# Crew State and Risk Model (CSRM) – Medication Impacts on Physiologic Models for Exploration Class EVA Predictive Modeling and Operations

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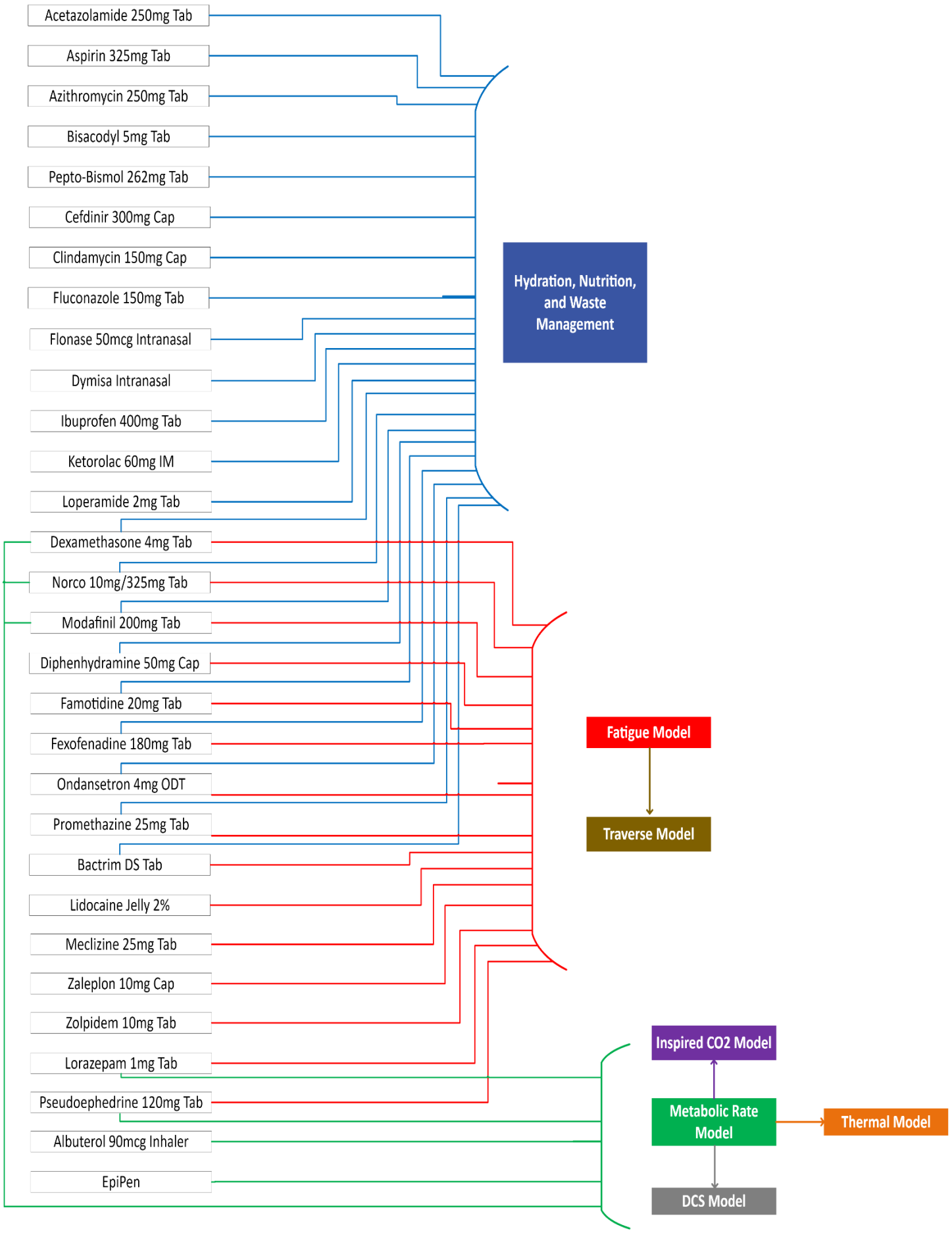

The Crew State and Risk Model (CSRM) is a collection of seven core physiologic models to predict crew readiness for EVA and state during tasks. Those seven core physiologic models are as follows:

- Metabolic Energy Expenditure
- Inspired $CO_2$
- Decompression Sickness (DCS)
- Human Thermal regulation
- Hydration, nutrition, and waste management (HNW)
- Traverse (defined as the metabolic cost of EVA ambulation)
- Fatigue (cognitive and physical)

Please see "Crew State and Risk Model (CSRM) – An Integrated Physiologic Map for Exploration Class EVA Predictive Modeling and Operations" authored by Dwyer Roche, DO for detailed information regarding specific modeling input definitions, expected outputs, and equations used for estimation.

**Scope:** EVA and Environmental Physiology Laboratory (EEPL) wanted to expand upon the previous CSRM Physiologic Map to visually demonstrate the impact of medications on various modeling inputs that map to the seven physiologic models. It is acknowledged various physiologic states present during EVA could impact drug pharmacokinetics (i.e. pressure changes, core body temperature), which could impact pharmacodynamics. However, that is outside the scope of this document. The medications below represent the authors' assumption of what medications will be available and able to impact an Artemis EVA and do not include the full ISS formulary, a final Artemis medical kit, or additional personal medications for individual crewmember's chronic medical conditions.

**Determining Medication Impact**

Medication impact was determined based on drug mechanism of action (MOA) and adverse drug reaction (ADR) profile. Below includes the modeled systems and the drug effects of concern. The affected inputs for the physiologic models are included in the right-most column. The drug effects are based on terrestrial drug pharmacodynamics due to lack of data during spaceflight and lack of reliable analog models.[1,2]

| Modeled Systems | Suboptimal Drug Effects | Affected Inputs |
|---|---|---|
| **Metabolic energy expenditure** | Dropping HR; increasing HR; increasing RR; decreasing RR | HR, RR |
| **Inspired CO2** | See inputs from metabolic rate | Metabolic rate |
| **DCS** | See inputs from metabolic rate | Metabolic rate |
| **Human Thermal Regulation** | Dropping HR; increasing HR; Blood flow changes (vasodilation or vasoconstriction) | HR; Skin temperature; Metabolic rate |
| **HNW** | Dehydration; fluid retention; electrolyte imbalances; AKI; Urinary Retention; appetite suppression; constipation; diarrhea; hypoglycemia | Thirst, Electrolytes, Renal Function, Creatinine Kinase, Glucose |
| **Traverse** | See inputs from Fatigue | |
| **Fatigue (cognitive)** | Stimulation, Sedation, sleep impacts (hallucinations, weird dreams) | Sleep/Wake cycles, Sleep quality |

| | | |
|---|---|---|
| **Fatigue (physical)** | Pain, stimulation, sedation | |

**Assigning Medications to Modeled Systems**

MOA and ADR profiles were taken from Food and Drug Administration (FDA) labeling documents and pharmacokinetic and safety studies. For FDA labeling, the most up-to-date brand name medication label was used per the Drugs@FDA database. If the drug had been on the market for some time or the product was over-the-counter (OTC), the most available, up-to-date label from Drugs@FDA was used.

