


Digital Therapeutics in Migraine Management: A Novel Treatment Option in the COVID-19 Era

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Abstract: Migraine is a chronic and often lifelong disease that directly affects over one billion people globally. Because access to migraine medical services is limited, only a minority of migraine patients are treated adequately. This situation worsened during the COVID-19 pandemic. Digital therapeutics (DTx) is an emerging therapeutic approach that opens up many new possibilities for remote migraine management. For instance, migraine management tools, online migraine diagnosis, guideline-based treatment options, digitally networked patients, and collecting anonymized information about migraine attacks and course parameters for scientific evaluation. Various applications of DTx in migraine management have been studied in recent years, such as the usefulness of digital migraine self-management tools in diagnosing and tracking migraine attacks, and the efficacy and safety of digital cognitive behavioural therapy. However, the development of DTx is still in its infancy and still faces many obstacles. The primary goal of this study is to review the latest research on DTx in migraine management, identify challenges, and outline future trends.

Keywords: migraine, digital therapeutics, COVID-19, innovative approaches, healthcare delivery

Introduction

According to the World Health Organization (WHO), migraine is the second most disabling condition in adults in disability-adjusted life years.¹ Migraine is a chronic and often lifelong disease that directly affects over one billion people globally, is a major global health challenge, and is the most common cause of disability in adults under the age of 50.^{2,3} Migraine treatment drugs are generally divided into drugs specifically for the treatment of acute migraine (including 5-HT receptor agonists and anti-CGRP drugs) and general analgesics (such as NSAIDs). It is worth noting that drugs targeting CGRP and 5-HT_{1F} receptor have been recently approved, indicating that drug development for new drug targets is still underway.⁴ Despite advances in migraine treatment, only a minority of these patients are adequately treated. It is estimated that 10–20% of patients with a diagnosis receive adequate treatment.^{3,5} This situation worsened during the COVID-19 pandemic.^{6–9}

Digital therapeutics (DTx) is an emerging concept for therapeutic approaches in healthcare system.^{10,11} This subdivision of digital health defines a healthcare system driven by the use of any form of digital technology to enhance the efficacy of healthcare delivery.¹² DTx is applied in the clinical field to aid diagnosis, clinical decision-making, treatment, and long-term management guidance,¹² which opens up many new possibilities for managing migraines remotely.¹³ For instance, migraine management tools, online migraine diagnosis, guideline-based treatment options, digitally networked patients, and collecting anonymized information about migraine attacks and course parameters for scientific evaluation (Figure 1). DTx can complement and support in-person diagnosis and treatment and ideally enable a direct link between practitioners and patients to soften the strict boundaries of outpatient clinics and patients in their day-to-day care,^{14,15} and meanwhile reduce the economic burden of repeated outpatient visits in migraine patients.¹⁶ In the era of COVID-19, headache management clinicians are trying to reduce face-to-face visits for migraine patients. This not only protects patients from the risk of exposure to COVID-19, but also avoids infection of medical staff and

