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Novel Indications for Commonly Used Medications as Radiation Protectants in Spaceflight

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Background

In the space environment, the traditional radioprotective principles of time, distance, and shielding become difficult to implement. Additionally, the complex radiation environment inherent in space, the chronic exposure timeframe, and the presence of numerous confounding variables complicate the process of creating appropriate risk models for astronaut exposure. Pharmaceutical options hold tremendous promise to attenuate acute and late effects of radiation exposure in the astronaut population. Pharmaceuticals currently approved for other indications may also offer radiation protection, modulation, or mitigation properties along with a well-established safety profile. Currently there are only three agents which have been clinically approved to be employed for radiation exposure, and these only for very narrow indications. This review identifies a number of agents currently approved by the U.S. Food and Drug Administration (FDA) which could warrant further investigation for use in astronauts. Specifically, we examine preclinical and clinical evidence for statins, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), metformin, calcium channel blockers, β adrenergic receptor blockers, fingolimod, N-acetylcysteine, and pentoxifylline as potential radiation countermeasures.

Keywords

radiation; protection; mitigation; modulation

High levels of radiation, particularly on exploration class missions beyond low Earth orbit (LEO), represent a major medical challenge for astronauts and their flight surgeons as the

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National Aeronautics and Space Administration (NASA) contemplates missions to Mars and beyond. Radiation protection has traditionally centered around the “as low as reasonably achievable” principles of time, distance, and shielding. However, in the space environment each of these principles becomes difficult to implement. Distance from the radiation source, in most cases the sun, is relatively fixed. Engineering, vehicle propulsion, flight time, flight trajectory, and orbital dynamics determine the timing of the exposure. Further, launching adequate shielding material into space quickly becomes prohibitively expensive. Both radiation dose and radiation quality factor increase at higher mission altitudes. Recent estimates state that with current technology an exploration-class mission as short as 100 d could increase cancer-related crew mortality to unacceptable levels with 95% confidence.²² Given the constraints on traditional techniques to manage radiation exposure, new methods are needed to protect astronauts as they venture beyond the protection of LEO.

One promising approach is the use of radiation protectors (compounds given before radiation exposure to reduce or prevent tissue injury), modulators (compounds given to increase baseline resistance of an organism to radiation), and mitigators (compounds given after radiation exposure to reduce or prevent tissue injury).⁹⁶ While several agents are currently under investigation, only a very few have ever been approved by the FDA to counter radiation effects, and those only for very specific indications. Amifostine was the first pharmaceutical approved as a radioprotector for radiation-induced xerostomia in head and neck cancers.⁶⁶ The thiol group in amifostine functions as a radical scavenger.⁶⁹ Thiols represent one of the most effective classes of radiation protectors; however, the side effect profile of some of this class makes them poorly tolerated and limits their dosage.⁶⁶ Common side effects include diarrhea, vomiting, and hypotension, all of which could be challenging to manage in the space environment.²⁷ More recently, filgrastim and its PEGylated counterpart pegfilgrastim have been approved for myelosuppressive doses of radiation. Both agents are granulocyte colony stimulating factors, inducing production of white blood cells.⁶⁶ These three agents are the only pharmaceuticals currently approved by the U.S. Food and Drug Administration (FDA) specifically for radiation mitigation. Clearly, NASA is in need of additional options for astronauts on exploration class missions.

Given that astronauts are generally healthy individuals, any pharmaceutical agent for consideration as a radiation protector/modulator/mitigator must have an established long-term safety profile. For that reason, we examined compounds which have already been approved by the FDA or other regulatory agencies and have a history of use in humans for other indications. Numerous experimental agents are currently being studied and their properties have been extensively reviewed elsewhere.^{101,124} This review aims to identify currently approved pharmaceuticals that may have relevance to the astronaut population and may merit further study.

Space radiation consists of multiple radiation types. Protons and γ rays make up the bulk of radiation emitted from the sun. Relatively low energy particle radiation is blocked by the aluminum/composite structure of spacecraft. Galactic cosmic radiation (GCR, very high energy particles of a wider variety of masses) contribute to astronaut exposure both through direct tissue interaction and through secondary radiation processes. Bremsstrahlung radiation and neutron-producing nuclear reactions also account for significant fractions of

astronaut radiation exposure. In particular, neutron doses represent a high linear energy transfer (LET) form of radiation. High LET secondary processes and galactic cosmic rays are better attenuated by hydrogen-rich shielding materials such as water or polyethylene. Hydrogen, which exists predominantly as the ^1H nuclide, can attenuate high energy particles without generating secondary neutrons. While surrounding the entire crew module with hydrogen-rich material is difficult, surrounding a smaller “storm shelter” with the mission water supply provides meaningful protection without increasing payload requirements. High LET radiation tends to have more profound biological effects than low LET; therefore agents which are successful in protecting tissues from low LET radiation, such as electrons and γ radiation, may not adequately protect from high LET radiation such as protons, neutrons, α particles, and higher Z particles.^{9,58} Low LET radiation produces cellular damage predominantly through the generation of reactive oxygen species. High LET radiation, on the other hand, damages the cell principally via direct interaction between the incident particle and the DNA. Additionally, space environments have increased UV radiation relative to terrestrial levels. UV radiation affects skin cancer incidence on Earth and could contribute to a variety of potential long term health effects in astronauts.^{15,16,59} Astronauts on the International Space Station (in LEO) are exposed primarily to GCRs with a secondary contribution from trapped radiation belts.²⁰ Required extra-vehicular activities (i.e., spacewalks) are scheduled around orbital position and space weather to minimize radiation exposure. Astronauts on exploration class missions would be exposed to a higher proportion of solar particle event (SPE) radiation with fewer scheduling techniques to minimize dose. While extensive experience with long term LEO exposures shows no pharmacological intervention is necessary, a 180-d flight to Mars would give four times the biologically equivalent dose as a comparable time on the International Space Station. The proposed 500-d stay on Mars would result in an exposure comparable to the 180-d transit and would add to the overall dose, which may approach 1.3 Sievert for the mission.^{40,42}

