National Aeronautics and Space Administration

Limitations in Predicting Radiation-Induced Pharmaceutical Instability during Long-Duration Spaceflight

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OVERVIEW

This presentation will discuss our current understanding of:

- Impact of space radiation on medication stability

We will further discuss opportunities for improved scientific understanding and research for future exploration spaceflight

PHARMACEUTICAL STABILITY

Radiation

Pharmaceutical Stability: Radiation

- Beyond LEO, the most important sources of space radiation consist of galactic cosmic rays (GCR), and Solar Particle Events (SPE).
  - GCR
    - Dose-rates ~0.3 mGy / day from GCR
  - SPE
    - Modeled intravehicular dose-rates: 0 – 2800 mGy / hr during large SPE in interplanetary space
      - Shielding can protect crewmembers AND pharmaceuticals

Pharmaceutical Stability

- Loss of drug stability caused by any alteration of *physical* or *chemical* properties can result in:

  - changed:
    - Appearance
    - Dosage form physical attributes and uniformity
    - Potency
    - Excipient composition

  - or promoted:
    - Excipient-active ingredient interactions
    - Toxic degradation

Pharmaceutical Stability

- To test for stability:
  - Concentration of Active Pharmaceutical Ingredient (API)
    - Acceptable ± limits defined by US Pharmacopoeia
  - API Release Characteristics
    - Dissolution (e.g. tablets, capsules) / Diffusion (e.g. ointments, creams)
  - Presence of degradation products
    - Some known / toxic products have USP-determined limits
  - Visible alteration of physical appearance

Stability Evidence: Flown Studies

References

Chuong 2012 | Cory 2017 | Wu 2016 | Du 2011 | Zwart 2009 | Wotring 2016

Terrestrial Radiation Arm

API (B Vitamin only)

Centrum Silver® Multivitamin*
Women's Once-A-Day® Multivitamin*

Ibuprofen
Levofloxacin
Phenytoin
Sertraline
Valacyclovir

Ibuprofen
Promethazine
Azithromycin

API, Physical Characteristics

Acyclovir
Amoxicillin/Clavulanate
Atorvastatin
Azithromycin
Cefadroxil
Ciprofloxacin
Clotrimazole
Dextroamphetamine
Epinephrine
Fluconazole
Furosemide
Ibuprofen
Imipenem/Cilastin
Levofloxacin
Levothyroxine
Lidocaine
Metoprolol
Metronidazole
Mupirocin
Nasal Cobolamine
Phenytoin
Progestin/Estrogen
Promethazine
Risedronate
Sertraline
Silver Sulfadiazine
Sulfamethoxazole/ Trimethoprim
Temazepam
Triamcinolone

API

Centrum Silver® Multivitamin •
Vitamin D Supplement •

API, Degradants

Aspirin
Acetaminophen**
Ibuprofen
Loratadine** †
Loperamide †
Pseudoephedrine
Melatonin
Modafinil †
Zolpidem †

* Drug tested only for Vit B API
** Drug would fail by today's API standard
† drug had unidentified degradant product

Altered Medication

Unaltered Medication

Pharmaceutical Stability: Radiation

- Risk of Radiation:
  - High-intensity electromagnetic radiation:
    - May cause significant loss of API – can reduce therapeutic effect
    - May initiate formation of degradation products
  - Is radiation contributing to the alterations observed in spaceflight? Or are other environmental factors?

Reference Doses (GCR, SPE)

Photolability

Du et al. 2011 Study Data

Environmental Conditions

- Flight vs. Ground Controls:
  - No significant difference in temperature
  - Minor alterations of humidity
  - Significant difference in radiation exposure:

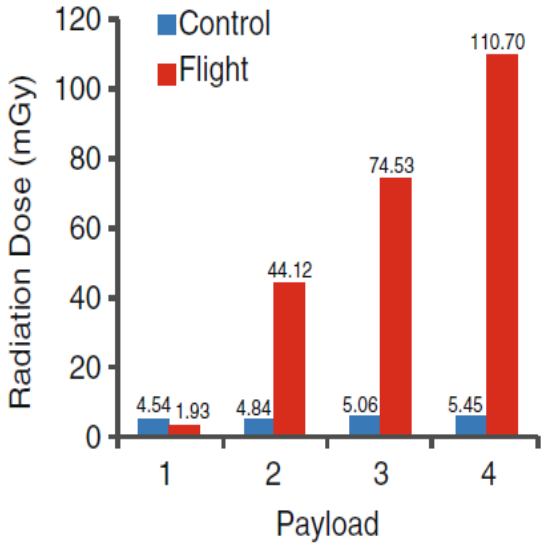


Fig. 7. Comparison of cumulative radiation dose between ground and spaceflight

Ground Control
Flight Samples

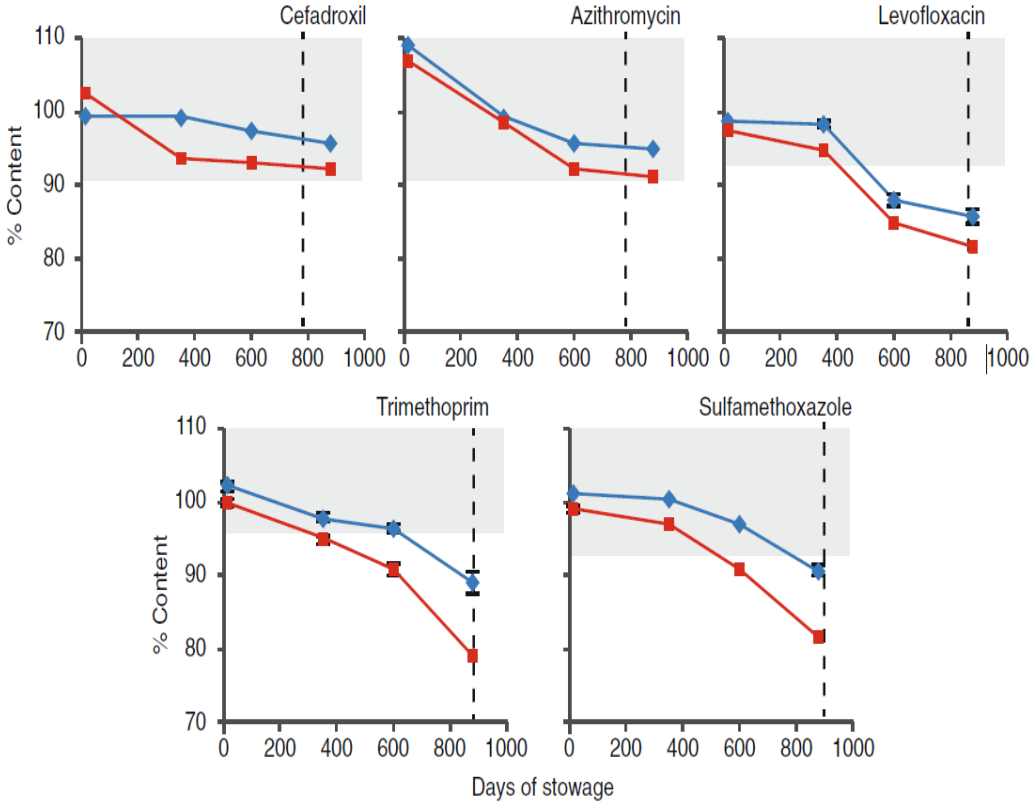


Fig. 5. Degradation of antibiotic tablets. Each data point represents one of four payloads. *Shaded area* represents USP range for label claim; *dashed lines* indicate labeled expiration date

