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National Aeronautics and Space Administration

Limitations in Understanding Use, Stability, and Effectiveness of Medications during Spaceflight

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Overview

This presentation will discuss our current understanding of:

- Medication usage during spaceflight
- Medication effectiveness in the space environment
- Medication stability in the space environment

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

Medication Usage

Subjective Efficacy

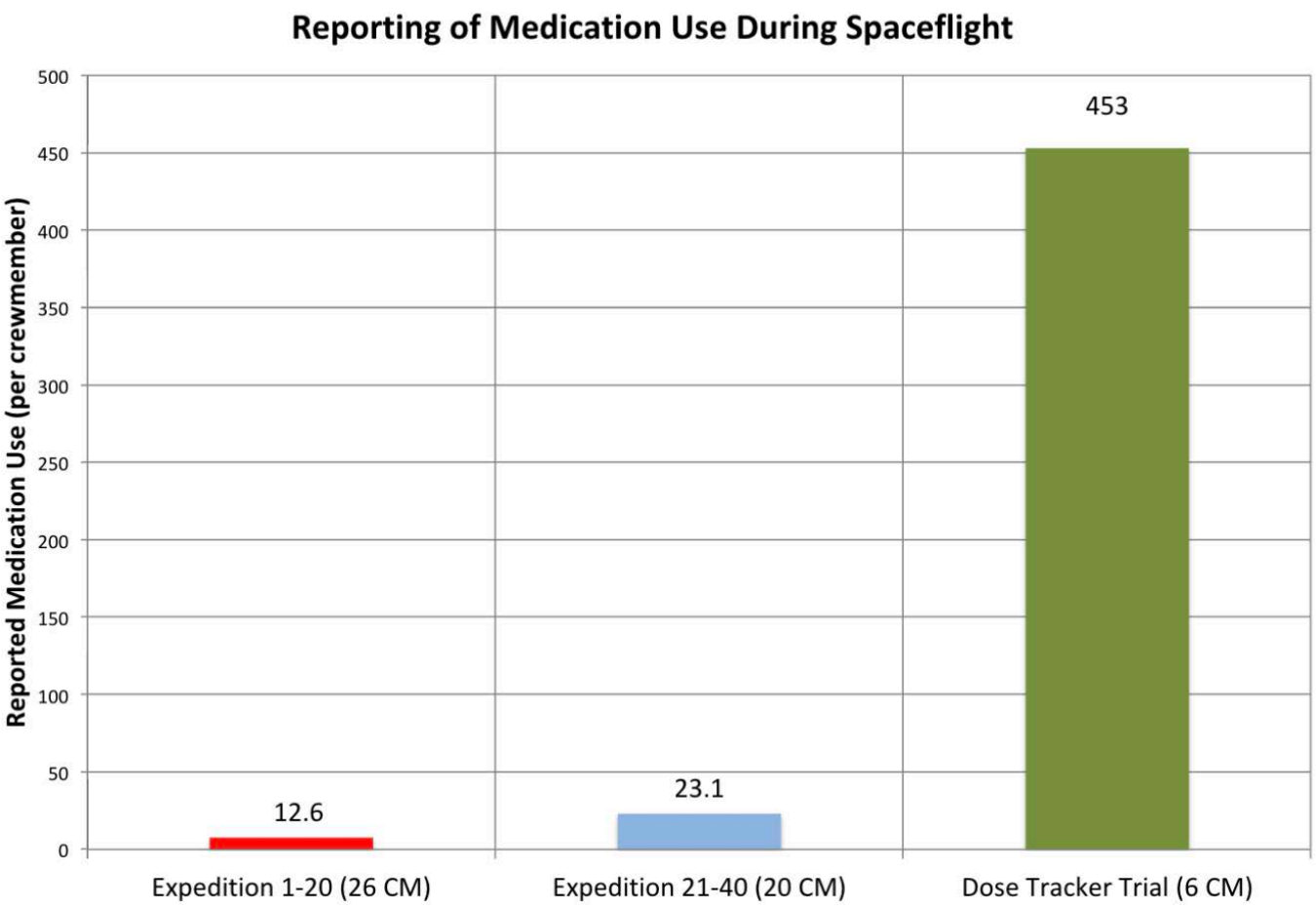
Retrospective Medication Use Evaluation

- Johnson Space Center Pharmacy Team conducted a review of inflight medication use data of:
  - Sleepers/Stimulants
  - Rash/Allergy
  - Headache/Congestion
  - NSAIDS