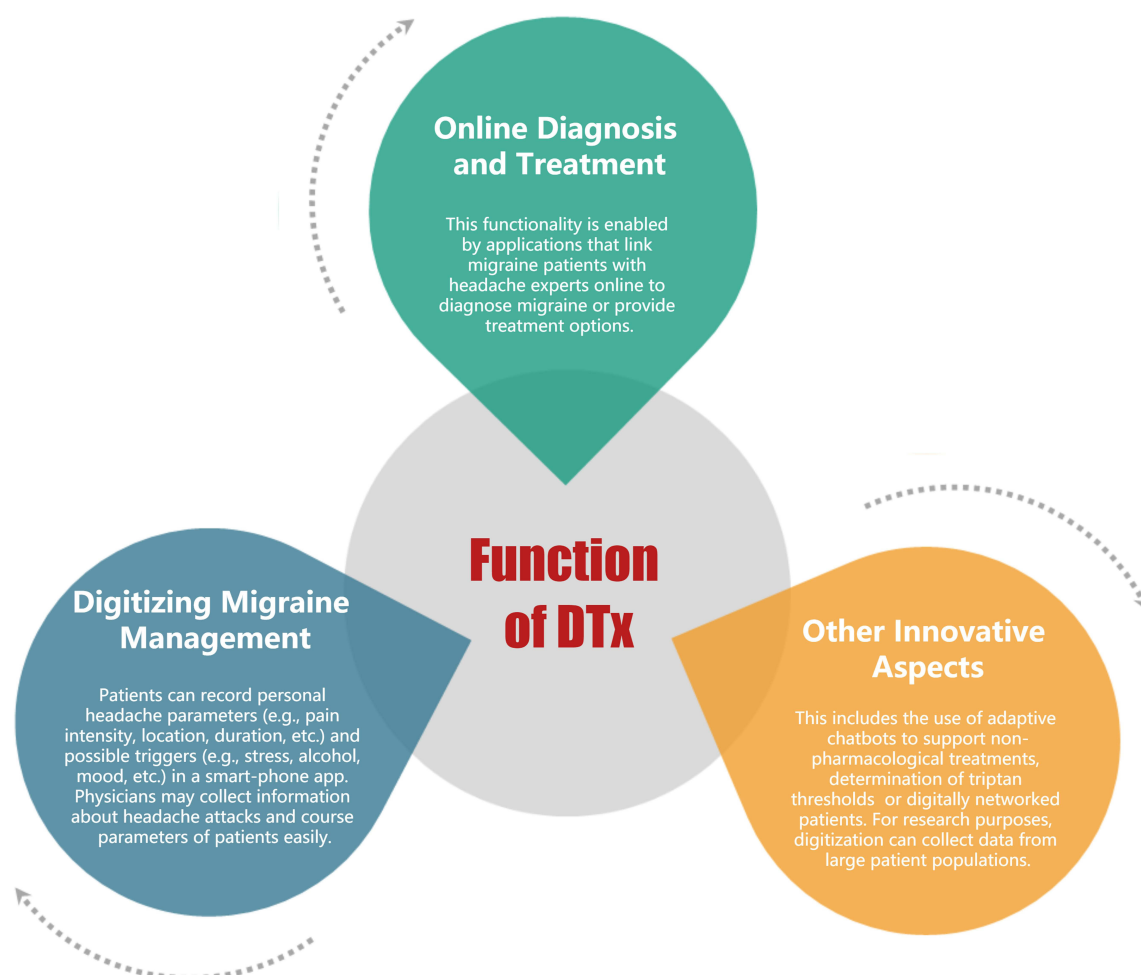


Figure 1 Functions of DTx in migraine management.

minimizes the additional demand for hospital infrastructure that is already over-saturated.¹⁷ DTx has been helpful in the COVID-19 era in the daily management of migraine as it breaks down physical barriers between patients and headache experts. In this paper, we reviewed the latest research on DTx in migraine management, identified challenges, and outlined future trends. The primary goal of this mini-review is to draw the attention of the academic community to DTx in migraine management.

DTx in Migraine Management

The use of computing power and the connectivity capabilities of smartphones, such as specific mobile applications, personalized patient education, digital cognitive behavioral therapy (dCBT), and virtual health coaches, are important features of digital therapeutics.^{18,19} Various applications of DTx in migraine management have been studied in recent years, including the usefulness of digital diaries and other digital migraine self-management tools in diagnosing and tracking migraine attacks, the efficacy and safety of digital cognitive behavioral therapy, and the usefulness of Internet/smartphone app-based surveys.^{20,21}

Digitizing Migraine Management Tools

Digitizing migraine management tools, particularly headache diaries, still predominate research on DTx in migraine management. Patients are allowed to enter personal headache parameters (eg, intensity, nature, pain location, and duration) and possible triggers (eg, stress, alcohol, and mood) in a digitizing paper-like form.^{22,23} A retrospective study found that the majority of patients wanted to use a smartphone diary app to assess what triggers versus relieves

Table 1 Main Clinical Trials, Meta-Analyses and Survey of DTx in Management Management

