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REVIEW ARTICLE

The Expanding Role of Digital Therapeutics in the Post-COVID-19 Era

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Abstract:

One of the few positive outcomes of the ongoing COVID-19 pandemic is that it has enhanced the pace of digitalisation of healthcare. Among various facets of digital health, Digital Therapeutics (DTx) is unique as it offers evidence-based interventions for preventing, managing, or treating specific disorders. It is different from wellness apps because it requires evidence from a clinical trial or real-world settings and is bound by regulatory approval and clearance. The DTx market is expected to grow exponentially in the post-COVID era, and there are multiple drivers for the same. After the onset of the pandemic, the viewpoint of various stakeholders of the DTx market, including the patients, prescribers, payers, and pharma industry, have changed significantly. Regulatory bodies have also started to realise the importance of DTx. This review provides an overview of the present status and future potential of DTx considering the COVID-19 pandemic.

Keywords: Digital therapeutics, COVID-19, DTx market, DTx regulations, mHealth, Digital health.

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1. INTRODUCTION

The arrival of the COVID-19 pandemic can be described as a watershed moment for the healthcare industry. It changed the manner of healthcare delivery dramatically, while exposing the lack of preparedness on the part of governments worldwide to adequately tackle a global healthcare emergency. Frontline health workers were involved in managing COVID-19 patients, but patients with other health conditions, especially chronic health conditions, experienced difficulties because of their in-clinic visits being postponed or avoided. At the same time, because the outcomes of COVID-19 among patients with comorbidities, especially obesity, heart complications, and diabetes, are worse than those without [1], these patients were asked to be additionally vigilant. The pandemic also brought a fair share of mental health disorders, including depression, anxiety, and withdrawals, and their management was a challenge because of the lack of face-to-face visits. These interconnected events have made healthcare providers look out for digital health solutions to tackle the ongoing health crisis [2].

Digitalisation of healthcare was already perceived to be inevitable, representing the future of healthcare delivery across the world. Numerous digital health solutions have been introduced for the purpose of general wellness and health upkeep, aiding in screening and diagnosis of diseases, providing therapy, and estimating prognosis. Out of all these solutions, the term 'Digital Therapeutics (DTx)' refers to evidence-based digital interventions that are intended to provide therapy for specific disease domains and work predominantly by inducing behavioural changes [3]. After the pandemic started, the adoption of DTx applications in various fields has accelerated many folds. The purpose of the present review is to explore the nature and development of various DTx applications in different therapeutic areas and their potential in the post-COVID era.

2. DIGITAL HEALTH AND STRIDE TOWARDS DTx

It is essential to understand the difference between a few related terms [3]. Digital health is a broad umbrella term that encompasses digital medicine, and within it, DTx. Digital health includes technologies, systems, and platforms that engage 'consumers' to maintain their lifestyle and wellness. Some digital health applications also support clinical operations or life sciences. Examples include wellness apps, telehealth, and clinical care administration and management tools. Digital health applications typically do not require clinical evidence. However, digital medicine applications usually involve evidence-based software or hardware products intended to measure (diagnosis) or intervene. Digital medicine products that are categorised as 'medical devices' require regulatory approval. Examples include digital diagnostics,

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remote patient monitoring software, and decision-support software [4].

DTx is different from both digital health and digital medicine in that DTx comprises evidence-based 'interventions' designed for the purpose of preventing, managing, or treating a particular disorder or health condition. In other words, DTx is like a digital pill which requires a similar level of clinical and real-world evidence, regulatory oversight, and clearance as it is required for conventional pharmaceutical products [4]. Thus, DTx products are not merely 'wellness apps' but are evidence-based specific interventions delivered digitally.

All DTx products generally adhere to a set of core principles. Their primary intention is to either prevent, manage, or treat a specific medical condition or a disease. This medical intervention delivered by the DTx product is driven by software and is delivered through software, complimentary hardware or medical device, medical service, or actual medication. Since there is collection and analysis of medical data of patients, DTx products must incorporate data privacy and security protections. All the efficacy is driven by evidence generated through randomized controlled trials (RCTs) or real-world data, which is reviewed, cleared, and approved by regulatory bodies as applicable. Finally, since DTx products are always evolving, they often collect and analyze real-world data and use analytics to improve product performance [5].