- Original Plan: Expedition 1 to 40

- After Review, Re-scope to include Expeditions 21 to 40 as a result of the way the data was captured (21-40 through more standard reporting)

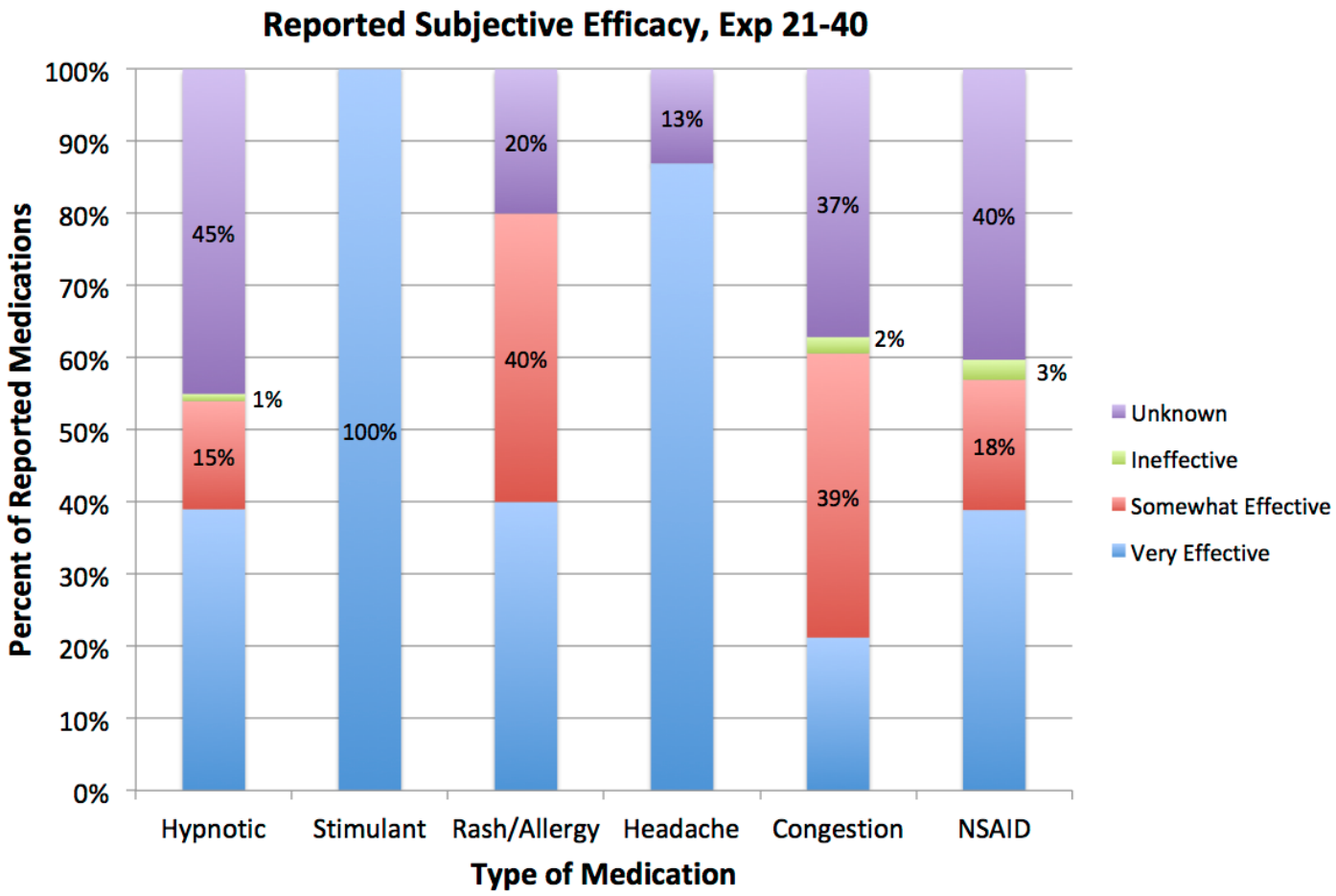
ISS Medication Usage



- Historically, we have had poor capture of medication usage data (which meds, effectiveness or response, side effects, etc)
- Data presented are AVERAGE reports per crewmember
- Short trial (5 subject) Dose-Tracker project: data shows a 20-60x increase in data points

Supplemental Data:
LSAH, Dose Tracker

Reported Subjective Efficacy



PMC tool doesn't 'ask' to capture this information.

