

NARRATIVE REVIEW

PAIN MANAGEMENT

Digital pain interventions: a promising new paradigm for pain control

Amara Nasir¹, Saiyid S. Mahmood², Syed Mahmood³

Author affiliation:

1. Amara Nasir, Department of Anesthesia, The University of Michigan, 325 E. Eisenhower Pkwy, Ann Arbor, MI 48108, USA; E-mail: amaranasir_93@hotmail.com ORCID: {0000-0001-6151-3609}
2. Saiyid S. Mahmood, California Northstate University College of Medicine, 9700 W Taron Dr, Elk Grove, CA 95757, USA; E-mail: sumairm@gmail.com
3. Syed Mahmood, University of Pittsburgh Medical Center, 8012 Bretz Drive, Harrisburg, PA 17112, USA; E-mail: hazique@gmail.com

Correspondence: Amara Nasir; E-mail: amaranasir_93@hotmail.com; Phone: +1 781 353 4711; Mobile: +1 7813534711

ABSTRACT

Background & Objective: A digitally enabled care environment offers a more holistic approach in managing pain in our patients and have the potential to fight the opioid crisis. Accordingly, several digital pain technologies have recently been introduced in our healthcare lexicon and are quickly transforming the healthcare industry. To our knowledge, no one has catalogued the use of these digital health technologies in the chronic pain patient population. The objective of this review article is to identify and classify the medical knowledge, concepts and properties of digital interventions that can be used to treat pain, and describe the most prominent trends in literature to guide future research.

Methodology: PubMed NCBI and EMBASE databases, Google Scholar and Google were searched for information on digital technology for pain management, individual devices, and to review studies describing each individual device. Manuscripts that explored the terminology, development or application of digital pain intervention technologies were selected. Eligible devices and manuscripts were assessed for quality features of relevancy in today's healthcare environment, relative promise of the technology, and maturity of products and/or approval status, and inclusion in current practice or guidelines.

Results: Several novel digital pain therapeutics were reviewed including their mode of action, specific role in pain management, clinical trials, FDA regulatory status, relevance and advancements compared to their predecessors.

Conclusions: Digital health interventions are poised to become an accessible means of alleviating pain. Improving our knowledge about these novel digital patient-centric approaches to treating patients' pain has the potential to transform our health system.

Key words: Pain; Digital Intervention; Food & Drug Administration; Wearables

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1. INTRODUCTION

Pain, as defined by International Association for the Study of Pain (IASP), is “an aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue damage”.¹ Chronic pain is defined as pain that persists beyond the expected normal tissue healing time which is considered to be about 3 months and is one of the leading causes of disability and addiction and a burden on the healthcare

system.^{2,3} Over 100 million Americans suffer daily from chronic pain and approximately \$17.8 billion are spent on pain medication prescriptions annually.⁴ This escalating opioid use and abuse has prompted researchers and clinicians to search for alternatives to manage their patients' pain.

With advances in technology and ubiquity of mobile devices, digital medicine may be employed as accessible adjuncts to alleviating pain in the general population.

Digital medicine is a field of medicine that uses technologies to prevent, monitor and manage an individual's health.⁵ These technologies are considered to be cost-effective, safe, easy to administer and encourage self-management. Further, recent studies have demonstrated improved health outcomes with the use of digital interventions.⁶ The digital health industry was worth \$25 billion in 2017, and is predicted to decrease healthcare cost by at least \$7 billion each year in the US.⁷ However, integrating this "digital health revolution" in the health system is a complex task. First, each digital intervention varies in terms of goals, properties and potential side effects and the data on systematic assessment and evaluation of these products is limited.⁷ Second, our healthcare system has not yet formulated a digital health strategy for the implementation of digital health services likely due to regulatory and reimbursement concerns. Regulatory bodies are focused on "traditional medicine" evaluations rather than digital medicine. More recently, entities such as FDA have started encouraging innovation and global organizations such as Global Digital Health Partnership (GDHP) have been formed to support the integration of digital medicine into our practices.⁸

Digital pain intervention is a subset of digital medicine that employs technological mediums such as smart phones, headsets, wearable electronic devices, internet and software to provide a means for pain management including self-care, monitoring, education and behavioral support remotely. A variety of new digital technologies offer hope for individuals living with pain.