Pertinent ADRs based on the above determinations are bolded. In the medical capability document for the ISS, medications have a possible side effects column, which is referenced in the accompanying documentation as "Adverse effects - Per Protocol". Other ADRs pertinent to EVA but not included in this "per protocol" section are referred to as "Adverse Effects – Additional". If incidence for ADRs was available, it was included in parathesis. Clinical significance to EVA was defined as >5%. However, as many medications did not have an easily identifiable percentage incidence, all pertinent ADRs were included for clarity and completeness. Below includes the rationale for the proposed modeled system assignment for each medication in the proposed Artemis medication kit was well as references.

**Future Research**

As ISS Medications are likely to inform future long duration missions, mapping all the ISS Formulary medications would be pertinent to inform future models. In this same regard, it may also be pertinent to map personal medications crew members that may be flying on missions to account for their pharmacodynamic impact.

Pharmacogenomics is another aspect of pharmacy risk management worth exploring. A considerable portion of medications at the JSC pharmacy have drug-gene interactions.[3] To better inform drug impacts on the CSRM model, understanding these impacts can better inform medication management.

<u>Acetaminophen (TYLENOL) 500 mg tablet</u>

Route: Oral; Labeled Purpose: Pain relief

MOA: By reversibly inhibiting COX-1 and COX-2 enzymes to reduce the formation of PGH2, acetaminophen decreases the concentrations of prostanoids produced by the downstream biosynthetic pathways, thereby reducing related pain signaling. It is postulated that the antipyretic effect is produced through action on the hypothalamic heat-regulating center.

ADRs: No significant side effects within prescribed dose

Rationale: Due to Acetaminophen's mechanism of action, it is less likely to impact any of the physiologic models.[4,5] Therefore, it was not assigned an aspect of the CSRM.

<u>Acetazolamide (DIAMOX) 250 mg Tablet</u>

Route: Oral; Labeled Purpose: Altitude Sickness

MOA: Inhibits carbonic anhydrase (which is responsible for hydration of CO2 and dehydration of carbonic acid). In the CNS, this stops the abnormal, paroxysmal, excessive discharge from the CNS neurons. It also

has a diuretic effect on the kidneys through the renal loss of HCO3 (which carries out Na, H2O, K ions). This offsets the hyperventilation-induced respiratory alkalosis and allows chemoreceptors to respond more to hypoxic stimuli at altitude.

ADRs - per protocol: Flushing, tingling sensation in extremities**, loss of appetite, increased urine output,** drowsiness, dizziness, confusion, photosensitivity, hearing disturbances, **kidney stones**; additional: **Na, K wasting**, hyperglycemia has been reported in diabetic patients

Modeled system/Rationale:

- *Hydration, Nutrition, and Waste Management model*. Acetazolamide has a diuretic effect on the kidneys, which can increase urine output and Na and K ion wasting. This impacts the electrolyte status and hydration status of the crew member. It also has appetite suppression due to taste disturbances, which can impact nutrition intake and in turn blood glucose.[6-8]

Albuterol (PROVENTIL HFA) 90mcg, 6.7gm Inhaler

Route: Inhaler; Labeled Purpose: Allergic Reaction

MOA: As a beta-2 AR agonist, albuterol mimics the activity of epinephrine to cause bronchodilation and reduced bronchiolar SMC relaxation to relieve the reduced airway caliber.

ADRs: **palpitations, fast heart rate, dizziness**, nervousness/tremors (7%)

Rationale: *Metabolic Rate Model*. Due to the MOA, albuterol can increase heart rate, impact the metabolic rate calculation. In turn, this can also impact *Inspired CO2 Model, DCS model,* and *Thermal Model*.[9] The MOA of Albuterol also leads to a momentary increase in FEV1 (duration of action as measured by 15% increase in FEV1 was 3-6hrs).[9] Due to this increase in FEV1, there would also be an increase in VO2 max, impacting the *metabolic rate model*, and all other models with a metabolic rate input.[10]

Aspirin 325 mg tablet

Route: Oral; Labeled Purpose: Pain Relief

MOA: Irreversibly inhibits the platelet COX-1 enzyme to reduce formation of TxA2 (activator of platelet aggregation), blocking platelet aggregation and decreasing thrombus formation that could lead to ASCVD progression or a CV event. Antipyretic activity is due to its ability to interfere with the production of prostaglandin E1 in the brain.

ADRs: **Upset stomach (dose related),** dizziness (reported in low dose aspirin), tinnitus, blood in stool (serious GI bleeds are rare)

Rationale: *Hydration, Nutrition, and Waste Management Model*. Aspirin irreversibly inhibits COX-1, the enzyme responsible for formation of prostaglandins. In the stomach, prostaglandins protect the lining. Inhibiting COX-1 decreases the number of prostaglandins, leading to stomach upset.[11] The effects of aspirin last for the duration of the platelet due to the irreversible bind to COX-1.

Azithromycin (ZITHROMAX) 250 mg tablet

Route: Oral; Labeled Purpose: Antibiotic

MOA: By binding to the 50S subunit, azithromycin blocks peptide bond formation and protein synthesis, which kills or stops the growth of bacteria that cause infections.

ADRs – per protocol: **Diarrhea (5-14%), nausea (3-18%),** abdominal pain (3-7%), **vomiting (2-7%);** additional – **QTc prolongation**

Rationale: *Hydration, Nutrition, and Waste Management Model*. Like most antibiotics, there is an incidence of diarrhea, increasing the concern for dehydration and electrolyte status.[12] Azithromycin carried a warning for QTc prolongation, especially in populations pre-disposed due to comorbidities or those taking other QTc prolonging medications in addition to Azithromycin.[12] This increase is dose and concentration dependent. As QTc prolongation impacts rhythm and not heart rate, it was not mapped to metabolic rate.

Bisacodyl (DUCOLAX) 5 mg tablet

Route: Oral; Labeled Purpose: GI Management

MOA: Stimulant laxative. Increases local irritation of mucosa and increases secretion of water and electrolytes into the small intestine.

ADRs – per protocol: Mild abdominal cramps (24%), nausea, **vomiting,** dizziness, **diarrhea (53%)**

Rationale: *Hydration, Nutrition, and Waste Management Model.* As it is a laxative, there is a high incidence of diarrhea, especially with over use and higher doses.[13, 14] While the MOA does increase secretion of electrolytes, based on multiple reviews, this does not lead to clinically relevant electrolyte loss.[13]

Bismuth Subsalicylate (PEPTO BISMOL) 262 mg

Route: Oral; Labeled Purpose: GI Management

MOA: Stimulates the absorption of fluid and Na and Cl to decrease fluid loss and inhibiting prostaglandins responsible for intestinal inflammation. Weak antacid properties by neutralizing gastric acid to increase gastric acid pH.

