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DIGITAL THERAPIES AND IMPROVING THE HEALTH RHYTHM

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Abstract : A relatively young subfield of digital health, digital therapeutics (DTx) relies significantly on computer programs. For clinical pharmacologists, this is incredibly interesting! In order to supplement existing medications, the US FDA has approved multiple DTx. Also included are guidelines for "prescription medication-related software." This has the potential to open the door to novel digital therapies that incorporate medication, leading to exciting drug-device combination products (DTx functions as a medical device). Since DTx are comparable to common medications, we can apply concepts from clinical pharmacology to them. Here is a great chance to help develop, implement, and oversee DTx regulations. For instance, cheaper biosimilars combined with DTx solutions are posing a serious threat to Humira® (adalimumab) in the market**.**

IndexTerms **- DTx, digital health, app based health care, medical device.**

I. INTRODUCTION

Through a "software as a therapeutic device" (SaMD) supervisory pathway, DTx are mobile therapeutic applications that have been approved by the US Food and Drug Administration (FDA) or another regulatory agency to treat or prevent specific medical conditions [1]. Combining disease treatment and prevention through pharmaceutical and digital health innovations is the most effective way to lessen the impact of chronic medical disorders [2]. Chronic illnesses affect about half of all Americans, contributing to 86% of the nation's yearly healthcare expenses. Numerous chronic conditions, including type 2 diabetes, hypertension, asthma, chronic obstructive pulmonary disease (COPD), and certain mental health conditions, including anxiety and depression, can be treated with digital therapeutics (DTx) applications. The majority of people with type 2 diabetes live in developing nations like China and India. Therefore, integrating digital technologies into the healthcare system may be a catalyst for enhancing public health generally [3].

DTx products are manufactured through regulated clinical research and have regulatory approval for particular indications. They are also prescriptible and reimbursable. Since DTx is composed of software and algorithms rather than a chemical or biological material, its active principle differs from that of a conventional medication. Drug + digital combination therapies can be developed in two steps:(1) Despite being a medical device, DTx was created using the "software as a medical device" regulatory process; (2) a DTx-Rx combo product was created [4].

II. COMPARISON TO PHARMACOTHERAPY.

Most clinical pharmacologists will be very interested in DTx when it is used to treat diseases that require the application of pharmacological concepts to the development and optimization of treatment regimens. Pharmacotherapy and DTx are comparable because they are both medical treatments. The primary difference, though, is that the therapeutic effects of DTx persist even in the absence of any active ingredient in the bloodstream [5].

Table 1: Conceptual comparison of pharmacotherapy and digital medicines from the perspective of clinical pharmacology

	Pharmacotherapy	Digital therapeutics
Pharmacokinetics		
Root of drug administration	Interface with user, panel for input to the systematic approach to management	circulation
Exposure	Dosage, dosing interval	Using time, frequency, duration
Elimination	Metabolism and Excretion. Described by half-life or clearance parameter	Hard to be quantified
Pharmacodynamics		

Mechanism of action	clear	unclear
Hysteresis or Tachyphylaxis	Can occur	Can occur
Safety		
Serious adverse events	Can occur	Less likely
Hypersensitivity	Can occur	None
Adverse Effect	Toxicity related to target or off-target of the drug	Related to using mobile device (eye, neck, finger, back pain) Other CNS effects (disturbance on sleep, etc)
Development and Clinical Use		
Therapeutic area	Not restricted	Mostly on neuropsychiatric disease
Development Strategy	Unmet medical needs Target identify	Amplification of existing non-pharmacological therapy

III. Technologies in DTx

After 2019, publications on digital therapeutics arranged the market's concept and trends and listed the kinds of cutting-edge technologies that could be used for further advancement. The primary viewpoints of developers and real service users can be used to assess the technology utilized in digital therapeutics. The key steps from the perspective of the DTx service developer are displayed on the upper side, along with the technologies that should be taken into account for each stage of implementation. Conversely, the technologies encountered from the perspective of the service user are displayed on the down side. The technologies that must be taken into account for DTx development and commercialization are compiled into several key categories in this section [6].

