INTRODUCTION

The field of digital therapeutics (DTx) has grown steadily over the past decade. The academic term “digital therapeutics” was first proposed in 2015 and defined as “evidence-based behavioral treatments delivered online that can increase accessibility and effectiveness of healthcare” [1]. In 2017, an application for managing substance use disorder known as reSET® (Pear Therapeutics) received authorization from the United States (US) Food and Drug Administration (FDA) [2]. Before reSET®, other digital healthcare software included Bluestar® (Welldoc Inc.), a type 2 diabetes management mobile application that received FDA authorization in 2010 [3]. Nevertheless, reSET® is considered the earliest FDA-approved DTx, as it was the first for which treatment benefits were claimed at the time of approval, with clinical trial evidence provided to support this claim. Treatment with reSET® involves a prescription from a physician, similar to traditional medical treatment.

Since the approval of reSET®, DTx have received increasing attention as a new paradigm for medical treatment. The purpose of this article is to examine the current and future roles of DTx in the field of sleep medicine. We first review definitions and background of DTx and then discuss use of DTx developed for insomnia and other sleep disorders, use of DTx for patients with sleep disorders who have psychiatric comorbidities, and regulations for DTx in various regions of the world. We review studies comparing DTx with existing treatments, describe challenges associated with the use of DTx, and discuss the future of DTx in sleep medicine.

DEFINITION AND BACKGROUND OF DIGITAL THERAPEUTICS

DTx are defined as products driven by high-quality software programs that provide evidence-based interventions to prevent, manage, or treat a medical disease. DTx are receiving increasing attention as a new therapeutic approach. Several DTx for insomnia are on the market, some of which have received approval by national regulatory agencies. DTx for insomnia are usually based on cognitive behavioral therapy for insomnia. No DTx for other sleep disorders, such as narcolepsy or sleep-related breathing disorders, have received regulatory authority approval as a medical device. DTx have the substantial benefits of being accessible and relatively low-cost. However, several issues related to DTx have not yet been fully resolved, and discussions regarding DTx are still in the early stages. To use DTx for sleep disorders as an effective treatment option in the future, considering the current status of DTx is necessary. This review discusses definitions and background of DTx; specific DTx for insomnia that have been developed; use of DTx for sleep and related psychiatric comorbid symptoms; global regulatory processes for DTx, including prescribing and medical billing issues; and remaining challenges regarding the use of DTx.

Keywords: Digital technology; eHealth; Software; Insomnia; Sleep disorder
promote optimization of their lifestyle, wellness, and health. DTxs are a subdivision of digital health. While digital health includes both hardware and software, DTxs involve only software. In this regard, DTxs can be considered a type of software as a medical device (SaMD), a term referring to software used for one or more medical purposes, without accompanying hardware [6]. The key characteristic that distinguishes DTxs from digital health or SaMDs is the purpose of DTxs: to prevent, manage, or treat medical diseases [4]. Because DTxs are used for therapeutic purposes, they require a higher level of evidence than other digital health products aimed at pure-play adherence, diagnostics, and telehealth [4]. As such, DTxs can be expected to have a higher level of clinical effects than general wellness digital health products.

The Digital Therapeutics Alliance (DTA) classifies a DTx into three categories according to its purpose: treatment, disease management, and health promotion [4]. DTxs for therapeutic purposes require validation of treatment efficacy and safety by a third party and may result in charges to insurance companies through prescriptions from medical professionals. DTxs for health promotion have fewer issues with medical billing, and validation issues related to effectiveness or safety are relatively less important. DTxs for promoting health have a lower risk of medical claims than DTxs for other purposes.

DTxs can also be classified as a digital companion or replacement therapy [7]. DTxs as a digital companion are products that provide therapeutic effects through indirect methods that improve convenience and effectiveness by supplementing traditional treatments, such as pharmacologic treatment. This form of DTx is used with traditional, existing treatments. Conversely, DTxs as a replacement therapy are products with their own therapeutic benefits. This form of DTxs can replace conventional treatment or be used in combination with usual therapy to enhance treatment effects. For any purpose, clinical evidence of therapeutic effects is required for products to be called DTxs.

