Electromagnetic Pain Relief/Blocking: Feasibility Assessment

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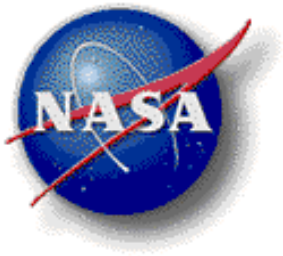

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ELECTROMAGNETIC PAIN RELIEF/BLOCKING: FEASIBILITY ASSESSMENT

1.0 ABSTRACT/EXECUTIVE SUMMARY

Context/Background: Astronauts use pharmaceuticals during spaceflight to manage acute and chronic pain, but use of analgesics will have drawbacks for exploration-class missions because the shelf life of these medications is limited, resupply will be curtailed, astronauts may develop tolerance and/or addiction to these medications, and side effects can include impairment of cognitive abilities. Electromagnetic devices have been developed that treat pain terrestrially by affecting neuromodulation–dubbed "electroceuticals", these devices have varied mechanisms of action that either stimulate or suppress neural activity in the central nervous system or peripheral nerves.

Objective/Purpose: The available literature was reviewed and FDA-approved pain treatments (both pharmacological and non-pharmacological), as well as those currently under development, were assessed for their suitability for use in exploration class spaceflight missions.

Data Sources: Due to the COVID-19 pandemic and the resulting closure of libraries, data sources were restricted to those available digitally. Online database searches included PubMed, U.S. Patent and Trademark Office, federal grant award databases (National Aeronautics and Space Administration (NASA), Department of Defense (DoD), National Institutes of Health (NIH)), and general internet searches. More than 1,600 records were reviewed in this effort.

Study Selection/Eligibility Criteria: Targeted searches included different aspects of pain management. Priority was given to review studies, to cover as much of the available literature as possible in this limited effort.

Study Appraisal and Synthesis Methods/Data Extraction and Data Synthesis: The titles of the studies and the awards that were obtained by searching online databases were reviewed and further information was sought for the relevant titles. Abstracts or award summaries were generally available online; for journal abstracts, full text articles were either available online or were requested via interlibrary loan.

Results: An overwhelming majority of the literature focuses on the treatment of chronic rather than acute pain because it is assumed that acute pain only rarely fails to resolve and instead transitions into chronic pain when the central nervous system becomes hypersensitized. The available electromagnetic devices marketed for pain treatment have varying levels of invasiveness, use different mechanisms of action, and have demonstrated varying efficacy when evaluated scientifically. A truly noninvasive, highly efficient device is desired for use during spaceflight. One portable, self-contained, FDA-approved device was identified that, from preliminarily assessment, best met these criteria; the device noninvasively applies pulsed shortwave therapy (PSWT) to modify pain signals from peripheral nerves, however, the device has limited battery life and the effects are relatively non-selective in type of neural signal modified.

Limitations: This current effort, although extensive, did not identify a comprehensive list of all alternatives for pain treatment. Once the pandemic limitations are lifted, a longer, more thorough effort may find additional options.

Conclusions/Implications: The ideal electromagnetic pain treatment device for use on exploration-class spaceflight missions does not yet exist, but it may be available soon. It is not feasible for NASA to develop medical devices due to the schedule constraints for pending exploration-class missions, but adapting a promising device that is already FDA-approved might be an option. Monitoring research that is ongoing at other federal agencies is recommended, and further review of the candidate PSWT device identified in this current effort may be warranted.

2.0 INTRODUCTION

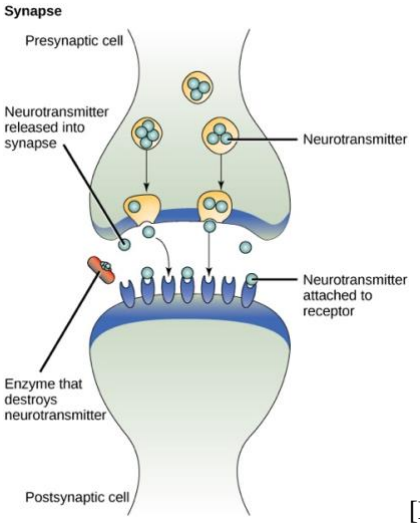
2.1 Rationale/Background

In the U.S., pain is the most common reason that patients consult with physicians [Cotler 2015]. It is reasonable then to assume that pain will be generally unavoidable during the extended mission durations planned for Artemis and beyond (up to 3 years). Common terrestrial pain treatment methods have potential drawbacks: ineffectiveness, development of tolerance and/or addiction, and side effects that can include impairment of cognitive abilities or organ damage [RxList 2020, Smith 2020, Nalamachu 2013, Vance 2014]. Exploration-class missions will have additional requirements: the mass and volume of payloads will be highly constrained, highly invasive procedures must be avoided, and medication will need to be stored for extended durations.