Du et al. 2011 Study Data

Ground Control

Flight Samples

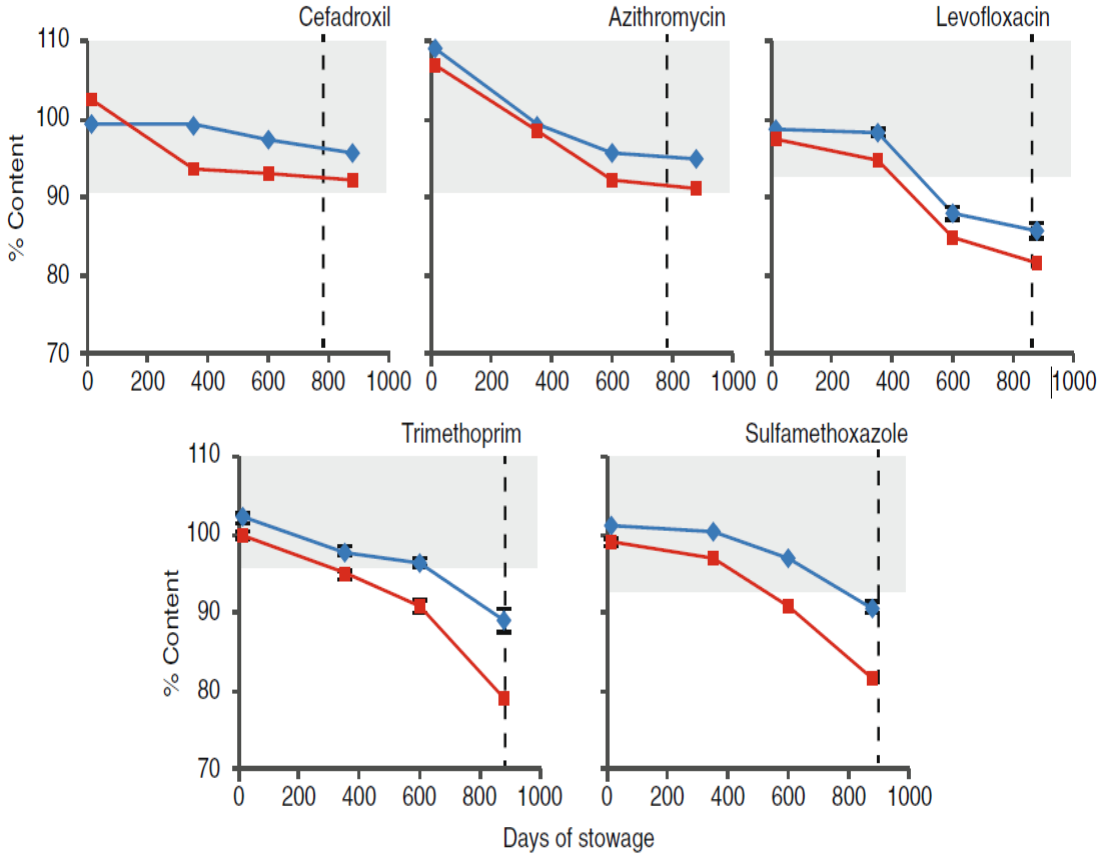


Fig. 5. Degradation of antibiotic tablets. Each data point represents one of four payloads. *Shaded area* represents USP range for label claim; *dashed lines* indicate labeled expiration date

Du et al. 2011 Study Data

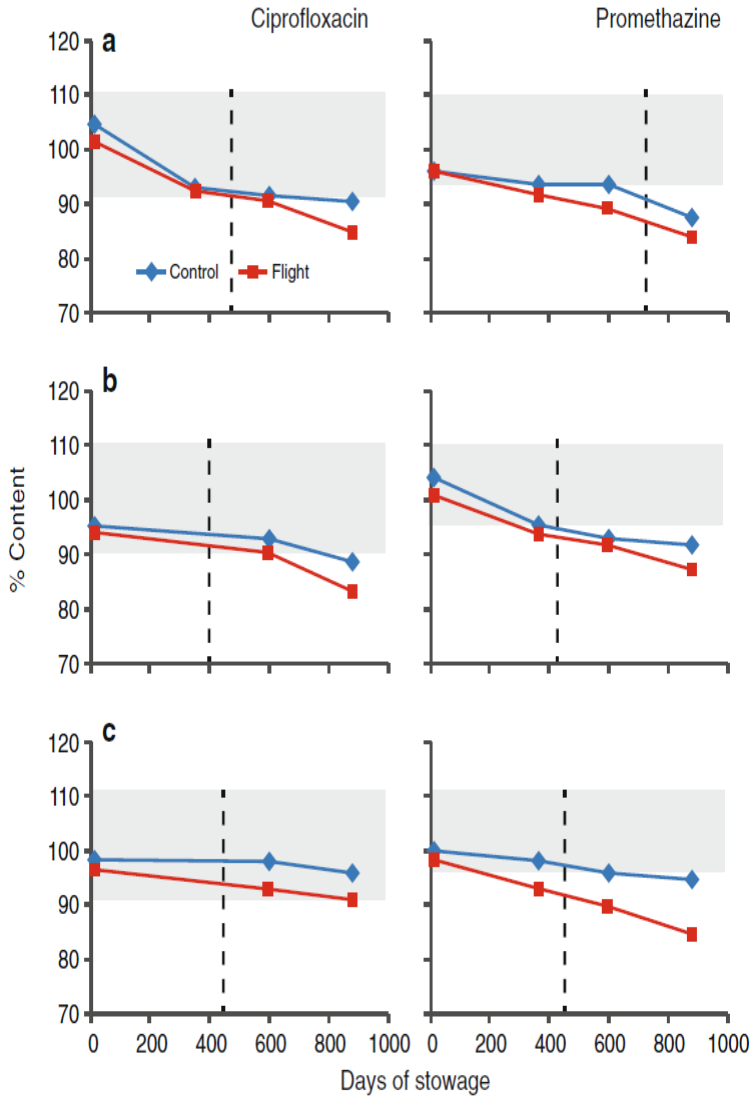


Fig. 4. Degradation of ciprofloxacin and promethazine dosage forms. **a** Solid, **b** semisolid, **c** liquid. Each data point represents one of four payloads. *Shaded area* represents USP range for label claim; *dashed lines* indicate labeled expiration date

