NASA-STD-3001 Technical Brief

Pharmaceutical Care

OCHMO-TB-006
Rev A

Executive Summary

Pharmaceutical Care refers to the dispensing of drug therapy to achieve outcomes that improve a patient's quality of life including management of a medical condition, elimination or reduction of patient symptomatology, and stopping or slowing disease progression or illness. The spaceflight environment leads to a host of factors that must be considered when choosing treatment, including anticipating medication needs to establish an optimal formulary, pharmaceutical shelf life and time to resupply, medication degradation and impurity considerations, and effective packaging. Vehicle constraints include weight and volume limits, storage, and inventory systems. Physiological considerations include alterations of pharmacokinetics and pharmacodynamics, response to gravity transitions, vibration, and radiation exposure. Low Earth Orbit (LEO) experience and studies have not shown changes in medication stability, dosing, or effectiveness leading to poor health outcomes. Further study is taking place regarding medication use and challenges during longer duration spaceflights beyond LEO.

Related OCHMO Technical Briefs

1. OCHMO-TB-016 Behavioral Health
2. OCHMO-TB-030 Bone Loss
3. OCHMO-TB-019 Orthostatic Intolerance
4. OCHMO-TB-037 Decompression Sickness
5. OCHMO-TB-013 Food and Nutrition
6. OCHMO-TB-020 Radiation Protection
7. OCHMO-TB-041 Sleep Accommodations
8. OCHMO-TB-027 Water

Relevant Technical Requirements

NASA-STD-3001 Volume 1, Rev C

[V1 3004] In-Mission Medical Care
[V1 4009] Sensorimotor Countermeasures
[V1 4016] In-Mission Hematological/Immunological Countermeasures
[V1 4027] In-Mission Bone Countermeasures
[V1 5001] Medical Training
[V1 5007] Support Personnel Training
[V1 6001] Circadian Shifting Operations and Fatigue Management
[V1 7001] Crew Health Results
[V1 7002] Crew Records Transmission
[V1 7003] Crew Records Security

NASA-STD-3001 Volume 2, Rev D

[V2 7038] Physiological Countermeasures Capability
[V2 7042] Orthostatic Intolerance Countermeasures
[V2 7043] Medical Capability
[V2 7045] Medical Equipment Usability
[V2 7115] Medical Treatment, Personal Supplies, and Impacts to Environmental Systems
[V2 7050] Stowage Provisions
[V2 7051] Personal Stowage
[V2 7052] Stowage Location
[V2 7055] Priority of Stowage Accessibility
[V2 7059] Inventory Tracking
[V2 11027] Suited Medication Administration
[V2 11125] Suit Materials Compatibility

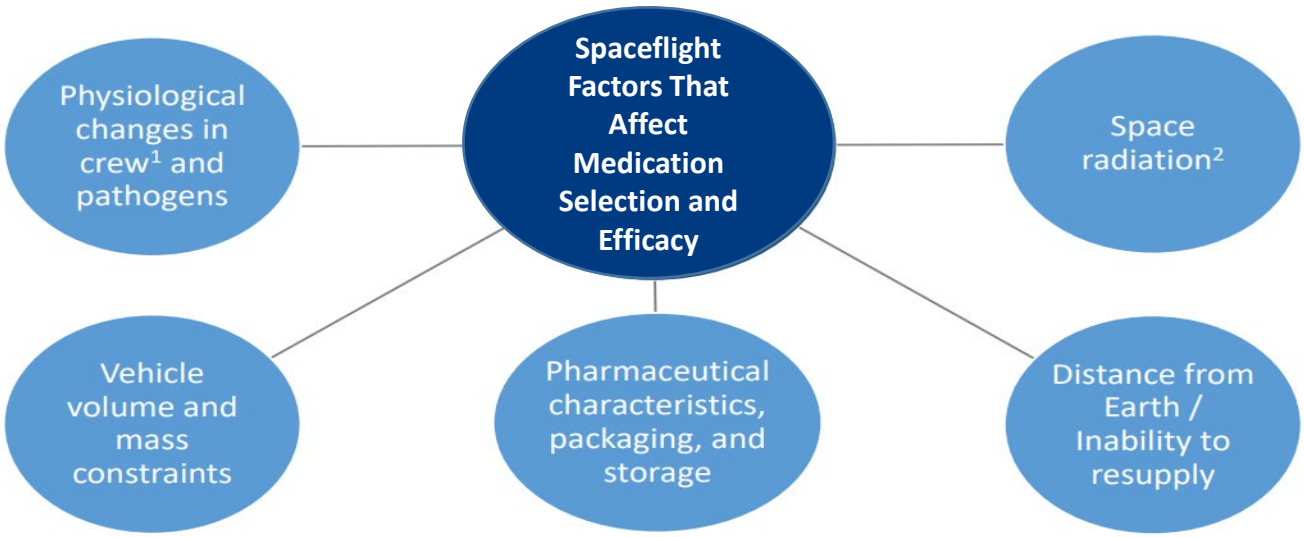
Overview

Medications for spaceflight are chosen based on individual crewmember needs, clinical practice guidelines, flight surgeon expertise, historical review, and probabilistic risk assessment (PRA) tools.

Choosing appropriate pharmaceuticals for flight is crucial as they significantly affect spaceflight human system risks including but not limited to those listed in the text, as interventions or countermeasures.

- Risk of Bone Fracture Due to Spaceflight-induced Changes to Bone
- Risk of Renal Stone Formation
- Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health
- Risk of Adverse of Health Event Due to Altered Immune Response
- Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders
- Risk of Spaceflight-Associated Neuro-Ocular Syndrome (SANS)
- Risk of Performance Decrements and Adverse Health Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload

Spaceflight Factors That Affect Medication Selection and Efficacy



[V1 3004] In-Mission Medical Care All programs shall provide training, in-mission medical capabilities, and resources to diagnose and treat potential medical conditions … including Medical kits (personal, routine, emergency, and survival) and resources, including appropriate pharmaceuticals, equipment, and supplies selected for ease-of-use, and personal protective equipment (e.g., biohazards and sharps containment). *From NASA-STD-3001 Vol 1, Rev C*

Overview

Medication Stability refers to how well a substance maintains consistent properties and characteristics within specified limits during use and storage. Stability concerns include if conditions of altered gravity, radiation, temperature/humidity, and the spaceflight environment effects the ability of medications to maintain their physical/chemical structure and effectiveness.

Crewmembers in LEO have not been affected by lack of medication effectiveness due to stability or radiation exposure. Studies have shown limited alteration in physical/chemical changes including increased rate of degradation, however most medications lost less than 20% of medication active pharmaceutical ingredients (API) in one study *(Du et al., Evaluation of Physical and Chemical Changes in Pharmaceuticals Flown on Space Missions),* and less than 5-10% degradation after 550 days on ISS for a select set of medications *(see page 4, Wotring, 2016).*

Expiration Concerns include long duration spaceflight planned for 1-5 years which will be beyond the current average medication expiration dates of 1-2 years.

Terrestrial studies show expiration dates of many medications extend long (1-10 years) after published expiration dates of 1-2 years (*US Food and Drug Administration Federal shelf-life extension program (SLEP) updated 04/2023)*.

Effectiveness Concerns include considering above situations/stability/expiration conditions that could adversely affect medication effectiveness

Studies have shown medications used in LEO are perceived by crew as >80-90% effective, with 85% experiencing no side effects (*Putcha et al., Pharmaceutical Use by U.S. Astronauts on Space Shuttle Missions 1999*).

Use How are medications being used, will we be able to treat medical conditions?

To date, medication use is similar to terrestrial ambulatory medicine with exception of sleep medication, which has increased use in space (*Putcha et al., Pharmaceutical Use by U.S. Astronauts on Space Shuttle Missions 1999, Wotring ISS Medication Use, 2015*).

Radiation Concerns include exposure to potentially damaging galactic cosmic rays (GCRs), solar particle events ejecting damaging high-dose radiation charged particles, and potential alteration of medication chemistry, especially in liquid pharmaceuticals thought to be more vulnerable to radiation exposure.

