



Research progress of digital therapy in pain management

Zhaoyang Yan^{1*}, Chunhui Qin^{2*}, Shuya Wang^{1*}, Zhaohui Xie³, Liyun Kong⁴, Lili Zhong⁵, Hong Wang⁵, Yun Cai⁶, Guohua Jiao⁷, Zhenwei Wang⁸, Qiwen Zhu^{9*}, Ruoyu Tang^{10*}

¹Shanghai Reacool Medical Technology Co., Ltd., Shanghai 200041, China. ²Department of Anesthesiology, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200437, China. ³Department of Pain Management, The First Hospital of Lanzhou University, Lanzhou 730000, Gansu Province, China. ⁴Department of Pain Management, The First Affiliated Hospital of Gan-nan Medical University, Ganzhou 341000, Jiangxi Province, China. ⁵Department of Anesthesiology and Pain Management, Wuhu Fifth People's Hospital (Anhui Province Wannan Rehabilitation Hospital), Wuhu 241004, Anhui Province, China. ⁶School of Health and Rehabilitation, Nanjing University of Chinese Medicine, Nanjing 210046, Jiangsu Province, China. ⁷Department of Pain Management, Tongxiang Hospital of Traditional Chinese Medicine, Tongxiang 314500, Zhejiang Province, China. ⁸Department of Respiratory Medicine, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200437, China. ⁹Department of Engineering and Computer Science, Syracuse University, New York State/Syracuse 13210, the United States of America. ¹⁰Department of Psychology, University of British Columbia (UBC), Vancouver V6T 1Z4, British Columbia, Canada.

*The authors contribute equally.

Corresponding authors: Lili Zhong and Zhenwei Wang.

Acknowledgement: This project was supported by the research on the application of digital therapy in the treatment of neuropathic pain caused by herpes zoster (2023yf004) and the Gansu Province Intelligent Pain Diagnosis and Treatment Industry Technology Center. The authors would like to thank all the guest editors and anonymous reviewers for their constructive advice.

Declaration of conflict of interest: None.

Received June 21, 2024; Accepted September 3, 2024; Published December 31, 2024

Highlights

- Analysis of collected data reveals that digital therapy offer new treatment methods and options in the field of pain management. After conducting research and analysis, it has been found that digital therapeutics offer new treatment methods and options, especially in the area of perioperative pain management.
- Multiple clinical studies indicate that digital therapy has significant effects in the treatment and relief of pain caused by various conditions.
- Domestic and international policies have positively influenced the development and progress of digital therapy.
- Ethical considerations require continuous evaluation, decision-making, and regulation, warranting ongoing reflection.
- Digital therapeutics, as an emerging intervention for pain, are propelling perioperative pain treatment towards a diversified and personalized comprehensive diagnostic and treatment model.

Abstract

Pain significantly impacts both the physical and mental well-being of individuals and imposes a substantial burden on society. Traditional pain management approaches are diverse but often fall short in adequately addressing patients' emotional and psychological experiences. In recent years, digital therapy has emerged as a rapidly developing field with significant potential in perioperative pain management. This innovative approach leverages digital technology, particularly cognitive-behavioral therapy, to alleviate pain and deliver more comprehensive, efficient, and personalized care. This study explores the applications and future directions of digital therapy in pain management, aiming to broaden understanding among healthcare professionals and patients, and to open new

Address correspondence to: Lili Zhong, Department of Anesthesiology and Pain Management, No. 2, Zhe-Shan East Road, Jinghu District, Wuhu 241004, Anhui Province, China. Tel: +86-180-0963-7377. E-mail: williyia@wnmc.edu.cn. Zhenwei Wang, Department of Respiratory Medicine, No. 110, Ganhe Road, Hongkou District, Shanghai 200437, China. Tel: +86-189-1875-7762. E-mail: wangzhenwei@shyueyanghospital.com.



avenues for pain treatment. The text combs through the synergistic empowerment of digital therapeutics in the perioperative period, discussing its multifaceted advantages such as optimizing analgesic effects, reducing mental anxiety, and improving psychological conditions. It also analyzes current challenges including privacy protection, data security, and technological adaptation, providing a reference for future research and application directions in digital pain treatment during the perioperative period.

Keywords: Pain, digital therapy, virtual reality, pain management, cognitive-behavioral therapy

Introduction

Pain is a prevalent health concern, with chronic pain, defined as pain persisting or recurring for more than three months, posing a particularly severe societal burden [1, 2]. Managing chronic pain has long been challenging, as traditional pain treatment methods, including pharmacological, physical, and surgical interventions, are often associated with side effects or limitations. Especially during the perioperative period, which is a critical accompaniment to surgical treatment, there are higher demands on the medical team. If pain management during the perioperative period is inadequate, it can lead to numerous complications for patients, increasing medical costs and the difficulty of recovery. In this context, digital therapy has garnered increasing attention as an innovative therapeutic option.