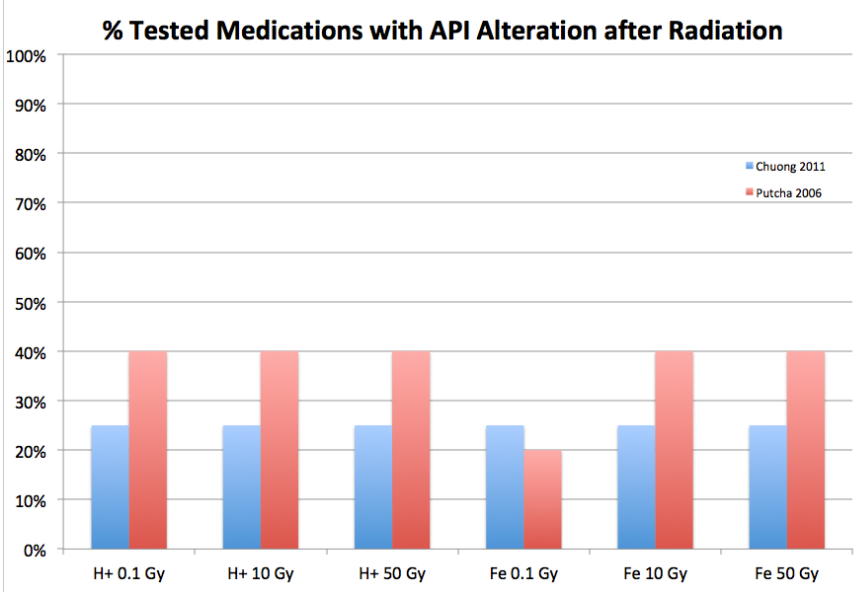
Terrestrial Evidence: Radiation

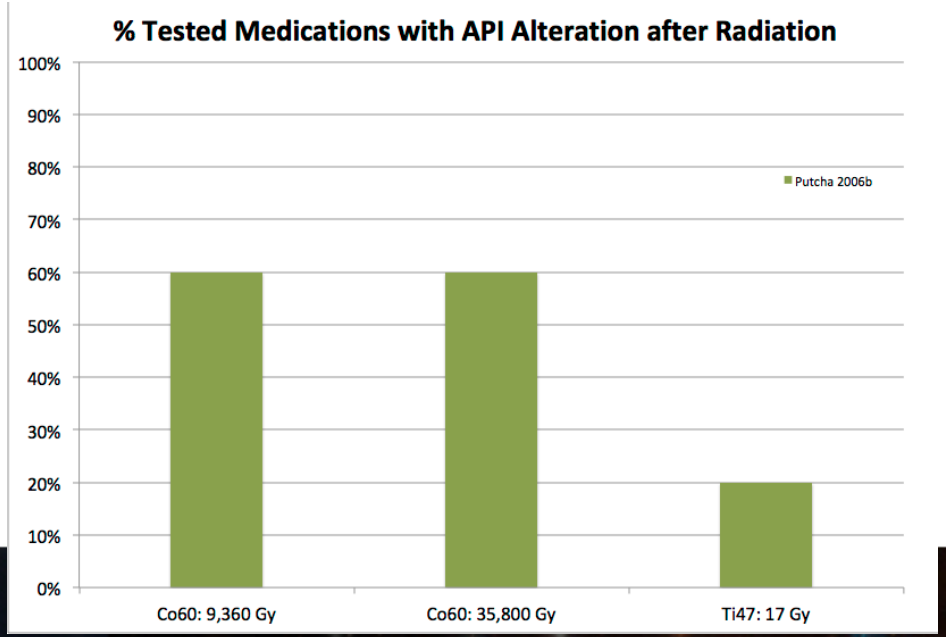
- Difficult to emulate space environment on Earth
  - Limitations:
    - Dose
    - Dose-rate
    - Type of exposure
    - Intravehicular / intrapackaging environment
    - No well-characterized validation studies (ground-to-space)

Supplemental Discussion:
Space Environment Emulation

Terrestrial Evidence: Radiation

- Few terrestrial irradiation studies of pharmaceuticals
  - All show at least some medications with API alteration
  - Study irradiation much higher than even cumulative mission doses
  - Minimal comparative study (Chuong)
  - Difficult to determine significance of irradiation from limited data

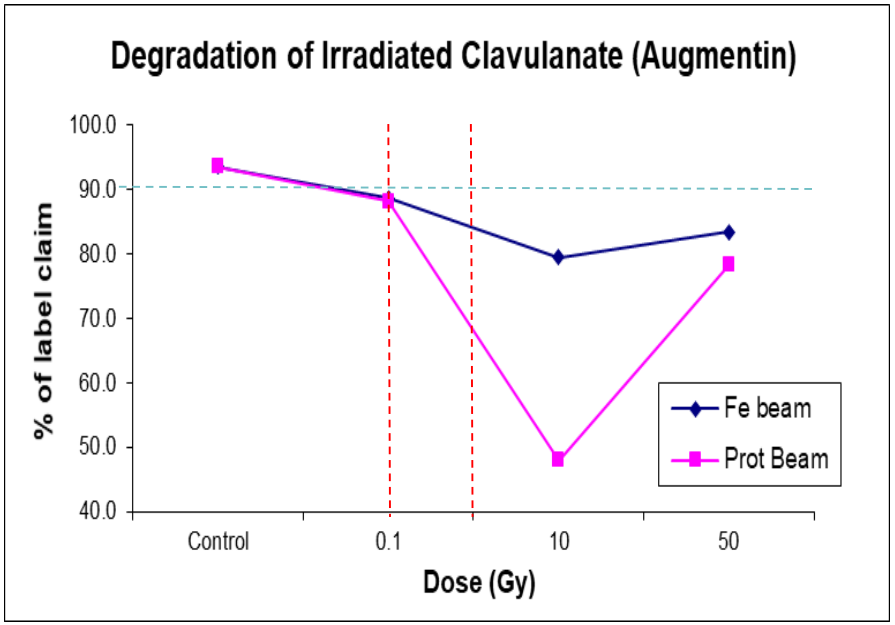




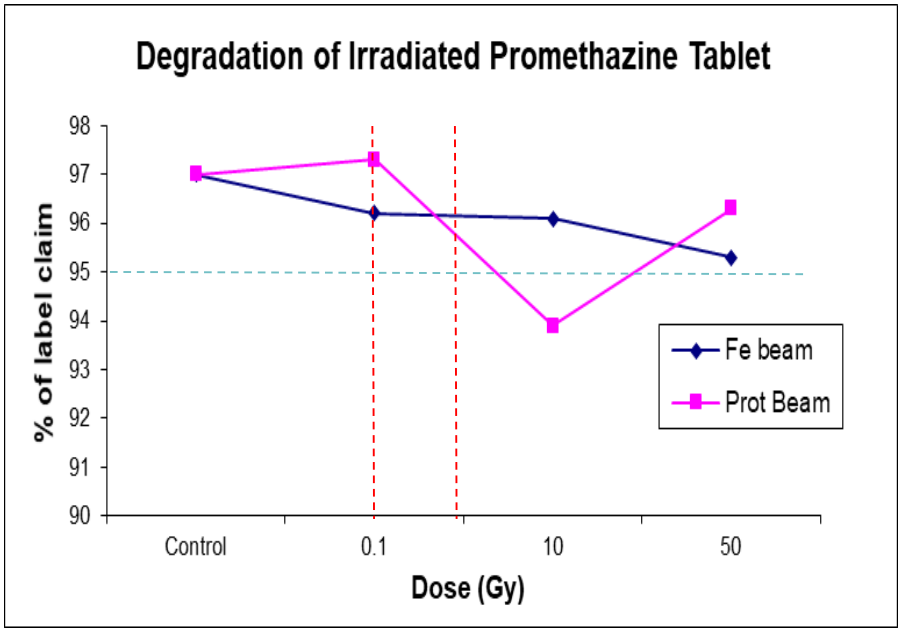
Supplemental data: BCM, NSRL, Chuong

Terrestrial Evidence: Radiation

Clavulanate API % content by dose received



Promethazine API % content by dose received



Why might drug stability following exposure to high-dose **radiation** not necessarily translate to drug stability following exposure to low-dose radiation?

Terrestrial Radiation: Conclusions

- **Uncertainty regarding space radiation**
  - Data points do not align with modeling projections that suggest little-to-no impact of radiation on drug stability
  - Terrestrial radiation studies have been limited
  - Minimal study of comparative effects of space radiation to ground analog radiation

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

1. We have insufficient data collection to understand the effect of the space environment on medications used during missions today

2. Our current understanding of pharmaceutical stability suggests that the interplanetary radiation environment may have a substantial impact on medication stability for long-duration exploration missions

To provide safe and effective medications for exploration spaceflight, we need to balance resources available with a standard of acceptable scientific evidence sufficient to characterize the risk

Recommendations

1. Crew tracking of pharmaceutical usage, effectiveness, and side effects should be encouraged and streamlined

2. Pilot research projects regarding initial characterization of the radiation-related stability issues that may be encountered in flight should be encouraged to build a foundational database from which the need for future, more detailed investigations can be evaluated.

3. NASA and industry / academic partners should actively pursue spaceflight exposures of medications to characterize with the best available evidence the environmental impact on pharmaceuticals in upcoming missions.

QUESTIONS?

BACKUP SLIDES

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Spaceflight Evidence – Pharmaceutical Stability

- Du B, Daniels VR, Vaksman Z, Boyd JL, Crady C, Putcha L. Evaluation of physical and chemical changes in pharmaceuticals flown on space missions. AAPS J 2011; 13:299–308.
- Chuong MC, Prasad D, Leduc B, Du B, Putcha L. Stability of vitamin B complex in multivitamin and multimineral supplement tablets after space flight. J Pharm Biomed Anal 2011; 55:1197–200.
- Wotring VE. Chemical Potency and Degradation Products of Medications Stored Over 550 Earth Days at the International Space Station. AAPS J 2016; 18:210–6.