In addition to the complex radiation environment in space, there are a number of practical considerations that make studying space-relevant exposures difficult. First, due to the small number of people who have traveled in space (and even fewer beyond LEO, those participating in the Apollo missions), it is difficult to get sufficient statistical power for epidemiological studies in the target population. Next, few facilities are even capable of generating the appropriate radiation fields, much less creating the mixed radiation environment seen in space. Thus, most studies are performed with low energy, nonparticulate radiation; what is often called “conventional” radiation. Hence, unless otherwise specified, the radiation used in referenced studies in this review is low LET, γ , or X-ray. Efforts are underway by NASA and other agencies/institutions to better simulate space-type radiation at Brookhaven National Laboratory and other accelerators with high LET or high-Z particles to mimic GCR, including iron particles and other heavier nuclei at energies in the GeV range. Further, the anticipated interplanetary space radiation exposure will be chronic, low dose rate GCR with a background of lower energy solar wind protons. Acute exposure associated with SPEs, commonly due to coronal mass ejections, may require a different strategy for radiation protection than chronic exposure as the energy and dose rate (due to high flux and fluence) will be different for SPEs than for both solar wind and GCR particles.¹⁰ Further, many of the late-onset radiation effects such as fibrosis are not

immediately evident. As such, long observation times postradiation are necessary to determine chronic outcomes of radiation exposure. The majority of the available literature (and of the studies presented in this review) examines the effects of a single, large dose of radiation in animal models or of fractionated doses given to radiotherapy patients over the course of several weeks. Neither of these scenarios may represent an adequate comparison to the primarily chronic low-dose radiation encountered by astronauts. One appropriate model system for chronic low-dose radiation may involve studying geographic areas on Earth with naturally high backgrounds. For example, due to high local concentrations of radon, residents in the Ramsar region of Iran receive an average of 6 mSv per year.⁴³

Radiation exposure can lead to numerous biological effects, both acute and chronic. Acute exposures in space result primarily from SPEs. Data from radiation monitors during space-flight can provide a good guide to the expected exposure levels in nominal and worst-case scenarios. If an event such as the 1972 SPE occurred, an astronaut traveling outside LEO while inside a spacecraft (approximated as a $5 \text{ g} \cdot \text{cm}^{-2}$ aluminum sphere) would receive a 2.69 Gy dose to the skin and 0.46 Gy dose to the blood forming organs. In contrast, an “average” SPE under these same conditions would give a dose of 10 mGy. If outside the spacecraft in a spacesuit (modeled as a $0.3 \text{ g} \cdot \text{cm}^{-2}$ aluminum sphere), the dose of a 1972 scale SPE would increase to 32 Gy to the skin and 1.38 Gy to the blood forming organs.⁴⁹ Travel in interplanetary space, even in the absence of SPE, still exposes spacefarers to 1.69–1.80 mSv/d.¹³¹ Ferrets, a model system for gastrointestinal radiation exposure, develop emesis at lower doses. High LET sources of radiation (⁵⁶Fe or fission neutrons) induce emesis in ferrets with ED₅₀ values of 0.35–0.40 Gy.⁶² Low LET sources require 0.77–1.38 Gy to achieve the same effect. Humans begin to exhibit mild prodromal effects (nausea, vomiting, anorexia, and fatigue) and mild damage to the hematopoietic system at doses of 0.5–1.0 Gy.⁷⁸ Further, the effects of acute radiation exposure may be exacerbated by reduced gravity. Mice that undergo partial unloading of their hindlimbs and are subsequently irradiated with high doses of proton irradiation demonstrate a greater loss of white blood cells, impaired immune function, and decreased ability to survive subsequent bacterial challenge when compared to fully loaded irradiated mice.⁶² Exposure to a high dose of protons from SPEs is very unlikely to occur; nevertheless, the space program must prepare to mitigate the acute radiation syndrome that could potentially occur.

Chronic low dose exposure to high-LET radiation is a very likely risk. Carcinogenic effects of radiation have been documented, while other long term effects such as cataracts, lung fibrosis, neural deficits, vascular disease, infertility, and impaired hematopoiesis are less understood.⁵⁶ Astronauts receiving lens doses of > 8 mSv have increased lifetime prevalence of cataract formation relative to those with lens doses of < 8 mSv.²¹ New evidence points to an even lower (0.5 Gy/yr) threshold for long term pathological damage.¹⁰⁵ Additionally, space travel (and likely associated radiation exposure) induced pulmonary fibrosis and respiratory dysfunction in murine disease models. Markers of fibrosis in mouse lung were increased immediately upon return from a 13-d flight on space shuttle mission STS-118.¹¹¹ These fibrotic changes eventually lead to hypoxemia in mice exposed to space relevant radiation (²⁸Si or ⁵⁶Fe).¹³ Radiation exposure also impairs the proliferative ability of neural precursor cells at doses as low as 1–2 Gy,^{1,2} which may be partially responsible for some of the cognitive deficits in children and adults who undergo radiation therapy for malignancies.