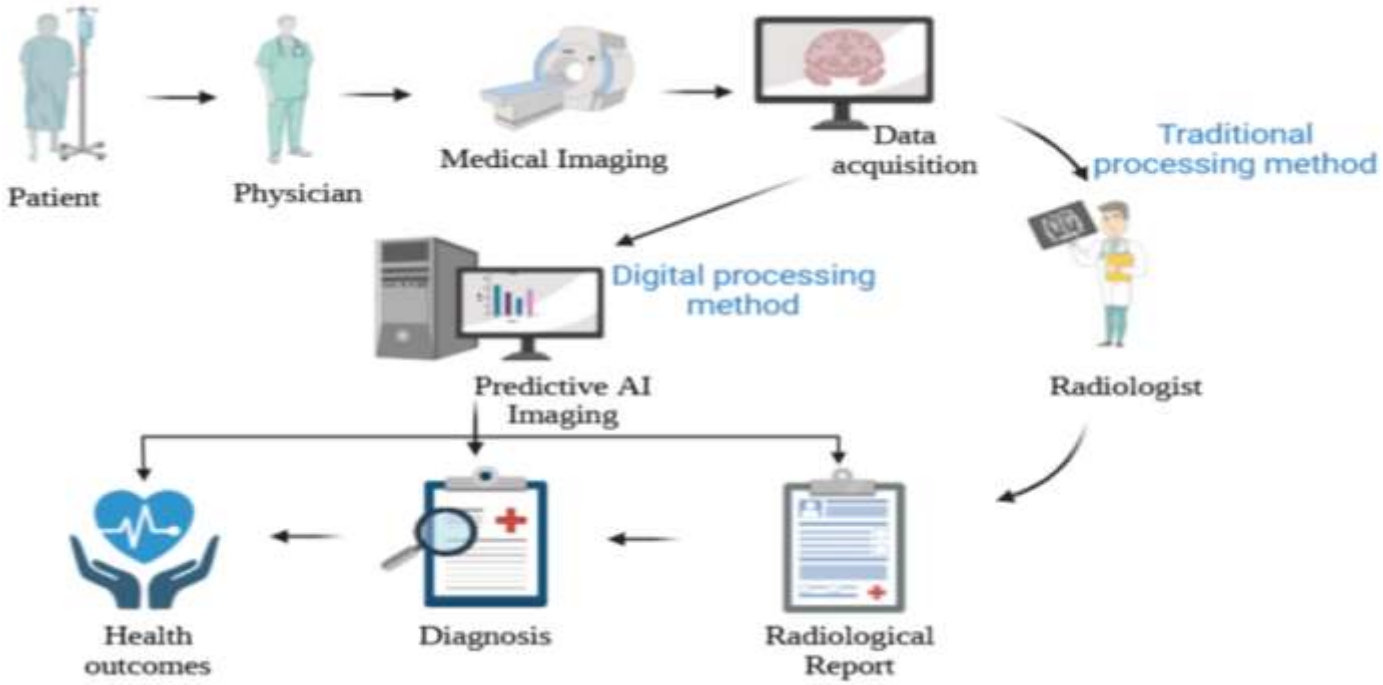
Development of Digital therapeutics	Digital therapeutics service
Treatment program design : program based on medical mechanism of action	Service subscription : use DTx service for specific disorder
Research data collection : data for program generation and evaluation	User data provide : provide required dataset to the system
Research data preprocessing : the development of user classification systems and data management algorithms from a data privacy standpoint	User classification : DTx classifies the user to give optimized program
Research data analysis & classification : generating analysis AI, ML algorithms for data feature groups, and user classification system	Personalized intervention : use DTx programs that personally designed for the user, based on the analysis results from user dataset
Personalized intervention design : algorithm design to match treatment programs and user classification results	Feedback to users : get information about the changes of user status

IV. Smarter Treatment and Recent Advancements:

According to George Savage, a Californian physician and co-founder of Proteus Digital Health, "efficacy is what a drug can do; effectiveness is how it works in the real world and right now we have a large efficacy-effectiveness gap." Approximately 25% to 50% of people worldwide do not take their prescription medications as directed, which is the main issue. An estimated $289 billion is spent annually on this, which has been linked to 125,000 deaths in the US alone. These can be reduced by using digital therapies, which use sensors to track user behaviour and document drug reactions. "This can be compared to a digital nurse," Savage says [7]. At the moment, the vast majority of digital therapeutics products available on the global market are proprietary software, such as mobile applications or medical platforms. According to national and international standards, an app called "Hypertension Digital Therapeutics" encourages lifestyle changes for non-pharmacological treatment elements that have been demonstrated to successfully lower blood pressure [8].

Among the few other digital health platforms and solutions that benefit both patients and physicians are digital stethoscopes that come with an electrocardiogram (ECG). Electronic medical records can be connected to these devices. the development of computational and experimental techniques to predict and evaluate responses to multimodal tumor therapy by combining 3D bioprinting and machine learning in a therapeutic context. Additionally, this integrative approach enabled the examination of the intricate tumor-immune microenvironment properties [9].

Fig : Digital therapies technique [13]



V. Distinctive Features of DTx Clinical Trials

Blinding for DTx is frequently challenging. A placebo medication that is exactly the same shape as the active treatment medication is frequently used in traditional drug clinical trials. However, a "placebo" is frequently impractical or impossible because DTx products are software in a variety of forms. Rather, a "sham control," which is sometimes employed in assessments of medical devices, is put into practice. Clinical trials are instead carried out using an open-label design with regard to the treatments because it is frequently challenging to establish blinding of the sham control. Blinding cannot be used unless a distinct sham control is created, especially when the two treatment groups are conventional therapy versus conventional therapy plus DTx

Furthermore, there are several types of comparators in DTx. As previously stated, a sham control is frequently used in DTx trials. Unlike the placebos used in drug trials, the sham control for DTx trials can vary widely. Sham controls can be designed so that only the auxiliary function remains after the primary components of the intervention are eliminated or altered. For instance, Somryst from Pear Therapeutics employed HealthWatch, a different piece of software without a sleep aid effect, as a sham control. Only minor components of the software being tested, such as the interactive interface, were included in the software's design [10].