**DIGITAL THERAPEUTICS FOR INSOMNIA**

Cognitive behavioral therapy for insomnia (CBTi) is recommended as first-line treatment for insomnia in many treatment guidelines. CBTi is a well-established effective nonpharmacologic therapy that adjusts maladaptive cognition and behaviors related to insomnia [8]. Despite similar or superior treatment effects when compared with pharmacologic therapy [9], CBTi has the disadvantages of lower accessibility and higher costs [10,11]. To resolve these limitations, ongoing efforts have focused on providing CBTi through online processes, which have shown significant results [10]. Most DTxs for insomnia are based on digital CBTi (dCBTi).

dCBTi is emerging as an ideal alternative to conventional treatment. It is provided through an online platform, with the content tailored according to different types of interactions and algorithms [12]. dCBTi is available in a number of versions. One version functions as ancillary therapy to enhance the treatment effects of existing face-to-face CBTi, another version provides feedback from a therapist online, and yet another version provides feedback based on a fully automated algorithm [13]. Advantages of dCBTi include immediate support, flexible scheduling, personalized content, and non-face-to-face interactions. The ability to visually present treatment progress or review past data is another advantage of dCBTi [13]. However, dCBTi relies entirely on the user’s motivation and involves self-training that is performed alone without a therapist or other participants, which can lead to lack of adherence and ultimate treatment failure. Over-generalized advice, technical problems, and privacy or confidentiality issues are other major drawbacks [12]. In addition, most published randomized clinical trials have focused on a specific race, people living in a specific continent, or middle-aged individuals. Very few randomized studies have been conducted in Asia, a continent with high smartphone and internet usage [10]. Further studies involving populations of different cultures, ethnicities, and ages are required. Additionally, many studies have been conducted in patients with only mild to moderate insomnia and have not reported longer-term results after the dCBTi study period (typically 4–24 weeks) [14,15]. The effects of dCBTi compared with conventional CBTi are also unclear, as most studies compared dCBTi with wait-list or sham controls. Of the very limited number of randomized clinical studies comparing dCBTi with face-to-face CBTi, one showed similar results between methods, whereas the other reported inferior results with dCBTi. Of note, the study with similar results demonstrated non-inferiority for only the primary outcome, with dCBTi being inferior for secondary outcome variables, including adverse events, remission, response rate, depression, and use of sleep medication. The increase in medical claims related to DTx prescriptions should also be considered. As with prescriptions for drugs or other health care, prescribing DTx will increase overall health care costs. However, the effects on the opportunity cost of accessing other health care are unclear and will likely be controversial.

Several DTxs for insomnia are currently on the market. Somryst® (Pear Therapeutics), an FDA-approved DTx for insomnia, is a mobile application based on CBTi, which consists of 6 core sessions for a total of 9 weeks of therapy [16]. Treatment effects of Somryst® were demonstrated in a randomized controlled trial that showed significant improvement of insomnia severity index (ISI) and sleep indicators, including sleep onset latency (SOL) and wake after sleep onset (WASO), compared with a patient education group [17]. SleepioTM (Big Health Inc.) was developed jointly in the United Kingdom (UK) and US and is available as a computer program or mobile application. SleepioTM is marked by Conformité Européenne (CE), indicating that it fulfilled safety, healthy, and environmental protection requirements of the European Union (EU) [18]. It consists of 6 core sessions for a total of 6 weeks of therapy. The therapeutic effects of SleepioTM were verified in a randomized controlled trial showing significant improvements in sleep indicators, including sleep efficiency and daytime func-
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USE OF DIGITAL THERAPEUTICS FOR SLEEP WITH PSYCHIATRIC COMORBIDITY

CBTt has demonstrated effectiveness in reducing insomnia symptoms in patients with psychiatric comorbidity [32], and these benefits persist with dCBTt. Effectiveness of dCBTt has been reported for depression, anxiety disorder, and substance use disorder [33,34]. Studies have also shown that CBTt improves comorbid psychiatric symptoms, including depression and anxiety [32,35,36], and dCBTt has likewise been demonstrated to improve comorbid depression and anxiety symptoms [33,37]. Use of Somnyst® significantly improved depression symptoms evaluated with the Patient Health Questionnaire-9 (PHQ-9), with benefits persisting for 6 months after treatment in patients with comorbid depression and insomnia [38]. In a study of Sleepio™, 68% of people with clinically significant elevated pre-treatment PHQ-9 or Generalized Anxiety Disorder-7 (GAD-7) scores had PHQ-9 or GAD-7 scores within the normal range after treatment [39]. Sleepio™ has also been reported to significantly decrease Beck Anxiety Inventory (BAI) scores [40]. Another randomized controlled study demonstrated that Sleepio™ significantly reduced the ISI and Quick Inventory of Depression Symptomology [41]. Furthermore, Sleepio™ has been shown to improve quality of life [42] and cognitive function [43]. Improvements in PHQ-adolescent version and GAD-7 were also reported in a pilot study using Sleep Ninja™ [24].