The objective of this review article is to identify and classify the medical knowledge, concepts and properties of digital interventions that can be used to treat pain, initiate a discussion about digital pain interventions as an accessible adjunct to establishing an optimal pain practice, and describe the literature to guide future research. In this manuscript, we will review the most promising of these digital interventions in clinical trials and with recent Food and Drug Administration (FDA) registrations and clearances. These include wearable devices, smart phone applications, virtual reality headsets, and implantable devices which may be controlled remotely.

2. METHODOLOGY

2.1. Data sources and search strategy

We searched databases including PubMed NCBI and EMBASE databases, Google Scholar and Google. To determine an optimal search strategy that identified the broadest results possible, multiple search terms and combinations of search terms were tested as inclusion

criteria.⁹ Literature was selected based on title, abstract and full article review.

Examples of search strings are as follows:

- PubMed NCBI and EMBASE databases search terms:

"digital pain" OR "digital therapeutics" OR "digital pain devices" OR "digital pain interventions."

- Google Scholar and 'Google Search' search terms:

"digital pain" OR "digital therapeutics" OR "digital pain devices" OR "digital health" OR "digital interventions."

Inclusion criteria were as follows: (1) included the key words 'pain' and 'digital', including both singular and plural forms of search terms identified additional publications, and (2) Limited to English language results. Before deciding on the search strings, consensus was reached among the authors.

Exclusion criteria were as follows: (1) Literature published prior to 2010. (2) Abstracts that did not have full articles. (3) Literature on pain in digits (digital pain) seen in our searches. (4) Literature on abdominal pain and digital rectal examination seen frequently in our searches. (5) Duplicate results. (6) We limited our review of search results to the first 10 pages. Studies on Google Search have suggested the search should be limited to the first few pages as the relevancy of the articles greatly diminished after 10 pages. Therefore, search results after the first 10 pages were excluded. To avoid problems related to a personalized search, we logged off from all Google accounts and cleared our cache to avoid personalization of search results.

The primary source of data in our study was a systematic search in PubMed, with searches in Google Scholar and Google Search as additional sources only.¹⁰ With digital pain therapeutics at the very forefront of medical science, we expected a low total number of "hits" on PubMed. We acknowledged that many of these novel devices and guidelines have not as yet been published in scientific journals. Our aim in this manuscript was to present a comprehensive search (rather than a representative search), bearing in mind the qualitative, not the statistical character of the study. Accordingly, we employed Google Scholar and Google Search engine as additional sources to capture any relevant "grey" literature.¹⁰ Grey literature encompasses informal scholarly publications outside the sphere of traditional academic publishers and can include dissertations, technical reports, conference proceedings articles from nongovernmental organizations and policy institutions; and many innovations in technology are initially published in these forums. Google Scholar and Google Search are regarded as significant sources of grey literature¹¹ and provide a more complete view of

available evidence.¹² Google Search is an imperfect tool to perform reviews; limitations include an unknown search algorithm that cannot be controlled and adapting the search to the individual user to personalize information. This “bubble effect” on Google Search¹³ is a form of selection bias, and, as a result, a query is probably not replicable. Although Google Scholar and Google Search have some shortcomings and should not be used as the only source for systematic reviews, they may be appropriate tools for some types of qualitative systematic reviews. We executed an explicit methodology in our grey review searches to be systematic, transparent and reproducible in the review process.¹³ As a result, Google Search identified many additional products, the FDA device classifications and approval basis and status for the devices.

2.2. Data extraction, synthesis and analysis:

Two reviewers (AN and SM) independently searched the online literature available on PubMed NCBI database, EMBASE database, Google Scholar and Google Search. The search was conducted electronically from July 2021 through December 2021. Data was initially abstracted into a standardized format entered into Microsoft Excel. Any disagreements were resolved through discussion by the two independent reviewers. If the reviewers could not reach a final decision, the literature was excluded. The selected literature was wholly reviewed again to extract requisite information. In the final step, we synthesized all of the collected information and evidence to support our analysis. As anticipated, most results were published recently, demonstrating a growing interest in this topic in with advancement in this technology.

