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The Emerging Role of Digital Therapeutics in Overcoming Medication Nonadherence

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Abstract: Medication adherence is the extent to which patients take medication as specifically prescribed by their healthcare professional. Given the significant and dramatic impact, both from a population health and actual direct and indirect cost perspective, nonadherence has been and will continue to be a significant healthcare system and societal burden. Nonadherence to prescription medication treatment is a multifactoral problem that is influenced by several different dimensions. While many stakeholders have sought to fix the problem, there is no panacea or universal solution to prevent nonadherence at present. In a digitally advanced society, digital health interventions have rapidly become a major area of innovation, particularly given their potential to increase medication adherence. Digital therapeutics (DTx) are rapidly expanding disruptive technology innovations which include technology, data and digital applications that inform medical practice and improve health through various platforms and systems that apply technological solutions to enhance healthcare delivery. This paper addresses the potential, challenges and risks faced by several specific DTx interventions that can drive significant improvements in both patient health outcomes and decreased healthcare system costs.

Key words: healthcare, digital health, digital therapeutics, digital pills, digital applications, adherence and persistence

JEL codes: I

1. Introduction: The Nonadherence Problem

The latest report on global healthcare expenditures by the World Health Organization (WHO) indicated that global health spending continues to accelerate and reached $9 trillion USD or 10.8% of global gross domestic product (GDP) (WHO, 2022). Nowhere was this more evident than in the United States where recent national health expenditures (NHE) reached $4.3 trillion USD (48% of global expenditure) yielding a 19.7% GDP. Also, U.S., drug spending increased 7.8% to $378.0 billion in the period. Looking long-term over the next decade, U.S. NHE and GDP are both projected to continue growing at a 5.1% rate resulting in even more pressure on the healthcare system (CMS, 2022).

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Medication adherence is the extent to which patients take medication as specifically prescribed by the healthcare professional (HCP). Nonadherence to medication has been a long-standing issue impacting patient health outcomes and driving significant healthcare spending. Research has indicated that 50%+ of patients do not take their medications as directed by their doctor, leading to thousands of preventable hospitalizations and preventable deaths each year. Overall nonadherence costs ~16% or $500 billion of the entire yearly U.S. healthcare spend, and accounts for $~650 billion in pharma revenue opportunity loss (Herrington, 2018). Nonadherence is a centuries old problem and one of the costliest issues the U.S. healthcare system faces, in both dollars and patient lives. In fact, nonadherence to medical treatment was reported to be the sixth leading cause of premature death in the United States in the year 2014 (Omcare, 2021). And it accounts for poor health outcomes such as 50% of treatment failures, ~125,000 deaths annually, and up to 25% of hospitalizations yearly in the United States alone (Kim, 2018).

Nonadherence to prescription medication treatment is a multifactorial problem that is influenced by five different dimensions: 1) social and economic factors, 2) therapy-related factors, 3) disease-related factors, 4) patient-related factors and 5) health care system-related factors. While many stakeholders have sought to fix the problem, there is no panacea or universal solution to prevent non-adherence at present.

2. The Potential of Digital Therapeutics

By definition, digital health includes technology and data that inform medical practice and improve health. Digital health encompasses various platforms and systems that apply technological solutions to enhance healthcare delivery. The use of technology for health and wellbeing has significantly increased over the past few years, as seen by the worth of the digital health market estimated to be $175 billion USD in 2019, and more recent data has projected the market to $660 billion USD by 2025 (Statista, 2022). In a digitally advanced society , digital therapeutics (DTx) have rapidly become a major area of innovation particularly given its potential to increase medication adherence, a long-standing public health issue associated with poor health outcomes and disease progression resulting in billions of dollars in excess spending and financial waste. Government and private payors, healthcare providers and administrators have all been challenged to contain costs by reducing waste and improving the effectiveness of care delivery. Consequently, this has led to an ongoing search for effective interventions to improve medication adherence.