With the rapid development of digital technology, digital therapeutics have demonstrated numerous advantages such as personalization, convenience, and remote monitoring, as well as unique potential in pain treatment. However, the application of digital therapeutics in pain treatment is still in a phase of continuous exploration and development, and further in-depth research is needed in terms of efficacy, safety, and reliability. Therefore, a comprehensive review of the research progress of digital therapeutics in pain treatment is presented, along with a graphical summary (see **Figure 1**). It is hoped that through this visual presentation, medical practitioners and researchers can quickly understand the cutting-edge dynamics in this field, providing new ideas for future research and clinical application in the field of pain treatment.

Current status of pain management

Statistics show that approximately 20% of patients globally experience pain, with chronic pain accounting for about 50% of these cases [3]. Chronic pain, characterized by its long-term and persistent nature, inflicts significant physical and psychological harm on patients. In China, the number of chronic pain patients exceeds 300 million and is rapidly increasing, with a trend towards younger patients [4]. This

trend is expected to worsen as the population ages. Despite the widespread and detrimental nature of pain, there remains a lack of focus on pain management across various specialties, and current clinical pain treatments have yet to fully satisfy both patients and healthcare providers.

According to guidelines and consensus from the Pain Society of the Chinese Medical Association, pain management begins with preventive strategies, lifestyle modifications, and rehabilitation as initial treatments [5]. Pharmacological treatments, including nonsteroidal anti-inflammatory drugs, opioid analgesics, ion channel blockers, and antidepressants, are commonly used for pain management [6, 7]. However, long-term use of medications inherently carries risks and potential dependency. When medications fail to alleviate pain or cause adverse effects, minimally invasive interventional pain techniques are available as alternatives [8]. Research indicates that 64% of chronic pain patients are dissatisfied with the pain relief achieved through various treatments, with complete relief rates of less than 20% [9].

The absence of objective measures for pain introduces significant variability in causes, tolerance levels, and treatment responses, presenting challenges for accurate diagnosis and treatment. Furthermore, the establishment of pain management departments in China is relatively recent, having developed only within the past decade, leading to limited awareness of pain management among both medical professionals and the public. Given these obstacles, pain management faces pressing questions: What specific problems and challenges does it confront? Should alternative methods be explored to improve treatment outcomes? There is an urgent need to explore new treatment options, with digital therapy emerging as a promising, effective approach for pain management.

Overview of digital therapy

Definition of digital therapy

Digital therapy (DTx) is a novel concept in the field of medical technology, driven by software programs and grounded in evidence-based

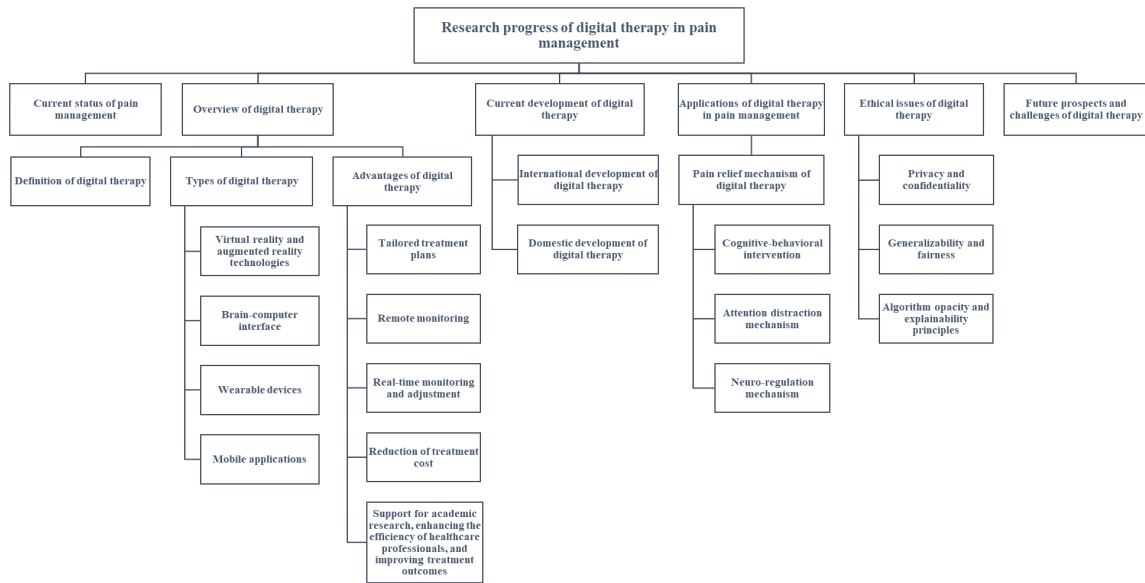


Figure 1. Digital therapeutics in pain treatment research progress analysis chart.