3. RESULTS

On PubMed NCBI and EMBASE databases, the search for the key word “digital pain” identified 2,889 results; “digital therapeutics” identified 13,626 results; “digital pain devices” identified 557 results; and “digital pain interventions” identified 2077 results. After removal of duplicate results, 61 entries met our criteria and were evaluated for our review. The studies covered a wide range of research designs including randomized controlled trials, systematic reviews and meta-analysis. This search was supplemented with Google Scholar and Google Search using the same key words, inclusion and exclusion criteria, and limiting our search to the first ten pages. As expected, multiple pages of results were seen per search term, and content displayed was a little different for each independent reviewer.

4. DISCUSSION

Digital pain is a subdivision of digital health, which is the convergence of digital technologies with health, healthcare, living, and society to help address health problems, enhance the efficiency of healthcare delivery and make medicine more personalized and precise. Digital health offers a comprehensive approach towards multiple challenges within the health sector including medication adherence, management of chronic conditions, care-coordination and patient well-being. Over 33 billion has been invested in digital health solutions over the last decade,¹⁴ and are being utilized by about 90 percent of the population in some form.¹⁵ Many digital technologies may be purchased over the counter. Since digital health devices help health-care providers manage patient outcomes and other measures of quality of care, reimbursement for digital health tools is already afforded within the provisions of the Affordable Care Act, where reimbursement is dependent on outcomes.¹⁶ However, decision-making in medicine is shaped by past experiences; therefore, we are slow to identify, adopt and understand the potential and limitations of digital health. Many digital technologies still lack conclusive research data and therefore are not included in evidence-based medicine guidelines. Furthermore, digital interventions may store patient data, and collect information from both patients and healthy individuals. In addition, some technologies require constant internet or bluetooth connectivity.¹⁷ Accordingly, there are concerns due to lack of research, patient privacy, dynamic government regulations and no clear path for implementation. As the field of digital health matures, access to high quality, reliable, data-driven personalized digital tools will become more prevalent.

Digital pain intervention is an emerging concept of using electronic tools, systems, devices and resources to generate, store or process data and to utilize pain reduction techniques for easing the suffering and improving the quality of life of individuals. Digital pain intervention is an evidence-based intervention that leverages a combination of software and devices such as wearable devices, smartphones, personal digital assistants, virtual reality, implantable devices, tablet computers or robotics with the intention to treat a specific clinical indication.¹⁸ This novel technological paradigm supports healthcare professionals in collecting, organizing, interpreting and using clinical data, diagnosing and managing several conditions, clinical decision making, monitoring the health of their patients, share information, engage patients, and integrate digital healthcare delivery with traditional pain practice. Moreover, this patient-centric technological revolution empowers individuals to venture beyond the traditional, physical constraints of healthcare delivery. Consumers can access instantaneous information pertaining to their health, empower themselves to become an active

participant and make informed choices about their care and healthcare delivery through understanding and managing their pain, and provide their physicians with

a different level of clinical evidence for a medical device depending on the novelty of the product and the risk the device poses if it malfunctions.¹⁷

Table 1: FDA classification for regulating medical devices.

Class I	present a low risk of harm to the user and most are exempt from a premarket review or notification requirements by the FDA but still must register with the FDA. Approximately 47 percent of medical devices fall into this category.	FDA registered or listed
Class II	are moderate-risk medical devices and the manufacturer must demonstrate before marketing to the FDA that the device is substantially equivalent in safety and efficacy to another legally marketed device that the FDA has already given clearance. About 43 percent of medical devices fall into this category.	FDA cleared
Class III	are the highest-risk devices and usually sustain or support life, are implanted, or present potential unreasonable risk of illness or injury; and accordingly, are subject to a rigorous review process by the FDA. These devices generally require FDA approval of a premarket approval application before marketing, where the manufacturer must demonstrate that the devices are safe and effective for their intended use with sufficient, valid scientific evidence that there is a reasonable assurance. About 10 percent of medical devices fall into this category.	FDA approved

real-time feedback that can potentially improve healthcare and health outcomes.