Whether or not the crewmember thought the medication worked is self-reported

Claim that we 'don't have a problem' is artificial - **we don't have good data to support that claim**

Supplemental Data:
LSAH, Dose Tracker

Reported Subjective Efficacy

Dose Tracker Data –unpublished Wotring/Smith

- Perceived efficacy was reported for 32 medications by 1- 3 subjects.
- Most medications were considered partially effective.
- Two subjects evaluated efficacy in both flight and Earth environments:
  - one found valacyclovir to provide “complete relief, but required continued dosing” in both situations, and
  - another found zaleplon to provide complete relief in a single dose, both flight and ground.
- One subject reported the absence of side effects during both flight and ground use for 8 medications.

Efficacy

- **Potential reasons for lack of efficacy**
  - Pharmacokinetics (PK) / Pharmacodynamic (PD) changes
  - Stability of medication

Pharmaceutical Stability

Shelf Life and Radiation

Pharmaceutical Stability

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

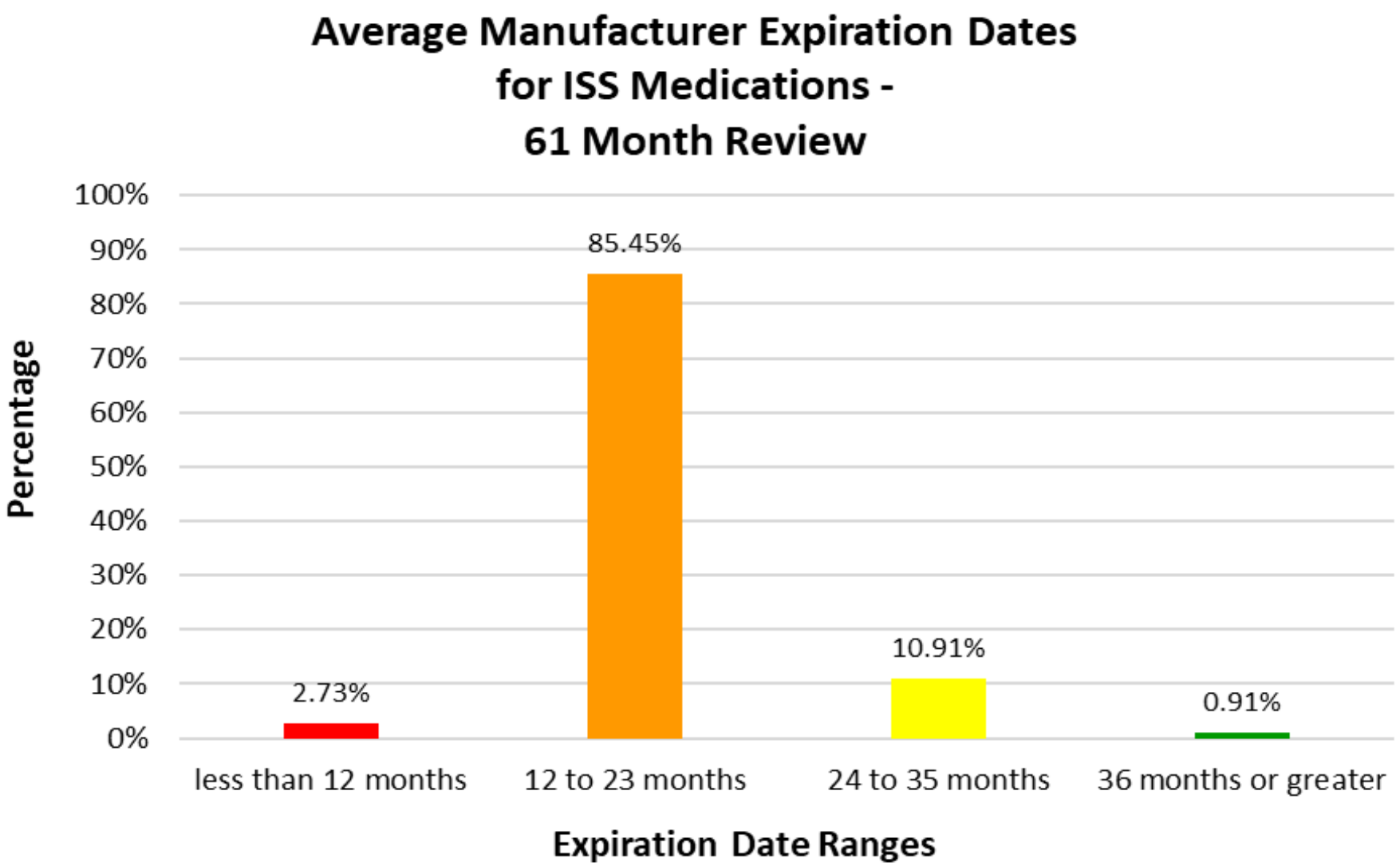
  - changed:
    - Appearance
    - Dosage form physical attributes and uniformity
    - Potency
    - Excipient composition