Ionizing radiation exposure in LEO, within the Earth's protective magnetic field which minimizes radiation exposure, has not been found to significantly interfere with the usability of medications. Limited radiation studies at Brookhaven NASA Space Radiation Laboratory (NSRL) found small alterations of API or physical characteristics. Most cases were within acceptable limits at the time for study analysis (*Blue et al., Limitations in predicting radiation-induced pharmaceutical instability during long-duration spaceflight*). Future long-duration missions will have a vastly different radiation environment than during LEO and will require additional considerations.

To date, LEO spaceflight experience and studies have shown limited changes in medication composition or crewmember physiology that adversely affect pharmaceutical stability, dosing, or effectiveness leading to negative health outcomes.

Background

Physiological Changes

Although medications have been able to treat medical conditions as they have arisen in LEO, long duration spaceflight beyond LEO introduces additional challenges including lack of resupply capability, prolonged exposure to the space radiation environment, and the absence of emergency medical return capability. These challenges as well as the physiological crewmember changes (shown below) that occur in all spaceflight must be considered when choosing medications for long duration spaceflight. **Reference** OCHMO-TB-007 Mission Duration

Physiological changes in the human body during spaceflight

- Fluid shifts – altered volume distribution
- Intracellular fluid alteration – altered metabolism; altered drug uptake and clearance
- Altered plasma protein concentration – altered free drug concentration; altered renal/hepatic clearance
- Cell membrane permeability – altered drug distribution and uptake
- Hepatic metabolism – altered hepatic blood flow; altered hepatic enzyme expression
- Gut motility and absorption – altered gastric emptying from space motion sickness (SMS) or medications to address SMS; faster and more variable intestinal transit rate
- Alterations in immune response
- Potential increased antibiotic resistance of spaceflight cultured bacteria

Environmental changes contributing to physiological changes

- CO_2 changes
- Pressure changes
- Gravity changes
- Radiation exposure
- Other atmospheric considerations (humidity, temperature, etc.)

Definitions

- **Pharmacokinetics (PK)** what the body does with a drug, including how medications are absorbed into the body, transported throughout, and degraded or eliminated. The extent of absorption can depend on route of administration and physical and chemical properties.
- **Pharmacodynamics (PD)** how a drug interacts with tissues, cells, and organs and if the drug formulation (i.e., tablet capsule, liquid, or aerosol) produces the desired effects.
- **Active Pharmaceutical Ingredient (API)** The ingredient or active pharmaceutical substances intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect. FDA establishes percentages of API for medications.
- **Degradation** products or unwanted chemicals that can develop during the manufacturing, transportation, and storage of drug products and can affect the efficacy of pharmaceutical products.

Background

Stability Studies

Medications aboard the International Space Station (ISS) have maintained usability in LEO gravity and radiation conditions and are restocked before their expiration dates. These conditions may be more challenging and resupply not possible on future long-duration missions. To help ensure future optimal use of medications, studies have, and continue to be performed, regarding medication use beyond expiration date and how alterations in environment affect concentration of API and possible degradation of pharmaceuticals in long-duration missions.

Wotring 550 Day study (2016) -- Analyzed nine medications for API content and degradant amounts after being flown on ISS for 550 days. Medications were repackaged prior to flight, and after return to Earth were tested at one time point, with results normalized to each medication's expiration date.

Hypothesis -- Medication degradation on ISS does not differ from that typically seen on Earth.

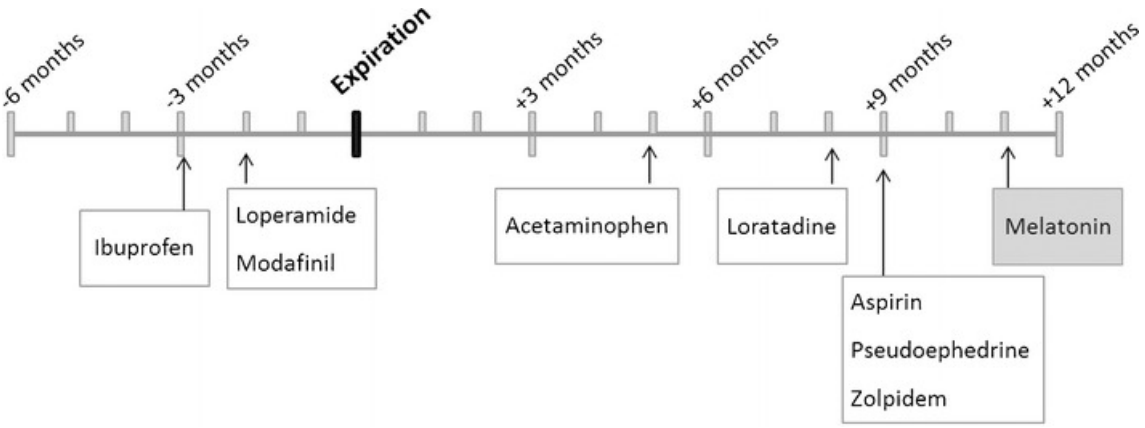
Results:

- All medications but one (Melatonin) found to contain API within USP guidelines (90-110%) of label claim. Only Melatonin had degradation products identified above USP limit.
- No unusual degradation products identified, some common degradation products with specific USP guidelines were noted in aspirin, ibuprofen, loratadine, and zolpidem. Other degradation products were noted in other samples, at amounts too small for further analysis with USP methods.

Results of 550 Day Study Medication API Assays

Medication	Results (mg)	% Label API
Aspirin 325mg	313.7±0.5	96.5
Acetaminophen 325	315.4±3.2	97.0
Ibuprofen 400mg	399.6±7.1	99.9
Loratadine 10mg	10.0±0.3	99.9
Loperamide 2.0mg	2.0±0.6	96.3
Pseudoephedrine 120mg	118.9±3.3	99.0
Melatonin 3mg	2.7±0.1	89.2
Zolpidem 10mg	10.07±0.09	100.6
Modafinil 200mg	201.2±2.4	100.6

- Samples for this study were opportunistically obtained, therefore no ground samples were available for analysis



Timeline (left) of medication ages relative to expiration dates. All medications aged on ISS for 550 days. Medications had varied expirations but were tested at 1 point, thus show different points on timeline. Melatonin had been expired by the most time (11 months) and was the only medication not to contain API within USP guidelines.

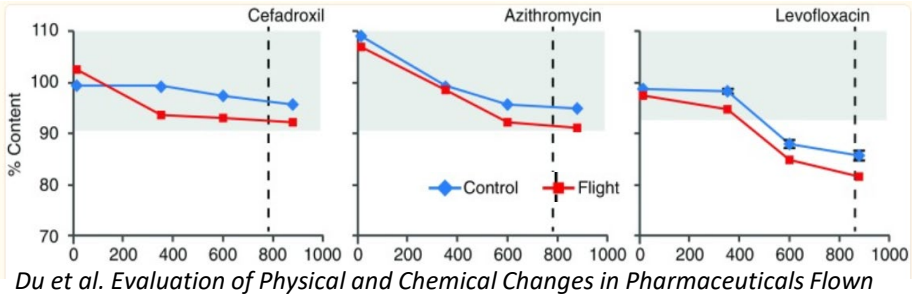
Source: Wotring (2016) Chemical Potency and Degradation Products of Medications Stored over 550 Earth Days

Background

Du et al. Pharmaceuticals Evaluation Study (2011) – Compared 35 pharmaceuticals commonly used in spaceflight med kits stowed on ISS and Earth, observed for physical and chemical changes at 4 check points (14, 353, 596, and 880 days) over a 28-month period.

- Quantities of each medication, from same lot were packaged in ground control and flight payload kits.
- Kits equipped with passive radiation dosimeters, temp and humidity recorders.
- Four kits were stowed onboard space transport systems for delivery to ISS, 4 matching kits stored at JSC

Photo: Du et al. Evaluation of Physical and Chemical Changes in Pharmaceuticals Flown on Space Missions (2011)



Du et al. Evaluation of Physical and Chemical Changes in Pharmaceuticals Flown on Space Missions (2011)

Examples of data (left) shows degradation of antibiotic tablets based on days of stowage. Each point represents one payload. The shaded area represents USP range for label claim. Dotted line is expiration date.