High doses of ionizing radiation exacerbate atherosclerotic disease processes, especially when combined with other risk factors. Low doses (< 500 mSv) appear to activate the immune response, which may be associated with either protection from or induction of atherosclerotic processes.⁶ Tragically, many women who battle cancer early in their lives suffer from premature ovarian failure and infertility following radiotherapy.⁸¹ Additionally, patients undergoing radiation therapy often suffer from hearing loss. The loss is sensorineural and therefore incurable with current capabilities.¹¹³ Although hematopoietic stem cells are sequestered within relatively dense bone, both acute and chronic ⁵⁶Fe irradiation alters hematopoietic stem cells, leading to leukemia and other blood diseases.⁸³ Proton doses as low as 1.0 Gy cause persistent damage to murine hematopoietic cells, leading to chronic sequelae.¹¹

In order to facilitate the approval process for radiation countermeasures since human clinical trials cannot always be ethically executed, the FDA established the “Animal Rule” through which a drug may be approved with demonstration of efficacy only in animal models.¹¹² Many animal model systems have been tested with space-like radiation to characterize the effects on healthy tissues.¹⁰⁰ However, a flight surgeon caring for astronauts must question whether a certain drug will truly be effective in protecting healthy tissues in humans. Unfortunately, clinical studies of healthy tissue radiation protectors in humans undergoing treatment for cancer cannot be easily translated to the astronaut population. Studies with sufficient statistical power are complicated by the fact that the patients are receiving very high doses of primarily low LET radiation (not space relevant), possibly concurrent with other modalities (i.e., chemotherapy, hyperthermia, immunotherapy, etc.) for their malignancies. It is possible that the pharmacodynamics and pharmacokinetics of medications differ in space. A handful of studies were performed in spaceflight and in bed rest, a ground-based analog for the fluid shifting occurring in microgravity. While there are some differences in the kinetics and plasma distribution, in general, medications do work in space and in bed rest.¹²⁶ A conscientious flight surgeon may hesitate to use approved medications until there is definitive evidence of efficacy and safety in humans for protecting healthy tissues against ionizing radiation damage. Hence, we undertook this survey of FDA-approved medications with known long-term safety profiles and examined the evidence for their potential use in protecting astronauts from space radiation.

Methods

Literature searches were performed between January 2014 and May 2015 using the PubMed database. Agents were identified by searching for “radiation protectants” or “radiation mitigants.” Promising articles were selected based on title and abstract and searched to identify FDA-approved compounds. Nonoral formulations were excluded. A more in-depth search was performed on each identified agent or class, including the term “radiation” combined with the class of drug (i.e., statins) or individual FDA approved medications within the class. Abstracts published in the last 30 yr were reviewed for relevance to the stated topic. Full text versions of articles with promising abstracts were downloaded and studied. If an adequate review of a class of drugs was identified, that review was cited in this publication, but articles predating that review were excluded.

This review examines preclinical and clinical evidence for radiation protection, modulation, and mitigation from medications approved by the FDA for other indications. Vitamins, chemopreventatives, nutraceuticals, and other natural substances (e.g., erythropoietin, EPO), while potentially useful in radiation recovery, are not discussed here. There are numerous references which evaluate the efficacy of nutrient cocktails, non-FDA approved, or experimental agents which have demonstrated some radiation protection.^{14,57,101,124} Compounds and classes of compounds that we selected to review include statins, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), metformin, N-acetylcysteine, calcium channel blockers, beta blockers, fingolimod, and pentoxifylline. There are psychoactive agents which could have activity in reducing possible central nervous system (CNS) side effects, e.g., selective serotonin reuptake inhibitors, based on early animal studies; however, the currently published human literature does not strongly support their use at this time.

Results/Discussion

Possible radiation defense agents were subclassified based on their primary therapeutic and “FDA-approved” uses and their associated potential radiation protection, modulation, or mitigation properties assessed and discussed by category.

Anti-Inflammatories

Perhaps the best studied FDA approved class of compounds for use in radiation protection is the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, i.e., the statins, possibly because a large number of the population (and hence radiotherapy patients) are taking these medications. Statins may be beneficial in general in the astronaut population due to both their antineoplastic and anti-inflammatory properties. Statins function as antiproliferative agents through activating pathways involving caspases 3 and 9 in dose dependent fashion. By promoting these apoptotic pathways, statins inhibit the proliferation of neoplastic cells.¹²³ Additionally, statins inhibit the upregulation of E-selectin in mesenchymal type cells. E-selectin, which is induced by ionizing radiation, is necessary for neoplastic cells to bind to the vasculature and to metastasize throughout the body.^{92,121} Neutrophil chemotaxis is also inhibited by E-selectin downregulation, reducing inflammation and subsequent fibrotic processes. Finally, statins exhibit marked anti-inflammatory effects which decrease vascular changes following radiation exposure.⁶⁰ By inhibiting the inflammatory and fibrotic responses, statins appear to be able to mitigate both short term and long term radiation sequelae in many tissues.⁹⁴ A thorough review can be found elsewhere.³² Highlights and new discoveries subsequent to that review are briefly detailed here.