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- Cory, W, James, V, Lamas, A, Mangiaracina, K, Moon, J. Analysis of degradation of pharmaceuticals stored on the International Space Station. 2017; presented at the HRP Investigator's Workshop, Galveston, TX.
- Wu and Chow, Degradation Analysis of Medications from ISS Using LC-MS/MS Assays – NSBRI RFA-15-01 First Award Fellowship, Final Report, Submitted by 11/29/16

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Limitations of Terrestrial Radiation Research

- Dose – cumulative mission dose delivered over a matter of minutes
- Dose-rate – Significantly higher dose-rate in terrestrial studies or radiostability analyses
  - Altered energy delivery = altered chemical reactions, short-term dosing = no propagation of reaction over time; may alter free-radical generation or exhaustion
- Type of exposure – single ion does not emulate the complexity of the space environment or the varied energy transfers of different ions
- Intravehicular / intrapackaging – added spallation (scatter) ions may alter chemistry or reactivity of exposed drugs

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- Hydrolysis vs. Direct – historically focused on water-based drugs re: increased production of free radical (oxygen species).
  - Direct impact to solid/powder drug lattice may trap free radicals, directly catalyze chemical reaction, or alter excipient structure

Pharmacokinetic / Pharmacodynamic Spaceflight Studies

Flown | Analog




Flown Human Studies

PHARMACEUTICAL STUDIES

Acetaminophen (1987 - 2-4d, 2009 - 1d)
Scopolamine / Dextro-amphetamine (1987 - 1-5d)
Promethazine (2009 - 1d)

Anecdotal reports of failure
1999:
Oxymetazoline (1/103, 1%)
Zolpidem (4/58, 7%)
Acetylsalicylic Acid (3/95, 3%)
Flurazepam (3/44, 7%)
Promethazine / Dextro-amphetamine (4/36, 11%)
Promethazine (15/148, 10%)
Temazepam (7/387, 2%)
Pseudoephedrine (5/129, 4%)
Thiethylperazine (2/5, 40%)
2014:
Zolpidem (76/411, 18%)
Zaleplon (21/66, 32%)

ENZYMATIC / HEPATIC MORPHOLOGY STUDIES

Flown Rodent Studies

P450 Enzyme (1985 - 7d, 1987 - 7d, 1990 - 14d, 1992 - 14d, 2015 - 30d)
Catalase (1998 - 8d)
Glutathione Reductase (1998 - 8d)
Glutathione-Sulfur-Transferase (1985 - 7d, 1998 - 8d)
cGMP Production (1999 - 17d)
Hepatic Cell Morphology (1992)
Hepatic Injury (2016 - 13d, 2017 - 13d)

Bedrest Human Studies

Penicillin (1980* - 7d)
Lidocaine (1980* - 7d, 1982, 1995 - 1-5d)
Benzylpenicillin (1967, 1986 - 4h)
Promethazine (2002)
Acetaminophen (1992 - 4h, 1999 - 7d, 2003 - 1d, 18d, 80d)
Ciprofloxacin (2005 - 3d)
Amoxicillin (1980)

Hind Limb Suspension Rodent Studies

Antipyrine (1995 - 3-7d)
Acetaminophen (2000 - 7d)
3H-Nicotine (1999 - 14d)

P450 (1995 - 3-7d)
cGMP Production (1999 - 17d)
Hepatic Cell Morphology (1992)
Hsp70 / Hsp70mRNA (2010 - 6-96h)

Hind Limb Suspension Model Validation Studies

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Terrestrial Evidence: Radiation

Chuong et al. 2011

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- Multivitamins irradiated, analyzed for Vit B content only
  - Large range in API allowed (90-150%)
  - Significant change in B1 in all irradiated samples and 2 controls
  - API decrease not seen as dramatically in ISS flown samples
- Unclear significance

Kit #	Treatment	Absorbed dose
0001	Heavy iron	10 cGy[a]
0002	Heavy iron	10 Gy
0003	Heavy iron	50 Gy
0004	Proton	10 cGy
0005	Proton	10 Gy
0006	Proton	50 Gy
0007	None	None

Table 2
Contents of vitamins B_1, B_2, B_3 and B_6 (% label claim) in the vitamin tablets retrieved from a payload containing ISS, OES and NASA ground control samples.

	Sample size	Vitamin B_1 (mean ± SD)	Vitamin B_2 (mean ± SD)	Vitamin B_3 (mean ± SD)	Vitamin B_6 (mean ± SD)
Irradiation					
0001	3	53.5 ± 8.3[c]	104.2 ± 11.8	132.2 ± 28.1	113.7 ± 21.5
0002	3	50.1 ± 6.3[c]	98.0 ± 9.3	123.2 ± 25.0	113.4 ± 21.3
0003	3	47.2 ± 6.7[c]	99.1 ± 6.9	128.1 ± 19.7	106.4 ± 20.9
0004	3	49.9 ± 14.9[c]	96.1 ± 9.6	131.2 ± 31.6	113.0 ± 15.6
0005	3	58.5 ± 14.8[c]	98.1 ± 4.8	130.0 ± 27.1	111.4 ± 19.7
0006	3	56.7 ± 12.3[c]	96.1 ± 4.8	127.2 ± 26.1	107.8 ± 20.4
0007	3	55.7 ± 12.6[c]	94.6 ± 3.9	125.5 ± 22.4	109.7 ± 26.8
0012	3	57.2 ± 11.7[c]	94.6 ± 3.9	130.6 ± 28.0	108.4 ± 22.8
G_0[a]	6	112.4 ± 3.8	136.0 ± 1.1	116.7 ± 3.4	147.5 ± 8.0
G_L[b]	3	104.6 ± 6.4	141.4 ± 0.4	119.5 ± 1.7	152.6 ± 1.1

	Sample size	Vitamin B_1 (mean ± SD)	Vitamin B_2 (mean ± SD)	Vitamin B_3 (mean ± SD)	Vitamin B_6 (mean ± SD)
Brand #1					
ISS	3	90.2 ± 34.0	136.0 ± 34.3	103.0 ± 20.3	140.6 ± 21.3

Terrestrial Evidence: Radiation

API content data analysis, BCM Simulation Radiation Study, L. Putcha et al, 2006

RADIATION SOURCE		Control		Gamma				Nucleon Titanium		USP CONTENT REQUIREMENT
IRRADIATION DOSE (KGy)		N/A		9.36		35.8		0.017		
DRUG FORMULATION		PERCENT LABELED CONTENT								
		%	STDEV	%	STDEV	%	STDEV	%	STDEV	
Augmentin® Tablets	Amoxicillin 875 mg	111.5	0.16	104.8	1.49	101.5	NR	109.1	NR	90-120
	Clavulante 125 mg	96.9	0.1	88.1	0.09	83.3	NR	94.5	NR	90-120
Promethazine 25 mg Tablets		98.2	NR	94	NR	NR	NR	96.3	NR	95-110
Promethazine 50 mg/ml Inj. Solution		98.3	0.26	96.8	NR	90.3	1.08	93.7	NR	95-110
Promethazine 25 mg Suppositories		97.6	0.53	95.8	NR	89.5	0.08	95.6	NR	95-110
Bactrim® Tablets	Sulfamethoxazole (800 mg)	97.9	1.27	94.2	NR	93.1	0.37	96	NR	93-107
	Trimethoprim (160 mg)	96.8	1.81	87.9	NR	81.4	3.17	93.6	NR	93-107

NR: No result provided in report

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Terrestrial Evidence: Radiation

API content data analysis, NSRL Simulation Radiation Study, L. Putcha et al, 2006

IRRADIATION DOSE (Gy)		Control	0.1		10		50		
RADIATION ION SPECIES		N/A	Iron	Proton	Iron	Proton	Iron	Proton	
DRUG FORMULATION		% Labeled API Content							USP API CONTENT REQUIREMENT
Acetaminophen 325 mg Tablet		98.8	96.2	96.7	94.7	95.2	94	94.8	90-110
Atorvastatin 10 mg Tablets		100.2	100.4	**97.3**	**97.8**	98.5	98.6	**96.0**	98-102*
Augmentin® Tablets	Amoxicillin 875 mg	116.1	116.2	115.6	109.8	112.0	115.9	114.4	90-120
	Clavulante 125 mg	93.5	**88.6**	**88.1**	**79.4**	**48.0**	**83.4**	**78.2**	90-120
Ciprofloxacin 0.3% Ophthalmic Solution		96.9	96	96.1	95.9	94.5	96.1	96.4	90-110
Ciprofloxacin 0.3% Ophthalmic Ointment		99	96.4	94.8	94.6	91.7	95	94.8	90-110
Ciprofloxacin 500 mg Tablets		99.1	100.9	100.3	100.1	99.3	100.2	99.5	90-110
Clotrimazole 1% Cream		99.5	98.6	98.8	98.8	98.9	98.7	98.2	90-110
Ibuprofen 400 mg Tablets		101.4	102.3	102.5	102.3	102.6	102.6	102.8	90-110
Levothyroxine 25 mcg Tablets		94.1	96.6	93.4	93.5	94.2	95.3	94.4	90-110
Mupirocin 2% Ointment		100.5	99.6	100.3	100.2	99.7	100.3	99	90-110
Phenazopyridine 100 mg Tablet		98.0	96.2	96.6	94.2	94.5	92.5	93.9	90-110
Promethazine 25 mg Tablets		97	96.2	97.3	96.1	**93.9**	95.3	96.3	95-110
Promethazine 50 mg/ml Inj. Solution		99.2	99.6	97.8	97.3	98.4	98.7	98.8	95-110
Promethazine 25 mg Suppositories		103.5	102.3	102.1	103.1	102.9	103.3	103.6	95-110
Riboflavin 100 mg tablets		100.8	99.6	100.4	98.7	98.8	96.9	97.7	95-115
Silver Sulfadiazine 1% Cream		98.6	97.7	98.0	96.8	97.1	95.9	96.5	90-110
Temazepam 15 mg Capsules		100.5	100.4	100.1	100.2	99.8	100.2	99.8	90-110
Bactrim® Tablets	Sulfamethoxazole (800 mg	100.7	97.5	100.5	95.9	97.5	96.2	96.5	93-107
	Trimethoprim (160 mg)	101.5	98.2	101.3	96.5	98.5	97.1	97.3	93-107

