affected by the space environment, making a potential role for radioprotection and cryopreservation of medications.
- Although additional research is needed, these factors may be considered when choosing pharmacologic agents for long-distance space missions.

8. Psychiatric disorders in deep space

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

9. A deep space psychiatric formulary

- Guidelines by Santy remain relevant for a psychiatric formulary capable of treating a range of conditions.
- Formulary will include antidepressants, mood stabilizers, antipsychotics, anxiolytics, and sleep aids.
- 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.

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 medication of preference.
- 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-diagnosed medication/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.