Author	Year	Design	Tool	Sample	Outcome
Schröder et al	2022	Retrospective cohort study	Digital health app	84	An individualized low-glycemic diet intervention combined with continuous online glucose measurements could be a promising approach for migraine prophylaxis. ⁴⁰
Lelleck et al	2022	Prospective observational study	sinCephalea	49	sinCephalea (a non-pharmacological digital migraine prophylaxis) induced therapeutic effects within the range of pharmacological interventions. ³⁹
Buse et al	2022	Two-arm observational study	GIER & REN	170	Combining guided intervention of education and relaxation with remote electrical neuromodulation (REN) treatment can improve therapeutic efficacy beyond that of REN alone. ²⁹
Ailani et al	2022	Real-World Analysis	REN	12,368	The real-world clinical data indicates that remote electrical neuromodulation (REN) provides an efficacious, stable, and safe treatment option for acute migraine, both as a standalone replacement of pharmaceuticals, as well as an adjunct to medications. ³⁰
van de Graaf et al	2021	Meta-analysis	Digital diaries, digital behavioral therapy, etc.	94,127	Many digital health tools for migraine patients regarding diaries have been described in the literature, their effectiveness has not been included in most studies. ²⁵
van Casteren et al	2021	Prospective observational study	E-diary	484	The E-diary, including algorithms differentiating headache and migraine days, was useful in diagnosing migraine. ²⁶
Minen et al	2021	Survey	Telehealth	225	Migraine patients were comfortable treating migraine patients via telehealth. ⁴³
Minen et al	2021	Single-arm prospective study	App-based PMR	51	Smartphone-based PMR introduced to patients who present to the emergency department for migraine is feasible and acceptable. ³⁸
Kuruvilla et al	2021	Survey	Social media survey	372	This study suggests the need for better education on the role of, and evidence for, complementary and integrative medicine (CIM) among headache care providers. ²⁸
Minen et al	2020	Retrospective study	mHealth app	288	The majority of patients wanted to use a smartphone diary app to assess what triggers versus relieves migraine. ²⁴
Hommel et al	2020	Single-arm observational study	Self-management digital therapeutic tool	36	Migraine Manager demonstrated the feasibility and preliminary efficacy of digital self-management tools for adolescents with migraine. ²³
Crawford et al	2020	Randomized control trial	dCBT-I	42	Digital cognitive behavioral therapy (dCBT) is effective in improving insomnia in patients with chronic migraine, and the study further suggested that dCBT is feasible and acceptable in migraine patients. ³⁶
Minen et al	2019	Single-arm pilot study	App-based PMR	51	The smartphone-based PMR intervention was associated with reduction in headache days. ³⁷
Friedman et al	2019	Randomized control trial	Synchronous video-based telemedicine	45	Telemedicine is a feasible mode of treatment and an effective alternative to in-office visits for follow-up migraine care. ⁴²
Drescher et al	2019	Web-based questionnaire	Web & smartphone app - Migraine Radar	1085	Saturday seemed to be the predominant day for migraine attacks for a greater proportion of participants (195 of 1085). ⁴¹
Dodick et al	2018	Modified Delphi study	Patient-facing smartphone-based migraine tracker	-	A digitizing system that captures critical data about migraine attacks and collects feedback from patients may offer benefits to both patients with migraine and clinical practitioners by facilitating more objective communication and optimizing management. ⁴⁴

migraine.²⁴ Although many digital health tools regarding diaries for migraine patients have been described in the literature, their effectiveness has not been included in most studies²⁵ (Table 1).

In addition to the simple diary with migraine tracking function, some management tools for diagnosing and managing migraines have been developed and researched in recent years. A single-arm observational study demonstrated the feasibility and preliminary efficacy of digital self-management tools for adolescents with migraine.²³ Furthermore, a prospective observational study revealed that the E-diary, including algorithms differentiating headache and migraine days, was useful in diagnosing migraine²⁶ (Table 1).

Digitizing Patients Education and Wearable Devices

To understand migraine attacks, patients must learn to distinguish between the cause of migraine, a special readiness of the brain to react, and the triggers of headache attack.²⁷ Complementary education via the Internet/smartphone app softens the strict boundaries of migraine patients' learning about migraine. A web-based survey suggested the need for better education on the role of complementary and integrative medicine (CIM) among headache care providers.²⁸ Furthermore, a recent two-arm observational study revealed that combining the guided intervention of education and relaxation with remote electrical neuromodulation (REN) treatment can improve therapeutic efficacy beyond that of REN alone.²⁹ The real-world clinical data indicates that remote electrical neuromodulation (REN) provides an efficacious,

stable, and safe treatment option for acute migraine, both as a standalone replacement of pharmaceuticals, as well as an adjunct to medications³⁰ (Table 1).

Digitizing Non-Pharmaceutical Migraine Prophylaxis

Cognitive behavioral therapy (CBT) and biofeedback are recommended for the preventive treatment of migraine.^{31,32} The aim of CBT is to reduce its frequency and intensity.²⁷ To achieve this goal, the general relationship between patients and clinical practitioners must be changed fundamentally.²⁷ Digitally delivered behavioral treatments for headaches are a potential solution for barriers to access.³³ Evidence-based studies on the effectiveness of digitized CBT (dCBT) using high-quality software and focusing on treatment have been investigated.^{34,35} A recent randomized control trial reported that dCBT is effective in improving insomnia in patients with chronic migraine, and the study further suggested that dCBT is feasible and acceptable in migraine patients.³⁶ Moreover, progressive muscle relaxation (PMR) is an under-utilized Level A evidence-based treatment for migraine prevention.³⁷ A single-arm pilot study revealed that the smartphone-based PMR intervention was associated with reduction in headache days.³⁷ In the following study, the team further proved that the app-based PMR is effective and feasible in emergency settings.³⁸ In addition, a prospective observational study revealed that a non-pharmacological digital migraine prophylaxis tool, sinCephalea, induced therapeutic effects within a range of pharmacological interventions.³⁹ In addition to dCBT, a retrospective cohort study suggested that an individualized low-glycemic diet intervention combined with continuous online glucose measurement could be a promising approach for migraine prophylaxis⁴⁰ (Table 1).