ADR – per protocol: may darken tongue and stool; additional: Bitter taste, nausea, **diarrhea**

Rationale: *Hydration, Nutrition, and Waste Management Model.* While bismuth subsalicylate carries side effect of diarrhea, it is important to remember it is FDA approved for mild diarrhea. Studies have shown that for severe diarrhea, it is not as effective as loperamide at resolving symptoms.[15] Due to this risk of unresolved diarrhea, bismuth subsalicylate could affect hydration status as well as electrolyte status.

Cavit or similar repair cement

Route: Topical; Labeled Purpose: dental management

ADRs: gum and skin irritation

Rationale: Due to Cavit's route of administration and location, it is less likely to impact any of the physiologic models. Therefore, it was not assigned an aspect of the CSRM.

Cefdinir (OMNICEF) 300 mg Capsule

Route: Oral; Labeled Purpose: Antibiotic

MOA: Bactericidal inhibition of cell wall synthesis

ADRs: **diarrhea (15%),** nausea (3%), Abdominal pain (1%), **vomiting (0.6%)**

Rationale: *Hydration, Nutrition, and Waste Management Model.* Due to the clinically significant incidence of diarrhea, there would be a concern for dehydration and electrolyte imbalance.[16]

Clindamycin (CLEOCIN) 150 mg Capsule

Route: Oral; Labeled Purpose: Antibiotic

MOA: Binds to the 50S subunit, blocking peptide bond formation and protein synthesis, which kills or stops the growth of bacteria that cause infections.

ADRs – per protocol: Abdominal pain, nausea, **vomiting, diarrhea**, rash

Rationale: *Hydration, Nutrition, and Waste Management Model.* Due to the incidence of diarrhea and vomiting, there would be a concern for dehydration and electrolyte imbalance.[17]

Cyanoacrylate (DERMBOND) 0.7 mL swap

Route: topical; Labeled Purpose: wound repair

MOA: cyanoacrylate adhesive that forms a strong bond between wound edges.

ADRs – per protocol: **Skin irritation, itching**

Rationale: Data for Dermabond's impact on electrode conduction is lacking but would defer to best practices surrounding not placing electrodes on broken skin. It would also be best practice to avoid placing sensors on areas where topical medication has been applied. Because of these minimal impacts, Dermabond is unlikely to impact any of the physiologic models. Therefore, it was not assigned an aspect of the CSRM.

Dexamethasone (DECADRON) 4 mg Tablet

Route: Oral; Labeled Purpose: Allergic reaction

MOA: inhibits inflammatory cytokines to decrease inflammation

ADRs: large doses can cause elevation in BP; long term can cause Cushing's syndrome via HPA Axis suppression; **immunosuppression; insomnia, increase HR; emotional irritability; Na and water retention, increased excretion of potassium and Calcium; hyperglycemia**

Rationale:

- *Fatigue (cognitive, and physical) Model*. Dexamethasone can cause insomnia and emotional irritability, impacting sleep/wake schedule and sleep quality.[19] It can also dysregulate the immune system through immunosuppression. Due to impact on fatigue, the *Traverse Model* would also be affected.

- *Hydration, Nutrition, and Waste Management Model.* Dexamethasone can cause sodium and water retention leading to edema as well as increased excretion of potassium and calcium.[18] This can impact electrolyte and hydration status of the crew member.
- *Metabolic Rate Model.* While chronic use of dexamethasone can cause increase in blood pressure, animal studies have shown it can acutely increase heart rate in adult rats.[18, 19] Changes in heart rate can impact metabolic rate, thereby impacting the *Inspired CO2 Model*, the *Thermal Model*, and the *DCS Model*.

<u>Diphenhydramine (BENADRYL) 50 mg Capsule</u>

Route: Oral; Labeled Purpose: Allergic Reaction

MOA: Antagonizes H1 receptors to prevent histamine binding

ADRs – per protocol: **Drowsiness /sedation (10-25%), inability to concentrate,** dry mouth, **blurred vision,** rash, headache, **rapid heart rate,** dizziness, **fatigue,** photosensitivity, **urinary retention,** ringing in the ears, nasal stuffiness

Rationale:

- *Fatigue Model (cognitive, physical).* In a small study done in healthy men, diphenhydramine produced significant feelings of drowsiness for up to 6 hours after the dose, whereas significant mental impairment was only apparent for 2 hours.[20] This effect appeared to be concentration dependent. Because of this impact on sleep/wake schedule as well as the effects on ability to concentration, this would impact *Fatigue Model* and, in turn, the *Traverse Model.*
- *Hydration, Nutrition, and Waste Management Model.* Antihistamines are anticholinergic, meaning they have drying properties (urinary retention, dry mouth).
- While diphenhydramine can impact HR, this effect does not occur frequently and was therefore not mapped to Metabolic Rate.

<u>Epinephrine (EPIPEN) 0.3 mg / 0.3 mL autoinjector</u>

Route: Intramuscular; Labeled Purpose: Allergic Reaction

MOA: Acts on alpha receptors to cause vasoconstriction to increase blood pressure and prevent loss of intravascular fluid. Acts on beta adrenergic receptors to relax bronchial smooth muscle to alleviate wheezing and dyspnea during anaphylaxis.

ADRs – per protocol: **Rapid heart rate and palpitations**, flushing, dizziness, headache, nervousness, dry mouth

Rationale: *Metabolic Rate Model*. Due to the MOA, epinephrine causes vasoconstriction, which cause changes in blood pressure and blood flow impacting the *Thermal Model*.[21,22] As heart rate is an important input in metabolic rate, epinephrine also impacts *Metabolic Rate Model*, and, in turn, *Inspired CO2 model, DCS Model,* and the *Thermal Model*.[21,22]

<u>Eugenol 1 mL Oral Syringe</u>

Route: Topical; Labeled Purpose: Dental anesthetic

ADRs – per protocol: Gum and Skin irritation

Rationale: Due to Eugenol's route of administration and location, it is unlikely to impact any of the physiologic models. Therefore, it was not assigned an aspect of the CSRM.

Eye Wash (DACRIOSE) or alternative equivalent eye irrigation capability

Route: Eye; Labeled Purpose: Eye Foreign Body

ADRs: irritation

Rationale: Due to route of administration and location, it is unlikely to impact any of the physiologic models. Therefore, it was not assigned an aspect of the CSRM.