GLOBAL REGULATORY PROCESSES FOR DIGITAL THERAPEUTICS

Discussions are ongoing regarding the establishment of standards for DTx regulation. DTA has stated that DTx used to treat or manage disease require third-party validation of effectiveness and safety claims by a regulatory or equivalent national body [4]. Since DTx have the characteristics of both SaMD and therapeutic agents, it is difficult to use existing regulatory methods for either medical devices or drugs. Several considerations exist regarding the regulation of DTx. Because DTx are in the form of software, and verifying practical functional methods, rather than operation methods, of these devices is necessary [4]. Also, because of the rapidly developing nature of digital technology, DTx products could possibly be outdated if the regulatory review period is prolonged. However, an excessively simplified regulatory process may result in insufficient clinical evidence [44]. In addition, because DTx are software, they require continuous updates and maintenance, which may lead to multiple regulatory review processes. Because DTx handle personal information of patients, cybersecurity must also be considered [45]. Lastly, although most DTx provide non-invasive treatment, and the possibility of toxicity or side effects is likely lower than that for other medical devices or drugs, confirming that there are no unexpected toxicities or side effects when DTx are used as therapeutic modalities is critical [5].

Regulatory methods for DTx are being established and developed worldwide. In the US, DTx have been granted approval or cleared by the FDA following submission of superiority trial data via either the de novo or 510(k) pathways, which are traditional regulatory process for medical devices [45]. The first FDA-approved DTx, reSET® (for substance use disorder), was certified via the de novo pathway, but the FDA subsequently recognized the limitations of regulating DTx using traditional regulatory processes for medical devices. It established a guidance for the clinical evaluation of SaMDs in 2017 [46], and a precertification pro-
program for new approval of DTx in 2018 [47]. This guidance considered DTx as having a higher risk of adverse effects than other SaMDs because of its therapeutic purpose and thus required DTx effectiveness and safety to be verified by independent clinical evidence. The pre-certification program for DTx was established to address concerns that prolonged regulatory processes would slow the speed of developing DTx and that regulation of maintenance and updates following product launch would be required. The core concepts of the pre-certification program are evaluation of the development process and manufacturing company, rather than evaluation of each program, and replacement of clinical evidence from clinical trials by real-world evidence, which can be obtained through real-life user experience. In the pre-certification program, which began as a pilot program in 2019 involving 9 companies, the overall authentication process involves evaluation of 5 core items: product quality, patient safety, clinical responsibility, cybersecurity responsibility, and proactive culture [47]. Somryst® was approved by the FDA via both the 510(k) pathway and precertification program.

The EU strengthened its SaMD regulations in 2017 by including SaMDs as a medical device in the new Medical Devices Regulation (MDR) released that year [48]. According to this new MDR, some software previously considered “low risk” could be up-classified, requiring notified body approval [49]. SaMDs were also required to receive CE marking, similar to other medical devices [50]. Overall, the regulatory processes for SaMDs were tightened in the revised MDR. Because of concerns that this revision could represent an overly burdensome regulatory process for rapidly changing digital health, the National Health Service-X (NHS-X) unit was created in the UK in 2019 to guide best practices for NHS technology, digital information, and data, including data sharing and transparency [51]. Under the leadership of NHS-X, all digital health products in the UK were classified according to the potential risk to patients, and guidelines were provided for minimum evidence requirements [52]. If a digital product is selected as a target by policy priority, the manufacturer could obtain support via an accelerated access pathway, allowing the product to be approved quickly [53]. In 2019, the Digital Healthcare Act was established in Germany, after which fast-track approval for digital health applications (DiGA) began [54]. By 2021, a total of 11 products were approved DiGA, including Somnio™.

In Korea, regulatory processes have been established for rapid and appropriate DTx regulation. In 2019, the Ministry of Food and Drug Safety (MFDS) announced guidelines for SaMD regulation and approval to improve the safety of the SaMD development and related contents [55]. The next year, the Medical Device Industry Promotion and Innovative Medical Device Support Act was announced by MFDS. With this act, some data required for approval could be exempted if the manufacturer submitted proper certification, similar to the precertification program in the US [56].