DTx is often described as being the 'fourth wave' of digital healthcare. The first three 'waves' hovered around remote patient monitoring, telehealth, and digital health applications but failed to generate a high level of patient engagement, and consequently, patients started to lose interest in the digital product rapidly. There were issues pertaining to integration into clinical workflows and acceptance by healthcare providers as well. Learning from these pitfalls, DTx solutions have tried to improve patient engagement and retention. With the incorporation of Artificial Intelligence (AI) and Machine Learning (ML) protocols, DTx products are always available, scalable, and adaptable based on patient requirements. Being evidence-based and bound by regulations, the acceptance by healthcare providers is also quite high. This is also aided by the fact that DTx solutions are not meant to replace doctors or conventional therapies but to augment and enhance their efficacy by means of behavioural modification of the patient. Thus, the approach of DTx is personalised, evidence-based, and comprehensive [6].

3. CHANGING PERSPECTIVE OF STAKEHOLDERS TOWARDS DTx

Ever since the onset of the pandemic, there has been a paradigm shift in the perception of DTx by various stakeholders. From the patient viewpoint, any innovation which can result in reduced interaction with the hospital and represents 'digitally delivered' healthcare, is a welcome innovation, and is viewed favourably. Further, for patients with chronic diseases, DTx offers a unique way in which not only their healthcare needs are fulfilled but also the risk of exposure to the SARS-CoV-2 by means of an in-person hospital visit is reduced. Finally, the realisation that the care provided by DTx can be more patient-centric and personalised than it has been with conventional management should further boost the interest of patients in DTx [7]. For the caregivers, DTx can potentially offer a way to connect, engage, and manage patients virtually, thus enabling them to focus their energies on patients who require a higher level of care and intervention. With an increase in DTx uptake, terms like home healthcare, self-care, and virtual care have become commonplace rather than an enigma. Finally, since interventions delivered through DTx are evidence-based, there is increased participation of caregivers who are also a part of the DTx product offering [8].

The payer mindset towards DTx has been described as 'fragmented', largely due to uncertainty on the part of the regulators to decide if DTx should be treated at par with conventional medicines. Reimbursement decisions for DTx products should follow a solid step in the categorisation of DTx products under a separate category and framing regulations that are unique for DTx products [9]. Multiple payment approaches have been conceptualised for providing patient access to DTx. Though the relatively easier model is the customer-pay model (wherein the patient pays to use DTx), the model in which all involved stakeholders are not felt left out is when the healthcare provider actively prescribes the DTx application, and there is reimbursement for the DTx product through the payer. In fact, the ground is well-set for reimbursement of DTx products, because by definition, DTx products are evidence-based and regulatory-bound. Thus, theoretically speaking, reimbursement of DTx products should be hassle-free. However, the ground reality is that the reimbursement scenario of DTx products is not as uniform or well-defined as it is for conventional therapies across the world [9].

On the part of the regulators, there is an increasing willingness to develop regulations and improve patient access for DTx products worldwide. Some regulators have been proactively bringing out guidelines and regulations for DTx products. In Europe, Germany became the first country to facilitate reimbursement for DTx products; the outlook for DTx regulatory clearance in other European countries, including Belgium and Italy, is also favourable [10]. The Korean ministry of food and drug safety published a guideline document for DTx products in August 2020 [11]. The USFDA has been proactive in formulating DTx regulations, especially in the wake of the pandemic. For example, in April 2020, the USFDA released a guidance document to improve the availability of DTx products for managing psychiatric disorders while at the same time reducing contact between the healthcare provider and user, thereby minimising COVID-19 exposure [12].