Famotidine (PEPCID) 20 mg tablet

Route: Oral; Labeled Purpose: GI Management

MOA: By blocking H2R activation by histamine, H2R antagonists decrease gastric acid secretion and reduce the irritation/damage in the stomach that is symptomatic of acid-peptic diseases.

ADRs – per protocol: Dizziness, headache**, insomnia (<1% incidence in clinical trials and post marketing experience),** abdominal discomfort, **blurred vision;** additional: diarrhea (>1%), constipation (>1%)

Rationale

- *Fatigue (cognitive) Model*. Famotidine carries the risk of insomnia, which could impact sleep quality and sleep/wake schedule inputs for the cognitive fatigue model. However, due to the <1% incidence, this is highly unlikely.[23]
- *Hydration, Nutrition, Waste Management Model*. Constipation and diarrhea are reported as >1% incidence in the FDA labeling, meaning a >5% clinical significance cannot be ruled.[23] These conditions impact the electrolyte status and hydration inputs related to crew members

Fexofenadine (ALLEGRA) 180 mg Tablet

Route: Oral; Labeled Purpose: Allergic Reaction

MOA: By acting as a reversible, orthosteric H1R antagonist in the periphery, fexofenadine blocks H1R activation by HA, thereby reducing bronchoconstriction, vasodilation, vessel permeability, and other symptoms associated with allergies and histamine-mediated inflammatory processes.

ADRs – per protocol: Headache, **vomiting, fatigue (1.3%), somnolence**, dizziness, fever, pain, **drowsiness (1.3%), diarrhea, nausea (1.6%),** upset stomach, **muscle aches, back pain (2.8%), pain in extremities**; Additional: dry mouth**, urinary retention, constipation**

Rationale:

- *Fatigue (cognitive, physical) Model*. Per the FDA label, due to its antihistamine properties, fexofenadine carries sedative effects.[24] However, per a meta analysis compared to both first and other second generation antihistamines, fexofenadine carried a significantly lower risk of sedative effects, most likely due to it not crossing the blood brain barrier, making its impact on the cognitive fatigue and *Traverse Model* minimal.[25] Fexofenadine also caries a risk of muscle

aches and pains, which occurred 2.8% of the time.[24] Its impact on *Physical Fatigue Model* would be minimal.

- *Hydration, Waste and Nutrition Model*. Fexofenadine has minimal anticholinergic activity, which would present as urinary retention or constipation.[24] This would impact the Fluid In/Out measurement for crew member. However, impact on this would be minimal.

Fluconazole (DIFLUCAN) 150 mg Tablet

Route: Oral; Labeled Purpose: Antifungal

MOA: inhibits fungal sterol synthesis leading to aggregation of 14 alpha-methyl sterols in the fungi, which is responsible for the fungistatic activity

ADRs - per protocol: Headache, dizziness, nausea (x1 dose 7%; >7 doses 3.7%), abdominal pain, **vomiting (>7 doses 1.7%), diarrhea (x1 dose 3%; >7 doses 1.5%),** rash

Rationale: *Hydration, Nutrition, and Waste Management Model*. The incidence of vomiting and diarrhea are low.[26] However, if there were to be an impact, it would be the HNW Model.

Fluticasone propionate (FLONASE) 50 mcg intranasal spray

Route: Intranasal; Labeled Purpose: Nasal Congestion

MOA: Exact mechanism is unknown. As a Glucocorticoid receptor agonist, fluticasone stimulates pleiotropic physiologic effects that attenuate inflammatory processes.

ADRs – headache, **pharyngitis (6-7.8%), epistaxis (6-6.9%),** nasal irritation, cough (more likely to occur with higher dose), **Nausea/vomiting (2.6-4.8%); development of glaucoma and/or cataracts (1.2%) –** post-marketing experience from long term administration

Rationale: *Hydration, Nutrition, and Waste Management.* The absolute bioavailbilty of intranasal fluticasone is <2% on average, leading to its minimal ADRs.[27] However, if it were to impact a physiologic model, it would be the HNW model.

Fluticasone Propionate 50 mcg / spray + Azelastine HCL 137 mcg or equivalent (DYMISTA) Intranasal Spray

Route: Intranasal; Labeled Purpose: Allergic Reaction

MOA: Azelastine - H1 receptor antagonist, blocking histamine release; Fluticasone - Glucocorticoid receptor agonist, stimulates pleiotropic physiologic effects that attenuate inflammatory processes.

ADRs: headache, **Somnolence (<1% incidence), epistaxis (2%), development of glaucoma and/or cataracts (1.2%) –** post-marketing experience from long term administration

Rationale: *Hydration, Nutrition, and Waste Management.* The absolute bioavailbilty of intranasal fluticasone is <2% on average when monotherapy, leading to its minimal ADRs. However, it is shown to be increased when combined with azelastine (44-61% higher). Still, minimal ADRs were reported in clinical trials.[28] There is some data surrounding glaucoma. In one study, one patient had increased intraocular pressure at month 6. In addition, three patients had evidence of posterior subcapsular cataract at month 6 and one at month 12 (end of treatment). In the fluticasone propionate group, three

patients had evidence of posterior subcapsular cataract at month 12 (end of treatment).[28] In space flight, long term use could be of concern. If Dymista were to impact any physiologic model, it would be the HNW model.

Hydrocodone 10 mg / Acetaminophen 325 mg (NORCO) tablet

Route: Oral; Labeled Purpose: Pain Relief

MOA: As an MOPR agonist, hydrocodone attenuates nociceptive pain signaling in the periphery and enhances pain-modulating signaling in the descending pathway to decrease the perception of and response to pain. See acetaminophen for MOA.

ADRs: **slower heart rate, Respiratory depression (BBW),** dizziness, **drowsiness, mental impairment, sedation, nausea/vomiting (most common in ambulatory patients), constipation (from extended use), urinary retention**

Rationale:

- *Metabolic Rate Model*. Due to the decrease in HR and respiratory depression, the metabolic rate equation will be impact.[29] In turn this will impact any model utilizing metabolic rate as an input (*DCS, Thermal, Inspired CO2*).
- *Fatigue (cognitive, physical*) *Model*. Norco is associated with drowsiness, mental impairment, and sedation, which will impact *Cognitive Fatigue* as well as *Traverse Models*.[29]
- *Hydration, Nutrition, and Waste Management Model.* Norco can also cause nausea and vomiting, especially in ambulatory patients, leading to dehydration and electrolyte imbalances.[29]

Ibuprofen (MOTRIN) 400 mg Tablet

Route: Oral; Labeled Purpose: Pain Relief

MOA: By reversibly inhibiting COX-1 and COX-2 enzymes to reduce the formation of PGH2, NSAIDS decrease the concentrations of prostanoids produced by the downstream biosynthetic pathways, thereby reducing inflammation and related pain signaling.