Arguably the most important subset of digital health is Digital Therapeutics (DTx). The Digital Therapeutics Alliance defines DTx as “delivering evidence-based therapeutic interventions to patients that are driven by software to prevent, manage, or treat a medical disorder or disease” (Dang, 2020). In this context, the term applies to all the technologies that engage patients in their health and well- being and includes concepts such as digital pills, mobile health (mHealth), telehealth (i.e., telemedicine), smart devices, sensors and wearable’s, and health information technology. The expansion of digital health has led to advancements in technology being approved by the Food and Drug Administration (FDA) as a result of evidence supporting improvements in patient health. Healthcare professionals that are on the front lines of patient interaction are likely to see the use of these digital health tools in order to obtain positive patient outcomes. The following sections will focus on the potential of several types of DTx to impact patient positive outcomes and the challenges and issues involved with integrating them into the lives of patients and healthcare professional practices.

3. Digital Pills (DPs) Offer Potential and Challenge to Overcoming Adherence

Digital Pills are important, rapidly expanding disruptive technology innovations that can drive significant improvements in both patient health outcomes and decreased healthcare system costs DPs, also known as smart pills or ingestible sensors, a sub-category of DTx, are an innovative technology used for monitoring medical adherence, imaging, sensing different types of gases, monitoring medication absorption of medication, and electrochemical signal sensing. This paper focuses on Medication Monitoring DPs, which combine traditional medications with an ingestible sensor to monitor medication intake. These DP monitoring systems (i.e., a drug and a device combination) automatically record data about medication adherence as well as patients' physiological data can potentially become a potential breakthrough enabling healthcare professional access to online patient data to monitor therapy adherence to provide not only data but an opportunity to reinforce the need to stay on therapy with the patient.

In November 2017, FDA approved the first and to date only approved Medication Monitoring DP, Abilify MyCite (aripiprazole tablets with ingestible sensor) for several mental illnesses. Proteus Health and Otsuka's Abilify MyCite is a drug-device combination product comprised of oral aripiprazole tablets embedded with an Ingestible Event Marker (IEM) sensor, including the drug, a Patch (wearable sensor), a smartphone "App", and web-based portals for HCPs and caregivers (FDA, 2017). The Abilify MyCite System records drug ingestion and communicates it to the patient and HCP. It can also collect data on activity level, as well as self-reported rest and mood which, with patient consent, can be shared with the HCP and selected members of the family and care team. The system provides a summary of drug ingestion over time to help enhance collaboration with healthcare providers who treat patients with certain serious mental illnesses.

FDA approved Abilify MyCite despite no prospective, double-blind, randomized, controlled trial, as such it launched without an indication for, or definitive data on, improved medication adherence. Despite its potential it has struggled commercially and therapeutically to achieve success. While some suggest its lack of commercial uptake is the result of a soft-launch and limited roll-out to select health plans and providers by Otsutka, the cost of Abilify MyCite is prohibitive (i.e., $1,625/month vs. aripiprazole at $20/month) to payers and patients alike, especially without strong adherence evidence (LaMattina, 2019). From a European Medicines Agency (EMA) point of view, the product was not approvable without better clinical data proving better adherence or patient outcomes, and as such Otsuka withdrew the application for marketing authorization on July 17, 2020 (EMA, 2020). Today, almost six years later, the clinical impact of Abilify MyCite has yet to be unequivocally demonstrated as clinical evidence has not proved its value despite its potential. For example, in the DIMES (DIgital MEdicine Study for Adults with Schizophrenia, Bipolar I Disorder, or Major Depression Currently Using Aripiprazole) trial, a Phase IV, 12-month, pragmatic trial designed to assess adherence in patients using ABILIFY MYCITE versus patients receiving treatment Abilify alone, there was no observed difference in refill rates, meaning that the data suggest there's no difference in adherence (Gonzales, 2022). However, an important Phase 3b, multicenter, prospective open-label trial to evaluate the impact of Abilify MyCite versus Abilify as the oral standard of care, noted that Abilify MyCite reduced inpatient psychiatric hospitalization rates for adults with mild-to-moderate schizophrenia (Cohen, 2022).