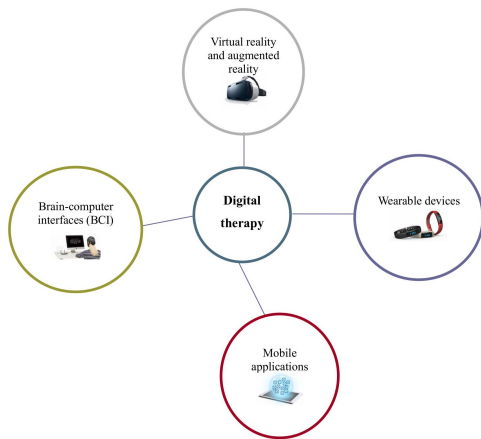


Figure 2. The main types of digital therapy.

medicine. It involves intervention schemes designed to treat, manage, or prevent diseases [10]. In terms of product form, the core of digital therapy is computer software that can be used independently or in conjunction with other medications. Diseases characterized by long management cycles, multiple intervention measures, poor patient adherence, low levels of patient self-management, and clear clinical guidelines are particularly suitable for the treatment with digital therapeutic products [11]. These are the primary application areas for digital therapy.

Types of digital therapy

At present, the main types of DTx include Virtual Reality (VR) and Augmented Reality Technologies, Brain-Computer Interfaces, Wearable Devices, and Mobile Applications (Figure 2). Since DTx covers a broad range, its main types

include but are not limited to the descriptions mentioned above, and also encompass sub-branches under the main types or other types that have not been explicitly classified.

1. VR and Augmented Reality Technologies [12]: VR is used in psychological therapy or rehabilitation training by immersing patients in therapeutic scenarios, thereby enhancing treatment efficacy. By leveraging big data and artificial intelligence, VR and Augmented Reality technologies can provide customized treatment plans based on individual patient characteristics and specific conditions.

2. Brain-Computer Interfaces [13]: This technology establishes a direct connection between the brain and external devices, allowing users to control external devices through conscious thought or brain signals. This “dialogue” between the brain and machines facilitates the acquisition of external information.

3. Wearable Devices [14]: Essential to digital therapy, wearable devices include smart wristbands, electrocardiogram monitors, and physiological trackers for sleep, heart rate, and blood pressure monitoring. They enable continuous health data recording and management, with features like vibration feedback supporting remote treatment by healthcare providers.

4. Mobile Applications [15]: These applications support mental health and disease management, promoting patient-centered care and autonomy in managing health conditions.

Advantages of digital therapy

Digital therapy leverages virtual reality technology and other digital tools, transforming real medical principles into software-driven interventions. They represent an innovative approach that extends beyond traditional treatment limitations and serve as a complement and optimization of conventional therapies [16].

VR technology is a novel alternative for pain management and has shown significant effectiveness in various acute pain treatments [17]. Despite the complex pathophysiology that drives the transition from acute to chronic pain, VR technology has also demonstrated benefits in managing chronic pain [18]. For instance, Sam et al. conducted a study on VR-based pain relief [19]. They recruited 15 volunteers, applied capsaicin to induce a pain model on their legs, and simulated chronic pain with electric shocks. Volunteers used VR to either experience an Arctic adventure or view static images to alleviate pain. The results showed that immersive VR reduced both pain and sensitivity, supporting the hypothesis that “immersive VR reduces pain by distracting attention.”

Compared to traditional therapies, digital therapy offer several advantages:

1. Targeted Treatment Plans: Provides targeted therapeutic options based on individual patient conditions.
2. Remote Monitoring: Enables disease intervention at home, making treatment more accessible and convenient.
3. Real-Time Monitoring and Adjustment: Facilitates timely interventions and adjustments through real-time data monitoring and recording.
4. Cost Reduction: Reduces treatment costs and lessens the economic burden on patients.
5. Support for Academic Research [16]: Enhances the of healthcare professionals’ efficiency, and improves treatment outcomes.

Current development of digital therapy

International development of digital therapy

With rapid advancements in science and technology, a new technological revolution, led by artificial intelligence, is driving a global innovation, including the integration of advanced technologies into healthcare. This integration aims to improve the current medical environment and has spurred the concept of digital therapy.

DTx, introduced by Joseph Kvedar, provides effective, evidence-based medical interventions driven by high-quality software [10, 20]. The approval of digital therapy prescription products by the U.S. Food and Drug Administration, such as the BlueStar® diabetes management platform depression treatment platforms, and treatments for substance abuse, marks the entry of digital therapy into clinical practice as an effective complement to traditional therapies [21-23].

Government support has significantly accelerated the progress of digital therapy. However, only a few countries have implemented related policies for the practical execution of digital therapy. The United States has a relatively mature registration and approval process for digital therapy products, having introduced the Digital Health Pre-Certification Program in 2017 and initiated pilot projects for digital health and certification [24]. In 2019, Germany proposed public access to digital therapeutic products free of charge, incorporating them in the health insurance reimbursement scope, while Belgium approved similar reimbursement schemes [25, 26]. In 2020, South Korea released approval guidelines, paving the way of digital therapy regulation [27]. Currently, digital therapies are widely used abroad in areas such as chronic diseases, mental health, neurological disorders, and other conditions, with national approval systems taking shape.

Additionally, countries like the UK, France, and Australia have adopted effective measures to ensure the legality and compliance of digital therapy, even without fully developed regulatory frameworks [28].

Domestic development of digital therapy

Compared to international advancements, digital therapy in China began later and remains in the early stages, with few mature solutions currently established. Globally, definitions and regulations for digital therapy are still evolving, and China has yet to adopt a clear official definition. In February 2017, the National Medical Products Administration categorized digital therapy as conventional medical devices in the “Guiding Principles for Technical Review of Mobile Medical Devices” [29].