As expected, retrospective epidemiological studies show decreased cancer incidence in subsets of the population taking statins. Statin use of over 5 yr is associated with a decrease in breast cancer risk with an odds ratio of 0.7 which approaches, but does not achieve, statistical significance (95% CI 0.4–1.0).⁷ Statins reduce overall cancer rates with an odds ratio of 0.80 (95% CI 0.66–0.96); this improves even further with use of 4 yr or more (OR 0.64, 95% CI 0.44–0.93) or with over 1350 statin doses (0.60, 95% CI 0.40–0.91).³⁸

Statins may protect endothelial cells from radiation damage. While statins do not prevent cell death in human fibroblasts and do not protect from DNA double strand breaks, they do temper the stress response in exposed human umbilical vein endothelial cells.⁹¹ After 5 and 10 Gy radiation doses, pravastatin mitigates the increase in inflammatory factors monocyte chemoattractant protein 1 (MCP-1), interleukin 6, and interleukin 8. These effects appear even when pravastatin is applied up to 14 d after the radiation insult.³⁵ Other studies of human umbilical vein endothelial cells indicate that after either a low (2 Gy) or a high dose (25 Gy) of radiation, levels of the anti-thrombotic protein thrombomodulin increased in statin-treated cells relative to untreated cells. Levels of protein C, another anti-thrombotic, also increased when treated with atorvastatin post-radiation, but decreased in untreated irradiated controls.⁹⁷ Pravastatin decreases levels of cell adhesion molecules such as MCP-1, E-selectin, and intercellular adhesion molecule 1. This effect is likely mediated by endothelial nitric oxide synthase, because the effect is abrogated in endothelial nitric oxide synthase knockout mice.⁴⁵

Statins may mitigate pulmonary fibrosis following thoracic radiation exposure. Lovastatin decreases lung T-cell counts and inflammatory markers such as MCP-1 in murine models after 15 Gy of total lung irradiation. T-cell counts in the lung indicate inflammation that precedes pulmonary fibrosis and are associated with collagen deposition. Lovastatin was efficacious both when administered at time of radiation or at 8 wk post radiation.¹²⁵ High dose (25 Gy) exposure of mice treated with simvastatin shows decreased radiation-induced lung injury, including decreased vascular leak, leukocyte infiltration, and oxidative stress when compared to untreated mice. Disease-related expression patterns of p53, nuclear factor erythroid 2 related factor, and sphingolipid metabolic pathways were also reversed by simvastatin.⁷⁶

Statins also show promise in relieving gastrointestinal symptoms resulting from radiation. Rats receiving pravastatin starting either 3 d before or 14 d after a high dose (19 Gy) of irradiation showed dramatic improvement in long term gastrointestinal tissue integrity (albeit with no improvement in acute symptoms). At 15 wk postirradiation, rats showed significant reduction of dystrophic (but not fibronectin) lesions. After 26 wk, 6 out of 10 rats showed complete recovery while the remaining 4 showed only minimal lesions. Murine models showed similar late benefits after treatment with simvastatin and exposure to 9 daily fractions of 5 Gy radiation.¹¹⁵

Within the central nervous system, some of the most radiosensitive cells are the neural progenitor cells. Atorvastatin combined with the ACEI ramipril administered 24 h after exposing rats to 10 Gy of whole brain irradiation synergistically mitigated destruction of doublecortin positive neural progenitor cells.⁵⁴

With the numerous preclinical studies using statins for radiation protection/modulation/mitigation and the high prevalence of patients incidentally taking statins, a number of groups have analyzed outcomes associated with statin use in radiotherapy patients. Most studies involve chart analyses of men treated for prostate cancer. Continuous statin users were at a decreased risk of all-cause mortality following radiotherapy, with a hazard ratio of 0.39 (95% confidence interval 0.37–0.94).⁶¹ Following radiation therapy, statin use was

associated with increased freedom from biochemical failure (defined as prostate specific antigen $2 \text{ ng} \cdot \text{mL}^{-1}$ over nadir), increased relapse free survival, and decreased need for salvage androgen deprivation therapy.⁴¹ Another study also found that men taking statins had increased progression free survival over nonstatin users, but that these differences became nonsignificant when adjusted for treatment year and other prognostic factors.¹⁰⁶ Decreases in all-cause mortality may reflect cardiovascular protective effects rather than specific radioprotective abilities inherent to statins. Similarly, freedom from progression may reflect antimetastatic properties of statins. The specific operative mechanisms in each case remain complex and need to be further elucidated. Side effects of statin use include myalgia and memory loss/dementia.¹¹⁰ Statins are generally well-tolerated and show potential as both a prophylactic agent and an acute exposure mitigator for gastrointestinal (GI) and CNS insults.

As statins work partly through their actions as anti-inflammatories, it stands to reason that NSAIDs may also be efficacious as radiation mitigators via similar mechanisms. These compounds have been reviewed for their role in radiation therapy and cancer treatment elsewhere.^{39,102} Since the time of these reviews, additional supportive studies have been published. The cyclooxygenase 2 inhibitor meloxicam decreases 30-d lethality in mice when given either before or 1 h after otherwise lethal 9 Gy whole body irradiation. Celecoxib, another cyclooxygenase 2 inhibitor, significantly reduces radiation pneumonitis in mice when given starting 80 d after irradiation. When started immediately or 40 d after irradiation, the decrease in pneumonitis was not as robust.⁵⁰ In clinical cases, those that did not use statins or acetylsalicylic acid following radiation therapy for prostate cancer had early biochemical failure and worse outcomes.¹³⁰ Acetylsalicylic acid reduced rates of distant metastases and improved overall survival.⁵¹

Adverse effects from NSAIDs stem primarily from prostaglandin inhibition. Lower levels of prostaglandins result in decreased gastric mucus production and resultant gastritis. Further, the kidney relies on prostaglandins to maintain blood flow and regulate electrolyte secretion.¹⁰⁹ High levels of NSAIDs can also produce analgesic nephropathy. Decreased renal function is particularly worrisome in the astronaut population.¹⁰⁹ Calcium levels rise with bone breakdown in microgravity. Decreases in renal blood flow can lead to renal calculi, which can quickly incapacitate crewmembers. While NSAIDs deserve more investigation in the acute setting, side effects stemming from their chronic use would likely limit their application as a prophylactic.