A brief summary of the anatomy and biophysics of pain

To understand how pain can be treated, it is first necessary to understand how pain is sensed and reported in the human body.

Specialized neurons in the peripheral nervous system (primary nociceptors) sense and transmit pain signals. These neurons, like other neurons in the body, are composed of cell bodies and axons. They communicate with other neurons by exchanging neurotransmitters at neural interfaces as shown in Figure 2-1.

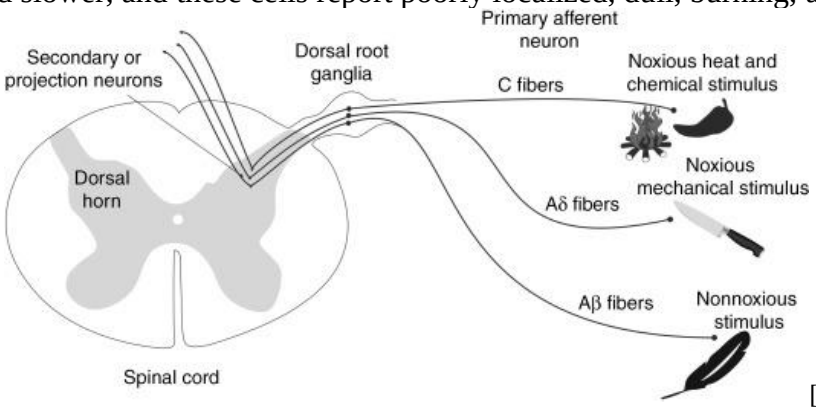


[Lumen, 2020]

Figure 2-1: Neurotransmitter pathway

Peripheral branch axons receive information from the body and transit it to the cell body, and central branch axons relay information from the cell body to the central nervous system (CNS). The cell bodies that receive information from the head reside in the ganglia near the brain, and

cells bodies that receive information from the body reside where the dorsal root ganglia enter the spinal cord. Primary nociceptors tend to be the smallest nerves in the body, and they contain little to no myelin covering, so signals are transmitted relatively slowly in these cells. Signal transmission is faster in Aδ-fibers because they have a thin myelin sheath, and these cells report well localized, sharp, stabling, prickling pain. C-fibers have no myelin sheath so signals are transmitted slower, and these cells report poorly localized, dull, burning, aching pain.



[Kulkarni 2017]

Figure 2-2: Neurons involved in pain reporting

Primary nociceptor axons carry a negative charge internally when at rest. A transmitted signal results when activated sodium channels (to transmit pain) or activated TRPV1 ion channels (to transmit heat) cause a depolarizing spike for a few milliseconds in the axon, then positive feedback activates neighboring channels and propagates the signal along the axon to the cell body. At the spinal cord, the primary nociceptors contact CNS neurons to communicate pain to the brain in a complicated and not necessarily completely understood network of neurons that can excite or inhibit other neurons. For example, the wide dynamic range neurons respond to nociceptors and other neurons (such as those that transmit touch), which is thought to explain why holding or rubbing a painful area lessens the pain (competing signals inhibit the pain signal). Descending pathways from the brain can inhibit pain signals. Endogenous opioids inhibit pain transmission by decreasing excitability of nociceptors and stimulating inhibitory descending pathways; pharmaceuticals enhance this effect [Abd-Elsayed 2018].

Nociceptors densely innervate peripheral tissues (skin, joints, respiratory, and gastrointestinal tract) and respond to mechanical, chemical, and thermal noxious stimuli. Nociceptors are also involved in the molecular and cellular interactions between the nervous system and the immune system: immune cells release mediators that modulate nociceptor neuron activity and pain sensitivity, and nociceptors release neuropeptides and neurotransmitters that modulate the function of innate and adaptive immune cells [Pinho-Ribeiro 2017].