  - 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

Average Manufacturer Expiration Dates



Terrestrial Evidence: Shelf-Life

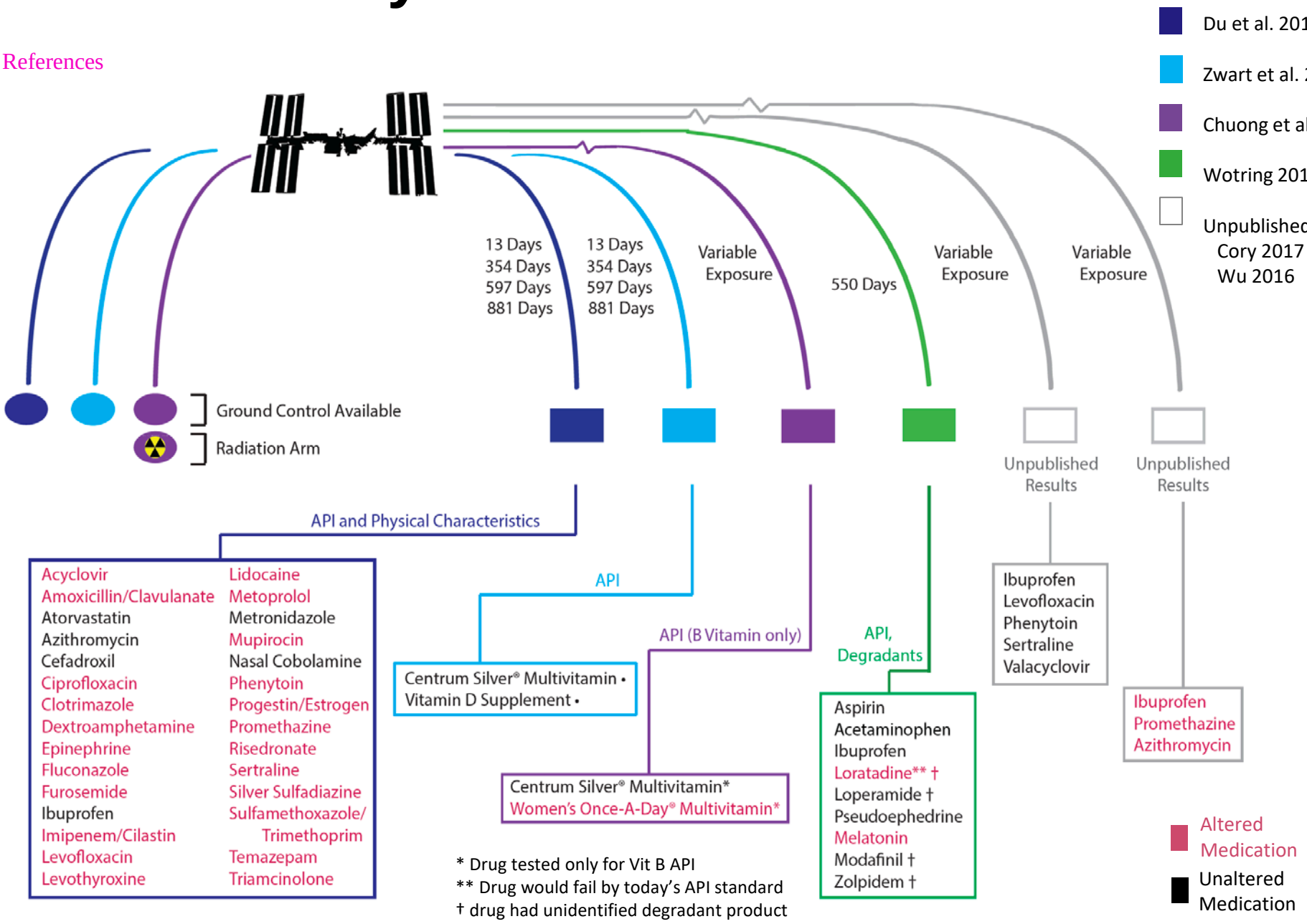
- Table: Medications flown in ISS formulary that have been tested by various **terrestrial** studies on shelf-life extension
  - FDA SLEP Program
  - Cantrell 2012
  - Matto 2013