From the viewpoint of the lay public, the post-COVID era has seen an increased proportion of digitization in all fields, and the healthcare sector is not an exception. There has been a trend of increasing adoption of digital health solutions by the general public, as evidenced by a 25% increase in health app downloads and a nearly 50% increase in fitness app downloads after the arrival of COVID-19. Interestingly, the highest increase in downloads was observed in India, with a 155% increase in downloading fitness apps [13, 14]. A similar trend can be anticipated with DTx products, which are more rigorously tested and have a stamp of approval from regulatory

authorities. In Germany, for example, DTx products were brought within the purview of reimbursement in September 2020; subsequently, the usage of DTx apps has been observed to increase [15]. This suggests that patients are keen to adopt the technology in DTx for their health management.

DTx, being virtual products, are not associated with safety concerns like traditional medicine. However, there are some risks that have been identified with DTx products. For example, there is a risk of overdependence on technology and the associated devices such as the smartphone. This observation gains significance especially since a large number of DTx products focus on various mental health conditions. Another concern, more so with digital health applications, includes unverified claims of benefit of the product. However, since DTx is by definition required to provide evidence to the regulator pertaining to the efficacy of the product in a particular situation, the risk of unverified claims does not assume significance in the case of DTx products. Nevertheless, since the field of DTx is an upcoming one, focussed research on the potential risks associated with DTx products is warranted [16].

Finally, the pharma industry has realised the potential in DTx as the future of healthcare delivery. For example, major pharmaceutical companies, including Boehringer Ingelheim, Novartis, and Sanofi, have already started investing heavily in DTx products [17]. Another interesting aspect that has piqued the interest of the pharma industry towards the DTx market is the fact that the cost of development of DTx solutions is considerably less than the costs involved in drug development [18]. Finally, since many aspects of healthcare delivery are driven by patient data, the fact that DTx provides near real-time access to health data from patients has also contributed to the increasing pharma interest in the DTx market.

With this background, and due to the ongoing pandemic, it is not a surprise that the DTx market is anticipated to flourish exponentially. The pandemic has joined the other major drivers for DTx growth, such as increased incidence of chronic diseases, enhanced focus on preventive healthcare, and affordable gadgets due to technological advancements. As per a recent report, the global DTx market is projected to grow at a CAGR of 26.7% between the period 2020 to 2025, and the value of the DTx market is estimated to grow to USD 6.9 billion in 2025, compared to USD 2.1 billion in 2020 [19]. As of August 2020, around 230 DTx solutions are currently available or under development, and the three most prominent therapeutic areas in which DTx products are being developed include neurological disorders (27%), mental health problems (24%), and metabolic disorders (22%). Generating evidence for DTx is also going on massively, with an estimated 80,000 patients enrolled in DTx clinical trials as of August 2020. North American and European regions are expected to dominate the market share of DTx at around 70%. The growth of the DTx market in Asia-Pacific is also anticipated to be quite fast, at 23.2%, by 2030 [20].

4. DTx IN MAJOR THERAPEUTIC AREAS

DTx applications have been tried in multiple therapeutic areas [21]. In this section, important DTx products in major therapeutic areas are briefly reviewed.

4.1. Diabetes

Diabetes is the dominant therapeutic area as far as the DTx market is concerned. It was estimated that 26.6% of the DTx market share in 2017 was held by diabetes, and the trend is expected to continue in the post-COVID era. This therapeutic area is also projected to have a growth rate of 22.0% between 2018 to 2025, and this is because of the rising global prevalence of diabetes [22]. DTx products targeting diabetes such as Bluestar, FareWell, Dario, and KYT-Adhere have shown varying degrees of success in bringing about glycemic control [23 - 26]. In 2014, BlueStar became the first prescription-only DTx app receiving USFDA marketing approval [23].

4.2. Psychiatry Including Addiction Medicine

The stigma surrounding mental health illnesses has been documented for a long time. While many approaches have been tried to break this stigma, the suddenly increased incidence of COVID-associated mental health conditions has contributed to the destigmatizing process. At the same time, the widespread nature of affliction of patients with mental health issues arising out of social distancing and isolation is an opportunity for DTx companies working in this therapeutic area [8].