How pain is measured

Pain is by its very nature subjective, and measuring pain consistently and as objectively as possible across patients is challenging. Multiple pain scales have been created to facilitate this effort [Ramirez 2020]:

- Numeric Rating Scale (NRS-11): 0-10 score for pain intensity
- Stanford Pain Scale: 0-10 score, with accompanying description, for pain intensity

- Brief Pain Inventory: 0-10 score for intensity and interference with activities of daily life, short (9-item) or long (17-item) versions
- Wong-Baker FACES Pain Rating Scale: graphical (emoji) pain intensity, designed for children
- Global Pain Scale: 0-10 score for intensity, feelings, and clinical outcomes
- Visual Analog Scale (VAS): continuous spectrum with descriptors
- McGill Pain Index: 0-50 score with comparative pain experiences

Irrespective of the scale is used, a 50% reduction in reported pain is considered the threshold for determining that the treatment is effective [Teater 2014]. Although this delta may initially seem excessive to establish proof of effect, placebo effects in the 20-30% range have been documented in analgesic studies [Staelin 2019].

2.2 Objectives

This study sought to survey and summarize the various terrestrial options currently available for pain treatment and to determine what options, if any, could be adapted to spaceflight.

3.0 METHODS

This research effort was a hybrid effort combining aspects of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach for systematic reviews with a traditional research literature review, market survey, and feasibility assessment. Section 4.1 discusses the information records surveyed and the down-select to relevant records incorporated into this review.

3.1 Information sources

This effort was a digital review because libraries were closed due to the COVID-19 pandemic. Multiple databases were interrogated: JSC library databases, PubMed article database, U.S. Patent and Trademark Office (USPTO) database (patents and patent applications), NASA task book (grants database for Human Research Program, Space Biology Program, etc.), Department of Defense (DoD) grants database (Congressionally Directed Medical Research Program (CDMRP) and Chronic Pain Management Research Program (CPMRP)), and National Institutes of Health (NIH) grants database (Helping to End Addiction Long-term (HEAL) Initiative).

Additional data sources included textbooks already on-hand, NASA technical briefs and medical technical briefs, and general internet (Google) searches.

All searches for this effort were conducted between July 19 and September 20, 2020.

3.2 Search

Table 3-1 lists the various searches conducted during the execution of this effort.

Database	Search keywords	Records Returned
Google	benchmark pain relief	4.95M
	pain scales	151M
	analgesic effectiveness chart	4.16M
	engineer model of pain	61.6M
	wearable pain monitor	14M
	laser treatment for pain	182M
	NASA light-emitting diode wound healing	564K
All JSC library databases	"pain management" + magnetic	35
	nerve magnetic sensing	13
PubMed	neuromodulation pain	3
	neuromodulation noninvasive dorsal	69
	neuromodulation pain noninvasive dorsal + full text	9
	neuron pain signal measure noninvasive + full text	9
	real-time nerve pain signal measure noninvasive + full text	1
USPTO	patents: pain noninvasive	74
	patent applications: pain noninvasive	77
NIH	HEAL	475
DoD	CPMRP	1
	grants: pain	455
NASA	taskbook: pain management	30
	Medical Tech Briefs: pain	375

Table 3-1: Summary of search efforts

The records identified during the search were examined for relevance. For scientific journals, this meant initially reading abstracts to determine relevance, and if an abstract was deemed relevant, then reading the full text article as available; due to COVID-19, information was only available digitally (interlibrary loan was not operational) so articles not available in full-text were only minimally useful. References listed within articles often led to additional records for review. For grants databases, if the title was relevant the grant summary was read, and this often led to targeted internet searches for further details.

4.0 RESULTS

This research effort identified many options for the treatment of pain.

Pharmaceutical treatments for pain

Pharmaceuticals that treat pain are generally called analgesics and typically interrupt the biochemical pathways that report pain. More than 100 discrete common analgesic drug formulations and combinations are currently available either over-the-counter (OTC) or by prescription. In order of increasing strength, classes of analgesics include salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics (including opioids), Cox-2 inhibitors, antimigraine agents, and combinations [Drugs.com 2020].