Since the advent of the opioid crisis, scientists have been ramping up efforts to develop digital technologies to address challenges faced by this patient population. FDA, too, is adapting its regulatory approach to help tackle the use and abuse of opioids. Accordingly, FDA has announced an innovation challenge on May 30, 2018 to encourage the development of medical devices, including digital health and diagnostic devices to fight the opioid crisis.¹⁹

4.1. Regulatory Considerations for Digital Devices

The FDA’s regulatory pathways for medical devices took shape in 1976, and the agency has acknowledged the need to modernize its procedures to better foster innovation, particularly in light of the iterative nature of digital products. In December 2017, the FDA issued new guidelines clarifying types of product that will no longer be deemed regulated medical devices, such as apps that promote general wellness.²⁰

In the United States, digital pain interventions fall under the Food and Drug Administration’s (FDA’s) definition of a medical device- which is anything other than a drug that is “intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease”- and must follow the regulatory pathways set up for medical devices. The FDA requires

The FDA classifies medical devices in one of three categories using a risk-based, tiered approach for regulating medical devices: Class I (low risk), Class II (higher risk), and Class III (highest risk). Accordingly, applicable FDA “label” classifications for the devices would be FDA registered or listed, to FDA cleared and FDA approved respectively (Table 1).²¹

4.2. Categories of Digital Pain Interventions

Upon review of results, five main categories of digital pain interventions emerged (Table 2). According to our research, many of the studies on digital pain interventions often targeted one of the main categories which led to our classification of digital interventions under these 5 headings. These five main categories for digital pain interventions were created based on popularity, and follow generally the same categories as other digital health technologies.^{22, 23, 24, 25}

4.2.1. Wearables: These are devices that can be worn on the body to benefit the patient’s health either by preventing, diagnosing, monitoring, data collection or delivery of care. They are further categorized based on the field of specialty and the purpose of the intervention. Wearable technologies could be sensors, neurostimulators, bio-feedback devices, or tracking systems. We did not include smart phones under the wearable category as it is often considered a separate

entity mainly because of the rise in the third part applications which offers consumers with innumerable options.

4.2.2. Implantable: These are devices that are placed inside the body and perform as sensors, data collectors,

stimulators and drug delivery systems. They can be modulated through wireless communication such as smart phones, internet or remote controls. The

Table 2: Digital pain interventions may be divided into 4 salient categories: Wearable devices, implantable devices, virtual reality, and miscellaneous. This table includes the most promising of these technologies along with their FDA regulatory status and if there is a need for prescription.

Digital intervention	FDA clearance	Prescription needed
WEARABLE DEVICES		
Quell	FDA 510(K) exemption (Class II medical device, (has an RCT), undergoing lawsuit)	No
JOGO	Pending FDA clearance	Yes, not for sale in US
Nervio Migra	De Novo, Class II medical device	Yes
Oska Wellness	Yes FDA registered, class I medical device, 510(K) exempt	No
IB-Stim device	FDA 510K, class II medical device	Yes
The NSS-2 Bridge device	Yes, De Novo	Yes
ActiPatch	Yes, 510(K), class II medical device	No
Wearable EEG readers	No	No
The iReliev® Therapeutic Wearable System	Yes, 510(K), class II medical device	No
The Game Ready System	Yes, 510(K), class II medical device	Yes
SPRINT Peripheral Nerve Stimulation System	Yes, 510(K), class II medical device	Yes
IMPLANTABLES		
SetPoint's bioelectronic therapeutic device	Under investigational device exemption	Yes
Proclaim XR	Yes, Premarket approval (has had an RCT)	N/A (physician performed)
Stimwave Freedom spinal cord stimulator (SCS) System	Yes, 510(K), class II medical device	N/A (physician performed)
VIRTUAL REALITY		
Virtual Exercise Rehabilitation Assistant	Yes, 510(K), class II medical device	Yes
Virtual Reality Headsets	Yes, 510(K), class II medical device (several organizations have received it)	Organization/corporation dependent
MISCELLANEOUS		
Photo biomodulation (Erchonia)	Yes, 510(K), class II medical device	N/A (physician performed)
Repetitive transcranial stimulation	Not for pain control except migraine	N/A (hospital performed)
Smart Pills (ID-Cap System)	Yes, 510(K), class II	Yes