- Some drugs found to be stable under SLEP terrestrial analysis have demonstrated instability or alterations in flown studies (Du et. al. 2011, Wotring 2016)

	DRUG	DOSAGE FORM	LOTS TESTED	MEAN EXT (mo.)	EXT. RANGE (mo.)
FDA SLEP	Amoxicillin	Tablet*	21	23	21-23
	Bupivicaine	Inj. Solution	3	88	79-95
	Ceftriaxone	Inj. Powder	4	60	44-69
	Ciprofloxacin	Tablet	242	55	12-142
	Cimetidine	Tablet	5	67	59-75
	Dexamethasone	Inj. Solution	7	61	24-93
	Diphenhydramine	Inj. Solution	12	76	33-126
	Doxycycline	Capsule	13	50	37-66
	Guaifenesin	ER Tablet	7	85	39-122
	Ketamine	Inj. Solution	6	64	42-87
	Meperidine	Inj. Solution	6	89	32-128
	Morphine	Inj. Solution	13	89	35-119
	Naloxone	Inj. Solution	10	77	60-95
	Phenytoin	Inj. Solution	5	63	29-100
	Promethazine	Inj. Solution	9	51	28-73
Cantrell 2012	Acetaminophen**	Tablet	-	-	336-480
	Caffiene**	Tablet	-	-	336-480
	Caffiene†	Tablet	-	-	336-480
	Hydrocodone*	Tablet	-	-	336-480
Matto 2013	Doxycycline	Tablet	3	179	144-204
	Amoxicillin	Tablet	2	138	132-144

Stability Evidence: Flown Studies

References



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

Conclusions and Recommendations

Conclusions

1. We have insufficient data collection to understand medication usage, side effects, and effectiveness in spaceflight today

2. Our current understanding of pharmaceutical stability suggests that most medications do not have sufficient labeled shelf life to last for planetary exploration missions

3. 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. Support pilot research projects regarding initial characterization of the 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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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

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Pharmaceutical Stability: Radiation

- 2004: European pharmacopoeia identified more than 250 drugs and adjuvants considered to be photochemically unstable (photolabile)
- In 2009, Hospital Pharmacy published a list of US approved oral medications, and injections in 2014 considered to be photolabile.
  - Of the medications included in the 2017 ISS medication kit formulary:
    - 35.6% of the oral medications were included on the list of oral photolabile drugs
    - 88% of the injection medications were included on the list of injection photolabile drugs

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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