Based upon the pioneering work of Proteus Health, in December 2019, the FDA approved EtectRx's ID-Cap system as a "smart pill" device via a 501k medical device submission. Unlike Abilify MyCite, it is registered as a device, not a drug-device combination product. Additionally, unlike Abilify MyCite which requires a skin worn

patch to transmit data, the new system utilizes a more patient-friendly wearable lanyard-based reader which sends data to a secure smartphone application and can be pushed to an HCP. At present the ID-Cap system is in clinical trials with therapeutics to establish data needed to appropriately market it. The very limited data thus far shows that the ID-Cap system has an overall adherence of 97.75% in its small investigational trial. The study supports the clinical validation of the EtectRx technology and feasibility for real-time reporting of medication adherence. (Flores) However, like Abilify MyCite, there are a number of similar challenges and issues to its use if and when it's approved with a specific drug for therapeutic treatment.

With many companies continuing DP clinical development looking at different innovative concepts, there are important lessons to be learned from DP development and commercialization thus far. Commercial and Clinical staff must focus on a large set of issues if this technology is to achieve its potential. Among the practicalities that must be addressed are the high-cost burden to payers and patients without strong outcomes data, patient acceptability, and willingness to take trackable DPs, provider and patient hesitancy and needed education, potential non-pill sensor adverse events, and a wide range of ethical concerns amongst many stakeholders which must be overcome to drive success. Additionally, from a regulatory standpoint, there's been a significant call for increased regulatory guidance on DTx, and specifically DP development with concerns being cited over the use of DTx/DPs for "evergreening" as a patent protection strategy by making changes to a product but offering no added benefit to the patient or healthcare system.

Among the specific recommendations moving forward are:

- Develop DPs for the right diseases and for the right patients especially where strict medication adherence is critical to outcome (e.g., HIV, HepC).
- DP clinical trials must evaluate specific outcomes measures beyond 'usual' efficacy and safety endpoints (e.g., increased medication adherence).
- Clinical development should include early patient, community-based provider and payer input given many ethical concerns.
- Create a compelling pharmacoeconomic and health benefit case for the payer given the high cost of therapy.
- Train and equip HCPs on better patient communications to ensure full understanding of the technology, privacy, confidentiality, and security issues given DP complexity and be cognizant of impacts on vulnerable populations.
- Develop more patient-centered Informed Consent forms/procedures to ensure better understanding of the technology and benefits.

4. Digital Therapeutic Applications Demonstrate Patient Medication Adherence Improvement

Digital therapeutics can include mobile applications used on cellular phones which assist the patient with their medication adherence and ultimately follow the therapeutic plan of the physician. Digital therapeutics includes products used to measure or intervene and have clinical evidence to their functionality and includes products that are used to treat or manage diseases and must also have clinical evidence to support their use and regulatory clearance. Digital therapeutics include technology such as mobile applications or devices which remind patients of medication administration time and dose. Smart phone applications provide similar services to text

messages, including reminders and educational videos, and adherence tracking. Some DTx help patients adhere to their medications. Other digital health technologies include groups on social networking services that patients with common disease states can join and share information. DTx helps physicians track medication adherence and prevent further complications that may result from non-adherence in their patients.

Developments in technology are quickly advancing within the healthcare industry, and its use for patient care has been increasing in various ways. Over 90% of hospitals in the United States have adopted the use electronic health records (EHR), which has changed the way patient information can be stored and shared. In terms of technology that is accessible to patients, there are currently over 300,000 digital health applications available for download, some of which are connected to external devices. There are devices that connect to the internet to form an integrated network. One example would be an application that receives data from electronic medication dispensers and sphygmomanometers which creates specific text messages for the patients. Another example would be an electronic pill box which alerts the users to take the medication and creates messages as a reminder for the patients. This significant change in healthcare delivery, including a shift towards telehealth use, has especially increased since the COVID-19 pandemic, which has been able to streamline patient care. Successes from advancements in technology have led to research looking into more personalized digital health tools for patients (Dang, 2020).

A meta-analysis of 16 randomized controlled trials showed that text messaging programs doubled the odds of medication adherence with statistical significance (OR 2.11; 95% CI: 1.52-2.93; $p < 0.001$) and an absolute increase of 17.8%. The text messages provide services such as medication reminders and education to address the non-adherence due to negative attitude towards medications (O'Hara, 2022).