Angiotensin Axis Modifying Agents

FDA-approved drugs that modify the renin-angiotensin system were also studied for their effects in radiation protection, modulation, or mitigation. As ACEIs and ARBs work via blockade of the conversion from angiotensin I to angiotensin II, they show most promise in areas with high levels of angiotensin-converting enzyme (lung tissue) or at the site of angiotensin II action (kidney). A comprehensive review of ACEIs was published following the Fukushima Daichi reactor incident.⁷ Interested readers are thus directed and we will focus on more recent results.

ACEIs may reduce radiation-induced damage to the cardiopulmonary system. Captopril administered after proton irradiation alleviates tachypnea in rats when the heart is included in the radiation field.¹¹⁴ Rats exposed to 11 Gy of radiation and captopril combined with the experimental antioxidant EUK-207 after radiation showed virtually no molecular radiation effects at 32 wk.⁷⁴ Survival in rats exposed to 10 or 13 Gy of thoracic radiation improved after receiving a short course of enalapril up to 2 wk (10 Gy) or 1 mo (13 Gy) after initial radiation.^{33,84} Rats treated with enalapril also showed decreased numbers of cholesterol containing clefts in the alveoli, a histological marker of radiation injury.³⁴ Fosinopril, like captopril and enalapril, was able to decrease collagen synthesis in rats when given starting 1 wk after exposure to 13 Gy thoracic radiation, but did not have comparable decreases in mortality.⁶⁸ Captopril in rats was found to have a dose modifying factor (DMF) of 1.07–1.17 with regards to survival and a DMF of 1.21–1.35 with regards to tachypnea.⁷⁹

The efficacy of ACEIs as radiation protectants has been examined in humans both retrospectively and prospectively. One study indicates a statistically significant decrease in radiation-induced pneumonitis in patients receiving thoracic radiation.⁶⁴ A second study showed a trend, but was not statistically significant ($P = 0.06$).⁶³ This second study noted that changes in pneumonitis were statistically significant in certain subgroups such as males and those receiving a mean lung dose under 20 Gy.¹¹⁸ A prospective clinical trial involving a small number of patients undergoing total body irradiation for bone marrow transplantation noted decreased deaths due to pulmonary complications in the ACEI treatment group; however, it showed no significant improvement in overall mortality.¹⁷ Pulmonary structural changes were also decreased following concomitant ACEI use in radiotherapy, as evidenced by post-treatment CT scans.⁵²

The effects of ACEIs on gastrointestinal radiation damage are mixed. An early report found that captopril was successful as a radiation protector in mice when given 7 d before exposure to either 9 Gy or 15 Gy of radiation. Intact intestinal crypt numbers were significantly higher in the mice receiving captopril.¹²⁹ A study in rats undergoing fractionated radiation doses as part of bone marrow transplantation protocol showed no improvement in gastrointestinal damage with administration of captopril starting 9 d before transplant.⁸⁷ In retrospective chart review, ACEIs and statins worked independently and in combination to reduce radiation-induced gastrointestinal damage in patients undergoing pelvic radiotherapy for malignancy.¹²²

ACEIs also appear useful in mitigation of radiation-induced brain injury. Ramipril given starting 24 h after 10 Gy (but not 15 Gy) whole-brain irradiation in rats significantly protects neural progenitor cell proliferation and neuronal differentiation.⁵³ ACEIs were also effective in preventing adverse effects of a larger, fractionated dose (40 Gy in 5 Gy increments over 4 wk). Rats receiving ramipril before, during, or after irradiation prevented declines in perirhinal cortex based cognitive function and increases in microglial activation in the dentate gyrus.⁷¹ A more comprehensive review on the mechanism and past use of ACEIs and ARBs for treatment of radiation-induced brain injury, including effects on the eye, can be found elsewhere.⁹⁸

Patients with chronic, progressive kidney disease regularly receive ACEIs and ARBs as therapies to reduce injury to the renal tubule and glomerulus. Much work has been done to determine if these agents would act similarly in protecting the kidney from radiation damage, and a review on this topic has been published.¹⁸ In the intervening years, animal studies have established similar DMFs for the ACEI captopril (1.23) and the ARB losartan (1.21).⁸⁵ Five different ACEIs (captopril, lisinopril, enalapril, ramipril, and fosinopril) at clinically relevant doses have been examined for efficacy as mitigators of radiation-induced nephropathy. All except fosinopril effectively abrogated radiation nephropathy, with captopril being the most effective.⁸⁶ Confounding this finding is a retrospective chart analysis in humans which correlated incidental use of ACEIs with increased acute kidney injury following radiation therapy for head and neck cancer. This increased kidney injury resulted in increased interventions during therapy and increased renal dysfunction following therapy.¹⁰³ It is possible that patients that used ACEIs already had varying degrees of kidney failure and were at a higher risk for additional injury from radiation. Prospective clinical trials found a statistically insignificant decrease in radiation nephropathy in patients undergoing whole body irradiation when given captopril.¹⁷