The World Health Organization (WHO) released a "Pain Relief Ladder" to guide physicians when they prescribe different analgesic classes to treat increasing pain intensity [Ventafridda

1985]; this guide was created initially for cancer pain but subsequently extended to other acute and chronic pain conditions [Jadad 1995]:

1. (mild pain) non-opioids ± anxiety medications
2. (mild to moderate pain) mild opioids + non-opioids ± anxiety medications
3. (moderate to severe pain) strong opioids + non-opioids ± anxiety medications
4. (no pain relief with prior methods) invasive and minimally invasive treatments

Biologics are a subclass of pharmaceuticals that are manufactured in, extracted from, or synthesized from biological sources. Although the origin or composition of biologics and traditional pharmaceuticals differ, they have similar actions

Neuromodulation as treatment for pain

Many types of non-pharmaceutical treatments are used to treat pain. These treatments may be invasive or non-invasive, and they include cognitive training, topical devices, and surgically implanted devices.

A summary of methods that are used currently or are being developed to relieve pain are listed in Table 4-1.

Pharmaceuticals		Neuromodulation	
Systemic		**Invasive**	
Traditional		***Moderate-Major***	***Minimal***
Acetaminophen	***Astrocyte antagonists***	Spinal cord stimulation (SCS)	Acupuncture
Aspirin/NSAIDs	***Kv7 Channel Openers (KVOs)***	Radiofrequency ablation	Electro-acupuncture
Opioids	***Agmatine***	Cryoablation	Percutaneous peripheral nerve stimulation (PNS)
Protein kinase C epsilon (PKCe) inhibitors	***Adenosine 3A receptor (A3AR) agonists***	Intrathecal pumps (drug delivery)	
Acetaminophen analogs	***Biologics***	**Non-Invasive**	
D-cycloserine (DCS)	***Gene Therapy***	***Cognitive-Behavioral***	***Engineering Solutions***
N-naphthoyl-ß-naltrexamine (NNTA)	***Antibodies (Na-channel blocker)***	Neurofeedback	Cortical Electrical Stimulation
sigma-1 receptor (S1R) antagonists	***Antibodies (K-channel blocker)***	Mindfulness/Meditation/Hypnosis	repetitive transcranial magnetic stimulation (rTMS)
Endosome receptor inhibitors	***Microglia antagonists***	***Exercise***	transcranial direct current stimulation (tDCS)
Cannabinoids	***Derivatives from marine organisms***	Physical Therapy	Transdermal Electrical Nerve Stimulation (TENS)
Opioid (+)-enantiomers	***Conopeptides***	Yoga / Tai Chi	Pulsed Shortwave Therapy (PSWT)
Site-specific			Ultrasound
Nerve block (anesthetic injection)	***Biologics***		Photobiomodulation (Laser, LED)
Corticosteroids (injection)	***Stem cells***		***Induced mechanical force***
Analgesic creams (topical)	***Neural progenitor cells***		
Polymeric delivery devices	***GABAergic cells***		
Long-Acting Local Anesthetics (LALA)			

Color key: FDA-approved ***investigational***

Table 4-1: Summary of methods that are used currently or are being developed to relieve pain

Potential synergistic efforts

In addition to conducting research motivated by the commercial marketplace, the DoD and the NIH have recently made major investments seeking alternatives to opioids for pain treatment, given that opioids can be addictive.

The DoD Congressionally Directed Medical Research Program (CDMRP) initiated the Chronic Pain Management Research Program (CPMRP) in 2019. The CPMRP's initial set of solicited research awards has been reviewed, and award recommendations totaling $8.2M are pending. Before the formation of the CPMRP, the DoD awarded 455 grants related to pain since 2014, totaling $535M–of these, 11 awards ($2.2M) were relevant to this current review effort, and 33 awards ($6.3M) were related to this review effort.

The NIH Helping to End Addiction Long-term (HEAL) Initiative was initiated in 2017, and it incorporates a federal partners workgroup. Of the 6 focus areas for the HEAL initiative, 2 under Enhancing Pain Management (Preclinical and Translational Research in Pain Management, and Clinical Research in Pain Management) are of specific interest to the current review effort. The NIH listed over 475 awards on their website, of which 13 awards were judged as applicable to this current review effort.

4.1 Study Selection

For the current review, records were methodically identified and screened as shown in Figure 4-1. Internet searches returned far more records than could be reviewed in this small project, so only the records that were ranked highest relevance by search engine were examined further.