The ability and opinions of the elderly to use available health technologies is a concern and was studied in a group older than 79.6 years of age to determine how the elderly view these available health technologies. Qualitative interviews were conducted on healthy older adults to better understand what can be done to improve effectiveness, safety, and user-friendliness. The study assessed the general value of devices, their usability, and ethical considerations. Overall, there was a positive outlook on the available technologies and the participants felt it could genuinely impact their overall health. Main concerns were due to safety and privacy of their personal information and losing direct patient interaction with their physician. Most participants were fairly familiar with existing digital health technologies, and most are frequent smartphone and computer users. It is particularly important to note that there was a significant drop-off in patients over 80 years of age. Those over 80 years of age had a decreased exposure to such technologies. The majority prefer applications that help to increase communication between healthcare providers (Ienca, 2021).

The effectiveness and opportunities for improvement are an area of study with digital therapeutic applications. A study conducted in 2014 with 128 patients with chronic diabetes were observed over 6 months. The Morisky Medication Adherence Scale (MMAS) was used to evaluate patients' adherence level in a TExT-MED group vs. control group. TExT-MED is a low cost, scalable, unidirectional text message service used for mobile health intervention. The MMAS increased from 4.5 to 5.4 in the Text-MED group vs -0.1 in the control group indicating improved adherence. In 2016, 1372 patients with hypertension were observed for adherence using prescription refill data. With the use of SMS-Text Adherence Support (StAR), the patients were divided into 3 groups, information only, interactive SMS and usual care. Refill rates were higher in the groups that received some kind of text messaging (156/248, 62.9% information only group/134/225, 59.6% interactive message group) vs. usual care group (94/190, 49.5%). 80 patients with type 2 diabetes using the "Messaging for Diabetes (MED)"

SMS messaging were observed for adherence changes over three months. Results showed that the adherence was improved in the first (adjusted OR 3.88; 95% CI: 1.79-10.86) and second (adjusted OR 1.49; 95% CI: 0.66-3.10) but not in the third month (Bobrow, 2016).

Medication adherence benefits using DTx applications include: 1) the ability to measure the level of medication adherence through one-way, or two-way, interactive reminders; 2) needed patient support to educate patients and ensure they are engaged with their treatment; 3) the ability to tailor applications and interventions to the population as well as be culturally adaptable; and 4) the sharing of data with patients and providers to encourage communication and dialogue.

However, there are some challenges to the use of digital applications which include: 1) patient engagement and consistency of interaction and action is required; 2) the cost of some applications might be prohibitive; 3) the ability of patients and providers to understand appropriate use and functioning of the DTx and next steps associated with the data outcomes; 4) the fact that not all stakeholders involved in the patient's health are provided the data, and 5) data security concerns.

Specific recommendations for continued digital application use and improvement in patient medication adherence based on the challenges/issues include:

- Development of DTx applications that are easy to use and allow for sustained adherence.
- Providing initial and ongoing training to both patients and healthcare providers.
- Promotion of application uses and benefits to healthcare providers and payors.
- Data sharing with pharmacies where patients had medications dispensed to enable interventions designed to help patients persist in their treatment.
- Providing free, discounted, or refundable DTx applications to encourage uptake and use. Additionally, considering a rewards structure depending on the DTx application to encourage use will be a win-win for all stakeholders.

5. Conclusion

Given the significant and dramatic impact, both from a population health and actual direct and indirect cost perspective, nonadherence has been and is likely to continue as a significant healthcare system and societal burden. Nonadherence to prescription medication treatment is a multifactorial problem influenced by five different dimensions and is quite individualized to specific patient phenotypes (e.g., the patient does not understand the importance of medication adherence to their health and well-being, the patient does not perceive the medication to have therapeutic efficacy or is debilitated by the side effects, or the patient has concluded the cost does not outweigh the potential benefit, etc.). Traditional methods to enhance adherence have not proved fruitful so the potential of DTx, in its many forms, needs to be welcomed by all stakeholders. Although DTx is still in its infancy, it's a rapidly emerging and evolving treatment approach that offers considerable opportunity to patients, HCPs, payers, healthcare systems, pharma and life science companies, and many others. The development of these innovative approaches is not without challenges and risk, but by looking at lessons learned along the journey, investment in DTx will undoubtedly show significant positive impact very soon.

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