** No USP monographic API content requirements available at time of analysis; current requirement shown*

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Dose-Dependent Stability

- Low dose = low nanomolar ion concentration
  - May alter pH more than higher doses
- ➢ Dose changes type and concentration of free radicals produced
  - Can alter reactivity or affect chemical reaction progression
  - Electron spin resonance (detects free radicals) evidence supports
- High dose rate may increase radical consumption
  - Radicals interact with each other at higher doses
  - Low dose paradoxically frees more radicals for chemical interactions with drug substrate
- Solid / powder drug formulations
  - Increased radical trapping in excipient lattices at lower doses
  - Longer free radical presence in solids / powders exposed to lower doses

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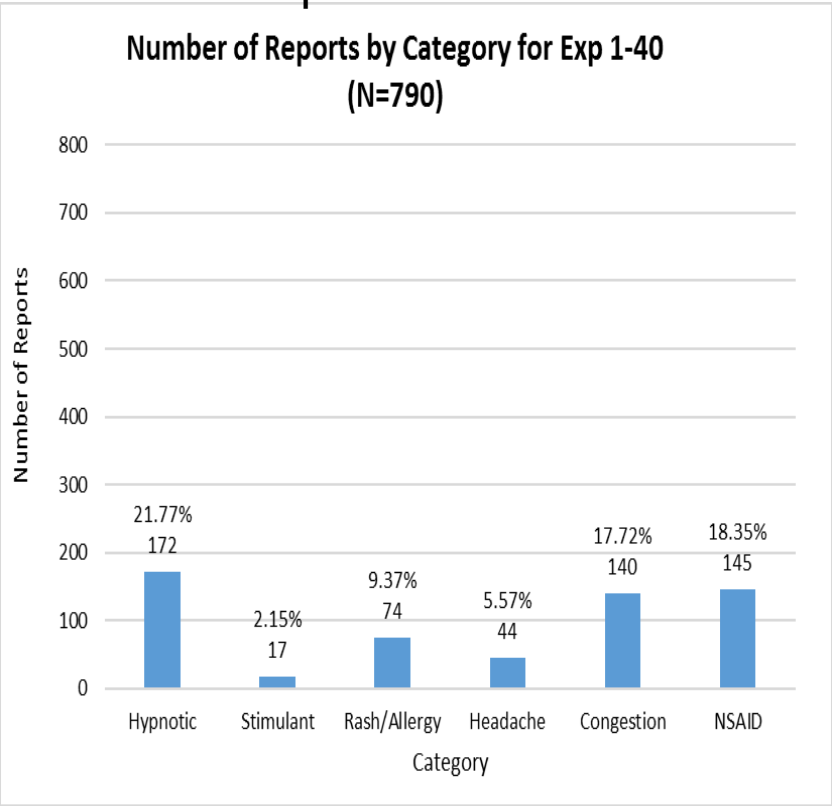
Medication Use Evaluation – LSAH Data

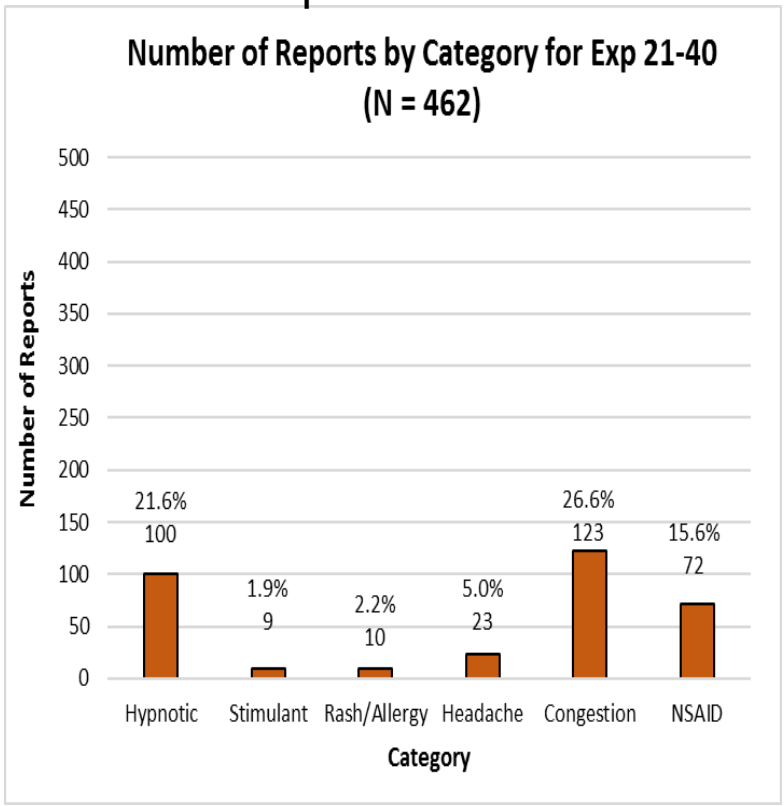
Data: Expeditions 1 through 40 (~107.5 months)