Even before the onset of the pandemic, many DTx products were introduced for a variety of mental health disorders. For example, a 2020 study observed that delivering warning alerts were given when irregular life patterns through a smartphone DTx app connected to a wearable device was associated with a reduced recurrence of mood disorders such as bipolar disorder and major depressive disorder when compared to using a wearable alone without the warning alerts [27]. Likewise, DTx products targeting addiction and substance abuse have also garnered interest. For example, a DTx smartphone app based on cognitive behavioural therapy was proven superior to usual treatment in achieving smoking cessation within 4 weeks of engagement [28]. Two prescription DTx programmes by Pear Therapeutics have been approved by the USFDA for the management of substance abuse (reSET) and opioid abuse disorder (reset-O) [29].

4.3. Cardiovascular

Various DTx products have been introduced in the cardiovascular therapy area and are expected to undergo much development and adaptation in the post-COVID era. For example, the BiovitalsHF platform uses a wearable component to capture parameters from patients suffering from heart failure and utilizes software to determine the optimal guideline-directed treatment algorithm. It also guides adherence to medication and monitors overall patient behaviour [30]. The 'Rhythm Analytics' is a machine learning-based platform which can detect over 15 types of arrhythmias by analysing ECG pattern. The platform which performs computer-aided ECG interpretation was granted USFDA clearance in April 2019 [31].

4.4. Wearables

DTx delivered through wearables have potential in the management of several disorders. For example, after successfully demonstrating the capability to manage acute migraine through a smartphone-controlled remote electrical neuromodulation delivered through a wearable device, the wearable DTx was granted marketing authorisation in both the US and Europe [32, 33]. A US-based cardiac specialty institute has initiated trials with wearable watches and pendants to monitor at-risk patients for signs of heart failure and provide treatment recommendations after analyzing the data, and also to create a digital prescription [34].

4.5. Neurological

The increasing prevalence of neurological conditions, partly attributable to the improved lifespan of adults, has also contributed to the growth in the DTx market in the neurological therapy areas. DTx can play a significant role in the management of neurological conditions such as Alzheimer's disease, Parkinson's disease, and epilepsy. According to a report, the Neurological DTx market was estimated to be over USD 737.5 million in 2018 and expected to grow at a CAGR of 31.6% between 2019 to 2030 [35]. DTx applications are also being developed for the management of post-stroke chronic walking impairments [36] and aphasia due to stroke or traumatic brain injury [37].

4.6. Other Therapy Areas

Various DTx products are in different stages of development and marketing across multiple therapeutic areas, and newer and innovative applications for DTx products are coming up with each passing day. For example, in managing patients suffering from chronic low back pain, it was proven in 2019 that a DTx application providing digital exercises and relaxation techniques to patients was superior to conventional physiotherapy exercises [38]. Likewise, a game-based DTx application was proven to be efficacious in reducing the severity of pediatric ADHD in comparison with a control application [39]. Following the publication of this study, this DTx product was granted USFDA marketing approval in June 2020 [40].

DTx is also being investigated in the management of insomnia. Among 303 patients with insomnia, a DTx delivering Cognitive Behavioural Therapy (CBT) was found to reduce the severity of insomnia, latency of sleep onset, and wake after sleep onset when compared to an active control group [41]. In another study involving 1149 patients with subclinical depression and insomnia, the same DTx product was shown to decrease depression, anxiety, and insomnia by 4 weeks of starting the intervention, and the effects were sustained for up to 18 months [42].

4.7. DTx and Clinical Trials

Because of the nature of the delivery of the DTx product, the way of conducting DTx clinical trials for evidence generation is different from conventional clinical trials. For the starters, blinding and placebo-controlling might not be feasible. Second, since interventions are delivered digitally, it might be possible to undertake remote patient recruitment and virtual monitoring of patient parameters. Also, ever since the beginning of the pandemic, stakeholders have observed an increased rate of patient enrolment in DTx clinical trials, indirectly indicating the growing patient interest in DTx products [8]. Regulators have also been quick to identify the merits of virtual clinical trials to minimise transmission of the COVID-19 pandemic. In March 2020, the USFDA emphasized in its clinical trial guidance document the importance of virtual visits, phone interviews, self-administration, and remote monitoring in clinical trials during the pandemic [43]. Other regulators are also expected to follow suit, thereby paving the way for increased use of DTx in clinical trials.