implantable system consists of two main parts, an internal component within the host which performs the

expected function and an external component which transmits communication to the internal system or provides it with power. With advances in technology, new developments address extending battery life, mode of charging, size, weight, and now with battery-less implants under investigation.

4.2.3. Applications: Apps are software that may be accessed via computers, mobile phones and other hand-held devices that provide an expected isolated functionality. In our manuscript, this category refers to applications that decrease, relieve or prevent pain. These applications can serve as pain trackers, patient education sources, home therapies, medication reminders. Traditionally, applications are not individualized or do not allow clinician involvement.²⁶ Recent apps have evolved to allow the integration of app data with a patient's electronic medical records and review by their healthcare providers.

4.2.4. Virtual reality: A simulated environment experienced through sensory stimuli that may be controlled through movement. VR technology consists of a computer simulated platform, head sets and motion trackers. Pain is thought to be managed through distraction therapy, graded exposure therapy, physical therapy and mindfulness.

4.2.5. Miscellaneous: These include digital therapeutics that do not fall under the above mentioned four categories. According to our searches, there is not enough data and devices that could qualify certain products to have their own individual categories yet.

4.3. Wearable devices

4.3.1. The Quell device is a wearable band that generates electric signals to stimulate the body to produce endogenous opioids to inhibit pain nerve signals. It is a form of transcutaneous electrical nerve stimulation (TENS). It is worn above the knee and used to ease chronic pain from conditions like fibromyalgia, diabetic neuropathy, sciatica, and osteoarthritis. It is an FDA-approved Class II medical device for symptomatic relief and management of chronic pain. It is available without a prescription. It is customizable and the stimulation intensity and pattern can be controlled via an app. Unlike other TENS units, this does not require wires and is lightweight. However, the electrode needs to be replaced every few weeks. Some patients have reported experiencing pain due to the device itself.

A recent study suggests that these can have a moderate effect in reducing pain and improving quality of life.²⁷

4.3.2. JOGO is a wearable wireless/EMG sensor that comes with a mobile app or tablet which provides protocols for muscle relaxation, movement coordination and neuromuscular re-education. It is a Tele-Rehab based prescription digital therapeutic product that is used for neuroplasticity training. Remote JOGO therapists provide rehab sessions via telemedicine. It not only helps patients with strokes but also individuals with chronic pain, incontinence, chronic constipation and several neuromuscular conditions. JOGO is pending FDA clearance. It is not for sale in USA yet.

4.3.3. Nerivio Migra is an electronic wearable device worn on the arm which deploys electrical signals to relieve acute migraines through neuromodulation/pain signal inhibition. It is controlled through a smartphone application. The app also consists of a diary to track the migraine history. A study done in 2019 shows "REN (remote electrical neuromodulation) provides superior clinically meaningful relief of migraine pain and MBS (most bothersome symptoms) compared to placebo, offering a safe and effective non-pharmacological alternative for acute migraine treatment." Nerivio Migra was granted de novo clearance in May 2019.²⁸

4.3.4. Oska Wellness is an over the counter pain relief device that uses a low level pulsed 22" diameter electromagnetic field (PEMF) to help reduce a user's pain. It is lightweight, portable and can be worn on any part of the body where there is pain. It does not need to be directly attached to the skin but simply near the area of pain to be effective. It has been FDA registered.

According to the company the therapeutic technology can be used not only to reduce pain, but also to increase range of motion and dilate blood vessels for inflammation reduction.