USP Content Acceptance Criteria

- Chemical potency or ≤10% decrease in percent content from label strength.
- Appearance, physical attributes (e.g., discoloration, phase separation), and physical performance test of hardness and friability.
- Acceptance criterion for pH (liquid formulations).
- USP limits for microbiological contamination (sterile liquid formulations).
- USP acceptance criteria for API dissolution performance.

Results

- Physical changes were observed but inconsistent.: No changes in ground samples 1-3, total of 21 changes in 13 medications in payloads 1-4, however changes not consistent. For example; medication changed in appearance in payload 1 but not in 2 or 4.
- Chemical content: Number of formulations that did not meet API requirements were higher among in-flight kits in all 4 payloads. After 880 days, 27% solid formulations met API of loss of less than 10% of label, however most medications lost less than 20% (see samples below).
- Rate of degradation faster in space but most meds still met USP standards for dissolution.
- Cumulative radiation dose was higher and increased with time in space.
- Temp and humidity environment of flight medications remained similar to ground medications.

Percent API Content in Unstable Formulations with Chemical Potency below Acceptable Limit (Partial list)

Payload (P)			14 Days (P 1)				353 Days (P 2)				596 Days (P 3)				880 Days (P 4)			
Medication	Label	USP	Control		Flight		Control		Flight		Control		Flight		Control		Flight	
Active Substance	(mg)	(%)	% [a]	±SD [b]	%	±SD	%	±SD	%	±SD	%	±SD	%	±SD	%	±SD	%	±SD
Amoxicillin/	875	90-120	116.2	0.35	116.0	0.14	100.1	0.05	102.3	0.33	97.2	0.37	88.0	0.68	96.4	0.47	87.0	0.41
/Clavulante	125	90-120	93.3	0.59	91.0	0.79	12.0	0.43	36.7	0.33	6.60	0.16	21.1	1.10	3.3	0.31	9.1	2.07
Ciprofloxacin (SS)	10.5	90-110	95.4	0.96	94.7	0.92					93.2	0.62	90.3	0.27	88.5	0.47	83.4	0.46
Ciprofloxacin (T)	500	90-110	104.8	0.87	101.5	0.31	92.9	0.15	92.1	1.19	91.5	0.03	90.6	0.34	90.9	0.30	84.4	0.49

Limits were set at 90-110% for these formulations in this study; Numbers in red indicate below lower limit of % chemical content.

Background

Medication Tracking

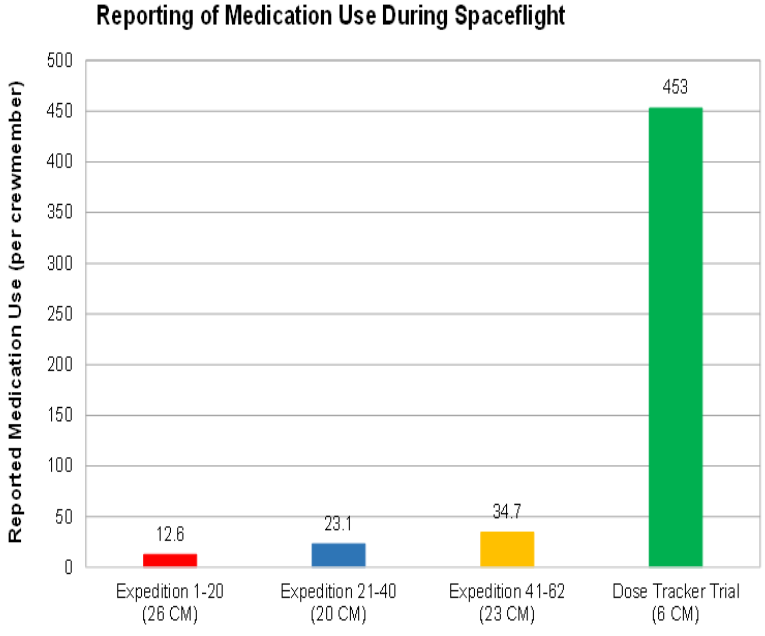
Medication use during spaceflight historically has not been comprehensively monitored due to conflicting crew time demands, effective tracking procedures, and crew preference. Crewmembers are able to take certain medications (mainly over-the-counter) without discussing with their flight surgeon, and while astronauts are encouraged to discuss medications with their flight surgeon, this discussion may occur without documentation. Studies have been performed to better discern crewmember use and effectiveness or perceived effectiveness of medications.

Dose Tracker Study

The Dose Tracker project was designed to more completely and efficiently track crew medication use and side effect information. "Dose Tracker" is an iOS application allowing easier recording of medication use and events. Six crewmembers were monitored during their 5 to 6-month missions on ISS. The study showed a large increase in reported medication use compared to previous reporting, which is believed to be a result of better reporting as opposed to increased use of medications**.**

- Expeditions 1–20, relied on crewmember volunteer reporting and flight surgeon documentation Documented 12.6 doses taken per crewmember per mission.
- Expeditions 21–40, crewmembers were queried during PMCs on medication use for documentation by flight surgeons. 20 crewmembers reported an average of 23.1 doses.
- In 2017, the Dose Tracker study monitored use by six crewmembers during their 5 to 6-month missions. An average of 453 medication uses were reported per crewmember during their missions, *approximately four medications per crewmember per week.*

Blue et al. (2019) Supplying a pharmacy for NASA exploration spaceflight: challenges and current understanding



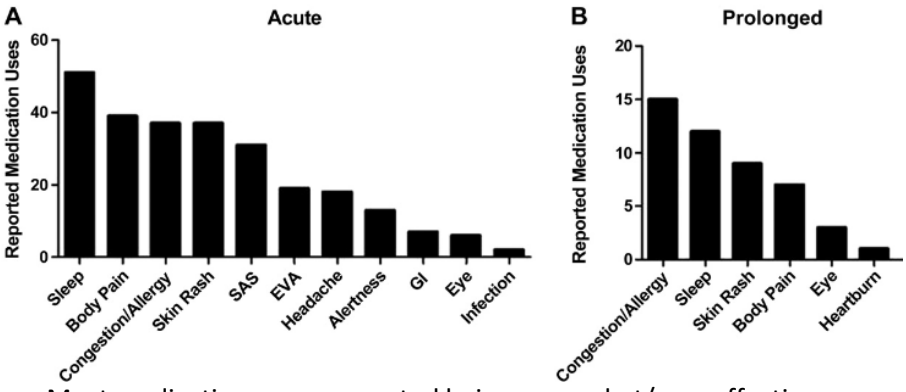
Updated since Blue et al, NPJ Microgravity (2019)5:14

"Dose Tracker Application uses an iPad for fast and efficient collection of data regarding crewmembers' medication use on a near real-time basis, eliminating the current problems associated with recall. The crewmember unstows their personal iPad and enters medication usage into the Dose Tracker Application. The questionnaire asks if the crewmember has used medications since the last entry, what prompted him/her to use the medication, how well it seemed to work, how frequently doses were repeated, and if the medication seemed to cause side effects. Specific questions regarding medication use are asked of each crewmember. The data is streamlined by using a programmed, computerized survey application reflecting the medication choices, the doses available, typical dosing frequency, and side effects associated with each medication." *Dose Tracker Application for Monitoring Medication Usage, Symptoms, and Adverse Effects During Missions NASA (Wotring, 2015).*

Background

Medication Use and Effectiveness

Wotring ISS Medication Use (2015) – Examined medication use during long duration flights (>30 days) to determine the effect spaceflight conditions (vibration, gravity transitions, radiation exposure) have on crewmember physiological conditions (PK/PD, immune, fluid shifting, muscle/bone, cell alteration) and medication effectiveness. Medication records were analyzed from 24 crewmembers on 20 missions over a 10-year period, observing trends in usage rates, efficacy, and adverse events.



- Most medications were reported being somewhat/very effective.
- 3 reports of ineffective medication use involved topical rash treatments.
- Medication reports were given retrospectively, some medication use may be complicated as the condition for the treatment may have been unclear, for example a headache can be caused by congestion, fluid shifts, elevated CO_2, or caffeine withdrawal and if given medication that treat the wrong condition, it may be incorrectly deemed as less or ineffective when it actually was an incorrect treatment.