Approval systems, clinical trial results, business models, and insurance reimbursement for digital therapy are still under exploration. However, with ongoing policy improvements and increasing market demand, digital therapy has gained attention, and prospects for development in

China appear promising.

Following the outbreak of COVID-19 in early 2020, digital technologies rapidly advanced in the healthcare field. That year, a digital therapy product in China received one of the first National Medical Products Administration approvals, permitting direct doctor prescriptions. Subsequently, the government initiatives like the “Healthy China 2030” Planning Outline and the “14th Five-Year Plan” for Bioeconomic Development, have emphasized the construction and application of innovative therapies, supporting the development and innovation of digital healthcare technologies [30]. With policy guidance and expert advice, domestic digital therapy companies have made progress in areas such as pain management. For instance, in 2023, Suzhou Reacool Medical Technology Co., Ltd. obtained the first national approval for a digital pain relief rehabilitation product [31].

Digital therapy not only reduces treatment costs but also facilitates the transformation of treatment methods, complementing or even substituting traditional therapies. According to ClinicalTrials.gov, as of July 2022, there were 5,291 clinical studies on digital therapy globally, with approximately 300 studies in China [32]. The shift toward clinical-oriented medical innovation and the integration of medicine and engineering is expected to drive the widespread adoption of digital therapy. As an emerging force in pain management, digital therapy is poised to gain prominence.

Application of digital therapy in pain management

According to the latest survey by Managed Markets Insight & Technology, LLC., a primary barrier to digital therapy is the perceived lack of “clinical value” [33]. As digital therapy evolves from concept to practice, stakeholders increasingly recognize that clinical trials play a crucial role in maturing digital therapy.

As of October 2021, data from E-Capital shows that there were 417 clinical trials related to digital therapy worldwide [33]. The number of trials grew over fivefold, from 16 in 2016 to 98 in 2020. In China, data from the Clinical Trial Registration Center indicates 60 trials involving “digital therapy,” “software,” and “virtual reality” between January 2021 and March 2023 [34]. Further analysis reveals that only 13 were conducted in 2021, while 37 were conducted in 2022, indicating a nearly threefold increase in clinical trials and a significant rapid growth trend [34].

Digital therapy is characterized by its evidence-based foundation, which necessitates high-quality clinical trials to demonstrate their safety and effectiveness in medical interventions. One randomized controlled trial showed that a digital program could serve as a viable model for alleviating chronic shoulder pain [35]. The study observed high acceptance, satisfaction, and adherence rates across groups, with significant clinical improvements. This trial highlighted the potential of digital therapy in alleviating chronic shoulder pain and considered its scalability and effectiveness. Another study also confirmed that combining virtual reality technology with local anesthesia and anxiety interventions provided additional analgesic effects [36]. This non-pharmacological intervention shows promise as an effective adjunct to pain management, reducing surgical pain and anxiety during procedures without serious complications.

Currently, VR is used in the treatment of various pain conditions, including burn pain, dental pain, ischemic pain, cancer pain, and chronic headaches [37-41]. It not only alleviates pain perception but also improves psychological well-being. Research confirms VR's effectiveness in relieving various types of pain, such as acute pain from surgical procedures and chronic pain from other causes [42-47]. A study on the efficacy of VR in reducing pain sensitivity in patients with lower back pain revealed that immersive VR effectively alleviated pain by distracting attention [48]. Moreover, VR's application extends to pediatric pain management. Wong et al. conducted a randomized controlled trial with children undergoing intravenous cannulation, showing that VR significantly improved pain and anxiety in these patients [49]. In digital health psychological intervention, adolescent pain management showed significant improvements over time, with participants reporting greater improvement post-treatment and during follow-up [50]. However, further research is needed to understand how digital health interventions can enhance treatment engagement and optimize implementation, ensuring the safety and reliability of digital therapy.

Digital therapy represents the empowerment of current medical methods through information technology and artificial intelligence, using innovative treatment methods to alleviate pain and modulate pain perception. The pain relief mechanisms of digital therapy include:

1. Cognitive Behavioral Intervention: Alters patients' negative perceptions and coping strat-

egies regarding pain, fostering a positive and optimistic mindset, thus breaking the “pain → negative emotion → pain” vicious cycle, and aiding in pain relief [51].

2. Attention Diversion Mechanism [52]: Uses virtual environments to attract patients’ attention, reducing their cognitive awareness of pain, thereby decreasing pain intensity and discomfort.

3. Neuroregulation Mechanism: Utilizes techniques such as electrical and magnetic stimulation to directly influence neural system activity and alleviate pain. Early research by Hoffman et al. on functional magnetic resonance imaging showed that VR technology could significantly reduce patients’ subjective pain perception and decrease brain activity in five pain-related brain regions [53]. However, the specific mechanisms by which VR alleviates chronic pain remain unclear and require further study.