Internet/Smartphone App-Based Questionnaire and Survey

Digitization not only provides online tools for migraine patients, but can also go beyond this, opening up new possibilities through the advantages of the Internet to collect anonymized data from large patient populations about migraine attacks and course parameters for research purpose.⁴¹ Some researchers have successfully obtained migraine patient information using this method. Drescher et al conducted a web-based questionnaire to study individual migraine attack patterns, and the study revealed that Saturday seemed to be the predominant day for migraine attacks in a greater proportion of participants.⁴¹ In addition, a randomized control trial was conducted using synchronous video-based telemedicine.⁴² Friedman et al suggested that telemedicine is a feasible mode of treatment and effective alternative to in-office visits for follow-up migraine care.⁴² Furthermore, another survey conducted through telehealth noted that patients were comfortable treating migraine patients via telehealth⁴³ (Table 1). In addition to the research purpose, it was also suggested that a digitizing system that captures critical data on migraine attacks and collects feedback from patients may offer benefits to both patients with migraine and clinical practitioners by facilitating more objective communication and optimizing management.⁴⁴

Current Challenges and Perspectives of DTx in Migraine Management

Medical regulators have generally adopted a cautious and strict attitude towards DTx, requiring digital health companies to provide reliable evidence such as randomized controlled trial results to ensure the safety and efficacy of DTx.⁴⁵ Meanwhile, DTx is a field in rapid development but still in its infancy, and DTx interventions (eg, applications, wearable devices, etc.) are rapidly developed and updated. Consequently, the literature published over the past five years is considered to be more representative. Peer-reviewed journal publications published between January 1, 2018, and July 31, 2022, were collected from various databases, including PubMed, Embase, and Google Scholar. The search was conducted using keywords, such as digital therapy, smartphone-based apps, telemedicine, digital diaries, and migraine. No language restrictions were applied. A total of 25 papers discussing DTx in migraine management over the past five years were identified. The number of publications is plotted by year (Figure 2). Notably, an initial upward trend in publications on DTx in migraine management has been observed over the past five years (Figure 2).

In addition, the current development of DTx still faces the following obstacles. (1) There is currently no consensus definition of DTx. Clinical studies of DTx lack standardized interventions, resulting in heterogeneity among the studies. (2) Similar to traditional treatments, DTx has not fundamentally addressed the problem of low patient compliance with migraine management. (3) Although the digital networking of patients information can facilitate access to research data,

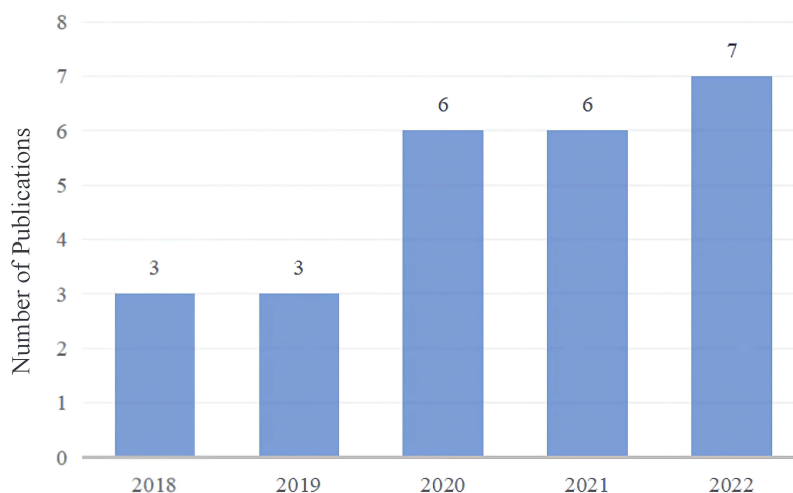


Figure 2 Number of publications in the field of digital therapy in migraine management over the last five years. “2022” only covers the first seven months of 2022.

it also generates a large amount of redundant medical data, and the interpretation and screening of these data brings a heavy workload to doctors.

As an emerging treatment method, DTx provides a novel treatment option for long-term migraine management and has the potential to significantly impact global healthcare services and the pharmaceutical markets.^{10,46,47} With the growing interest in DTx from medical societies, its potential is expected to be revealed in the near future.

Conclusions

DTx has been used in many aspects of migraine management and ideally enables a direct link between practitioners and patients to soften the strict boundaries between outpatient clinics and patients in their day-to-day care. Clinical research on DTx is an emerging field, and the number of publications on the topic of “DTx in migraine management” has revealed an initial upward trend. Most studies support the feasibility or effectiveness of DTx in tracking and recording migraine attacks, self-diagnosis, treatment, and long-term management guidance. However, further large-sample studies are needed to confirm the effectiveness of DTx in migraine management.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors have no conflicts of interest to declare for this work.

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