Medication Class	Crewmembers Reporting Use (%)	Reported Efficacy
Sleep aids	71	Somewhat-very effective
Alertness aids	21	Very effective
Pain relivers		
For back pain	21	Somewhat-very effective
For joint pain	46	Somewhat-very effective
For muscle pain	21	Somewhat-very effective
For headache	54	Somewhat-very effective
Congestion/allergy treatments	55	Somewhat-very effective
Rash treatments	25	Ineffective (2 reports)
SAS treatments	21	Ineffective (1 report)
SAS prophylaxis	25	Very effective

Medication use by U.S. crewmembers on the International Space Station Wotring 2015

Results

- Medication use was similar to space shuttle and adult ambulatory medicine, with exception of sleep aids which were used 10 times more during spaceflight.
- Medications used for </= 7 days were used for ordinary complaints and use was comparable to any healthy group of adults.
- 3 reports of apparent treatment failures occurred, all in cases of skin rash.
- 71% of crewmembers reported using sleep medications.
- Most medication use linked to EVA, exercise protocols, or equipment and operationally driven schedule changes (lighting and schedule-shifting).
- This was a retrospective study with medication data based on medical records and physician notes. OTC or previously prescribed medications were not formally monitored, possibly introducing errors.

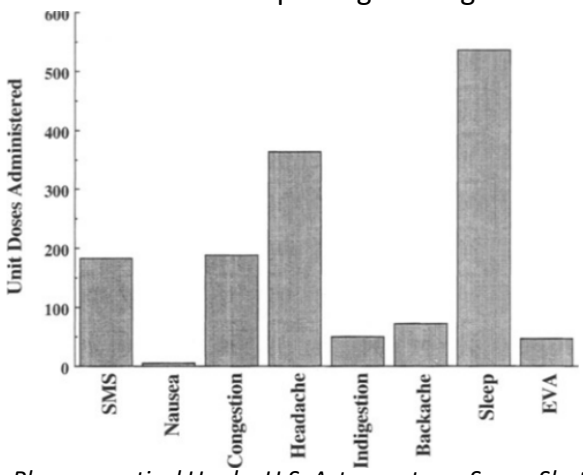
Background

Medication Effectiveness

Gravity transitions, radiation, and a variety of potential physiological changes all are concerns that can potentially impact medication effectiveness during spaceflight. The previously mentioned underreporting of medication use as well as lack of metabolism half-life, or peak concentrations, has complicated medication effectiveness reporting. Studies have occurred that describe crewmember feedback regarding effectiveness or perceived effectiveness of medications.

Putcha et al. Pharmaceutical Use Study (1999) – Evaluated crewmember reporting after 79 shuttle missions and 219 reports which showed 94% of crewmembers used medications, 85% doses had no side effects, 80% doses perceived effective by recipient. Medication ineffectiveness reporting was highest in the first day.

- Doses in order of use were sleep, headache, congestion, and space motion sickness (SMS).
- 47% took SMS formulations (most often the first day).
- 44.7% used sleep aids (throughout the mission).
- Pain medications most often in first 4 mission days.
- Decongestants used throughout.
- When effectiveness and side effects were examined simultaneously over the course of the missions, most of the adverse events were found to occur during the first mission day.



Pharmaceutical Use by U.S. Astronauts on Space Shuttle Missions 1999

Drugs taken were most often reported as effective, with 54% reported as being "very efficacious," 30% "moderately efficacious," and 7% "mildly efficacious." Only 8% of all drug treatments were reported as "not efficacious" (see below). Non-effectiveness can also occur when medications are used for the wrong purpose – e.g., fluid shifts to the head can appear as nasal congestion but will not be relieved by decongestants.

TABLE II. DRUG-DOSE EVENTS RATED "NOT EFFECTIVE" OR "MILDLY EFFECTIVE."

Drug Names	# "Not Effective"/ Total # Doses	%	# "Mildly Effective"/ Total # Doses	%
Afrin (nasal spray)	1/103	1	not reported	N/A
Ambien (zolpidem)	4/58	7	1/58	1.7
Aspirin (acetylsalicylic acid)	3/95	3.2	3/95	3.2
Dalmane (flurazepam)	3/44	6.8	3/44	6.8
Phen/Dex (promethazine and dextroamphetamine)	4/36	11.1	not reported	N/A
Phenergan (promethazine)	15/148	10.1	2/148	1.4
Restoril (temazepam)	7/387	1.8	6/387	1.6
Sudafed (pseudoephedrine)	5/129	3.9	not reported	N/A
Torecan (thiethylperazine)	2/5	40	not reported	N/A
Dulcolax (bisacodyl)	not reported	N/A	5/34	14.7
Entex (phenylephrine/phenylpropanolamine)	not reported	N/A	6/48	12.5
Phazyme (simethecone)	not reported	N/A	6/14	43
Tylenol (acetaminophen)	not reported	N/A	9/244	3.7

Pharmaceutical Use by U.S. Astronauts on Space Shuttle Missions 1999

Background

Drug Expiration and Shelf Life

Medication expiration poses a big challenge to providers of health care for long duration spaceflight. Many medications expire within 1-5 years and without resupply, medication availability and usability is in question.

Expiration date: The final date at which the manufacturer can still guarantee the full potency and safety of the drug when stored under proper conditions.

Shelf-life: Date determined by drug manufacturers expressed as an expiration date after which time the manufacturer cannot guarantee the stability or potency of the medication.

**Neither shelf-life nor expiration date state that medications are harmful if used beyond the identified date, and currently there is very little information regarding this topic. One medication, Tetracycline, is associated, but not strongly proven, with potential harm of increased risk of kidney damage (Fanconi Syndrome) when used beyond expiration (see *Wegienka et al., 1964*).

History of Expiration Dating

In 1979 the U.S. Food and Drug Administration (FDA) passed the law "Current Good Manufacturing practice for finished pharmaceuticals, expiration dating" to ensure people would only use medications that were safe and guaranteed to work as intended under proper storage conditions.

This protection also caused some difficulty. The Department of Health and Human Services (HHS), which stockpiles certain medications for emergency or in the interest of national health, found that they were often needing to replace stockpiles of unused medications at significant expense based on expiration dates.

1986 Federal Shelf-Life Extension Program (SLEP)

This program was Developed by the Department of Defense in conjunction with the FDA to defer cost of drug waste by studying if drugs can be safely used beyond expiration (Lyon et al., 2006). The study demonstrated that many medications, when maintained in original and unbroken packaging, may last significantly longer than labeled expiration dates. Testing showed 88% of medication lots could be extended beyond their stated expiration (stability varied between samples of the same drug, manufacturer, and lot). As a result, some government stockpiled medications can be stored beyond the original expirations for emergency use only.

eMC - A similar study occurred in the UK with the electronic Medicines Compendium (eMC), which contained drug information from UK pharmacy companies.

Many eMC medication shelf lives were changed by manufactures and extended for public use up to 3-6 years (practice is not yet adopted by FDA).

Sample of SLEP medication extensions

Drug name	Extension (avg months)
Morphine Sulfate injectable	89 (35-119)
Naproxen Tablets	52 (46-62)
Ciprofloxacin Tabs	55 (12-142)
Doxycycline Caps	50 (37-66)

Source: Lyon et al. 2006

Other Concerns

Some medications may be more susceptible to bacterial growth or loss of stability including nitroglycerin, eye drops, liquid antibiotics, and insulin, and are less likely to qualify for extended shelf-life program.