ADRs: Dizziness, nervousness, **upset stomach, nausea (3-9%), vomiting**, rash (3-9%), ringing in the ears (<1%)

Rationale: *Hydration, Nutrition, and Waste Management Model*. Due to the COX-1 inhibition of NSAIDs, it results in decrease prostaglandins, which protect the stomach lining, leading to stomach upset.[30]

Ketorolac (TORADOL) 60 mg pre-filled syringe or single dose vial

Route: Oral; Labeled Purpose: Pain Relief

MOA: By reversibly inhibiting COX-1 and COX-2 enzymes to reduce the formation of PGH2, NSAIDS decrease the concentrations of prostanoids produced by the downstream biosynthetic pathways, thereby reducing inflammation and related pain signaling.

ADRs: Headache, **nausea (>10%), upset stomach, diarrhea (1-10%)**, dizziness, **drowsiness (1-10%)**, elevated blood pressure (1-10%), swelling (<1%)

Rationale: *Hydration, Nutrition, and Waste Management Model*. Due to the COX-1 inhibition of NSAIDs, it results in decrease prostaglandins, which protect the stomach lining, leading to stomach upset. Ketorolac is incredibly COX-1 selective compared to other NSAIDs, meaning there is more incidence of nausea.[31]

Lidocaine Jelly 2%, 30 mL tube

Route: Topical; Labeled Purpose: Urinary Anesthesia

MOA: acts by binding to voltage-gated sodium channels on the inner surface of the neuronal cell membrane, leading to a decrease in the influx of sodium ions, which inhibits depolarization and ultimately leads to the blockage of conduction

ADR – per protocol: Irritation, itching, rash

Rationale: *Physical Fatigue Model.* A majority of studies involving topical lidocaine focus on its use for local pain reduction. Use of topical lidocaine for pain reduction during EMG and other conduction studies has been tested with mixed clinical results. Regarding electrode impact, one study suggested that while it may interfere with conduction due to its blocking abilities, the nerves undergoing stimulation are relatively deep compared to the absorption of lidocaine, making interference less likely.[32] Based on this, it is it unlikely to impact the EMG input in the *Physical Fatigue Model*, but it cannot be ruled out.

Loperamide (Imodium) 2 mg Tablet

Route: Oral; Labeled Purpose: GI Management

MOA: Synthetic peripheral opioid receptor agonist; it inhibits peristalsis and antisecretory activity and prolongs intestinal transit time reduces fecal volume, increases viscosity and bulk density, decreases fluid volume and electrolyte depletion.

ADRs – per protocol: Abdominal discomfort, nausea, vomiting, constipation (2.6%-5.3%), drowsiness (1.4%), dizziness, dry mouth; Additional: BBW for cardiac adverse events at higher than recommended doses.

Rationale: *Hydration, Nutrition, and Waste Management Model*. Due to the MOA of loperamide, it slows intestinal transit time causing constipation.[33]

Lorazepam (ATIVAN) 1 mg Tablet

Route: Oral; Labeled Purpose: Behavioral Health

MOA: As an allosteric modulator, lorazepam binds to GABA-A receptors on the postsynaptic neuron within the CNS. Lorazepam enhances the inhibitory effect of GABA, thereby increasing neuronal membrane permeability to chloride ions, which results in neuronal hyperpolarization, inhibition of the action potential and a decrease in neuronal excitability.

ADRs – per protocol: **Drowsiness, slowed breathing, low blood pressure (0.1-2.4%), sedation (15.9%),** dizziness, headache, **memory impairment, nausea,** changes in appetite, visual disturbances

Rationale:

- *Fatigue (cognitive, physical) Model*. Due to lorazepam's MOA, there is clinically significant sedation and memory impairment, affecting the sleep/wake schedule.[34] Due to its impact on fatigue, the *Traverse Model* would also be impacted.
- *Metabolic Rate Model*. The MOA of lorazepam depresses the CNS, leading to its sedative effects.[34] This also slows respiratory rate and HR, impacting the metabolic rate model, and in turn, *DCS, Thermal, and Inspired CO2 models*.

Meclizine (ANTIVERT) 25 mg Tablet

Route: Oral; Labeled Purpose: Nausea / Vestibular Adaptation

MOA: As an H1R antagonist, meclizine blocks H1R activation by histamine, thereby suppressing neurotransmission in the vestibular system that results in motion sickness including nausea and vomiting. Meclizine also acts off target as a mAChR antagonist, thereby working as an anti-emetic by blocking cholinergic activation of GI SMC contraction necessary for emesis.

ADRs – per protocol: **Drowsiness,** headache, **fatigue,** nervousness, dizziness, dry mouth, **blurred vision (rare)**

Rationale: *Fatigue (cognitive, physical) Model*. Meclizine has some anticholinergic activity and is a first generation Histamine 1 Receptor antagonist, leading to some sedative effects.[35] Therefore, sleep/wake schedule would be impacted. Due to impact on fatigue, the *Traverse Model* would be impacted as well.

Modafinil (PROVIGIL) 200 mg Tablet

Route: Oral; Labeled Purpose: Circadian Management

MOA: Mechanisms for wakefulness unknown. In vitro, binds to dopamine transporter and inhibits dopamine reuptake to increase extracellular dopamine levels. In humans, produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants.

ADRs: Headache (34%), nervousness, dizziness, anxiety, **insomnia (5%),** chest pain, **rapid heart rate (2%), diarrhea (6%),** upset stomach, dry mouth, **lack of appetite (4%)**

Rationale:

- *Fatigue (cognitive, physical) Model*. In one study looking at cognitive impacts on healthy male patients, there was no significant effect of modafinil on self-reported fatigue, declarative memory 24 hours after learning, sustained attention.[36] On study looked at subjective effects of modafinil on fatigue in fighter pilots and found it was used preventively 33% of the time for fatigue with minimal impacts to sleep quality.[37] However, due to its clinically significant ADR of insomnia, sleep/wake schedule would be impacted. In turn, *Traverse Model* would also be impacted.
- *Hydration, Nutrition, and Waste Management Model*. The clinically significant diarrhea could lead to dehydration and electrolyte abnormalities in crew members. As modafinil is a stimulant, it exhibits appetite suppressive effects, which could nutritional status of crew members.[38]
- *Metabolic Rate Model*. Per the package insert, modafinil can cause tachycardia and palpitations in 2% of patients. While it unlikely, its impact cannot be ruled out. [38]

Moxifloxacin (VIGAMOX) 0.5%, 3 mL Bottle

Route: Eye; Labeled Purpose: Eye Foreign Body

MOA: inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV

ADRs – per protocol: **Dry eye**, eye pain, **itching eye, tearing, visual acuity decreased (occurred in approximately 1-6% of patients)**

Rationale: Fluoroquinolones as a class carry a risk of tendon rupture. Estimated daily exposure AUC (45 ng·hr/mL) values were 1,600 and 1,000 times lower than the mean Cmax and AUC reported after therapeutic 400 mg oral doses of moxifloxacin.[39] Therefore, the risk of tendon rupture is unlikely. Due to route of administration and location, it is unlikely to impact any of the physiologic models. Therefore, it was not assigned an aspect of the CSRM.