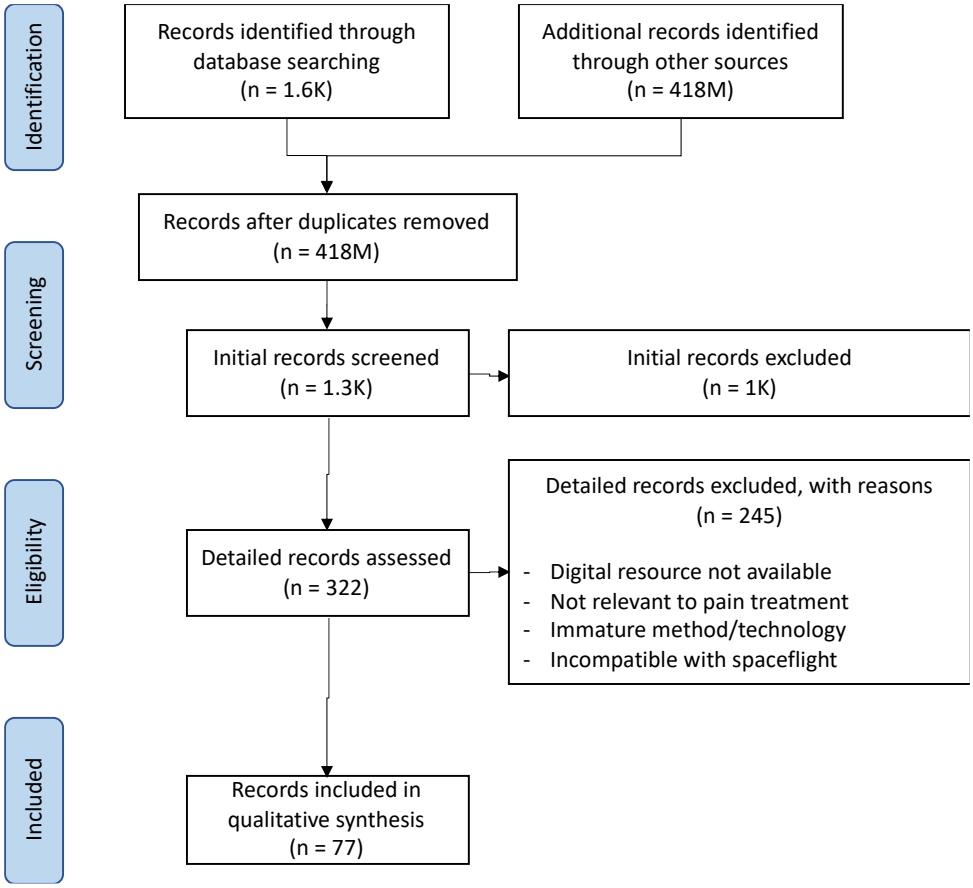


Figure 4-1: Summary of source data selection

4.2 Synthesis of results

The current effort identified many classes and types of remedies for treatment of pain as summarized in Table 4-1. All approaches essentially either distract or disrupt pain signals.

The action of pharmaceuticals generally blocks either the transit of neurotransmitters across neuronal gap junctions or the action of ion channels along the nerve fiber (axon) to propagate the pain signals. Systemic medicines are administered away from the site of pain (typically administered orally or injected), and to modify pain signals the medicines must migrate either to the affected area or to an area involved in pain transmission. Site-specific medicines are administered at the site of pain and act locally to modify pain signals. Many novel non-opioid analgesic drugs are being developed and evaluated with funding from the NIH, the DoD, or commercial entities; additional current research focuses on different delivery methods and the duration of therapeutic effect.

Neuromodulation refers to the specific modification of neural signals by a targeted non-pharmaceutical approach. A brief description of each class/type of neuromodulation method, as listed in Table 4-1, follows.