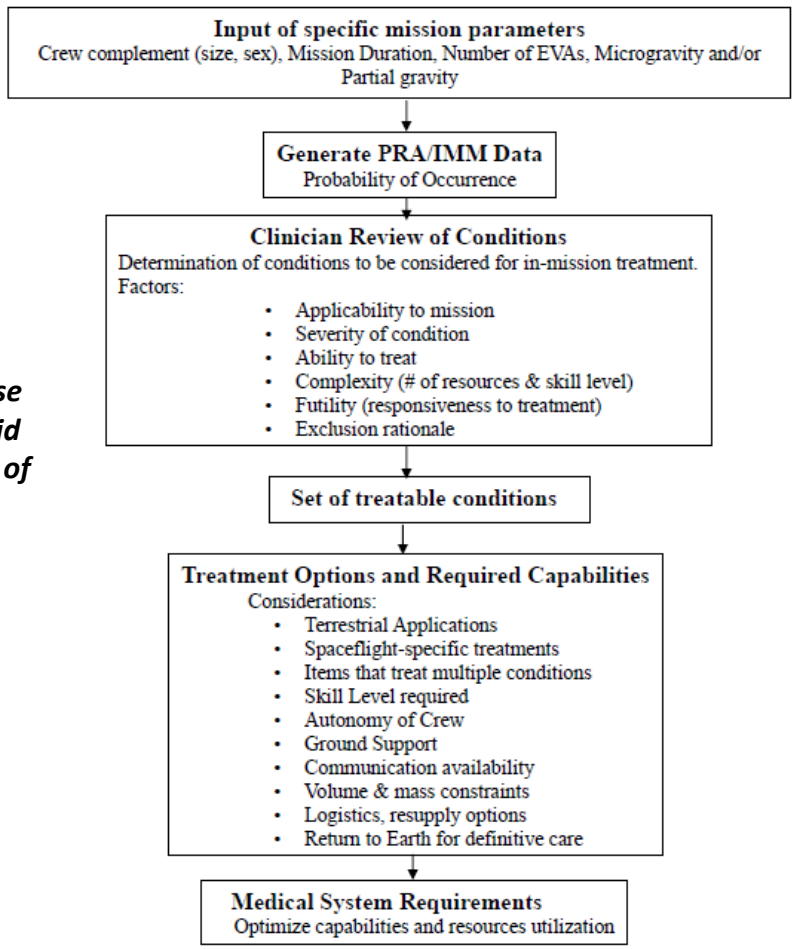
Application

Choosing Pharmaceuticals for Spaceflight

In addition to considering crewmember physiological aspects, information obtained from probabilistic risk assessment (PRA) aids in determining optimal formulary. The PRA tool helps predict medication needs and limitations for each specific vehicle and mission. PRA is a comprehensive, structured, and logical analysis method used as a decision support tool aiding clinical stakeholders and mission planners in providing probability of occurrence of medical conditions based on past spaceflight experience coupled with terrestrial occurrences of medical conditions. Disease states and medical conditions are identified through individual needs, clinical practice guidelines, flight surgeon recommendations, and flight surgeon knowledge. These disease states are fed into an analysis program (PRA/ Integrated Medical Model (IMM)) which considers many simulations ultimately identifying cases that will be at a higher risk for occurring in spaceflight. Once the most likely medical needs are identified, the needed pharmaceuticals or treatment options can be considered, including evidence-based effectiveness, storage requirements, size and weight, and expiration date optimization.

[V2 7043] Medical Capability A medical system shall be provided to the crew to meet the medical requirements of NASA-STD-3001, Volume 1. *From NASA-STD-3001 Vol 2, Rev D.*

Outline for the Use of PRA Data to Aid in the Generation of a Medical Conditions List



Application

Integrated medical model (IMM) - A type of PRA developed by the Human Research Program; a stochastic decision support tool that is available for use by clinical stakeholders, spaceflight mission planners, and medical system designers to aid in assessing risks and optimizing medical systems.

Sample IMM Output

	Medical Condition	Likelihood
1	Late Insomnia	13.85 per mission
2	Skin Abrasion	9.86 per mission
3	Skin Rash	9.83 per mission
4	Eye Abrasion	7.42 per mission
5	Late Headache	5.25 per mission
6	Space Motion Sickness (SAS)	4.37 per mission
7	Diarrhea	3.53 per mission
8	Nasal Congestion	3.51 per mission
9	Respiratory Infection	3.46 per mission
10	Back Injury	3.41 per mission

Sample of medical conditions identified during spaceflight

Musculoskeletal conditions	Acute arthritis Acute compartment syndrome Back injury (sprain/strain) Dislocation (finger, elbow, shoulder) Fingernail delamination (EVA related) Fracture (finger, hand, wrist/arm, distal leg, hip/proximal femur, thoracolumbar spine, cervical spine) Hand injury (EVA related) Joint sprain/strain (shoulder, elbow, wrist, hip, knee, ankle) Lower extremity stress fracture Muscular sprain/strain Neck injury (sprain/strain) Overuse injury – Upper or lower extremity Paresthesia Subungual hematoma Suit contact injury (EVA related) Vertebral disc injury
Dermatological conditions	Burn – Chemical, skin **Cellulitis – Bacterial skin infection *** Herpes zoster (Shingles) **Skin abrasion *** **Skin laceration *** **Skin rash *** Toxic dermal exposure Viral/fungal skin infection

Conditions noted with an asterisk (*) should be addressed on every mission regardless of the DRM parameters.

Background

Medication Storage and Packaging

NASA must consider logistical factors such as stowage and inventory, as well as formulary needs, when packing medication kits.

Considerations for Medical Kit Content

- Volume
- Mass
- Waste (excess packaging)
- Stability and sterility
- Storage conditions
- Pharmaceutical issues - PK/PD toxic metabolites
- Drug delivery systems ability in space
- Drug availability - shortages
- Packaging/repackaging effect on stability
- Astronaut personal medications
- Vehicle and suit environmental impacts

A medical technician surrounded by medical kits for the ISS Crew. *Source: NASA*

[V2 7050] Stowage Provisions The system shall provide for the stowage of hardware and supplies, to include location, restraint, and protection for these items.
[V2 7055] Priority of Stowage Accessibility Stowage items shall be accessible in accordance with their use, with the easiest accessibility for mission-critical and most frequently used items.
From: NASA-STD-3001 Vol 2, Rev D

Onboard Personal Medical Kit Crewmembers are allowed to bring a personal supply of medications or medical supplies. These are currently referred to as ISS Medical Accessory Kits (IMAKs). This name will vary depending on the program, for example, future medical kits for Orion are referred to as Orion Medical Accessory Kits (OMAKs). The medical team needs to consider this content ahead of time to evaluate any potential medication interactions.