4.8. DTx and Medication Adherence

Poor adherence to prescribed medication is consistently associated with poor treatment outcomes and consequently increased healthcare costs [44]. Various approaches have been tried to improve medication adherence, and DTx is also a potential solution for this problem. A recent study reported adherence to hepatitis C antiviral medication of 95% among hepatitis C patients with documented poor medication adherence after administration of a DTx in the form of an ingestible sensor, which sent adherence information to the provider [45]. DTx in the form of electronic sensors attached to inhalers was found to improve asthma outcomes by improving medication adherence by 58% after 1 month of use which was 55% after 6 months of use [46]. By providing integrative medication reminders and financial incentives, the DTx application KYT Adhere was found to improve medication adherence by 22.9% and a mirroring improvement in glycemic control by a reduction in Hba1c of 1.2% over a period of 3 months [26]. In the post-COVID era, where in-clinic contact between patients and physicians and the consequent positive reinforcing effect on medication adherence is expected to diminish, the potential of DTx in improving medication adherence gains even more value.

4.9. DTx Supporting Hospitalisation at Home

Hospitalisation for chronic conditions and end-of-life care is associated with many unwanted outcomes such as hospital-acquired infections, depression, and increased cost of care, all of which lower the quality of life and morbidity. There are several strong drivers for favouring hospitalisation at home. For example, the societal, social, and economic pressures that arise due to hospitalisation can be avoided by home hospitalisation. Further, people favour staying at home and receiving medical care over institutionalisation, even for a short duration of time [47]. DTx products have a role in supporting hospitalisation and care at home. DTx products have the potential to provide preventive care, monitor patient's health status, assist with behavioural change, including medication adherence, support with improving mental health and cognitive conditions, and also help in health data collection [47]. Hospitalisation in the home is especially relevant in the post-COVID era, where the priorities in hospitals have shifted to accommodate patients with COVID-19. Patients increasingly prefer home isolation and quarantine even for COVID-19 management. Thus, DTx has a prominent role in

supporting home hospitalisation for all possible health conditions.

5. DTx IN INDIA

The DTx market in India is yet in its nascent stages. DTx has a vast scope in India by virtue of its population and increased prevalence of DTx-amenable conditions such as diabetes, addiction, mental health conditions, and other chronic disorders. However, the main hindrance in India is in the form of regulations. In 2017, the Government of India drafted the National Health Policy, which contained, among other things, the National Digital Health Blueprint, with an intention to provide universal healthcare to all Indian citizens based on digital technologies to achieve higher effectiveness. The National Digital Health Mission (NDHM) was subsequently announced in August 2020, with an aim to "support the integrated digital health infrastructure of the country." Even though NDHM includes ambitious components such as Health ID, Digi Doctor, Health Facility Registry, Personal Health Records, and Electronic Medical Records, the NDHM would be more comprehensive when it includes DTx among its services [48]. The creation of NDHM has increased hopes among DTx stakeholders in India, and only time will tell if amendments in NDHM will pave the way to strong and reasonable DTx regulations in India.

CONCLUSION

Digitisation of healthcare is a certainty, and the COVID pandemic has accelerated it. The increasing preference to virtual healthcare delivery and tendency to opt for in-person clinic visit only for emergencies that has been observed in the wake of the pandemic is bound to continue even in the post-COVID era. DTx has already started to be a dominant player in the digital health industry, and its scope is bound to increase and expand in the light of regulators bringing out guidelines for the development and marketing approval of DTx products. With many market reports predicting an impressive growth for the DTx market in the next decade, it remains to be seen as to which among all therapeutic areas will benefit the most from the DTx boom. The potential of DTx to make healthcare delivery more personalised than before needs to be realised by all stakeholders. The COVID pandemic has unified even the most reluctant players in favour of digital health, and more specifically, adoption of DTx.

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CONFLICT OF INTEREST

The authors are founders of KYT Adhere, a prescription digital therapeutic smartphone application for improving medication adherence through behavioural modification.

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