Mupirocin (BACTROBAN) 2%, 22 gm Tube

Route: Topical; Labeled Purpose: Antibiotic

MOA: inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl-transfer RNA (tRNA) synthetase

ADRs – per protocol: **Skin irritation, itching**

Rationale: Lotions, creams, and oils are recommended to be avoided prior to electromyography. During one study aboard the ISS of surface EMG, use of lotion prior to placing the electrodes resulted in poor adhesion, but conduction was still good.[40] It would also be best practice to avoid placing sensors on areas where topical medication has been applied. It is unlikely to impact any of the physiologic models. Therefore, it was not assigned an aspect of the CSRM.

Ondansetron (ZOFRAN) ODT 4 mg Tablet

Route: Oral; Labeled Purpose: Nausea / Vestibular Adaptation

MOA: As a 5-HT3R antagonist, ondansetron blocks 5-HT from activating 5-HT3R located on enteric neurons connecting to inhibitory vagal afferents, and thereby prevents depolarization of the neuron and increases normal GI contractility to reduce the reverse contraction necessary for vomiting. Ondansetron also blocks activation of 5-HT3R located on CTZ neurons to prevent depolarization of the neurons and reduce vomiting signaling in the CNS

ADRs – per protocol: Headache**, fatigue (13%), drowsiness**, dizziness, anxiety, **constipation (9%), diarrhea (6%), urinary retention, itching (1%)**. Additional: QTc Prolongation

Rationale:

- *Fatigue (Cognitive, physical) Model*. Ondansetron carries a significant side effect of fatigue and drowsiness, impacting sleep/wake schedule.[41] This in turn would affect the *Traverse Model*. QTc prolongation was reported in post-marketing as well as Clinical monitoring. In one clinical study, 8mg of ondansetron infused over 15min did not prolong QT interval to any clinical relevant extent. [38] These studies were done in healthy adults. Impact on physical fatigue monitoring would be minimal but cannot be ruled out.

- *Hydration, Nutrition, and Waste Management*. Clinically significant diarrhea and constipation occurred with ondansetron, which could impact hydration and electrolyte status of the crew member.[38]
- As QTc prolongation is affecting rhythm and not heart rate, it was not mapped to metabolic rate.

Oxymetazoline (AFRIN) 0.05%, 15 mL bottle Intranasal Spray

Route: Intranasal; Labeled Purpose: Nasal Congestion

MOA: Acts on the alpha adrenergic receptors in the arterioles of the nasal cavity to cause constriction. This results in decreased blood flow and congestion.

ADRs – per protocol: Transient burning, stinging, dryness of the nasal mucosa, sneezing, cough

Rationale: Due to oxymetazoline's route of administration and location, it is unlikely to impact any of the physiologic models. Therefore, it was not assigned an aspect of the CSRM.

Promethazine (PHENERGAN) 25 mg Tablet

Route: Oral; Labeled Purpose: Nausea / Vestibular Adaptation

MOA: As an H1R antagonist, promethazine blocks H1R activation by histamine, thereby suppressing neurotransmission in the vestibular system that results in motion sickness including nausea and vomiting.

ADRs: **Sedation, inability to concentrate, drowsiness (most commonly reported),** dizziness, **blurred or double vision,** nausea, dry mouth, **urinary retention, constipation**, rash, agitation, photosensitivity, **uncontrolled muscle spasms**

Rationale:

- *Fatigue (cognitive, physical) Model*. Promethazine has clinically significant drowsiness and sedation due to H1 receptor antagonism, impacting sleep/wake schedule.[42] This in turn would impact the *Traverse Model*. There are also some EPS, but this is not as common and would have minimal impact on the physical fatigue.
- *Hydration, Nutrition, and Waste Management*. Promethazine causes some constipation and urinary retention, which would affect the Fluid ins/outs of crew members.

Pseudoephedrine (SUDAFED 12 HOUR) 120 mg Tablet

Route: Oral; Labeled Purpose: Nasal Congestion

MOA: Indirectly stimulates alpha receptors causing a release of NE while directly stimulating beta adrenergic receptors. In the mucus membranes, alpha 1 stimulation causing constriction of the vessels to improve congestion.

ADRs: Dizziness, **rapid heart rate, high blood pressure**, restlessness, tremor, headache, loss of appetite**, may impair ability to concentrate,** dry mouth, **insomnia (>30%),** photosensitivity

Rationale:

- *Metabolic Rate Model*. Pseudoephedrine causes modest increases in blood pressure and heart rate, impacting the metabolic rate calculation.[43] This would also impact *Inspired CO2, Thermal, and DCS models* that use metabolic rate as an input.
- *Fatigue (cognitive, physical)*. There is a clinically significant incidence of insomnia, which would impact sleep/wake schedules and sleep quality.[44] This in turn could impact Traverse.

Sodium Chloride (AYR SALINE) 0.9%, 22 mL Bottle Intranasal spray

Route: Intranasal; Labeled Purpose: Nasal Congestion

ADRs: No significant side effects within prescribed dose

Rationale: Due to the route of administration and location, it is unlikely to impact any of the physiologic models. Therefore, it was not assigned an aspect of the CSRM.

Sulfamethoxazole 800 mg / Trimethoprim 160 mg (BACTRIM DS) tablet

Route: Oral; Labeled Purpose: Antibiotic

MOA: Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with paraaminobenzoic acid (PABA), while trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase.

ADRs – per protocol: Headache, dizziness**, insomnia**, stomach upset, **diarrhea,** nausea, **vomiting**, photosensitivity, rash; additional**: High doses of TMP can cause reversible hyperkalemia**

Rationale:

- *Hydration, Nutrition, and Waste Management Model*. Diarrhea and vomiting can cause fluid loss, leading to dehydration and electrolyte shifts in crew members in addition to the increased potassium caused by the TMP component.[45]
- *Fatigue (cognitive)*. While not as common as GI disturbances, Bactrim can cause insomnia in some patients leading to impacts on sleep quality and sleep/wake schedule.[45] In turn, this would impact *Traverse Model.*

Tetracaine 0.5%, 15 mL bottle

Route: Eye; Labeled Purpose: Eye Foreign Body

MOA: blocks sodium ion channels required for the initiation and conduction of neuronal impulses thereby affecting local anesthesia

ADRs – per protocol: **Burning, stinging, redness of the eye, light sensitivity, tearing**

Rationale: Due to the route of administration and location, it is unlikely to impact any of the physiologic models. Therefore, it was not assigned an aspect of the CSRM.