Ethical issues in digital therapy

In the past 20 years, the digital transformation of healthcare has relied on deep learning and simulation computing, primarily applied to medical diagnostics, remote care, and data monitoring, aiming to provide more convenient and adaptable care models for the public [54]. However, with the rapid development of digital medical technology, certain ethical risks and challenges have emerged. Addressing these ethical concerns requires intervention and management not only from a legal perspective but also from an ethical standpoint [55].

Privacy and confidentiality

Compared to traditional patient-doctor interactions, digital therapy platforms introduce new risks related to patient information leakage. Training digital intervention models requires collecting large amounts of patient data, and the instability and vulnerability of networks may exacerbate the risk of data breaches. If privacy protection systems are flawed, there is a potential for violating individuals’ property rights, personal rights, or leading to intellectual property disputes [56]. As more personal information appears in large online databases, data aggregation and analysis raise the risk of re-identification, making complete privacy protection challenging. Thus, data security and privacy are fundamental and crucial ethical issues in digital therapy.

When collecting, using, and storing data, strict adherence to laws, regulations, and ethical

standards is essential. Privacy issues should be addressed through rigorous scientific research and ethical design, with sensitive data subjected to appropriate de-identification or encryption to prevent unauthorized access or misuse. Patients’ rights to informed consent and choice must be fully protected, and data should be collected and used only within the minimum necessary scope [57]. Comprehensive data privacy protection measures and security standards must be established to effectively safeguard the development of digital therapy.

Generalizability and fairness

While digitalization brings convenience to daily life, it also creates a “digital divide” disproportionately affects populations with limited information technology skills, such as the elderly [58]. Older adults are a high-risk group for diseases, with declining physical functions, weakened immune systems, and frequent medication use. They often recover more slowly and have greater healthcare needs. However, the “digital divide” poses significant barriers to their access to healthcare. Additionally, factors such as educational levels and economic conditions in remote areas may affect their ability to benefit from digital health services.

The development of digital therapy should consider broad applicability and respect for special groups and cultural differences. Recognizing that older populations may have limited familiarity, learning capacity, and acceptance of new technologies, digital therapeutic products should incorporate age-friendly services [59]. Simple and intuitive interface design, user-friendly digital therapeutic platforms, and tools should be prioritized to improve the overall health status of diverse populations.

Algorithm opacity and explainability principles

Digital therapeutic technologies are software-based, and due to algorithm opacity or technical and commercial confidentiality, their reliability and safety undergo testing in a “black box” manner. This “black box” characteristic is one of the main obstacles to the application of digital therapy in the medical field [58]. For various digital therapeutic domains, validating product safety and reliability depends on the source of research evidence and must be scientifically rigorous. When developing digital therapeutic systems, ethical issues must be carefully considered to ensure that artificial intelligence products meet corresponding ethical requirements during clinical trials. For example, ChatGPT is programmed with source code to

adhere to OpenAI's ethical and moral standards, avoiding actions that could result in adverse outcomes when responding to abnormal instructions [60].

As digital medical technologies become increasingly crucial for public health and personalized healthcare, their global adoption is accelerating. The healthcare sector's digital transformation, often referred to as "Health 4.0," signifies a shift into a new era where digital healthcare will face unique challenges and opportunities.

Future prospects and challenges of digital therapy

According to the latest report by Markets and Markets, the global artificial intelligence market is expected to reach USD 11.03 billion in 2023 and USD 51.8 billion by 2028, with a compound annual growth rate of 35.6% [61]. FORTUNE BUSINESS INSIGHTS predicts that the digital health market size will reach \$1,965.3 billion by 2030, with a compound annual growth rate of 23.3% from 2023 to 2030 [62]. Insider Intelligence forecasts that digital therapy will become a USD 56 billion global opportunity by 2025 [28]. Between December 1, 2022 and December 22, 2023, Chinese central government issued 66 policies related to digital health [61]. The alignment of global market trends with supportive local policies is expected to refine the digital therapy framework, establishing a solid foundation for the industry's healthy development. Moreover, the latest report by the Peterson Health Technology Institute indicates that digitally guided therapy programs offer cost-effective solutions, providing outcomes to face-to-face therapy at lower costs. For patients with commercial insurance, virtual or remote digital solutions can save at least USD 737 to 1,306 in medical expenses annually [63].

Digital therapy is rapidly evolving, with ongoing developments in disease management and regulatory approvals, holding immense potential. Although recent investment data have been less than ideal, with overall decline in market investment, reflecting a normal fluctuation cycle [63]. The domestic prospects for digital therapy are broad, but the industry remains in its infancy and faces several challenges. First, ensuring the safety and efficacy of digital therapy in China requires rigorous clinical trials and robust regulatory mechanisms to better support these trials. Given the potential technical differences among various digital therapeutic products, there is an urgent need to establish unified standardized protocols for digital therapy. Additionally, patient data privacy and security must

be prioritized, as safeguarding personal information and data security is crucial. Despite the advantages of digital therapy over traditional methods, achieving comprehensive solutions remains challenging. The promotion of digital therapy may involve issues related to medical costs and the willingness of doctors and patients to adopt new technologies, which could hinder widespread adoption. Therefore, exploring suitable payment models and increasing awareness and acceptance among healthcare professionals and patients are essential.