In-flight Medication Considerations

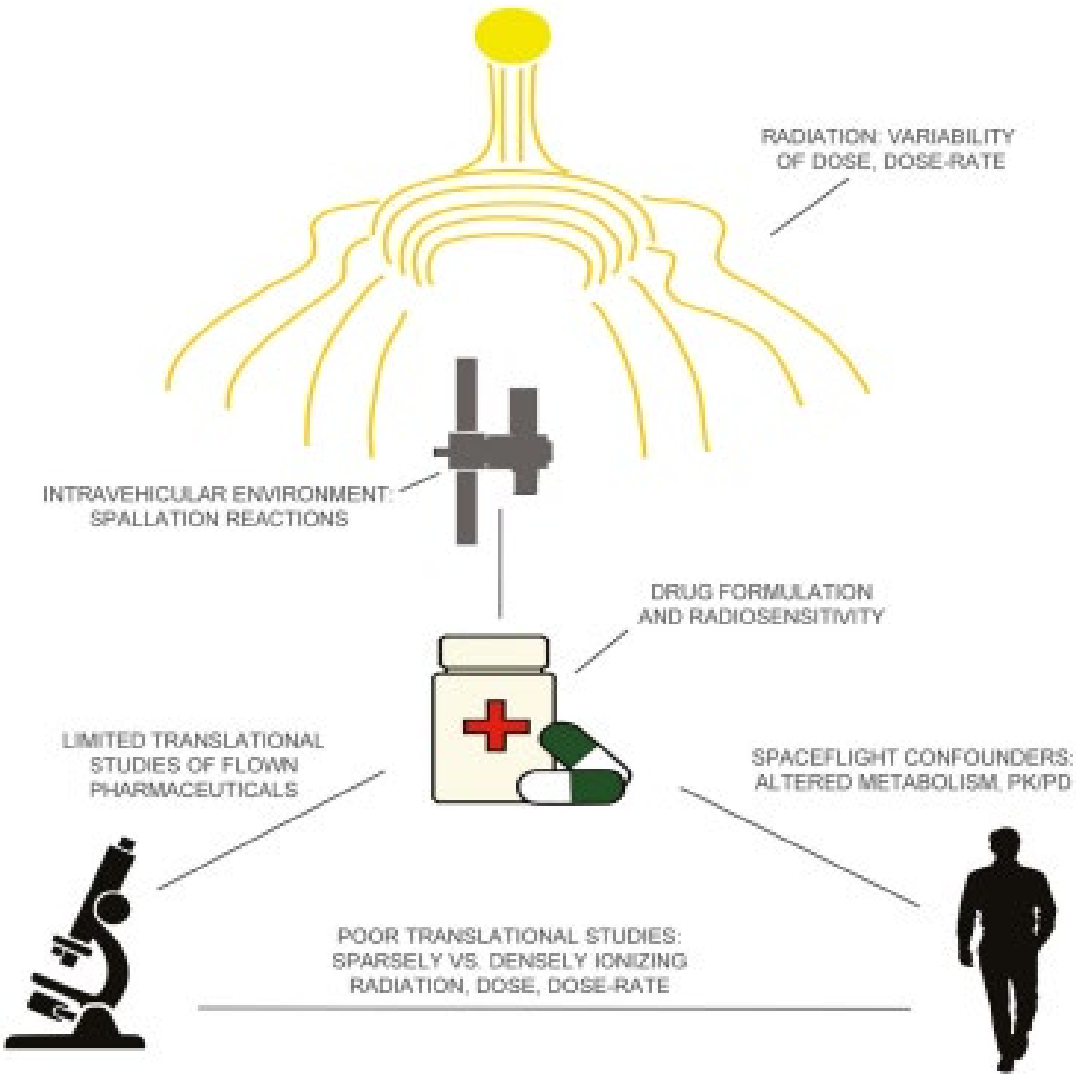
- Shelf life is a driver of medication as expiration is a limiting factor when flying medications. We can only legally pack medications that have manufacturer expiration data.
- Need to consider the time it takes to pack and transport to launch site.
- Toxicology considers all medications for active and inactive ingredients as possible toxic exposure.
- Shipping happens during prelaunch timeframe, need to ensure storage chain requirements are followed.
- Predict any side effects and interactions, including personal medications.
- Provide education regarding all medications.
- Consider administration, absorption, metabolism, elimination, clinical response, toxicity, and effectiveness.
- Consider any physiological change that can cause medications to work differently.
- International medications – may need additional information such as education and storage if not familiar.
- Inventory management—ensure medications are packed to be accessible and designed to best manage expiration parameters.
- May have multiple medication packs depending on mission design.

Background

Radiation

The uncertainty of the effect radiation exposure has on pharmaceuticals during spaceflight is a subject of concern and study. During spaceflight, radiation can potentially cause direct or indirect damage to biological cells by disrupting genetics and biochemistry. **Ionizing radiation exposure in LEO as well as the Earth's protective magnetic field creates an environment that thus far has not been found to significantly interfere with the usability of medications.** Long duration flights in deep space, however, will experience more dangerous galactic cosmic rays (GCR) and without the Earth's magnetic field protection, it is unknown whether this will affect drug stability or produce potentially toxic byproducts in medicines.

Uncertainty regarding radiation exposure during long duration spaceflight



Supplying a pharmacy for NASA exploration spaceflight: challenges and current understanding Blue et al. (2019)

Background

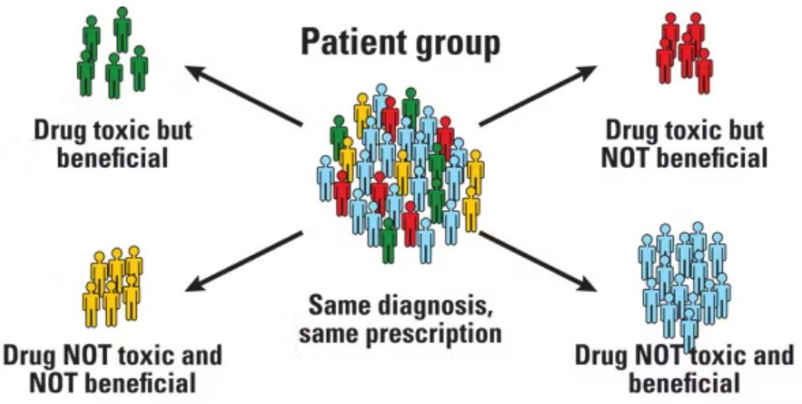
Pharmacogenomics The study of how a person's genes affect their response to medications. Medication effectiveness can vary among patients, some will attain the desired effects with no problems while others may have an adverse drug reaction or receive no benefit from taking the medication. One cause of medication reaction variability is the fact that patients can have differences in enzymes which help to metabolize medications into usable products. Patients with enzymes which are more active have increased metabolism and may break down the medication too quickly to be able to work in the manner designed. If the patient enzymes are less active, medication is not broken down quickly enough and patient may be exposed to unexpected chemicals for longer periods of time which can cause adverse or toxic effects. Studies have also found particularly strong variances among specific cultural populations.

Pharmacogenomics and Spaceflight Pharmacogenomics information is not currently being used to choose spaceflight medications but is being studied as it could be helpful when choosing the optimal effective medications to include in each mission medication kit.

Pharmacogenomics Study Stengl et al. (2014) study explored 78 drugs permanently available on the ISS to determine variability the elimination of medications among crewmembers, and if this variability would require individual dose changes in order to prevent therapy failure or exposure to toxic adverse effects.
Results: 24 drugs showed metabolism is affected by polymorphic metabolizing enzymes, but not enough evidence was present on how polymorphisms affects drug exposure to predict therapeutic recommendations or dose adjustments to make genetic testing a requirement at this time.

Pharmacogenomics Examples Although we do not have enough information at present to base medical kit formulary choices on pharmacogenomics, we can still be aware of possible impacts. For example, enzyme CYP2D6 has been studied and found to have significant variability with patients ranging from poor metabolizers, through ultrarapid metabolizers. CYP2D6 is involved in the metabolism of 11 medications currently on the ISS medical formulary including metoprolol, a heart medication, which when taken by poor metabolizers (PM) can lead to symptoms of bradycardia and by ultrarapid metabolizers cause twofold higher clearances, not treating patient's symptoms or disease properly. Pharmacogenomics is new in its use and not standard practice in spaceflight crews at this time but is something being studied for effectiveness for future long-distance spaceflight.

Example of Pharmacogenomics



Source: Journal of Solid Tumors, 2012

Background

History of Medication Kits

Mercury Medications were available for emergency auto injectors:

- Cyclizine for motion sickness, epinephrine for injury or shock, meperidine for pain, dextroamphetamine sulfate for alertness and response time.

Gemini Higher quantities of medications for longer missions, included a first-aid kit:

- Medications added included pseudoephedrine for congestion, as well as tetracycline for infection or diarrhea and eye drop medication.

Apollo Continued to adjust and add medications per needs assessed after each flight:

- Included lunar module kit to accommodate crew split and medication for sleep disruption, cardiac dysrhythmias, eye, ear, multivitamins, decongestant/antihistamine, antibiotics, analgesics, GI, sedative, and stimulant medications.

Skylab Longer missions required larger and more comprehensive medical packs:

- Medications similar to Apollo, introduced additional medical kits including dental kit, diagnostic kit including hematology, urinalysis, and therapeutic kit including laryngoscope and airway equipment. Astronauts received 80 hours of paramedic training prior to launch.

Space Shuttle Program Crew Medical Officer on each flight:

- Three kits including medication kit, medication and bandage kit (MBK), and emergency medical kit (EMK); kits contained subpacks to further organize and make medications accessible.

International Space Station Two medical kits, one for the Russian segment and one for the US segment:

- Contains 190 medications to treat anticipated medical conditions, medical officer trained in first aid and emergency medical and include personal medication kits for crew (IMAK).

Sample Medication Kit Lists

Mercury-4	Gemini-10	Apollo-30
Cyclizine	Cyclizine	Acetaminophen
Dextroamphetamine	Dextroamphetamine	Ampicillin
Epinephrine	Diphenoxylate	Aspirin
Meperidine	Pseudoephedrine	Atropine
	ASA/phen/caffeine	Bacitracin
	Meperidine	Cyclizine
	Methyl Cellulose	Dextroamphetamine
		Simethicone
		Tetracycline
		Tetrahydralazine

See next page for additional medication lists

Medication list from Principles of Clinical Medicine for Spaceflight, Michael Barratt Chapter 6 Spaceflight Medical Systems Pg 201-231.