- 43 unique crewmembers (7 women, 36 men)
- 790 total reported medication uses

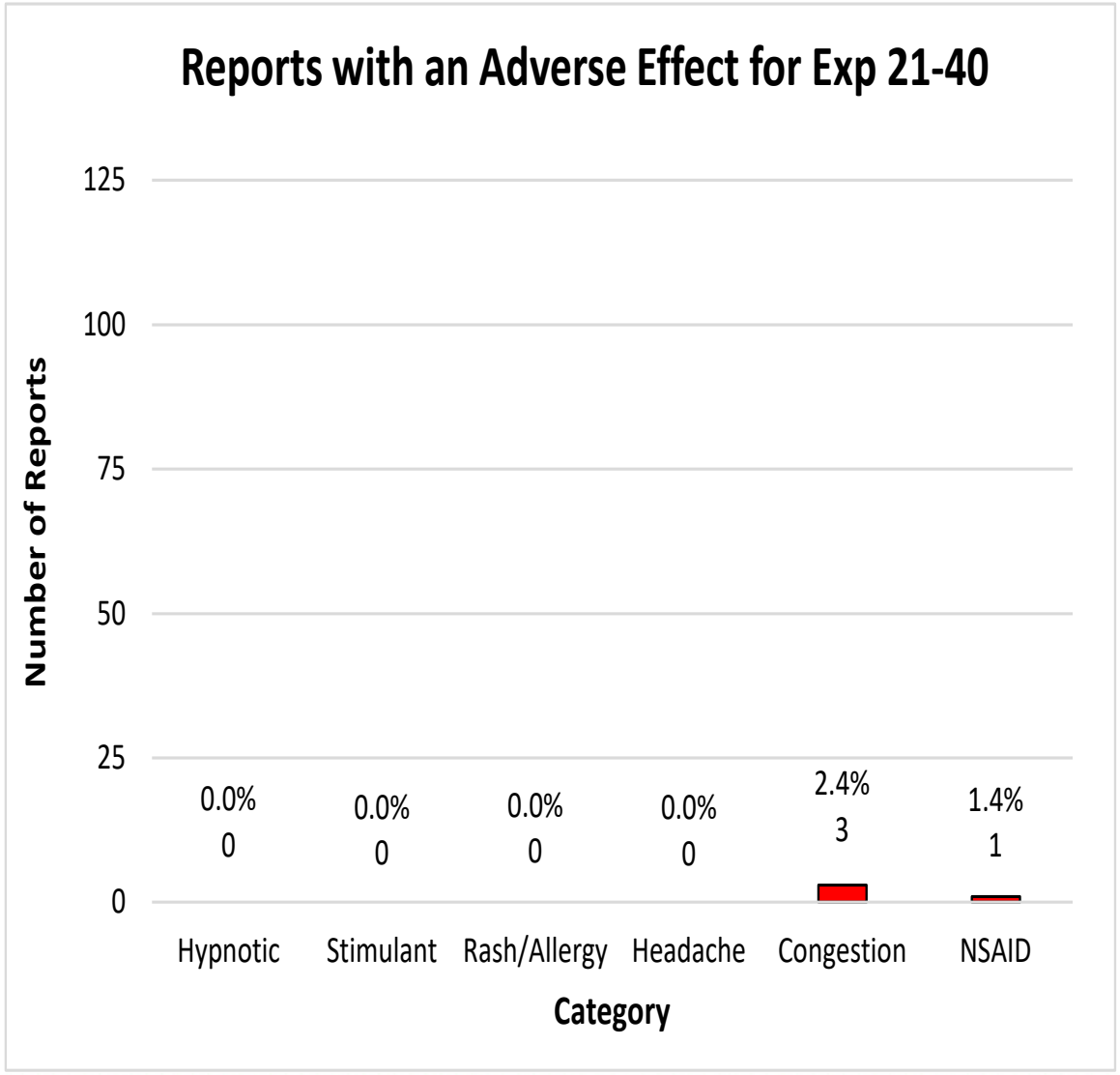


Data: Expeditions 21 through 40 (63.5 months)

- 20 unique crewmembers (5 women, 15 men)
- 462 total reported medication uses



Pharmacotherapeutics: Adverse Effects



- PMC tool doesn't 'ask' to capture this information.
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- Adverse effects self-reported

- A Zero in this graph does not mean that there weren't adverse effects, **only means there is no documentation.**

Potential Drug-Drug Interactions

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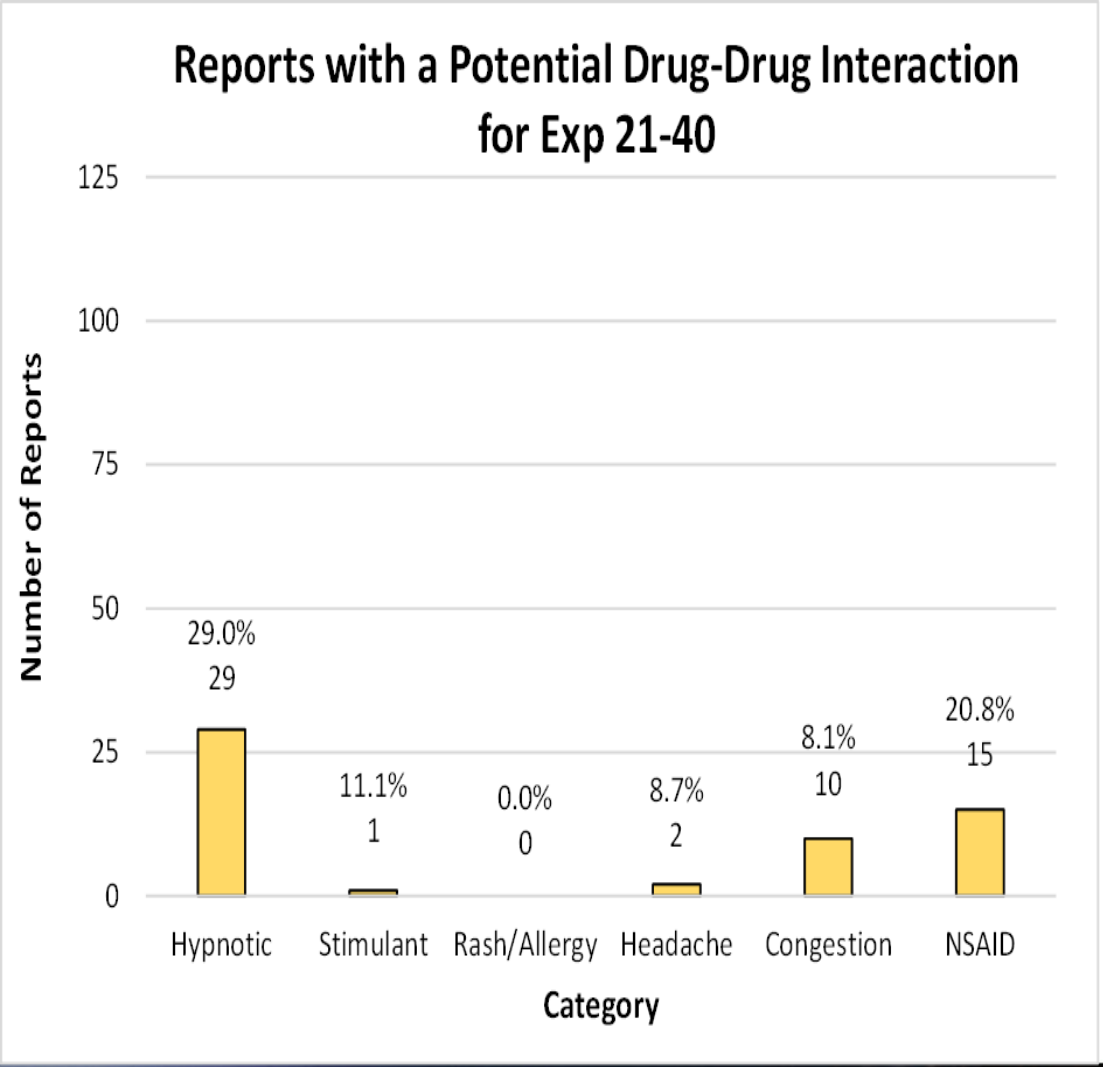

- Potential DDI
  - Medications taken concurrently during the reporting period
    - 28 of the 29 due to 2 sleepers reported use within the same reporting period.
  - Interactions between different classes of drugs
- Underestimated: the fidelity of data doesn't support this level of review
  - Multiple days of possible interactions within each reporting period
  - Lack of dosing specificity as a contributing factor (i.e., timing of drugs taken during the reporting period)

Dose Tracker Insights

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- Dose Tracker pilot project:
  - Collected data on 6 crewmembers during ISS missions
  - As of February 2017, DT collected over 224 weeks of medication usage data
    - 128 weeks inflight, 96 weeks on the ground
    - >5800 recorded medication entries (3049 inflight, 2717 ground)
    - Average of 961 entries per subject (453 inflight, 508 ground).

- Inflight average of 453 medication entries per subject
  - 20x increase over average 23.1 / CM reported Exp 21-40
  - 60x increase over average 7.6 / CM reported Exp 1-20

- 49 reports of no medication use in a given week of data collection
  - POSITIVE confirmation of no medication use
  - Previous efforts rely on possibly incorrect assumption that no report = no medication use

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Barger 2014: Med Usage and Reporting

Roughly three-quarters of shuttle crew members reported taking sleep-promoting drugs in-flight (table 1).

- Use of sleep drugs was reported on 500 (52%) of the 963 in-flight nights, with two doses of sleep drugs on 87 (17%) of 500 nights on which such drugs were taken
- Use of sleep drugs was reported on 60% of nights before extravehicular activities (table 1).

Of the 21 ISS crew members, more than a third (n=8) declined to answer the question about drug use on the sleep log at some point during the mission, which prevented the question being asked in future logs.

- Three of those eight participants indicated sleep promoting drug use in the mission before declining to answer the question.
- Sleep drugs were reported as being used on 96 (11%) of 852 sleep logs. On **18 (19%) of 96 days when sleep-promoting drugs were used, two doses were reported**."