The challenges extend beyond clinical trials and regulatory issues, as further development is also needed in areas such as mechanism exploration and delivery technology. While some well-known international digital therapeutic companies, such as Pear in the U.S. and Babylon in the U.K., have encountered financial difficulties and even bankruptcy, the outlook for digital therapy in China remains optimistic. Local governments, particularly in Hainan, have shown strong support for digital therapy industry, issuing the first policy documents to facilitate its growth and conducting pilot projects to accelerate digital health transformation in Hainan Province [64]. Strengthening international collaboration and incorporating innovative practices from other countries can help shape a digital therapeutic model suitable for China's unique healthcare needs and national conditions.

Conclusion

Amid rapid technological advancements, digital therapy is playing an increasing prominent role in modern medical diagnosis and treatment. Many countries and regions have introduced policies and regulations to encourage the innovation and application of digital therapy. Alongside a favorable policy environment, substantial research and clinical trials have proven the effectiveness and safety of digital therapy, providing scientific evidence for their application value.

Digital therapeutic interventions for pain management offer significant clinical and social values. Given the limitations of traditional treatment methods in meeting the needs of pain patients, digital therapy emerges as a promising solution. Future research and development will further drive the application and innovation of digital therapy in the field of pain management. While our current understanding continues to evolve, the outlook for digital therapy is promising, with significant potential to transform pain management in the years ahead.

Author contributions: Zhaoyang Yan: Proposing the theme and ideas of the article, designing the content and structure of the article, as well as revising and submitting the manuscript. Chunhui Qin: Leading the conception of the research direction and the overall framework, and putting forward innovative research ideas. Shuya Wang: Responsible for the main writing of the manuscript, literature review, manuscript revision and submission. Zhaohui Xie: Conducting the final review of the full text of the manuscript to ensure the accuracy of the research content, logical rigor and reasonable conclusions. Liyun Kong: Carefully revising and polishing the language expression, logical structure and grammatical errors of the manuscript. Lili Zhong: The corresponding author of this article, the person in charge of the industry-university-research cooperation project, and responsible for the medical scientific review. Hong Wang: Discovering research topics, sorting out the academic context, and putting forward the core arguments. Yun Cai: Proofreading details, supplementing domestic and foreign references, and improving the scientific nature of the paper. Guohua Jiao: Participating in the design of the article's content and structure, and putting forward key suggestions and improvement opinions. Zhenwei Wang: The corresponding author of this article, the person in charge of the industry-university-research cooperation project, and responsible for the medical scientific review. Qiwen Zhu: Translating and proofreading the full text of the manuscript. Ruoyu Tang: Translating and proofreading the full text of the manuscript.

References

- [1] Chen J, Wang JL. International Association for the Study of Pain's Revision and Systematic Classification of Chronic Pain in WHO ICD-11. *Chin J Pain Med* 2019;25(5):323-330.
- [2] Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. *Lancet* 2021;397(10289):2082-2097.
- [3] Barke A, Korwisi B, Jakob R, et al. Classification of chronic pain for the International Classification of Diseases (ICD-11): results of the 2017 international World Health Organization field testing. *Pain* 2022;163(2):e310-e318.
- [4] Fan BF. Report on the Development of Pain Medicine in China. Beijing (China). Tsinghua University Press, 2020.
- [5] Ma K, Jiang W, Wang YX, et al. Expert consensus of the Chinese Association for the Study of Pain on pain treatment with the transdermal patch. *World J Clin Cases* 2021;9(9):2110-2122.
- [6] Peng BG, Liu YQ, Ma K. Editorial for the special issue of the Chinese Association for the Study of Pain. *World J Clin Cases* 2021;9(9):2022-2026.
- [7] Liu Y, Zhang D, Fu ZJ. Standards for Diagnosis and Treatment in Chinese Pain Medicine. Beijing (China). People's Medical Publishing House, 2021.
- [8] Ma K, Ji Y. Minimally Invasive Interventional Pain Management to Promote Precision Treatment and Comprehensive Management of Chronic Pain Conditions. *Chin Med J* 2021;101(43):3521-3524.
- [9] Borsook D, Sava S, Fau - Becerra L, Becerra L. The pain imaging revolution: advancing pain into the 21st century. *Neuroscientist* 2010;16(2):171-185.
- [10] A New Category of Medicine. Available at: <https://dtxalliance.org/understanding-dtx/>
- [11] The application status and future prospect of digital therapy. Available at: <https://www.ewit-key.cn/cms/show-22566.html>
- [12] Wu C, Zhang L, Ma C, et al. Research Progress of Virtual Reality Technology in the Field of Pain Treatment. *Xiehe Med J* 2024;15(02):272-278.
- [13] Chai X, Cao T, He Q, et al. Brain-computer interface digital prescription for neurological disorders. *CNS Neurosci Ther* 2024;30(2):e14615.
- [14] Digital Psychosomatic Medicine Collaborative group of Psychosomatic Medicine Branch of Chinese Medical Association, Chinese expert consensus writing group of digital therapy for insomnia. Chinese Expert Consensus on Digital Therapy for Insomnia (2024 edition). *Chin Med J* 2024;104(9):650-661.
- [15] McDarby M, Llana D, George L, et al. Mobile Applications for Advance Care Planning: A Comprehensive Review of Features, Quality, Content, and Readability. *Am J Hosp Palliat Care* 2021;38(8):983-994.
- [16] Cheng ZX, Li Y. Application of Digital Therapy in the Field of Chronic Pain. *Chin J Pain Med* 2023;19(05):835-839.
- [17] Chan E, Foster S, Sambell R, et al. Clinical efficacy of virtual reality for acute procedural pain management: A systematic review and meta-analysis. *PLoS One* 2018;13(7):e0200987.
- [18] Feizerfan A, Sheh G. Transition from acute to chronic pain. *Continuing Education in Anaesthesia Critical Care & Pain* 2015;15(2):98-102.
- [19] Hughes SW, Zhao H, Auvinet EJ, et al. Attenuation of capsaicin-induced ongoing pain and secondary hyperalgesia during exposure to an immersive virtual reality environment. *Pain Rep* 2019;4(6):e790.