Zaleplon (SONATA) 10 mg Capsule

Route: Oral; Labeled Purpose: Circadian Management

MOA: Modulates the GABA BZ receptor complex to induce the sedative, anxiolytic, muscule relaxant, and anticonvulsant effects.

ADRs – per protocol: Headache, dizziness, **drowsiness (5%), short-term memory impairment (2%), lack of coordination,** nausea (6%), upset stomach**, muscle weakness (<1%);** Additional: **BBW: Complex sleep behavior**

Rationale: *Fatigue (cognitive, physical) Model*. Due to its MOA, zaleplon produces significant drowsiness and some rebound insomnia the night after discontinuation. For memory impairment, healthy subjects experienced short term memory impairment, sedation, impairment of psychomotor function at 1hr with greater effect at doses >20mg. It was no longer present as early as 2hr post dosing and in none of the studies after 3-4h. Risk of next day amnesia was 3% in larger clinical trials.[46] Rebound insomnia was minimal following 5-10mg doses of Sonata on the first night after discontinuation and resolved completely by the second night.[46] This would affect sleep/wake schedule and sleep quality. In turn this would affect *Traverse*.

Zolpidem (AMBIEN) 10 mg Tablet

Route: Oral; Labeled Purpose: Circadian Management

MOA: Binds to the BZ1 receptor with a high affinity for alpha 1/5 subunits. No myorelaxant or anticonvulsant effects.

ADRs – per protocol: **Drowsiness (2%-8%),** dizziness, headache**, abnormal dreams, insomnia, memory impairment, visual and attention disturbance (<1%);** additional: withdrawal with abrupt discontinuation. **BBW: Complex sleep behaviors**

Rationale: *Fatigue (cognitive, physical) Model.* Risk of next day psychomotor impairment is increased if not taken 7-8h prior to waking, if higher than recommended dose is taken or if taken with other CNS depressants or OH. There are also PK difference based on gender as females do not clear zolpidem as fast as males.[47] PK studies showed a significant increase in maximum concentration and exposure in females compared to males at the same dose.[47] These ADRs impact sleep quality and sleep/wake schedule. In turn, this impacts *Traverse*.

**Sources**


1. Blue RS, Bayuse TM, Daniels VR, et al. Supplying a pharmacy for NASA exploration spaceflight: challenges and current understanding. *NPJ Microgravity*. 2019;5:14. Published 2019 Jun 13. doi:10.1038/s41526-019-0075-2
2. Dello Russo C, Bandiera T, Monici M, et al. Physiological adaptations affecting drug pharmacokinetics in space: what do we really know? A critical review of the literature. *Br J Pharmacol*. 2022;179(11):2538-2557. doi:10.1111/bph.15822
3. Diaz T, Mathew S, Bayuse TM. Impacts of Pharmacogenomics on NASA Ground Support and Spaceflight Pharmaceutical Care. Aerospace Medicine Clerkship October 2023.
4. Acetaminophen (TYLENOL) Tablets. [Package Insert]. McNeil Consumer Healthcare; 2021 https://pdf.hres.ca/dpd_pm/00062135.PDF
5. Court MH, Zhu Z, Masse G, et al. Race, Gender, and Genetic Polymorphism Contribute to Variability in Acetaminophen Pharmacokinetics, Metabolism, and Protein-Adduct Concentrations in Healthy African-American and European-American Volunteers. J Pharmacol Exp Ther. 2017;362(3):431-440. doi:10.1124/jpet.117.242107
6. Acetazolomide (DIAMOX) Tablets USP. [Package Insert]. Teva Pharmaceuticals; 2024 https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/008943s053,009388s039lbl.pdf
7. Van Berkel MA, Elefritz JL. Evaluating off-label uses of acetazolamide. Am J Health Syst Pharm. 2018;75(8):524-531. doi:10.2146/ajhp170279
8. Leaf DE, Goldfarb DS. Mechanisms of action of acetazolamide in the prophylaxis and treatment of acute mountain sickness. *J Appl Physiol (1985)*. 2007;102(4):1313-1322. doi:10.1152/japplphysiol.01572.2005
9. Albuterol Sulfate (PROVENTIL HFA) Inhalation Aerosol. [Package Insert]. Merk Sharp & Dohme Corp; 2017 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020503s054lbl.pdf
10. McNeill J, Chernofsky A, Nayor M, et al. The association of lung function and pulmonary vasculature volume with cardiorespiratory fitness in the community. *Eur Respir J*. 2022;60(2):2101821. Published 2022 Aug 4. doi:10.1183/13993003.01821-2021
11. ASPIRIN Tablets. [Package Insert]. Bayer; 2022 https://www.bayer.com/sites/default/files/2020-11/aspirin-pm-en.pdf
12. Azithromycin (ZITHROMAX) Tablets. [Package Insert]. Pfizer Inc; 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/050670s036,050710s051,050711s050,050784s037lbl.pdf
13. Corsetti M, Landes S, Lange R. Bisacodyl: A review of pharmacology and clinical evidence to guide use in clinical practice in patients with constipation. Neurogastroenterol Motil. 2021;33(10):e14123. doi:10.1111/nmo.14123
14. One trial: Kamm MA, Mueller-Lissner S, Wald A, Richter E, Swallow R, Gessner U. Oral bisacodyl is effective and well-tolerated in patients with chronic constipation. Clin Gastroenterol Hepatol. 2011;9(7):577-583. doi:10.1016/j.cgh.2011.03.026
15. Gorbach SL. Bismuth therapy in gastrointestinal diseases. Gastroenterology. 1990 Sep;99(3):863-75
16. Cefdinir (OMNICEF) Capsules. [Package Insert]. AbbVie Inc; 2015 https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050739s017,050749s023lbl.pdf
17. Clindamycin Hydrochloride (CLEOCIN HCl) Tablets. [Package Insert]. Pfizer Inc; 2020 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/050162s102lbl.pdf
18. Dexamethasone (DECADRON) Tablets USP. [Package Insert]. Merk & Co., Inc; 2029 https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/011664s064lbl.pdf