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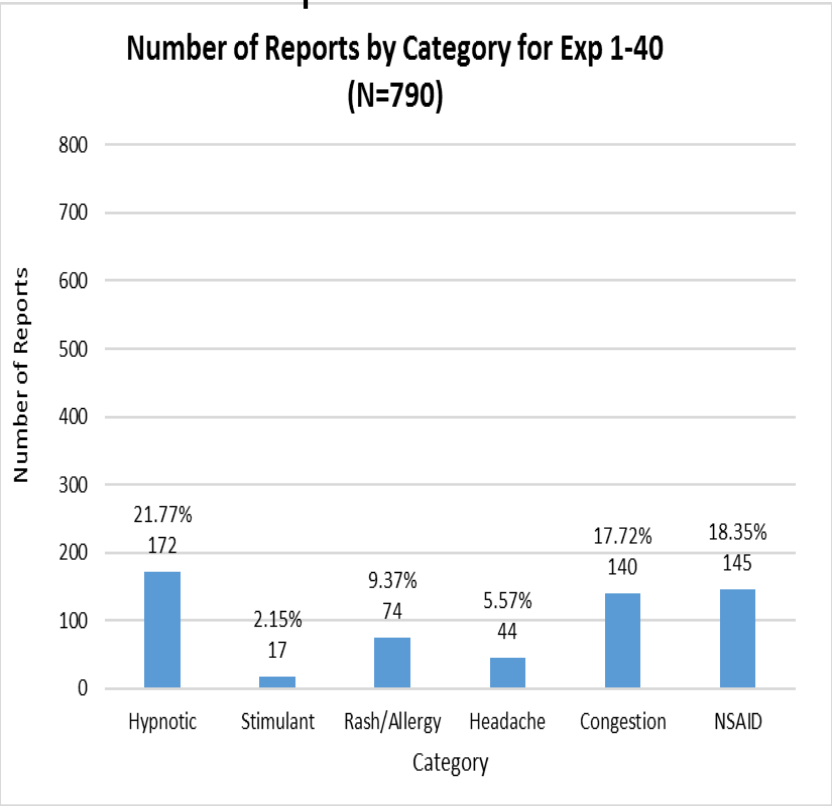
Medication Use Evaluation – LSAH Data

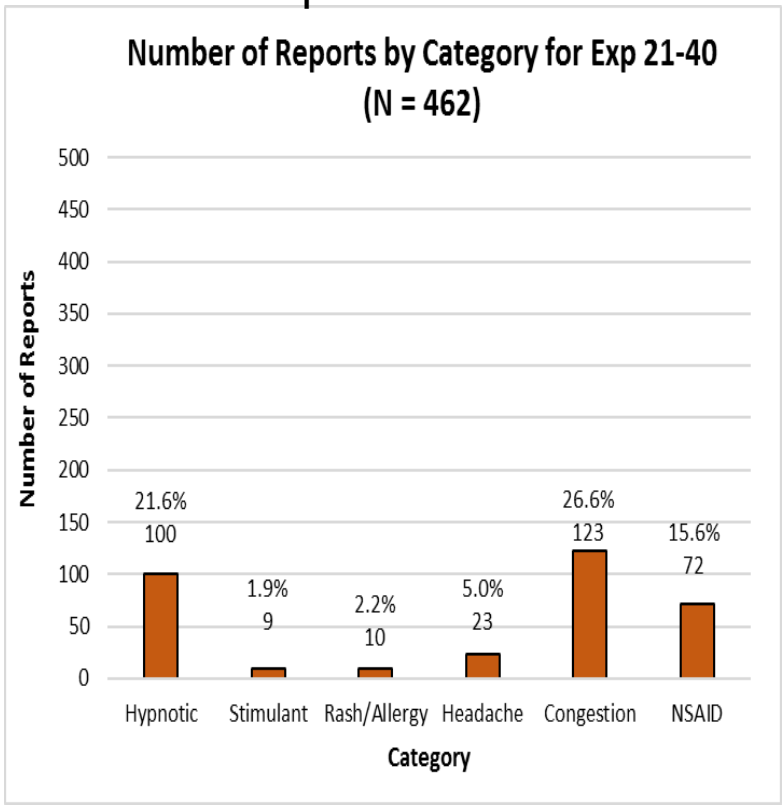
Data: Expeditions 1 through 40 (~107.5 months)