- [20] Dang A, Arora D, Rane P. Role of digital therapeutics and the changing future of healthcare. *J Family Med Prim Care* 2020;9(5):2207-2213.
- [21] FDA clears WellDoc for diabetes management. Available at: <https://www.mobihealthnews.com/8539/fda-clears-welldoc-for-diabetes-management/>
- [22] Digital therapeutics:Catalysing the future of health. Available at: <https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-digital-therapeutics.pdf>
- [23] Pear Therapeutics Obtains FDA Clearance of the First Prescription Digital Therapeutic to Treat Disease. Available at: <https://www.prnewswire.com/news-releases/pear-therapeutics-obtains-fda-clearance-of-the-first-prescription-digital-therapeutic-to-treat-disease-300520068.html>
- [24] Digital Health Software Precertification (Pre-Cert) program. Available at: <https://www.fda.gov/medical-devices/digital-health-center-excellence/digital-health-software-precertification-pre-cert-pilot-program>
- [25] Want to see the future of digital health tools? Look to Germany. Available at: <https://hbr.org/2020/12/want-to-see-the-future-of-digital-health-tools-look-to-germany>
- [26] As of January 2021,medical apps can now be submitted for reimbursement in Belgium for the first time. Available at: <https://www.medicaldevice-network.com/analyst-comment/mhealthbelgium/>
- [27] Wang C, Lee C, Shin H. Digital therapeutics from bench to bedside. *NPJ Digit Med* 2023;6(1):38.
- [28] Yao HM. Research on the Development Trend of Global Digital Therapy. *Compet Intell* 2022;18(02):57-63.
- [29] Interpretation of the Guiding Principles for Technical Review of Mobile Medical Device Registration. Available at: <https://www.nmpa.gov.cn/directory/web/nmpa/xxgk/zhcjd/zhcj-dylqx/20171229135401582.html>
- [30] 2023 China Digital Therapy (DTx) Industry Insight Report. Available at: <https://www.36kr.com/p/2140041445640583>
- [31] Core Medical. Available at: <https://www.szreacool.com/>
- [32] ClinicalTrials.gov. Available at: <https://classic.clinicaltrials.gov/>
- [33] In the World of Digital Therapy, How Far Have Pear, Akili, and Others Come? Available at: <https://www.cn-healthcare.com/articlewm/20220606/content-1373035.html>
- [34] Triple Growth Rate and Four Major Challenges! Digital Therapy Clinical Trials in Progress. Available at: <https://www.cn-healthcare.com/articlewm/20230414/content-1536918.html>
- [35] Pak SS, Janela D, Freitas N, et al. Comparing Digital to Conventional Physical Therapy for Chronic Shoulder Pain: Randomized Controlled Trial. *J Med Internet Res* 2023;25:e49236.
- [36] Joo Y, Kim EK, Song HG, et al. Effectiveness of virtual reality immersion on procedure-related pain and anxiety in outpatient pain clinic: an exploratory randomized controlled trial. *Korean J Pain* 2021;34(3):304-314.
- [37] Carrougner GJ, Hoffman HG, Nakamura D, et al. The effect of virtual reality on pain and range of motion in adults with burn injuries. *J Burn Care Res* 2009;30(5):785-791.
- [38] Furman E, Jasinevicius TR, Bissada NF, et al. Virtual reality distraction for pain control during periodontal scaling and root planing procedures. *J Am Dent Assoc* 2009;140(12):1508-1516.
- [39] Magora F, Cohen S, Shochina M, et al. Virtual reality immersion method of distraction to control experimental ischemic pain. *Isr Med Assoc J* 2006;8(4):261-265.
- [40] Chirico A, Lucidi F, De Laurentiis M, et al. Virtual Reality in Health System: Beyond Entertainment. A Mini-Review on the Efficacy of VR During Cancer Treatment. *J Cell Physiol* 2016;231(2):275-287.
- [41] Shiri S, Feintuch U, Weiss N, et al. A virtual reality system combined with biofeedback for treating pediatric chronic headache—a pilot study. *Pain Med* 2013;14(5):621-627.
- [42] Tejera DM, Beltran-Alacreu H, Cano-de-la-Cuerda R, et al. Effects of Virtual Reality versus Exercise on Pain, Functional, Somatosensory and Psychosocial Outcomes in Patients with Non-specific Chronic Neck Pain: A Randomized Clinical Trial. *Int J Environ Res Public Health* 2020;17(16):5950.
- [43] Garcia LM, Birkhead BJ, Krishnamurthy P, et al. An 8-Week Self-Administered At-Home Behavioral Skills-Based Virtual Reality Program for Chronic Low Back Pain: Double-Blind, Randomized, Placebo-Controlled Trial Conducted During COVID-19. *J Med Internet Res* 2021;23(2):e26292.
- [44] Deo N, Khan KS, Mak J, et al. Virtual reality for acute pain in outpatient hysteroscopy: a randomised controlled trial. *Bjog* 2021;128(1):87-95.
- [45] Weynants L, Chys B, D'Hulst P, et al. Virtual reality for pain control during shock wave lithotripsy: a randomized controlled study. *World J Urol* 2023;41(2):589-594.
- [46] Merlot B, Elie V, Périgord A, et al. Pain Reduction With an Immersive Digital Therapeutic in Women Living With Endometriosis-Related Pelvic Pain: At-Home Self-Administered Randomized Controlled Trial. *J Med Internet Res* 2023;25:e47869.
- [47] Gold JI, SooHoo M, Laikin AM, et al. Effect of