- Moderately-to-Majorly Invasive
    - Spinal cord stimulation (SCS)–a pair of electrodes are implanted on opposing sides of the spinal cord that, when energized, decrease pain transmission; an initial surgery to test placement efficacy is required, then after a week of verified positive results, the implantation is completed for long-term use [Abd-Elsayed 2018]
    - Radiofrequency (RF) ablation–a probe inside an inserted large bore needle delivers RF energy that heats and creates a lesion within neural tissue that decreases pain transmission; typically effective for 6-12 months [Abd-Elsayed 2018]
    - Cryoablation–nitrous oxide gas delivered from inside a large bore needle delivers extreme cold to create a lesion within neural tissue that decreases pain transmission [Abd-Elsayed 2018]
    - Intrathecal pumps (drug delivery)–an established and common method (since 1800s); an implanted catheter linked to a drug pump administers pain medication to the appropriate location along the spinal cord; limited set of FDA-approved medications for use; similar to SCS, requires an initial surgery to test placement efficacy then a final implantation for long-term use [Abd-Elsayed 2018]
- Minimally Invasive
    - Acupuncture–thin needles are placed through skin at strategic points to affect neural trigger points [Abd-Elsayed 2018]
    - Electro-acupuncture–similar to traditional acupuncture but includes small, measured electric current delivered via the acupuncture needles to stimulate the tissue around the inserted needle [Mao 2014]
    - Percutaneous peripheral nerve stimulation (PNS)–a lead is implanted along a localized peripheral pain pathway to reduce transduction of pain signals; similar to SCS, requires an initial surgery to test placement efficacy then a final implantation for long-term use [Abd-Elsayed 2018]
- Non-invasive
    - Cognitive-Behavioral
        - Neurofeedback–direct information regarding brain activity (EEG or fMRI) is provided to patients to help them reduce processing of nociceptive information, and increase relaxation and down-regulation of pain; moderate gains have been demonstrated in pilot studies; assumes that brain oscillations in certain bandwidths indicate pain and that training can alter those oscillations [Jensen 2014]
        - Mindfulness/Meditation/Hypnosis–patients focus on an object, thought, or activity to train attention/awareness that induces a mentally and emotionally clear, calm state that reduces stress, anxiety, and pain [Abd-Elsayed 2014]; typically used in combination with medication; benefits can improve sleep quality, creativity, confidence, mood, and social behavior with no notable adverse side effects reported [Jensen 2014]
    - Exercise

        - Physical Therapy–patients perform function and goal-based therapy that counters reflexive response to reduce physical activity that causes pain (typically protective for acute pain, but counterproductive for chronic pain); efforts increase power or endurance strength, as well as improve stretching and posture [Abd-Elsayed 2014]
        - Yoga / Tai Chi–patients perform martial arts derivatives that improve range of motion through controlled movements, poses, and meditation [Abd-Elsayed 2014]
    - Engineering Solutions
        - Cortical Electrical Stimulation–treatment applied over the motor cortex contralateral to the painful area is thought to send an inhibitory signal directly to the thalamus that reduces perception of pain [Jensen 2014]
            - repetitive transcranial magnetic stimulation (rTMS)–cortical stimulation is applied via a magnetic coil on scalp above the target area, with magnetic field penetrating the skull; high-frequency (≥5Hz) lowers neuronal firing thresholds (enables signal transmission), low-frequency (≤1Hz) increases firing thresholds (inhibits signal transmission); trains of pulses of varying lengths can vary intensity and duration of therapeutic effect [Jensen 2014]
            - transcranial direct current stimulation (tDCS)–a 1-2mA current is typically applied directly to the scalp for 20 minutes a day during 5 daily sessions; firing threshold is lowered in the neurons in the cortex area below the anode, making them more excitable (neurons become less excitable under cathode) [Jensen 2014]
        - Transcutaneous electrical nerve stimulation (TENS)–electrical current is applied atop the dermal layer near the source of pain to induce endorphin release, thereby affecting the same biochemical pathways as pharmacological interventions that reduce pain; treatments can be high-frequency (HF) or low-frequency (LF) [Vance 2014]
        - Pulsed Shortwave Therapy (PSWT)–RF MHz-range transmitter adjacent to biological tissue at maximum output (saturation) causes modulation of peripheral nerve activity; could be useful for both acute and chronic pain [Staelin 2019]
        - Ultrasound–penetrating soundwaves are applied to produce deep mechanical stimulation that increases circulation, reduces inflammation, and pushes nutrients through cellular structures [Lewis 2014]
        - Photobiomodulation–light of specific wavelengths is applied atop the dermal layer but penetrates the tissue; at low energy, photons absorbed by cellular photoreceptors trigger chemical changes; at high energy, bradykinins are reduced decreasing nerve sensitivity and endorphins and enkephalins are released for analgesic effect [Cotler 2015]
            - Laser–long history, dating back to 1903 Nobel Prize awarded for contribution to treatment of diseases with concentrated light radiation [Cotler 2015]; “cold” (Class III, <500mW) or “warm” (Class IV, >500W); has been effective in treating nociceptive and neuropathic