19. Duchatsch F, Constantino PB, Herrera NA, et al. Short-term exposure to dexamethasone promotes autonomic imbalance to the heart before hypertension. *J Am Soc Hypertens*. 2018;12(8):605-613. doi:10.1016/j.jash.2018.06.004
20. Gengo F, Gabos C, Miller JK. The pharmacodynamics of diphenhydramine-induced drowsiness and changes in mental performance. Clin Pharmacol Ther. 1989;45(1):15-21. doi:10.1038/clpt.1989.3
21. Epinephrine Injection (EPIPEN). [Package Insert]. Mylan; 2023 https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/019430Orig1s106Lbl.pdf
22. Epinephrine Injection USP. [Package Insert]. Belcher Pharmaceuticals LLC; 2021 https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/205029s006lbl.pdf
23. Famotidine (PEPCID) tablets. [Package Insert]. Valeant Pharmaceuticals North America LLC; 2018 https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019462s040lbl.pdf
24. Fexofenadine HCL (ALLEGRA) Tablets. [Package Insert]. Aventis Pharmaceuticals Inc; 2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/20786se8-014,20872se8-011,20625se8-012_allegra_lbl.pdf
25. Huang CZ, Jiang ZH, Wang J, Luo Y, Peng H. Antihistamine effects and safety of fexofenadine: a systematic review and Meta-analysis of randomized controlled trials. BMC Pharmacol Toxicol. 2019 Nov 29;20(1):72
26. Fluconazole (DIFLUCAN) Tablets. [Package Insert]. Pfizer Inc; 2024 https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/019949s072lbl.pdf
27. Fluticasone Propionate (FLONASE) Nasal Spray. [Package Insert]. GSK; 2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020121s045lbl.pdf
28. Azelastine HCL and Fluticasone Propionate (DYMISTA) Nasal Spray. [Package Insert]. Meda Pharmaceuticals Inc; 2012 https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202236s000lbl.pdf
29. Hydrocodone Bitartrate and Acetaminophen (NORCO) Tablets. [Package Insert]. Allergan; 2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/040148s073lbl.pdf
30. Rainsford KD. Ibuprofen: pharmacology, efficacy and safety. Inflammopharmacology. 2009;17(6):275-342. doi:10.1007/s10787-009-0016-x
31. Ketorolac Tromethamine (KETOROLAC) Injection. [Package Insert]. Almaject, Inc; 2020 https://www.accessdata.fda.gov/spl/data/5c1c882c-6204-47f8-a47f-b9bc82cc5d83/5c1c882c-6204-47f8-a47f-b9bc82cc5d83.xml
32. Al-Hayk K, et al. Effect of 2% Topical Lidocaine Gel on Discomfort from Electrical Stimulation During Nerve Conduction Studies- A Prospective Double-Blind Placebo-Controlled Study. Local Reg Anesth. 2023;16:153-163. Published 2023 Sep 26. doi:10.2147/LRA.S426076
33. Loperamide HCL (IMODIUM) Capsules. [Package Insert]. Johnson & Johnson Consumer Care; 2016 https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/017694s052lbl.pdf
34. Lorazepam (ATIVAN) Tablets. [Package Insert]. Bausch Health US, LLC; 2023 https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/017794s049lbl.pdf
35. Meclizine HCl (ANTIVERT) tablets. [Package Insert]. Casper Pharma LLC; 2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/010721s063lbl.pdf
36. Repantis D, Bovy L, Ohla K, Kühn S, Dresler M. Cognitive enhancement effects of stimulants: a randomized controlled trial testing methylphenidate, modafinil, and caffeine. *Psychopharmacology (Berl)*. 2021;238(2):441-451. doi:10.1007/s00213-020-05691-w

37. Wingelaar-Jagt YQ, Wingelaar TT, Riedel WJ, Ramaekers JG. Subjective Effects of Modafinil in Military Fighter Pilots During Deployment. *Aerosp Med Hum Perform*. 2022;93(10):823. doi:10.3357/AMHP.6072.2022
38. Modafinil (PROVIGIL) Tablets. [Package Insert]. Teva Pharmaceuticals; 2015 https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf
39. Moxifloxacin HCl (VIGAMOX) opthalmic solution. [Package Insert]. Bayer AG; 2023 https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/21598_vigamox_lbl.pdf
40. Ochia RS, Cavanagh PR. Reliability of surface EMG measurements over 12 hours. *J Electromyogr Kinesiol*. 2007;17(3):365-371. doi:10.1016/j.jelekin.2006.01.003
41. Ondansetron HCl (ZOFRAN) ODT. [Package Insert]. Novartis Pharmaceuticals Corporation; 2021 https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020103s038,020605s022,020781s022lbl.pdf
42. Paton DM, Webster DR. Clinical pharmacokinetics of H1-receptor antagonists (the antihistamines). Clin Pharmacokinet. 1985;10(6):477-497. doi:10.2165/00003088-198510060-00002
43. Salerno S.M., Jackson J.L., Berbano E.P. Effect of oral pseudoephedrine on blood pressure and heart rate. Arch. Intern. Med. 2009;6:1686–1694. doi: 10.1001/archinte.165.15.1686
44. Głowacka K, Wiela-Hojeńska A. Pseudoephedrine-Benefits and Risks. Int J Mol Sci. 2021;22(10):5146. Published 2021 May 13. doi:10.3390/ijms22105146
45. Sulfamethoxazole and Trimethoprim (BACTRIM) DS Tablets. [Package Insert]. Sun Pharmaceutical Industries; 2024 https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/017377s084lbl.pdf
46. Zaleplon (SONATA) Capsules. [Package Insert]. Pfizer Inc; 2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020859s016lbl.pdf
47. Zolpidem Tartrate (AMBIEN) Tablet. [Package Insert]. Sanofi-aventis; 2022 https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/019908s40s044s047lbl.pdf
48. Johnson & Johnson. DERMABOND ADVANCED and Mini Topical Skin Adhesives. Published 2023. Accessed October 2024. https://www.jnjmedtech.com/en-US/product/dermabond-advanced-mini-topical-skin-adhesives
49. Loew, D., Schuster, O. & Graul, E.H. Dose-dependent pharmacokinetics of dexamethasone. Eur J Clin Pharmacol 30, 225–230 (1986).
50. Paton DM, Webster DR. Clinical pharmacokinetics of H1-receptor antagonists (the antihistamines). Clin Pharmacokinet. 1985;10(6):477-497. doi:10.2165/00003088-198510060-00002
51. Casale TB, Ellis AK, Nowak-Wegrzyn A, Kaliner M, Lowenthal R, Tanimoto S. Pharmacokinetics/pharmacodynamics of epinephrine after single and repeat administration of neffy, EpiPen, and manual intramuscular injection. J Allergy Clin Immunol. 2023;152(6):1587-1596. doi:10.1016/j.jaci.2023.08.007
52. Mupirocin (BACTROBAN) ointment. [Package Insert]. GSK; 2017 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050591s034lbl.pdf
53. Giannakopoulos H, Levin LM, Chou JC, et al. The cardiovascular effects and pharmacokinetics of intranasal tetracaine plus oxymetazoline: preliminary findings. J Am Dent Assoc. 2012;143(8):872-880.
54. Tetracaine HCl Ophthalmic Solution. [Package Insert]. Alcon Laboratories, Inc; 2022 https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208135s005lbl.pdf