Discussions are ongoing to establish guidelines for the prescription and billing of DTx. DTA guidelines recommend that DTx designed for treating diseases be used with a doctor’s prescription [4]. Use of Somryst®, a DTx approved by the US FDA, requires a physician’s prescription [16]. However, a clear standard has not yet been established with regard to the billing for DTx in the US. If the product is recognized as sufficiently valid and necessary, a review of insurance coverage will occur, which is the same process used for existing medical devices. To qualify for insurance reimbursement, manufacturers should submit an application with documents indicating the target population, purpose of use, and instructions for use [57]. In the UK, it is recommended that medical devices used for treatment purposes be prescribed by a physician [52]; however, Sleepio™ can be used without prescription by focusing on improvements in life style, including sleep [18]. Billing for DTx use is determined by collecting and evaluating data after product review in the UK [58]. In Germany, DTx approved via DiGA can be prescribed and billed for. For the first year after release of a product, the manufacturers can set the medical fee; thereafter, the fee may be changed by negotiation with German health insurance [54,59]. In Korea, no guidelines exist regarding the prescription or billing of DTx. As with existing medical devices, all decisions about how to charge and pay for DTx should consider various factors, including the opinions of experts, academic opinions, medical feasibility, clinical significance and therapeutic effectiveness, cost effectiveness, cost burden to the patient, and social benefits [60,61].

**CHALLENGES OF DIGITAL THERAPEUTICS**

The main target of DTx is chronic disorders, including insomnia. This is because health-risk behaviors and poor adherence to medical regimens can have major effects on the development and management of chronic disease. Self-regulation (the ability to manage cognitive, motivational, and emotional resources that enable individuals to act according to their long-term goals) is an important determinant of health behavior and outcomes. As self-regulation is a major subject of interventions for chronic disease, engagement in the use of DTx is a very important consideration. Although the abovementioned dCBTi is effective not only for insomnia symptoms but also for psychiatric symptoms, such as depression and anxiety, these results were obtained under specific experimental conditions and may not reflect real-world situations. It is generally known that use of DTx in real-world settings is decreasing, and engagement with DTx remains the most important issue to address [62]. Studies on the treatment of depression and anxiety with DTx found that participants’ adherence to internet-provided cognitive behavioral therapy varied from 6% to 100% [63]. Similarly, reviews of DTx as a digital companion found that engagement varies widely [62,64] and may be lower than that of traditional treatments [65]. User engagement refers to the user’s understanding and ongoing interaction with digital interventions. User engagement includes expression of interest (such as registering for DTx), active use of DTx (such as participation in research), and contin-
used use of DTx, even after the minimum period required for research participation has elapsed [66]. User factors that can influence engagement include demographic characteristics, personality, psychiatric comorbidity, attitude toward mobile application use, and familiarity with mobile devices. Program factors that may influence engagement include the quality of the content provided through DTx, method of delivery, level of recommendations, and presence of peer support. Technical factors include confidentiality and privacy issues, as well as how accurately and easily the program functions.

**SUMMARY**

As a software-based therapeutic intervention, DTx represent a new treatment paradigm. DTx provide opportunities for healthcare professionals to offer digitalized, personalized medicine to help patients manage their own diseases. This characteristic of DTx as a form of personalized medicine could be especially important in the field of sleep medicine because sleep disorders are typically chronic diseases closely related to a person’s lifestyle. Today, the most well developed and widely used DTx in the sleep field are DTx for insomnia. Considering the possible side effects of long-term use of hypnotics and the low accessibility of traditional CBTi, DTx for insomnia could be a particularly useful approach for treating chronic insomnia.

However, a number of issues remain unclear regarding the clinical use of DTx in the field of sleep medicine. Firstly, DTx for sleep disorders other than insomnia have not yet been sufficiently developed. Further research is necessary to provide sufficient clinical evidence of the effectiveness and safety of the treatment effects of DTx for these other disorders. Secondly, issues related to regulation of DTx have not yet been clarified. Each country or region has established a system for regulation, prescription, and medical billing of DTx, but these systems are still in the early stages. Lastly, user engagement must be considered a core feature when developing DTx. Because of their focus on cognitive and behavioral modifications, DTx typically require more time and effort than pharmacotherapeutics, which may limit their use in the real world if user engagement is inadequate. Nevertheless, with continued interest and efforts of healthcare professionals in the field of sleep medicine to address the issues related to DTx, these technologies could become widely used as an effective therapeutic option for sleep disorders in the future.

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**Conflicts of Interest**

The authors have no potential conflicts of interest to disclose.

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