- 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

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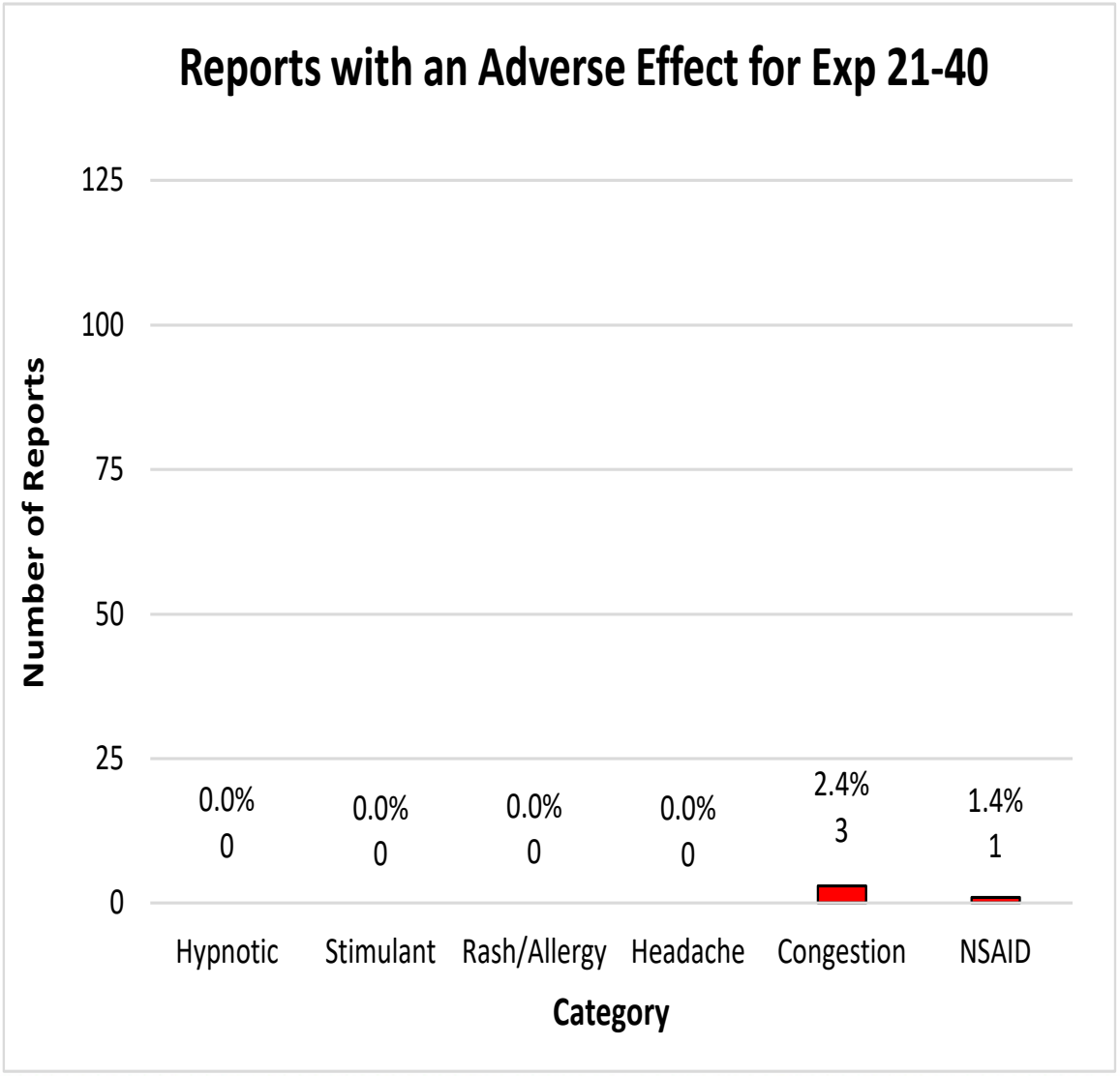

- PMC tool doesn't 'ask' to capture this information.
- Adverse effects self-reported
- A Zero in this graph does not mean that there weren't adverse effects, **only means there is no**