pain [Cotler 2015]; cold laser stimulates acupoints like the needles used for acupuncture, without piercing the skin [Pietrangelo 2019]
    - LED–benefits initially discovered during NASA plant growth research for ISS in 1990s; typically red and near infrared wavelength light applied topically induces penetrating cellular response that increases perfusion, reduces inflammation, and speeds healing [Dompe 2020]
- Induced mechanical force–"mechanoceuticals"; mechanical stimulation is applied that causes cell proteins to change ion flow, trains cells to adapt, and reduces pain signals (very preliminary, *in vitro* only) [Tech Brief Aug 2020]

5.0 DISCUSSION

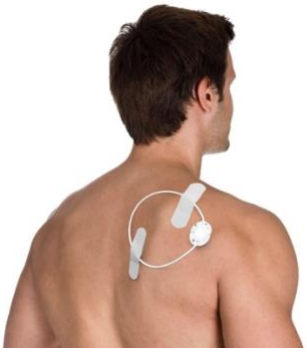
5.1 Summary of evidence

Pharmaceutical and biologic methods for treating pain were surveyed and summarized for completeness in the current effort, but they were not the focus; it is assumed that the NASA Human Health and Performance Medical Operations Group will monitor drug development for novel formulations that could be incorporated into the mission medical kit. Similarly, treatment by exercise or neuro-cognitive methods is beyond the scope of the current review. Operational concerns for spaceflight dictate that invasive methods are not desired, leaving the focus of the current review only on electromagnetic methods of neuromodulation. Furthermore, treatment of the central nervous system (i.e., brain) is undesirable during spaceflight due to the complexity of performing these procedures, so this discussion focuses on the currentlyavailable non-invasive neuromodulation engineering solutions identified through this effort.

Table 5-1 lists the key information for the 4 identified classes of non-invasive neuromodulation devices that act on the peripheral nervous system; the devices are ranked in order of perceived ability to implement during spaceflight, and examples of COTS devices are included.

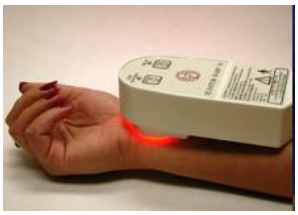
Rank Order	1	2	3	4
Method	PSWT	Ultrasound	Photobiomodulation	TENS
COTS equipment (manufacturer)	ActiPatch (BioElectronics Corp)	SAM Pro 2.0 (ZetrOZ)	PainAway (MultiRadiance)	Quell 2.0 (NEUROMetrix)
Evidence base	strong	strong	strong	Weak
Ease of use	easy	easy	easy	easy
Approval	FDA	FDA	FDA	FDA
Availability	OTC, home use	Rx, home use	OTC, home use	OTC, home use
Unit cost	$30	~$4K	~$3K	~$300
Therapeutic locations	all	all	all	lower leg
Treatment size	~15 cm^2	variable	~10 cm^2	~33 cm^2
Battery life	720hr disposable	6hr rechargeable	8hr rechargeable	multi-day rechargeable
Treatment sensation	none	none	none	just sub-pain threshold

Table 5-1: Summary of non-invasive neuromodulation engineering solutions



The treatment method ranked first in this review was pulsed shortwave therapy (PSWT), a low-power RF (MHz range) transmitter operated adjacent to biological tissue at maximum output (saturation) to modulate peripheral nerve activity. ActiPatch is a very small wearable PSWT device that is FDA approved for "adjunctive treatment of musculoskeletal pain" [Anwar-Deen 2020]. It is low cost, low power, and boasts 97% efficacy in reducing pain (85% over a 6-month period) [Staelin 2019]. The device can be secured to the body by physio tape and the area causing pain is bounded by the device's ring. The device can be turned on and off, and the non-rechargeable battery is capable of 720 hours of operation (one month continuous use). ActiPatch is sold OTC in local pharmacies for ~$30 [ActiPatch 2020].