VI. Commercialization of DTx

reSET is a prime example of a commercially available DTx (Pear Therapeutics Inc., MA, USA). The first interactive DTx approved by the FDA for use in cognitive-behavioral therapy for patients with drug and alcohol addiction is called reSET. Based on the findings of a patient self-questionnaire, reSET offers both in-person treatment with medical staff and a professional online counseling service. Moreover, EndeavorRx (Akili Interactive Labs Inc., MA, USA), a DTx for pediatric ADHD, has received FDA-510(k) clearance and a CE mark after proving that it can raise a patient's attention index (API) by stimulating and activating the prefrontal cortex through video games.

When used with asthma and COPD patients, respectively, Teva Pharmaceuticals' Propeller Health (ResMed (Propeller Health), WI, USA) and ProAir Digihaler (Teva Pharmaceuticals Inc., NJ, USA) medication reminders with inhalers have been shown to reduce inhaler use by 79% and have received FDA-510(k) certification [11].

VII. Evaluation with Real-World Data

Claims-based clinical evaluations can assess long-term clinical effects that clinical trials may not be able to assess. Several cases have been identified in which retrospective data was used to evaluate DTx. A cost-effectiveness analysis of Pear Therapeutics' reSET and reSET-O was conducted on 351 opioid use disorder patients using post-market insurance claims data. Retrospective cohort data were used to analyze the therapeutic effects and economic impact of DTx for patients with type 2 diabetes and hypertension.

Long-term clinical effects are also assessed using DTx usage data for managing chronic conditions or optimizing medication compliance. NaturalCycle has received market approval for the management of menstrual cycles and contraception; an analysis of 18,548 person-years of menstrual cycle data from 22,785 women confirmed the accuracy of its menstrual cycle predictions. Based on information gathered from application users, Perx Health's mobile application to enhance medication adherence also verified improvements in medication compliance. Given that these DTx types could easily gather vast volumes of usage data, it is anticipated that usage data will be used more frequently in clinical evaluations [10].

VIII. Obstacles in the DTx Adoption Process

Despite the substantial evidence supporting their clinical value and the significant solutions they have provided to poorly addressed conditions, DTX entities have not yet made a significant impact on mainstream healthcare. The two primary barriers to wider adoption of DTx are:

- Inequitable incentives in the healthcare sector; and
- Difficulty differentiating DTx from the more general health and well-being applications in the general digital health market.

Millions of dollars have been invested, and as of 2017, there are over 315 thousand health-related applications on the market. It can be challenging for both medical professionals and consumers to distinguish between applications with established therapeutic value and those that are low-value or unproven. Many digital therapies now require adjustments to healthcare providers' workflows, which adds to the workload of physicians due to the volume of data and necessary interpretation. Furthermore, given the constraints of the US private health insurance market, payers would prefer to reimburse digital therapy upon achieving improved clinical outcomes within a certain time frame [12].

IX. Use of DTx in India

In order to improve their market presence and better handle the shifting market dynamics, numerous Indian pharmaceutical companies are currently altering their business models, strategies, and product portfolios.

Businesses are now aware of the amazing value proposition that DTx's goods and services provide. It is thought that DTx services could lower the cost of producing drugs while also benefiting insurers by enabling them to tailor their offerings to the requirements of their clients. DTx is still uncommon in India, though, and some businesses intend to invest and enter the DTx market. For example, a major Indian pharmaceutical company wants to make it easier to treat cardiovascular conditions with prescription medications and AI-powered digital treatments [12].

X. DISCUSSION AND CONCLUSION

10.1 Discussion

As computer technology and software platforms like mobile applications proliferate globally, human disease diagnosis and treatment approaches are also evolving in a novel way called digital therapeutics. By 2025, the DTx market is anticipated to grow to USD 7.1 billion. Research on DTx, however, has only examined the efficacy of its own clinical solutions or the constraints of clinical regulation thus far. Consequently, ongoing development will be required to offer the best solutions to satisfy the rising demand.

From gathering user data for DTx development and service to returning treatment to the user, the field is progressively evolving through the use of the newest technologies. Data anonymization, deidentification, and federated learning are used for secure data processing; feature extraction is used to observe hidden data characteristics; various machine learning analyses are used for effective outcomes; and recommendation systems are used to give users optimal treatment processes. In this manner, a new medical platform for the target disease is completed by integrating the technologies at every stage.

As it approaches the start of clinical trials in the Republic of Korea, the DTxplatform for major depressive disorders described in this paper is presently undergoing software certification in the development stages. Since it is outside the purview of the overall architecture introduction, specific details about the types of extracted data features, instances of tailored treatment plans, and the precise number of classes used for the DTx user classification were not revealed in this paper.

10.2 Conclusion

In contrast to traditional clinical approaches, the market for digital therapeutics offers sophisticated hardware and software-based solutions. It is essential to create a method that can dynamically provide the best management, treatment, and diagnostic solutions while also gathering data in a variety of scenarios. In order to educate solution developers and providers, this study compiled technologies and examples that must be used at every stage and suggested a comprehensive architecture.

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