Potential Drug-Drug Interactions

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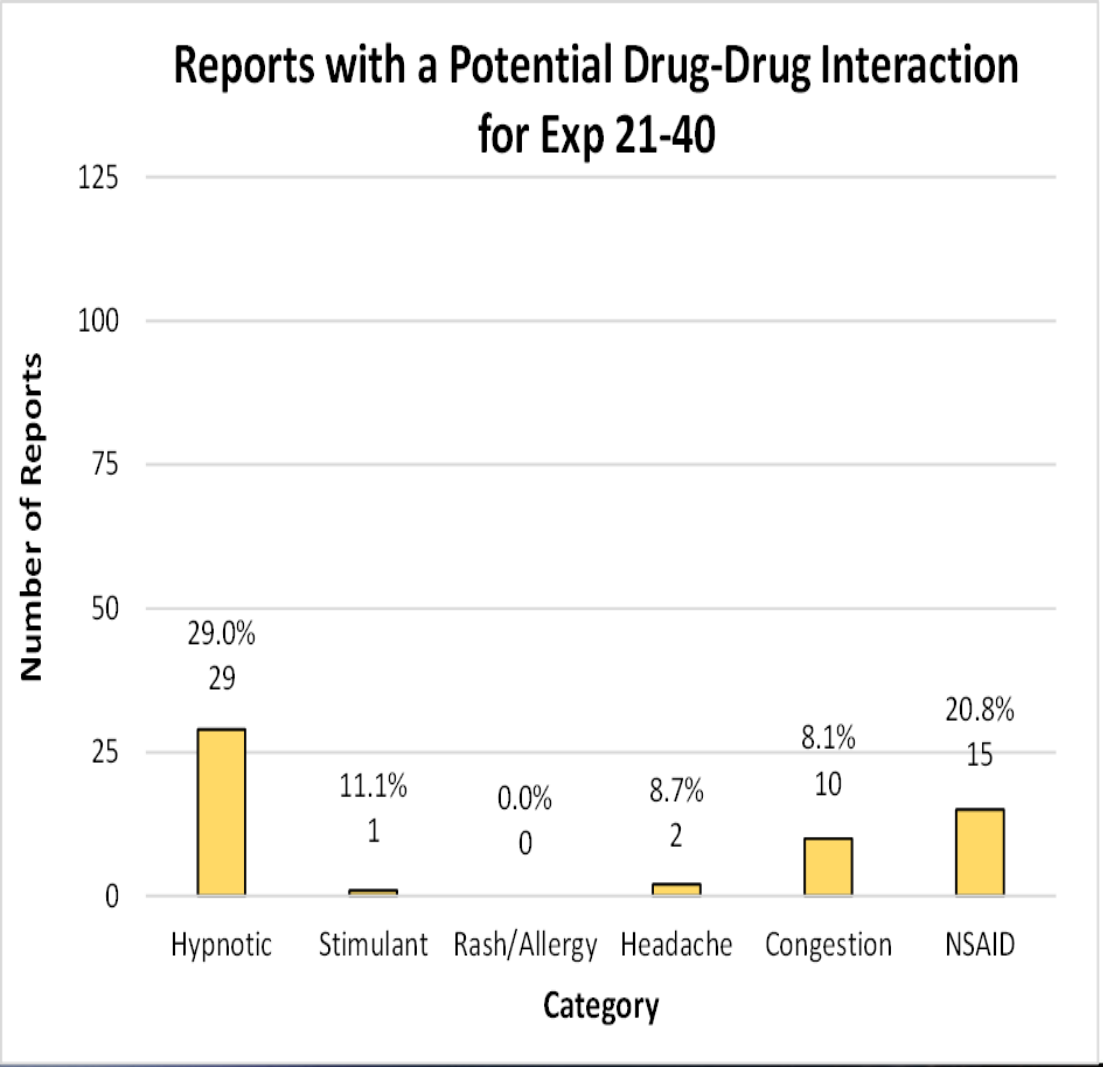

- Potential DDI
  - Medications taken concurrently during the reporting period
    - 28 of the 29 due to 2 sleepers reported use within the same reporting period.
  - Interactions between different classes of drugs
- Underestimated: the fidelity of data doesn't support this level of review
  - Multiple 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