The second ranked treatment method was ultrasound that produces deep mechanical stimulation, increasing circulation, reducing inflammation, pushing nutrients through cellular structures. Although ultrasound as a diagnostic modality has been used in spaceflight for many years, this is fundamentally different. SAM Pro 2.0 is a small wearable ultrasound device that is FDA approved for long-duration treatment of musculoskeletal and joint pain (previous devices had a 30 minute limit due to tissue overheating) [Lewis 2014]. The manufacturer claims include repair of soft tissues as well as reduction of chronic pain. The 2 electrodes are worn such that the target tissue is located between them. SAM has 6-hour battery life before recharge is necessary. SAM is available for purchase with prescription for ~$4K.



The third ranked treatment method, photobiomodulation, was "discovered" by happenstance during NASA plant experiments that sought to enhance plant growth by applying certain light wavelengths; the investigator realized that near-infrared light not only accelerated plant growth but also accelerated repair of skin tissue. The light energy is absorbed by cell's mitochondria and transformed into biochemical energy. PainAway is a portable handheld super-pulsed cold laser device with 3 lasers (640nm, 875nm, 905nm) and 3 power settings. The device is powered by a lithium battery that allows 8 hours of use before recharge is necessary; the device works in 5-minute episodes. PainAway is available for purchase OTC for ~$3K [Mantonya 2020].

The final ranked treatment method was TENS. TENS stimulates A-beta nerve fibers, causing the affected neuron to send non-pain signals to the brain. Quell 2.0 is a portable wearable device that is designed to be worn on the upper calf for treating pain in the leg, foot, and knee. The stimulation level required to induce a therapeutic effect is just below pain threshold, which can be a cause for complaint by patients. The device has a rechargeable lithium ion battery that can last for days in

normal use, and the device can be worn continuously. Quell is available for purchase OTC for ~$300 [Quell 2020].

5.2 Limitations

Information retrieval was ultimately incomplete for this effort due to the inability to obtain records other than digital records because of facility closures related to the COVID-19 pandemic.

Information on company websites may be classified more as marketing than science, so any claims sourced from these websites should be further vetted with evidence located in scientific publications before being fully trusted.

5.3 Conclusions

The information obtained in the execution of this review effort leads to 2 recommendations for forward work:

1. Tie into DoD and NIH research funding efforts to improve pain treatment: the NIH has a federal partners workgroup for their HEAL Initiative that could conceivably be joined by NASA, and the DoD CPMRP's initial solicitation only recently completed so that program is young and potentially synergies could be identified with NASA.
2. Obtain an ActiPatch device for evaluation and determine whether it could be beneficial and adapted to spaceflight use.

6.0 FUNDING

This effort was funded as a competed selection under the 2020 Innovation Charge Account program administered by the JSC Chief Technologist's Office. The JSC Biomedical Research and Environmental Sciences Division overhead resources, including the Bioastronautics Library, were used to conduct this study.

7.0 APPENDICES

7.1 Appendix A: Acronyms and Abbreviations

CDMRP	Congressionally Directed Medical Research Program
CNS	Central Nervous System
COTS	Commercial-off-the-Shelf
COVID-19	Coronavirus Infectious Disease – 2019
CPMRP	Chronic Pain Management Research Program
DoD	Department of Defense
EEG	Electroencephalogram
FDA	Food and Drug Agency
fMRI	Functional Magnetic Resonance Imaging
HEAL	Helping to End Addiction Long-term
HF	High Frequency
Hz	Hertz
ISS	International Space Station
JSC	Johnson Space Center
LED	Light Emitting Diode
LF	Low Frequency
mA	milliAmp
mW	milliWatt
NASA	National Aeronautics and Space Administration
NIH	National Institutes of Health
NSAID	Nonsteroidal Anti-inflammatory Drug
OTC	Over-the-Counter
PNS	Peripheral Nerve Stimulation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSWT	Pulsed Shortwave Therapy
RF	Radiofrequency
rTMS	Repetitive Transcranial Magnetic Stimulation
SCS	Spinal Cord Stimulation
tDCS	Transcranial Direct Current Stimulation
TENS	Transcutaneous Electrical Nerve Stimulation
TRPV1	Transient Receptor Potential Cation Channel Subfamily V Member 1
US	United States
USPTO	US Patent and Trademark Office
VAS	Visual Analog Scale
WHO	World Health Organization

7.2 Appendix B: References

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