	2 weeks about 3 months before launch	11 days before launch	In-flight	7 days after return to Earth	p value	Night before EVA
Space Transportation System shuttle						
Time in bed (diary; h)	7·40 (0·59)	7·35 (0·51)	7·35 (0·47)	8·01 (0·78)	<0·0001	7·47 (0·60)
Sleep episode time (actigraphy; h)	7·27 (0·61)	7·00 (0·62)	6·73 (0·46)	7·90 (0·81)	<0·0001	6·61 (0·90)
Total sleep time (diary; h)	6·86 (0·57)	6·73 (0·47)	6·32 (0·53)	7·23 (0·71)	<0·0001	6·33 (0·84)
Total sleep time (actigraphy; h)	6·29 (0·67)	6·04 (0·72)	5·96 (0·56)	6·74 (0·91)	<0·0001	5·94 (0·96)
Sleep latency (diary; min)*	15·54 (8·82)	16·44 (9·29)	23·63 (14·75)	13·67 (8·98)	<0·0001	28·47 (27·62)
Sleep quality (diary)†	67·91 (13·37)	65·88 (13·35)	63·70 (13·35)	69·23 (13·13)	<0·0001	61·77 (18·01)
Alertness (diary)†	65·17 (15·51)	64·30 (14·56)	64·92 (13·51)	67·46 (12·83)	<0·0001	64·81 (16·29)
Proportion of crew members reporting use of sleep-promoting drugs (%)	21/79 (27%)	56/79 (71%)	61/78 (78%)	19/76 (25%)	<0·0001	23/33 (70%)
Proportion of nights on which sleep-promoting drug use was reported (%)	58/1155 (5%)	272/832 (33%)	500/963 (52%)	19/76 (8%)	<0·0001	50/83 (60%)
International Space Station						
Time in bed (diary; h)	7·37 (0·83)	7·14 (1·16)	7·46 (1·22)	8·34 (1·14)	<0·0001	..
Sleep episode time (actigraphy; h)	7·27 (0·60)	6·77 (0·99)	6·84 (0·75)	8·17 (0·88)	<0·0001	..
Total sleep time (diary; h)	6·77 (0·71)	6·33 (0·76)	6·54 (0·67)	7·17 (0·85)	<0·0001	..
Total sleep time (actigraphy; h)	6·41 (0·65)	5·86 (0·94)	6·09 (0·67)	6·95 (1·04)	<0·0001	..
Sleep latency (diary; min)*	12·99 (5·87)	14·41 (9·46)	13·74 (10·64)	15·29 (15·15)	0·8903	..
Sleep quality (diary)†	67·51 (14·02)	62·32 (15·64)	66·51 (13·43)	66·87 (11·13)	0·0084	..
Alertness (diary)†	61·68 (17·76)	55·98 (19·46)	57·69 (18·73)	61·40 (17·55)	0·0026	..

Data are mean (SD), based on raw data, or n/N (%); p values are from statistical models. *We excluded latency times of >240 min. †Ratings are from a 100 mm non-numeric visual analog scale. EVA=extra-vehicular activity.

Table 1: Sleep outcomes

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Physiology: References

- Fluid shifts
  - Altered volume of distribution
    - Guyton and Hall 2006
    - Hargens and Watenpaugh 1996
    - Diedrich 2007
    - Montgomery 1993
    - Drummer 1993
    - Leach 1991
- Intracellular fluid alteration
  - Altered metabolism, altered drug uptake and clearance
    - Leach 1996
- Altered plasma protein concentration
  - Altered free drug concentration
  - Altered renal/hepatic clearance
    - Rice 2001
    - Larina 2017
- Cell Membrane Permeability
  - Altered drug distribution and uptake
    - Sumanasekera 2007
- Hepatic metabolism
  - Altered hepatic blood flow
  - Altered hepatic enzyme expression
    - Racine 1992
    - Hargrove 1985
    - Hollander 1998
    - Merrill 1992
    - Merrill 1990
    - Merrill 1987
- Gut motility and absorption
  - Altered gastric emptying from SMS or medications to address SMS
  - Increased GI wall edema = decreased absorption
  - Faster and more variable intestinal transit rate
    - Rowland 1975
    - Katzung 2007

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Stingl 2015: Medications with Genetic Polymorphisms

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- Crewmembers may have altered responses to medications due to individual genetic polymorphisms
- May suggest benefit of tailoring pharmacy to individualized response

CYP2D6 substrates on ISS drug list	Indication	Information about polymorphic enzymes in the drug label	Dosing Guidelines: CPIC/ GWPG	References	Level of evidence*
Metoprolol	Heart failure, hypertension	FDA: warnings about pharmacogenetics and drug interactions	PM: 75% UM: up to 250%	[10, 11]	3
Diphenhydramine	Vomiting, allergic rhinitis	Warning about drug interactions with drugs metabolized by CYP2D6		[12]	3
Cetirizine	Vomiting, allergic rhinitis	Information about drug metabolism via CYP2D6		[13]	1
Loratadine	Vomiting, allergic rhinitis, urticaria	Information about drug metabolism via CYP2D6		[14]	1
Meclizine	Vomiting, allergic rhinitis	Information about drug metabolism via CYP2D6		[15]	1
Ondansetron	vomiting	Information about drug metabolism via CYP2D6		[16]	3
Promethazine	Rhinitis, urticarial, Sedation, vomiting	Information about drug metabolism via CYP2D6		[17]	3
Tamsulosin	Prostate hyperplasia	Information about drug metabolism, high exposure in PM as compared to EM		[18]	2
Acetaminophen	Pain, fever	Warning about interaction potential with CYP2D6 substrates		[19]	1
Hydrocodone	Pain	CYP2D6 involved in activation; PMs less efficacy		[20]	1
Venlafaxine	Depression	Metabolism of venlafaxine to the active metabolite, total active moiety not affected by polymorphism	80% in PMs 170% in UMs or select an alternative drug, Cardiotoxic risk higher in PMs	[21, 22]	3
Aripiprazole	Psychosis	Dose recommendations in FDA label, and interaction warning	Reduce dose in PMs to 67% UMs no recommendation	[23]	2
CYP2C19 substrates					
Diazepam	Sleep disturbances	Information about drug metabolism and interaction via CYP2C19		[24]	2
Sertraline	Depression	Information about drug metabolism via CYP2C19	Reduce PM dose to 50% UMs no recommendation	[6]	2
Omeprazole	Reflux	Drug interactions	UM dose 100–200% increased	[25]	3
CYP2C9 substrates					
Ibuprofen	Pain, Fever	CYP2C9 and CYP2C8 involved in metabolism	*CYP2C8 and 9 combined genotype involved in GI bleeding side effects*	[26]	3
Phenytoin	Epilepsia, seizures	PMs: enhanced risk of toxicity	PMs: 50%, higher risk for skin toxicity; IMs: 75% of dose	[27]	3
Ketamine	Anesthesia, pain	Minor enzyme involved in metabolism		[28]	1
Acetylsalicylic acid	Pain, fever, cardiovascular	Minor enzyme, Drug interactions	CYP2C9 PM higher risk for urticaria	[29]	1
Sulfamethoxazole	Antibiotic	Information about m via CYP2C9	Risk of hemolysis in Glucose 6 phosphatase dehydrogenase deficiency	[30]	1
Loperamide	Diarrhea	Interaction warning		[31]	1
CYP1A2					
Melatonin	Daytime sleep, insomnia	Metabolism, Interactions		[32]	3
Caffeine	Sleepiness	Metabolism, Interactions		[33]	3
Lidocaine	Anaesthetic	Interactions		[34]	3

* Level of evidence: 1: in vitro data only, 2: in vivo pk data, 3: clinical data on efficacy and/or side effects

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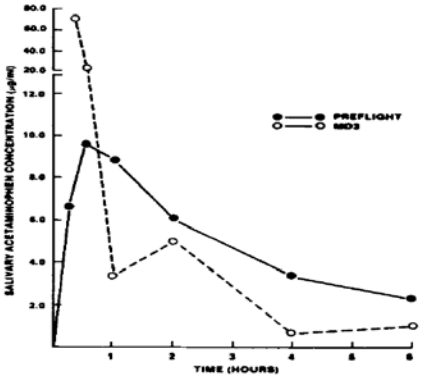
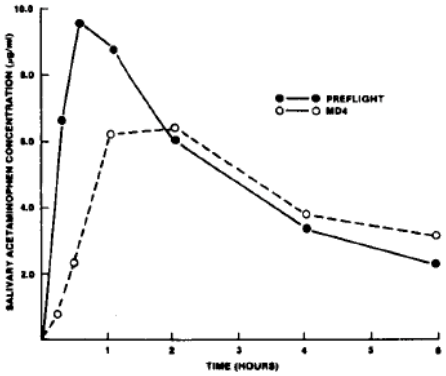
Cintron 1987: PK / PD
Acetaminophen / Scopolamine