Background

Space Shuttle Medication List

Proparacaine eye drops	Meperdine	Immodium	Nitrostat SL	Acetaminophen with Codeine
Zolpidem	Eugenol	Verapamil	Pepto Bismal	Diazepam
Amikacin	Marcaine/bupivacaine	Triamcinolone	Phazyme 125	Vidarabine
Amoxicillin	Dextroamphetamine	Lidocaine	Promethazine	Vosol HC otic
Anusol HC	Acetazolamide	clotrimazoe	Polysporin	xylocaine
Ascriptin	Bisacodyl	Lubricant	Povidine iodine	Azithromycin
Atropine	Cefadroxil	Morphine Sulfate	Albuterol inhaler	
Sulfamethoxazole/trimethoprim		Ibuprofen	Phenazopyridine	
diphenhydramine	Entex LA	Clotrimazole	Refresh eye drops	
Ciloxan eye drops	Epinephrine	Mylanta	Temazepam	
Ciprofloxacin	Metronidazole	Naloxone	Rimantadine	
Loratadine	Gentamicin	Neosporin Plus	Silvadene	
Cyclogyl/cyclopentolate	Haloperidol	Nitroglycerin parch	Acetaminophen	

Medication list from Principles of Clinical Medicine for Spaceflight, Michael Barratt Chapter 6 Spaceflight Medical Systems Pg 201-231.

Background

The ISS medication kit includes nine individual packs with medications and supplies: Emergency Medical, Convenience Med, Oral Med, Topical and Injectable Med, Diagnostic, Minor Treatment, Medical Supply, IV Supply, and Physician Equipment Pack. Shown below are the medications:

Convenience Med Pack	Emergency Pak		Topical /Injectable Med Pak	
Bacitracin	Atropine	Venlafaxine	Benzocaine Swabstick	Eugenol
Loperamide (Imodium)	Epinephrine	Lisinopril	Tetracaine	Carbamide Peroxide (Debrox)
Fexofenadine (Allegra)	Lidocaine	Metoprolol XL	Lidocaine and Epinephrine	Cyclopentolate (Cyclogyl)
Loratadine (Claritin)		Nitroglycerin	Lidocaine (Xylocaine)	Fluorescein Strip
Olopatadine (Pataday)	**Oral Pak**	Pseudoephedrine	Lidocaine Jelly	Tropicamide (Mydriacyl)
Oxymetazoline (Afrin)	Acetazolamide (Diamox)	Medroxyprogesterone	Bacitracin	Glycopyrrolate
Pseudoephedrine	Amoxicillin	Norgestrel and Ethinyl Estradiol	Ceftriaxone	Ketamine
Carboxymethylcellulose (Refresh Plus)	Azithromycin	Hydrocodone and Acetaminophen	Ciprofloxacin and Dexamethasone	Hydromorphone
Hypromellose (Nature's Tears)	Clindamycin	Meclizine	Ertapenem	Ketorolac
Mineral Oil and White Petrolatum (Refresh PM)	Doxycycline	Ondansetron	Erythromycin	Promethazine
Sodium Chloride (AYR Saline)	Levofloxacin	Promethazine	Moxifloxacin	Dexamethasone
Acetaminophen (Tylenol)	Metronidazole	Methylprednisolone	Mupriocin	Fluocinonide
Aspirin	Sulfamethoxazole Trimethoprim	Prednisone	Tobramycin and Dexamethasone	
Ibuprofen (Motrin)	Fluconazole	Modafinil	Clotrimazole	
Melatonin	Diphenhydramine	Bismuth Subsalicylate	Cromolyn (Nasalcrom)	
Zaleplon (Sonata)	Fexofenadine	Omeprazole	Diphenhydramine	
Zolpidem (Ambien)	Phenytoin	Ranitidine	Aripiprazole	
Hydrocortisone	Valacyclovir	Tamsulosin	Diazepam	
Caffeine (Vivarin)	Aripiprazole		Albuterol Proventil	
Modafinil (Provigil)	Lorazepam		Fluticasone Flovent	
Bisacodyl (Dulcolax)	Sertraline		Salmeterol Serevent	

National Aeronautics and Space Administration (NASA) Emergency Medical Procedures Manual for the International Space Station (ISS) [partial], 2016

Application

Medication Challenges

In-Suit Medication Use

Historically, a crewmember would plan to spend no more than 6 hours in a pressurized spacesuit for an EVA and would not need to take medications while in-suit. In future missions, situations may arise that require crewmembers to stay suited for longer periods and take medications while suited. For example:

- Long duration missions have longer transit times (i.e., return from the Moon can take 144 hours or more). Crewmembers must have the capability to stay suited for long periods of time in the event of unplanned cabin depressurization and ability to take medication if needed.
- Crewmembers may have much longer EVA capacity or be traveling in an unpressurized rover, requiring them to be suited for long periods of time and need the capability to access medications.

[V2 11027] Suited Medication Administration The system shall provide a means for administration of medication to a suited, pressurized crewmember for pressurized suited exposures greater than 12 hours.
From: NASA-STD-3001 Vol 2, Rev D

Medication Delivery Options

NASA is studying many options to find the best way to provide medications to suited crewmembers. Injections and oral medications are both options being considered but each have their own challenges.

Injectable Medication Challenges

- The ability to physically use the medical delivery device at the desired location while the astronaut is gloved and possibly seated is challenging.
- Not all medications are available as injectables so this method can decrease treatment options.
- Behavior of the fluid in a off nominal pressure/temperature environment can make injections difficult, for example, when giving an injectable medication the bubble within a syringe will expand as pressure decreases, including complete vaporization at very low pressures/vacuum.
- Require additional suit opening that can disrupt suit integrity, posing safety risks.

Oral Medication Challenges

- The capability to provide an easily accessible, and administrable delivery of oral medication compatible with a pressurized suit is challenging.
- Programs are currently considering using hand-held tools to assist with oral pill port type medication delivery which can pose a challenge when the astronaut has a gloved hand.
- The oral delivery device limits what size of tablets/capsules can be administered, limiting medication options.
- Oral medication can potentially introduce residue contamination.

Air Force U-2 suits have a port for food and pills in the hard shell.

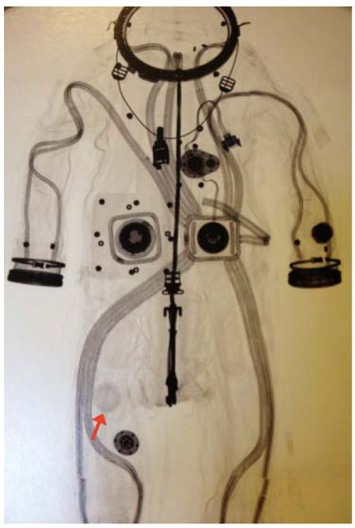
Toxic off gassing Another challenge is to ensure medications do not introduce off gassing or toxicity that may be damaging to the crew or vehicle.

[V2 7115] Medical Treatment, Personal Supplies, and Impacts to Environmental Systems Medical treatment, including pharmaceuticals, non-pharmaceutical crew care items, and related supplies, shall be evaluated for impacts on vehicle systems.
From: *NASA-STD-3001 Vol 2, Rev D*

Application

History Apollo In-Suit Medication

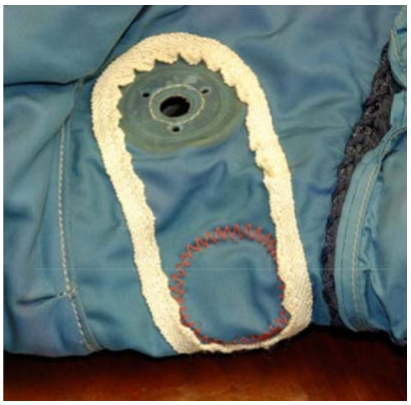
When Apollo spacesuits were designed, the needs differed from the Mercury and Gemini programs because the transit time lengthened from hours to days. The suit needed to address additional risks imposed by the longer duration including if a contingency situation required the crew to remain in pressurized suits, they must be able to administer an injection while suited in the event of illness or injury. The Apollo Program identified a requirement (see below) for the Apollo EMU to have a biomedical injection patch to facilitate the injection while in a pressurized suit. This patch is no longer in use, however in-suit medication administration options are currently being studied.