4.3.5. IB-Stim device is a prescription-only percutaneous nerve stimulator which fits around a patient's ear and delivers low-frequency bursts of electricity designed to stimulate certain cranial nerves to disrupt dysfunctional autonomic feedback loops that cause pain in patients with IBS. It emits low-frequency pulses over the course of five days, after which it can be replaced by a new device. It may be used for up to three consecutive weeks. It is FDA cleared for the treatment of functional abdominal pain associated with IBS in patients aged 11-18 when combined with other therapies for IBS. Reported side effects include mild ear discomfort and adhesive allergy at the site of application. Contraindications include hemophilia, psoriasis vulgaris, and the presence of a cardiac pacemaker.²⁹

4.3.6. The NSS-2 Bridge device works in a similar fashion to the IB stim device. A small battery powered electrical nerve stimulator placed behind the patient's ear to stimulate branches of certain cranial nerves. These

stimulations may provide relief from opioid withdrawal symptoms. It can be used for up to five days during the acute physical withdrawal phase. Opioid withdrawal causes acute physical withdrawal symptoms including sweating, gastrointestinal upset, agitation, insomnia and joint pain. It has been FDA cleared.

4.3.7. ActiPatch is a pulsed shortwave therapy (PSWT) device that helps reduce the intensity of musculoskeletal pain. Unlike a TENS unit, it claims that the individual does not feel heat or vibration and is rather sensation free and is also able to be mobile while wearing the device. It is available over the counter and has been cleared by the FDA.

4.3.8. Wearable EEG readers with sensors assess pain and present them on tablets that come with it which also attempts to lessen that pain with distracting content. The patient can then agree or disagree to arrive at the pain level that's sent to doctors and nurses. The tablet or smart phone device also features content for meditation to help them relax.

4.3.9. The iReliev® Therapeutic Wearable System is a wireless rechargeable TENS unit used by individuals suffering from chronic pain like arthritis or acute pain symptoms like a strain or sprain. Though Transcutaneous Electrical Nerve Stimulation devices have existed for decades, they usually come with the hassle of dealing with wires and replacing batteries. These devices provide a non-invasive drug-free method of pain relief by blocking the pain signals from traveling to the brain through low voltage pulses to the skin. As a result, it produces endorphins, the body's feel-good chemical. "The system comes with 14 preset programs, 8 TENS programs for pain relief and 6 electrical muscle stimulation (EMS) programs for muscle conditioning. Treatment times can be set in 5-minute increments for up to 60 minutes per session." This is an over the counter, FDA cleared digital tool.

4.3.10. The Game Ready System 2.1 Pro delivers targeted cold, intermittent compression, rapid contrast or heat therapy through anatomically designed wraps to help to reduce pain, swelling, and opioid consumption. It is usually used in acute injury or post-operative recovery.

4.3.11. SPRINT Peripheral Nerve Stimulation (PNS) System, is a percutaneous device designed to stimulate nerves around the affected part of the body to achieve pain relief.

It has been FDA cleared for both chronic and acute pain, including post-operative, post-traumatic pain, inoperable joint pain, lower back pain and complex regional pain syndrome (CRPS). The SPRINT PNS System leads are implanted by a physician during an outpatient procedure without surgery, incisions, tissue destruction or anesthesia, and are connected to a wearable stimulator

that delivers stimulation for up to 60 days of therapy, after which the leads are withdrawn. Studies show that the SPRINT system has demonstrated $\geq 50\%$ reductions in average weekly pain at 12 months compared with placebo.³⁰

4.4. Apps

4.4.1. Hinge health is a remote monitoring program that includes wearable sensors, an app and real-time health coaching and feedback for guided exercise therapy, education, cognitive behavioral therapy, weight loss, and psychosocial support. The purpose of the intervention is to provide an alternative to surgery, reduce opioid use, increase adherence to treatment for chronic musculoskeletal disorders and reduce healthcare costs.

4.4.2. The app, **Empower by Axial Patient** helps patients identify pain triggers and provides suggestions for alternative therapies to manage their pain. It also provides access to educational articles to help cope with chronic pain and opioid overuse as well as deal with them. The platform is working on incorporating a network of care teams as well as peer support.