- an Immersive Virtual Reality Intervention on Pain and Anxiety Associated With Peripheral Intravenous Catheter Placement in the Pediatric Setting: A Randomized Clinical Trial. *JAMA Netw Open* 2021;4(8):e2122569.
- [48] Chen TB, Wang J, Du D, et al. Clinical Efficacy of Virtual Reality-Induced Pain Reduction in Patients with Chronic Non-Specific Low Back Pain. *J Med Sci Kunming Univer* 2022;43(9):59.
- [49] Wong CL, Choi KC. Effects of an Immersive Virtual Reality Intervention on Pain and Anxiety Among Pediatric Patients Undergoing Venipuncture: A Randomized Clinical Trial. *JAMA Netw Open* 2023;6(2):e230001.
- [50] Palermo TM, de la Vega R, Murray C, et al. A digital health psychological intervention (Web-MAP Mobile) for children and adolescents with chronic pain: results of a hybrid effectiveness-implementation stepped-wedge cluster randomized trial. *Pain* 2020;161(12):2763-2774.
- [51] Gupta A, Scott K, Dukewich M. Innovative Technology Using Virtual Reality in the Treatment of Pain: Does It Reduce Pain via Distraction, or Is There More to It? *Pain Med* 2018;19(1):151-159.
- [52] Li J, Yang H, Xiao Y, et al. The analgesic effects and neural oscillatory mechanisms of virtual reality scenes based on distraction and mindfulness strategies in human volunteers. *Br J Anaesth* 2023;131(6):1082-1092.
- [53] Hoffman HG, Richards TL, Coda B, et al. Modulation of thermal pain-related brain activity with virtual reality: evidence from fMRI. *Neuroreport* 2004;15(8):1245-1248.
- [54] Yang YH, Su GY. Ethical Dilemmas and Practical Boundaries in the Application of Digital Medical Technology. *Med Philos* 2023;44(13):34-39.
- [55] Xu WJ, Sun HQ, Xu LZ, et al. Research on Ethical Review Issues in Clinical Research of Digital Healthcare. *Med Philos* 2023;44(20):1-4,21.
- [56] Zhang QJ, Jiang H. Ethical Design and Principle of Medical Artificial Intelligence Application. *Med Philos* 2021;42(4):22-26,31.
- [57] Wei YR. Privacy Risks of Intelligent Connectivity: Legal Challenges and EU Regulations. *Soc Sci Abroad* 2020;7(2):106-116.
- [58] Sun W, Xu LL, Xiao SP, et al. Current Status of Digital Therapy Research and Analysis of Ethical Issues. *Med Philos* 2023;44(20):5-8.
- [59] Shao Y, Fan MQ, Cai B, et al. Research on the Current Situation and Governance Approaches to the Digital Divide in Healthcare Access for the Elderly in the Context of Digital Healthcare. *Med Philos* 2022;43(24):73-76.
- [60] Wu JR. Three Challenges Faced by Artificial Intelligence Expert Systems in Clinical Applications. *Med Philos* 2023;44(1):4-5.
- [61] White Paper on Large AI Models Empowering the Healthcare Industry (2023). Available at: <https://zhuanlan.zhihu.com/p/684771573>
- [62] Digital health market size, share and Industry analysis. Available at: <https://www.fortunebusinessinsights.com/zh/industry-reports/digital-health-market-100227>
- [63] Industry Report Evaluates Insights on the Medical Effectiveness of Digital Health and Digital Therapy. Available at: <https://www.163.com/dy/article/J4A6Q5MV05149U3U.html>
- [64] The People's Government of Hainan Province. Available at: <https://www.hainan.gov.cn/>