Preclinical murine data also suggest that the ACEI captopril may be able to improve the response of hematopoietic cells to radiation insult. Captopril given 1 h prior to 2 Gy - γ irradiation prevented clastogenic effects in bone marrow erythrocytes two-fold relative to controls. The authors attributed this protection to increased free radical scavenging and reduced lipid per-oxidation/DNA damage.⁴⁷ In addition, captopril appears to decrease EPO transiently in nonirradiated controls and to increase EPO levels postirradiation if started prior to radiation exposure. When administered after a 7.5 Gy whole body irradiation dose, captopril induced quiescence in hematopoietic stem cells, protecting them and leading to improved recovery postirradiation.⁴ Captopril may work through regulating the cell cycle, differentially sensitizing or protecting hematopoietic cells based on the time of administration.²³ The isoflavone genistein appears to work synergistically with captopril, improving the 30-d survival in mice receiving both drugs from 0 to 95% after 8.25 Gy total body irradiation. The combination therapy reduced anemia and increased the number of circulating hematopoietic cells.²⁴ Perindopril, another ACEI, also increases recovery of the hematopoietic system following irradiation, with higher numbers of granulocyte macrophage colony forming units, erythroid burst forming units, and megakaryocyte colony forming units compared to controls.¹²

In one of the few studies involving particles heavier than electrons, keratinocyte cells showed increased radiation protection from neutron radiation when exposed to thiol containing drugs, including captopril.¹⁰⁷ Rats receiving γ radiation showed moist desquamation of epithelial cells, a hallmark of loss of integrity of the epithelial barrier and decreased oncotic pressure following a 30 Gy exposure. When treated with captopril, rats showed significantly less moist desquamation and were much less likely to develop malignancies during the following year.¹²⁰ Cardiac tissue does not appear to be protected from radiation damage with captopril administration, as pathology and heart function were unchanged from controls in mice studies involving a single dose of 20 Gy.¹²⁸ Overall survival in rats is higher after 11–12 Gy whole body irradiation when treated with any of the ACEIs captopril, enalapril, or fosinopril starting 1 wk postirradiation.⁸⁰ Clinically,

retrospective chart reviews indicate that incidental use of ACEIs is associated with poor tumor control in irradiated areas following thoracic radiation for treatment of nonsmall cell lung cancer.¹¹⁷

Side effects due to ACEIs and ARBs pertinent to the astronaut population include decreased renal perfusion and angioedema. The consequences of decreased renal perfusion have already been discussed. Angioedema, a rare side effect associated with ACEIs and ARBs, results from increased levels of bradykinin, which increases capillary permeability.^{5,30} During spaceflight, astronauts develop venous blood pooling in the absence of gravity, particularly in the pelvic, splanchnic, and cephalic areas.³ It is possible that increased levels of bradykinin due to ACEI/ARB use could transform this venous pooling to clinically relevant edema. Given the dangers of prophylactic use regarding edema and renal perfusion, ACEIs and ARBs would likely make poor prophylactic agents for the astronaut population. They may deserve further investigation for acute prevention of radiation pneumonitis, CNS damage, and bone marrow toxicity.

Metabolic Agents

Metformin is a pharmaceutical used predominantly for the treatment of type II diabetes mellitus. Its capacity to protect from the damage of reactive oxygen species makes it a potential radiation protector/modulator/mitigator. When given 24 h after exposure to 4 Gy of radiation, metformin increased survival of mouse embryo fibroblasts, human microvascular endothelial cells, and a mouse sarcoma cell line.⁸² Further, in vivo spleen assays measure the DMF of metformin as 1.8 when given 24 h following a 7 Gy radiation exposure. Metformin also works synergistically with N-acetyl-cysteine, captopril, or mesna to provide DMFs ranging from 2.0–2.8.⁸² Further in vivo tests measured the ability of metformin to protect from radiation-induced sensorineural hearing loss in guinea pigs. After a very high dose of 70 Gy delivered over 20 d, guinea pigs treated with metformin suffered a statistically insignificant lower degree of hearing loss than the control irradiated animals. Metformin on its own was not found to be ototoxic.⁸⁸ Decades of clinical use have demonstrated that metformin is generally well-tolerated and safe even in prediabetics as a preventative agent.⁴⁸ Adverse effects, when they occur, are generally gastrointestinal in origin.⁶⁷ While less evidence exists in support of metformin, its high DMF combined with its benign safety profile merit further investigation.

N-acetylcysteine is a thiol-containing antioxidant approved for acetaminophen overdose and as a mucolytic. This agent works across a wide variety of tissues by scavenging free radicals and decreasing levels of caspase-3.⁷² Treatment with n-acetylcysteine also improves wound healing¹⁰⁸ and anastomoses²⁶ after irradiation of rat models. These effects may be due to protection of immune cells following radiation.¹²⁷ After exposure to 40 Gy of radiation, rat femurs showed a larger cross sectional area, increased load bearing capability, and increased energy absorption capacity when pretreated with n-acetylcysteine.²⁹ Administration of n-acetylcysteine in rat models further decreases toxic metabolite formation in the liver (6 Gy)⁶⁵ and radiation dermatitis in the skin (18 Gy).²⁸ N-acetylcysteine also appears to decrease radiation-induced changes to the gastrointestinal tract and improve overall survival in mice when given starting 4 h before or 2 h after irradiation.⁵⁵ Side effects of n-

acetylcysteine appear almost exclusively in overdose or due to anaphylaxis.⁷⁵ N-acetylcysteine deserves further study as a prophylactic agent to counter immunosuppression in space as well as an acute preventative for GI and bone toxicities.