4.4.3. PainScale app has been developed with the needs of today's chronic pain patients in mind. The app helps log pain symptoms, but it also provides access to a wealth of insights and content targeted for your condition. The app also facilitates easy-to-create reports for your doctor, as well as daily health tips for living a full life with chronic pain.

4.4.4. The Kaia app provides users with online videos that cover education, physiotherapy and psychological strategies. It also tracks motion with the help of a smartphone to table to ensure proper form for exercises. It also features a chat function to connect to a musculoskeletal specialist if needed.

4.4.5. Ella provides mindfulness training to help deal with pain and the anxiety or stress from the condition. It provides its users with an online coach and online classes with other peers. Sessions range from 2.5 minutes to 20 minutes.

4.4.6. Curable is an online pain psychology program that provides users with access to a virtual coach, Clara. "Clara is like text messaging a friend. Except in Clara's case, it's a friend who wants to talk to you about your pain, has a lot of scientific information at her fingertips, and sends you interesting new lessons and exercises that help you reverse the cycle of pain going on your brain." The lessons or exercises usually last between 5 to 20 minutes. A biopsychosocial i.e. physical, psychological, and emotional approach is used to addresses the pain.

4.4.7. The selfBACK project is a healthcare program for self-management of low back pain to prevent chronicity, recurrence and pain-related disability. It delivers tailored information and advice to the patients through a smartphone app for their personalized self-management plan.³¹

4.4.8. Enter Avella is a pharmacy which created a mobile app for providers to support management of chronic pain and opioid overuse in individuals. It provides access to latest evidence-based medicine guidelines, other non-narcotic options, new pain medications and access tools like opioid converters along with drug dosage calculators.

4.4.9. reSET-O is an FDA cleared mobile app to help individuals with opioid use disorder. This is a prescription-based app that provides cognitive behavioral therapy intended to be used in addition to outpatient treatment in conjunction with treatment that includes buprenorphine and contingency management. Studies have not shown reduction in illicit drug usage but have proven to increase retention in an outpatient treatment program. The app includes a compliance reward system— such as earning special prizes within the app.

4.5. Implantables

4.5.1. SetPoint's miniature bioelectronic therapeutic device is an implantable MicroRegulator used for inflammatory arthritis. It is a wireless charging collar or band that is implanted on the left vagus nerve to activate the innate inflammatory reflex to produce a systemic anti-inflammatory effect. This helps regulate the immune system. It suppresses a range of inflammatory cytokines rather than eliminating them thus reducing inflammation without causing significant immunosuppression which is seen with the usage of biologic drugs used in inflammatory diseases. It may be used in conditions such as rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease. It comes with iPad-based prescription application. It is still under trial and pending FDA approval.

4.5.2. Proclaim XR is a spinal cord stimulator which works by delivering targeted low electric pulses signals to and from the spinal cord which change the pain signals as they travel between the spinal cord and the brain. The delivery of lower doses of stimulation help extend the system's battery life for approximately up to 10 years. It can also help physicians identify the lowest dose needed for the individual's pain relief. This device can also be controlled through smart phones. It has been a part of a randomized clinical trial which shows its efficacy in chronic pain.³²

4.5.3. Stimwave Freedom spinal cord stimulator (SCS) System is a small device implanted into the spine via a minimally invasive outpatient procedure. It is controlled through a wireless battery device or a smartphone. The device differs from existing spinal cord stimulator systems as it does not contain any leads or implanted pulse generator, but instead relies on power and telemetry provided by an external radiofrequency transmitter. Stimwave has received FDA clearance of 10,000 Hz neuromodulation. The StimQ Peripheral Nerve Stimulator (PNS) System utilizes the same technology as the Freedom SCS System but instead acts on peripheral nerves to treat chronic pain.