X-ray image of David Clark Apollo A-IC suit. *Source: Smithsonian Institute Image*

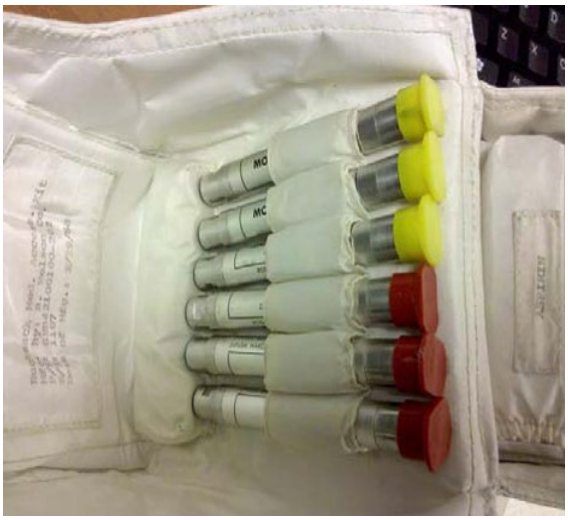
Right: Apollo Suit Injection Requirement. Apollo space Suit Assembly Design and Performance Specification, October 12, 1964.

Medical Injection Provisions - The PGA shall provide the capability for the crewman to administer to himself hypodermic injections utilizing a spring-loaded plunger type needle, while in a pressurized PGA. The PGA shall provide, in a location to be determined by NASA, features which shall allow insertion of the needle and subsequent withdrawal, without endangering the pressure integrity or reliability of the suit, and shall be self-sealing to prevent the loss of gas at the site of the needle penetration. Best location for medical injections is on the ventrolateral aspect of the thigh, approximately half-way between the knee and the hip. An alternate location would be the deltoid area of either arm.



Apollo suit medication injection patch. *Source: NASA*

The Apollo medical kits housed pre-filled medical syringes inside a pressurized aluminum tube. Injections were activated by pressing a button at the top of the device, which caused the syringe and needle to displace, driving the needle through the seal on the device and the injection patch on the EVA suit into the muscle.



Source: NASA

Back-Up

Major Changes Between Revisions

Original → Rev A

- Updated information and standards to be consistent with NASA-STD-3001 Volume 1 Rev C and Volume 2 Rev D.
- Added introduction with additional content, updated standards, added images of more current med kits.
- Deleted back risk and inflight medical risk for accuracy, added “other environmental factors” to space radiation bubble.
- New page with image “effects of space on the human body”, added wording regarding physiological, environmental, and immunologic changes information.
- Added additional information and graph regarding In-Mission Medication Effectiveness.
- Added additional detailed information regarding medication selection.
- Added Information and graph regarding Dose Tracker Study.
- Added additional information regarding Medication storage, packaging, shelf life, Onboard medical kit, Federal Shelf-Life Extension Program.
- Removed inflight medical kit image.
- Removed Apollo application information.
- New slide regarding radiation effects on medication.
- Added new slide analog and spaceflight to study medication use information.
- Added new slide history of medication kits.
- Added new slide information regarding pharmacogenomics.
- Added new slide regarding medication delivery and suited medication challenges.
- Added new slide with images regarding in suited medication administration.

Referenced Technical Requirements

View the current versions of NASA-STD-3001 Volume 1 & Volume 2 on the OCHMO Standards website

NASA-STD-3001 Volume 1 Revision C

[V1 3004] In-Mission Medical Care All programs shall provide training, in-mission medical capabilities, and resources to diagnose and treat potential medical conditions based on epidemiological evidence-based PRA, individual crewmember needs, clinical practice guidelines, flight surgeon expertise, historical review, mission parameters, and vehicle-derived limitations. These analyses consider the needs and limitations of each specific vehicle and design reference mission (DRM) with particular attention to parameters such as mission duration, expected return time to Earth, mission route and destination, expected radiation profile, concept of operations, and more. In-mission capabilities (including hardware and software), resources (including consumables), and training to enable in-mission medical care, and behavioral care, are to include, but are not limited to: (see NASA-STD-3001 Volume 1 Rev C for full technical requirement).

[V1 4009] Sensorimotor Countermeasures Countermeasures shall maintain sensorimotor function within performance limits.

[V1 4016] In-Mission Hematological/Immunological Countermeasures In-mission countermeasures shall be in place to sustain hematological/immunological parameters within the normal range as determined by direct or indirect means.

[V1 4027] In-Mission Bone Countermeasures Countermeasures shall maintain bone mineral density of the hip and spine at or above 95% of pre-mission values and at or above 90% for the femoral neck.

[V1 5001] Medical Training Medical training shall be provided to crewmembers, flight surgeons (FSs), mission control support staff, and other ground support personnel (GSP).

[V1 5007] Support Personnel Training Supervised training programs shall be implemented for individuals including but not limited to NASA personnel, international partners, and commercial/private space programs, who require knowledge of space medicine or flight medical procedures, such as flight directors, medical consultants, and/or other personnel deemed appropriate as part of the Medical and Crew Health Technical Requirements Document.

[V1 6001] Circadian Shifting Operations and Fatigue Management Crew schedule planning and operations shall be provided to include circadian entrainment, work/rest schedule assessment, task loading assessment, countermeasures, and special activities.

[V1 7001] Crew Health Results The results of all crew health monitoring shall be kept in a permanent retrievable format for evaluation including trend analysis.

[V1 7002] Crew Records Transmission The method of transmission of crewmembers' medical health data shall meet the medical operational needs of the program.

[V1 7003] Crew Records Security The method for handling, storing, and transmission of crewmembers' medical health records shall be secured.

NASA-STD-3001 Volume 2 Revision D

[V2 7038] Physiological Countermeasures Capability The system shall provide countermeasures to meet crew bone, muscle, sensorimotor, thermoregulation, and aerobic/cardiovascular requirements defined in NASA-STD-3001, Volume 1.

Referenced Technical Requirements

View the current versions of NASA-STD-3001 Volume 1 & Volume 2 on the OCHMO Standards website

NASA-STD-3001 Volume 2, Revision D

[V2 7042] Orthostatic Intolerance Countermeasures The system shall provide countermeasures to mitigate the effects of orthostatic intolerance when transitioning from weightlessness to gravity environments and during Az (head-to-foot) vehicle accelerations defined in the sustained acceleration limits.

[V2 7043] Medical Capability A medical system shall be provided to the crew to meet the medical requirements of NASA-STD-3001, Volume 1.

[V2 7045] Medical Equipment Usability Medical equipment shall be usable by non-physician crewmembers in the event that a physician crewmember is not present or is the one who requires medical treatment.

[V2 7115] Medical Treatment, Personal Supplies, and Impacts to Environmental Systems Medical treatment, including pharmaceuticals, nonpharmaceutical crew care items, and related supplies, shall be evaluated for impacts on vehicle systems.

[V2 7050] Stowage Provisions The system shall provide for the stowage of hardware and supplies, to include location, restraint, and protection for these items.

[V2 7051] Personal Stowage The system shall provide a stowage location for personal items and clothing.

[V2 7052] Stowage Location All relocatable items, e.g., food, EVA suits, and spare parts, shall have a dedicated stowage location.

[V2 7055] Priority of Stowage Accessibility Stowage items shall be accessible in accordance with their use, with the easiest accessibility for mission-critical and most frequently used items.

[V2 7059] Inventory Tracking The system shall provide an inventory management system to track the locations and quantities of items (including hazardous trash) throughout the mission.

[V2 11027] Suited Medication Administration The system shall provide a means for administration of medication to a suited, pressurized crewmember for pressurized suited exposures greater than 12 hours**.**

[V2 11125] Suit Materials Compatibility Pharmaceuticals, topical treatments and cleaning materials shall be compatible with suit materials (internally and externally).

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