Anti-Hypertensives

As radiation protection agents, calcium channel blockers are effective mitigators of vascular changes induced by oxidative stress in disease processes such as atherosclerosis. They prevent these changes by both inhibiting low density lipoprotein oxidation at high concentrations and a direct cellular protective effect (mechanism unknown) at lower concentrations.⁹⁰ Calcium channel blockers have not yet been studied as radioprotectants of cardiovascular tissues, but they have shown efficacy in other tissues. Appetite suppression and taste aversion are side effects of radiation exposure. Rats showed significant taste aversion to a saccharin solution with absorbed γ doses of 1 Gy. At doses equal to or higher than 10 mg · kg⁻¹, the calcium channel blocker diltiazem on its own also caused dose dependent taste aversion. However, rats exposed to both radiation and low doses of diltiazem (5 mg · kg⁻¹) show decreased taste aversion.⁸⁹ Finally, the calcium channel blockers diltiazem, nifedipine, and nimodipine administered by a variety of routes to animals exposed at half of the LD₅₀ dosage provide protection against radiation-induced mortality at the otherwise uniformly lethal 10 Gy radiation dosage. Additionally, the protective effects as measured by overall survival appear to be synergistic when calcium channel blockers are combined with dimethyl sulfoxide or zinc aspartate.³¹

The most common side effects of calcium channel blockers result from vasodilation.⁹⁹ Similar to ACEIs and ARBs, there is potential for increased edema in the astronaut population, particularly in the first 2 wk of microgravity. While calcium channel blockers may be useful in reducing taste aversion and appetite suppression associated with an acute exposure in the astronaut population, this limited benefit is likely too minor to place a high priority on further studies. Calcium channel blockers would have to show efficacy in other organ systems or in additional mortality studies before meaningful consideration as an acute intervention. No evidence currently exists for prophylactic use.

Beta adrenergic receptor blockers have also shown promise as radiation protectors, modulators, and mitigators, though the mechanism is unknown. While few preclinical studies on beta blockers and radiation have been performed to date, clinical chart reviews indicate that incidental beta blocker use may have a positive effect on prognosis. Patients receiving radiation therapy for nonsmall-cell lung cancer while on beta blockers showed significant improvements in distant metastasis free survival, disease free survival, and overall survival.^{116,117} Common adverse effects from beta blockers stem directly from induced hypotension (fatigue, dizziness). This is a concern given the neurosensory changes that astronauts must adapt to when transitioning between different gravitational states. Additionally, beta blockers can mask the signs of hypoglycemia in diabetics (a lower concern for the physically fit astronaut population than for the burgeoning population of space tourists) and exacerbate respiratory distress in asthmatics.⁸ Beta blockers need significantly more studies before consideration in astronauts, most likely as a prophylactic agent.

Neural and Pain Modulators

Fingolimod, a naturally occurring structural analog of sphingosine, also shows promise in the treatment of radiation-induced side effects. It is approved for treatment of multiple sclerosis, where it acts as a functional antagonist of sphingosine-1-phosphate receptors.⁴⁴ As an antagonist, fingolimod inhibits lymphocytic exit from lymph nodes, thus reducing inflammation. This drug also augments recovery of glial and precursor cells in the CNS.⁴⁶ Recent in vitro work indicates that fingolimod administered at clinically relevant concentrations provides protection from a 6 Gy dose to neuronal stem cells.

Oligodendrocytic differentiation from neuronal stem cells was not affected by the radiation, but as a monotherapy, fingolimod increased the oligodendrocytic differentiation of the stem cells in a radiation-independent manner. In contrast, control neuronal stem cells showed a greater than 50% decrease in neuronal proliferative capacity following radiation. After administration of fingolimod, a higher fraction of neuronal stem cells survived the radiation exposure.¹⁰⁴ In addition to its action as a neuro-protectant, fingolimod prevents radiation-induced ovarian failure and infertility. Female monkeys exposed to 15 Gy of ovarian irradiation demonstrated premature ovarian failure. After pre-treatment with fingolimod, irradiated monkeys showed higher follicle numbers, more rapid resumption of menstrual periods, and more regular fertility patterns after irradiation than those not treated with fingolimod. Human ovarian xenografts in the monkeys also showed drastically improved oocyte numbers following irradiation in the fingolimod treatment group relative to controls.¹³² Of note, fingolimod was not able to protect against radiation-induced lung fibrosis in a murine model; but two other preclinical sphingosine receptor modifiers tested in the same study were able to successfully decrease radiation-induced lung fibrosis.⁷⁷ Pertinent fingolimod side effects include macular edema, immunosuppression, and cardiac conduction abnormalities when taken with beta blockers or calcium channel blockers.¹⁹ In the astronaut population, macular edema is particularly worrisome as astronauts already experience visual changes. Immunosuppression associated with spaceflight has been established and could potentially be exacerbated by fingolimod. While cardiac effects are rare, they become more likely when fingolimod is combined with other agents mentioned in this review. Given that its side effects exacerbate many known issues in spaceflight, fingolimod might not be the safest choice presented here. While other agents may be better choices for lung protection, fingolimod is the only agent with evidence for fertility protection in female astronauts.

FDA approved for alleviation of muscle pain in those with peripheral artery disease due to its effects on blood viscosity, pentoxifylline also has anti-inflammatory properties. Its anti-inflammatory effects are believed to be through the inhibition of fibroblast growth factor 2 (FGF2). Following 8 wk of pentoxifylline treatment, the majority of patients undergoing radiotherapy showed increased active and passive range of motion, improved muscle strength, and decreased edema. Roughly half had decreased pain as well. These findings corresponded with a twofold drop in FGF2.⁹³ A similar study using a double blind placebo controlled study of pentoxifylline in combination with vitamin E given 1-3 mo after radiation showed significant improvement in lymphedema.⁷³ A third double blind placebo controlled study showed no difference compared with placebo in any of the measured parameters; however, this study was performed with patients at a median of 15.5 yr

postirradiation.³⁷ Due to its inhibition of FGF2, pentoxifylline should theoretically be most effective during the early stage postirradiation exposure as fibrosis is initiated.