Acetaminophen

Mission Day 3

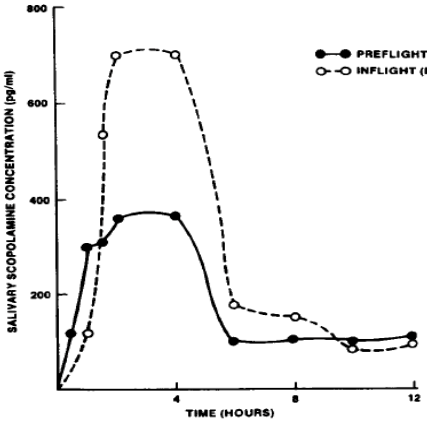


Mission Day 4

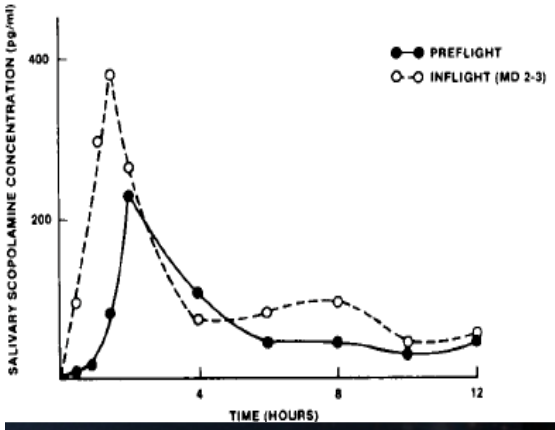


Scopolamine

Mission Day 1-2



Mission Day 2-3



- **Two flown studies (acetaminophen – 5 subjects, scopolamine – 3 subjects)**
  - Saliva sample collection by convenience – no time consistency, variable results
- **Crewmembers demonstrated altered PK / PD in flight – in general:**
  - Early mission: faster absorption, faster peak concentration, more rapid clearance
  - Later mission: slower absorption, lower peak

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Boyd 2009: Promethazine PK / PD

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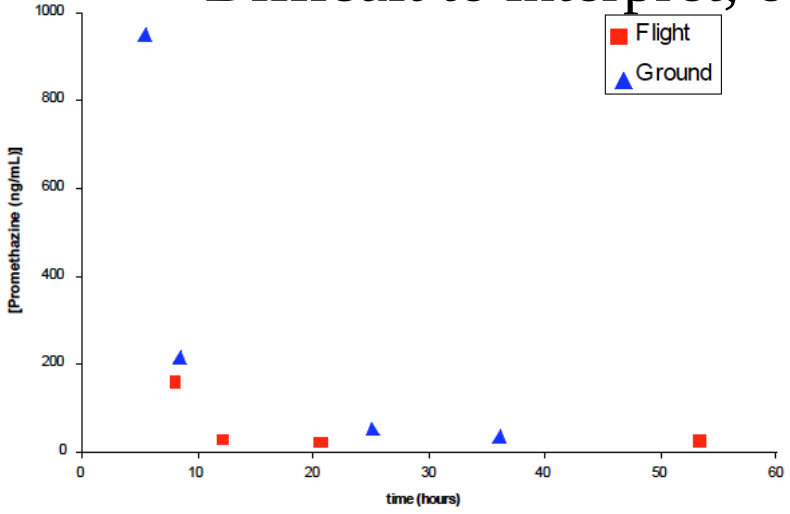
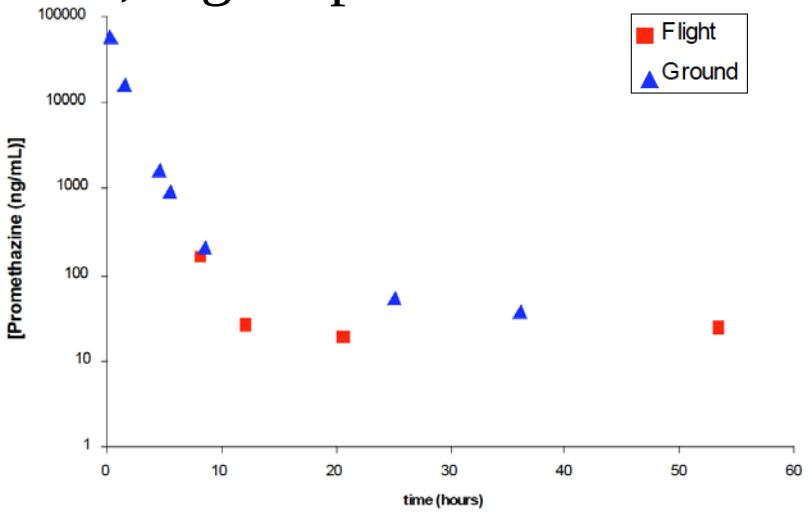
- Unpublished study
- 6 crewmembers, took 1 dose of promethazine on mission day 1
- Monitored saliva concentration for 72h
  - Variable sample retrieval (see graphs below)
  - Difficult to interpret; overall, higher peak concentration, shorte





Putcha 1999: Anecdotal Reporting

- **Anecdotal reporting of "not effective" and "mildly effective" medications by crewmembers**

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

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Barger 2014: Anecdotal Reporting

- **Anecdotal reporting of use of more than one drug or dose for sleep-promoting medications**

- **On the ISS, sleep drugs were reported as being used on 96 (11%) of 852 sleep logs.**
  - On 18 (19%) of 96 days when sleep-promoting drugs were used, two doses were reported.

- **Seventy-eight percent of shuttle mission crewmembers (61/78) reported taking sleep medications inflight.**
  - Sleep medications use was reported on 52% of the inflight nights (500/963)
  - 2 doses of sleep medication on 17% of nights that sleep medications were taken

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Animal Model Validation: Enzyme Activity

- **Carcenac 1999: validation study of hindlimb suspension vs. flown animals, studied cGMP production**
  - Significant increase in basal choroid cGMP levels after flight
  - Suspended rats demonstrate *atrial naturetic pepctic (ANP)-dependent cGMP* increase – NOT SEEN in flown animals
  - Suggests poor correlation between spaceflight and suspension model

- **Racine 1992: validation study of hepatic cellular morphology**
  - Flown cells larger, increased glycogen and lipid storage, than suspended animals
  - Decreased Kupffer cells (decreased defense capacity) in flown animals
  - Suggests poor correlation between spaceflight and suspension model

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eflight Evidence: PK/PD

- Additional reports of therapeutic failure
  - Antibiotic cultures
    - *E. coli:* demonstrated increased resistance to colistin, kanamycin (3 studies 1985, 1 study 1994)
      - Additional concern for dihydrostreptomycin – inconclusive resistance studies
    - *S. aureus:* demonstrated increased resistance to oxacillin, chloramphenicol
    - In some cases required DOUBLE the antibiotic dose to meet antibiotic effect

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Bacterial Antibiotic Response

- **Tixador 1985:**
  - Flown cultures of *Staphylococcus aureus* and *Escheria coli* demonstrated increased antibiotic resistance (increased “minimal inhibitory concentration” of antibiotics)

TABLE I. MINIMAL INHIBITORY CONCENTRATION FOR STAPHYLOCOCCUS AUREUS IN $\mu g \cdot ml^{-1}$.

	Control	Inflight
Oxacillin	0.16	0.16<MIC <0.32
Chloramphenical	4	4 <MIC <8
Erythromycin	0.5	0.5 <MIC <1

TABLE II. MINIMAL INHIBITORY CONCENTRATION FOR E. COLI IN $\mu g \cdot ml^{-1}$.

	Control	Inflight
Colistin	4	MIC>16
Kanamycin	4	MIC>16

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eflight Evidence: PK/PD

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- Human Flown
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strial Evidence: PK/PD

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