4.6. Virtual Reality

4.6.1. Virtual reality headsets are gaining popularity and may be considered by some to be a complementary adjunct to one's pain. Several apps have been created to distract an individual from his/ her pain. The brain engages in the immersive three-dimensional experience provided by this technology facilitating distraction from the individual's pain. Studies show that immersive distraction provided by VR can de-escalate chronic pain. However, some people may experience dizziness or nausea while using a VR headset which usually resolves once the headset is taken off.³³

4.6.2. Virtual Exercise Rehabilitation Assistant is an FDA cleared in-home interactive device that guides patients through exercises and records them in 3-D video for measuring movement and form as they move. An avatar provides instruction and feedback in real time. The platform enables tele visits with clinicians as well as virtual visits with a physical therapist, who can also review videos of the patient doing the exercises. "VERA seamlessly educates, demonstrates, measures, analyzes, and records patients' movements at home, all without the need for patients to apply or wear any sensors or monitoring devices." It is HIPAA compliant and secure.³⁴

4.7. Miscellaneous

4.7.1. Photo biomodulation therapy provided by a spinal exoskeletal robot is being studied for chronic low back pain due to arthritis. It plays a role in damaged tissue regeneration, decreasing inflammation, relieving pain and boosting the immune system. Using a robot also helps with precision when applying Class IV laser for therapy.

4.7.2. Repetitive transcranial stimulation, a non-invasive neuromodulation technique that has been used to treat depression is being studied for its role in pain management. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are two noninvasive brain stimulation techniques that can

modulate activity in specific regions of the cortex. It works by placing a charged coiled wire over the head which creates a magnetic field which stimulates axons to generate action potentials that have the potential to influence the brain pain circuits. Contraindications include nearby ferromagnetic or electronic implants. Possible adverse effects may include head aches and rarely seizures. There have been small studies with results showing improvement in pain scores, more so in the population suffering from fibromyalgia. However, their effects may be short-lasting. Further studies are needed to determine the efficacy of TMS and tDCS. Though repetitive transcranial stimulation has been approved by FDA for the management of depression and obsessive-compulsive disorder, it has not yet been approved for pain management other than treating migraines.

4.7.3. Smart Pills contain edible sensors to track medication adherence. Once ingested, these electronic sensors send wireless notification message to electronic devices. Originally approved by FDA to monitor real time ingestion of aripiprazole, it has gained attention in the chronic pain industry to tackle opioid drug abuse. A study conducted on the measurement of opioid ingestion patterns using digital pills revealed an accuracy of 87.3%.³⁵ Further studies are needed to determine their safety, feasibility and efficacy against standard of care drugs.

5. LIMITATIONS

Digital pain interventions are still in their infancy, therefore there is a lack of data on databases such as MEDLINE and PubMed; and grey literature had to be used for our searches. These searches may be biased based on the extent of advertisements by companies trying to launch/ sell their ideas and products. This is a form of selection bias, and, as a result, a query is probably not replicable. Availability of a limited number of trials decreases the ability to analyze the various characteristics and efficacy of digital pain interventions. Due to the lack of trials, we were also unable to make direct comparisons. Our study did not aim to analyze the various characteristics of each therapeutic such as its effective dose, duration, repeating frequencies, and targeted certain areas which may play a role in relieving chronic pain.

6. CONCLUSION

Digital health interventions are poised to become an accessible means of alleviating pain in the general population and improve quality of life in individuals living with pain. Although the healthcare industry is one of the last industries to adopt digital technologies, the digital revolution is quickly transforming the healthcare

industry and we are headed towards a universal digital future in healthcare. Digital health does not only provide an integrated digitally-enabled care environment where healthcare providers can connect, understand, monitor and treat an individual's pain but also offers the patient access to their healthcare information and autonomy to manage their pain.³⁶ Since digital pain intervention is still in its infancy, improving our knowledge about these novel digital patient-centric approaches to treating patients' pain has the potential to transform our health system. We hope that this manuscript will serve as a foundation for developing and applying digital pain interventions in clinical practice, familiarize us with the knowledge needed to decide how to evaluate digital health interventions and their implications on patient care, the health system, and society.

7. Conflict of interests

None declared by the authors.

8. Authors contribution

1. AN: Concept, data acquisition
2. SS: manuscript editing, data acquisition
3. SS: manuscript editing

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