Pentoxifylline has been studied in relation to radiation-induced pulmonary fibrosis and mandibular osteonecrosis. A placebo-controlled, double blind study showed lower toxicities, increased diffusion capacity of carbon monoxide, and a noticeable reduction in pulmonary radiologic anomalies in breast cancer patients treated concurrently with pentoxifylline and radiotherapy.⁹⁵ A phase II trial in which patients with osteoradionecrosis of the mandible were treated with pentoxifylline, clodronate, and vitamin E showed universal improvement at 6 mo with an 89% complete recovery rate.²⁵ Gastrointestinal symptoms are most common with pentoxifylline, which occur at the same rate as placebo.¹¹⁹ Evidence exists for lung, bone, and range of motion protection with a well-tolerated safety profile. These potential uses make pentoxifylline a promising agent for further study in the acute exposure setting.

Conclusions

FDA approved drugs are commonly used clinically for indications different than that for which they were approved. A variety of currently approved agents show preclinical and clinical efficacy in preventing or reducing acute and chronic sequelae of radiation exposure (Table I). Many of these agents can be combined with vitamins, chemopreventatives, nutraceuticals, and other endogenous substances with synergistic effects.^{57,58} The FDA-approved compounds reviewed above seem to be reasonable candidates for radioprotective consideration, as they have the advantage of established safety profiles and minimal, or at least well understood, side effects. Potential side effects will have to be weighed by the flight surgeon alongside the potential radiation risk and protection benefit.

Agents selected for further study should ideally meet a number of criteria. First, the medications should possess a long history of safe use in humans with minimal side effects. Further, any side effects present should not exacerbate known health hazards of space travel (i.e., immunosuppression, macular edema, bone loss, etc.) Second, potential side effects of the medications should be easily monitored by a crew with minimal health care experience. Thirdly, the medications themselves should be able to be easily administered (preferably orally) and possess a long shelf life in the space environment. Finally, the medication should treat known hazards of the space environment. A medication which treats acute symptoms of GI distress would have more promise than a comparably effective medication which treats range of motion. A single agent which treats multiple systems would decrease the possibility of medication interactions, making a multifunctional agent more valuable. Medications which have already been extensively studied would require less additional study to establish sufficient confidence for use.

Applying these criteria to the potential agents allows for a risk/benefit analysis of the potential agents. Due to their wide applicability and minimal side effects, statins are the most promising agent for future studies as a prophylactic agent. Despite many studies establishing mechanism of action and animal efficacy they have not yet been examined in prospective, randomized clinical trials in humans for radiation protection. In terms of agents to protect against acute radiation exposures, we recommend n-acetylcysteine for further consideration. Like statins, n-acetylcysteine prevents or ameliorates a number of radiation-

associated conditions with minimal side effects. While there have been little to no studies of radiation mitigation effects in humans, n-acetylcysteine has been used clinically as an antioxidant to counteract lung fibrosis and gastritis.³⁶ Female astronauts' flight time in space is often limited by reproductive organ radiation exposure.⁷⁰ Fingolimod is unique among the examined agents in its protection of ovarian function and deserves further study as a prophylactic agent in this context.

Even if subsequent experiments establish the efficacy of these agents for radiation protection purposes, numerous questions remain. Each would need to be validated for its performance during spaceflight. Formulations must remain stable after exposure to radiation and microgravity. Further, changes in drug distribution and clearance during spaceflight would need to be accounted for in dosing regimens. Finally, an easy and convenient method of monitoring side effects would need to be developed. For instance, liver toxicity is one of the more common side effects of statin use, yet drawing blood and measuring liver enzyme concentrations during spaceflight is currently impractical. Many medications used prophylactically could be started on Earth and side effects measured before spaceflight. Finally, further studies to determine the number of doses required to receive potential prophylactic benefit are required.

While this review was intended to identify agents for use in the spacefaring population, it is applicable for terrestrial populations exposed to chronic or accidental radiation, either occupationally or environmentally derived. More prospective and retrospective studies should be advocated to better determine the efficacy of these and other potential radioprotective agents and how they can best be employed to reduce the toxic effects of radiation on healthy tissues, both on Earth and in space.

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Table I

Summary of Medications Considered and Evidence.

PHARMACEUTICAL OR CLASS	EVIDENCE AVAILABLE	POTENTIAL USES
Statins *	Extensive preclinical and clinical evidence	pulmonary fibrosis, gastrointestinal damage, neural protection
NSAIDs *	Extensive preclinical and clinical evidence	Pneumonitis, overall survival, prevention of metastasis
n-acetylcysteine	Extensive preclinical evidence	Wound healing, immune protection, dermatitis, liver protection, GI protection
ACEIs/ARBs *	Extensive preclinical and clinical evidence	Radiation mitigator only: pneumonitis, gastrointestinal damage, neural protection, nephropathy, hematopoiesis
Metformin	Limited preclinical evidence	Hearing, vasculature
Calcium channel blockers	Limited preclinical evidence	Vasculature, appetite
β -blockers	Limited clinical evidence	Overall survival, metastasis prevention
Fingolimod	Limited preclinical evidence	Neural protection, ovarian failure/infertility
Pentoxifylline	Limited clinical evidence	Pulmonary fibrosis, osteonecrosis, lymphedema

* indicates separate review available.