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COMMENTARY

The Rise of Prescription Digital Therapeutics in Behavioral Health

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ABSTRACT

Medicine is evolving to incorporate digital technologies of all kinds—technologies that may improve patient health, reduce clinician workload, lower costs, reduce health disparities, and expand access to needed treatments. Prescription digital therapeutics (PDTs) are an emerging technology with particular potential. These are software-based treatments delivered on mobile devices that address the behavioral dimensions of many diseases and conditions. Unlike health and wellness apps, PDTs are rigorously evaluated for safety and effectiveness and are authorized by the US Food and Drug Administration (FDA). Nine PDTs are currently authorized to treat conditions such as substance use disorders, attention-deficit disorder, and chronic insomnia. The findings reported in two recent research papers published by *Advances in Therapy* related to use of PDTs for substance use disorder and opioid use disorder provide real-world evidence of clinical and cost effectiveness, strengthening the evidence base for these technologies and suggesting a role for these technologies in the efforts to help patients recover from these often-chronic and deadly conditions.

Keywords: Opioid use disorder; OUD; Prescription digital therapeutic; PDT; Sub stance use disorder; SUD

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Key Summary Points

Prescription digital therapeutics (PDTs) are FDA-authorized software-based treatments delivered on mobile devices that address the behavioral dimensions of many diseases and conditions and may help address provider shortages and reduce economic impacts.

Nine PDTs are currently authorized to treat conditions such as substance use disorders, attention-deficit disorder, and chronic insomnia.

Findings recently reported in *Advances in Therapy* related to use of PDTs for substance use disorder and opioid use disorder provide real-world evidence of clinical and cost effectiveness.

Work remains to facilitate full integration of PDTs into clinician and organizational workflows, to ensure coverage of these treatments for patients, and to streamline the steps required to prescribe and implement PDTs for patients who need them.

COMMENTARY

The prevalence of substance use disorders (SUDs) has increased, fueled by the COVID-19 pandemic, which contributed to substance use risk factors including widespread isolation and increased mental health burden [1]. Morbidity, including nonfatal overdose, and most notably mortality driven by overdose deaths have had large year-over-year increases peaking in 2021 with over 100,000 people dying from a drug-related overdose [2]. Over 75,000 of those deaths involved opioids as a consequence of the increasingly common exposure to high potency synthetic opioids [2]. Additionally, there were increases in deaths related to psychostimulants and multiple substance involvement [3]. These devastating costs in loss of human life and functioning are also accompanied by significant increases in healthcare costs related to utilization of acute care services [4].

Despite these alarming changes, the need for high-quality, evidence-based treatment for SUD has outpaced the supply of care. Factors contributing to this significant treatment gap include stigma, limited access to treatment due to segregation of SUD programs from other medical and surgical care settings, a shortage of clinicians trained in SUD management, high cost, limited coverage of SUD treatment services by insurance and third-party payers, and poor retention of patients in treatment [5–7]. The majority of the estimated 40.3 million people aged 12 years or older who met criteria for SUD in 2020 did not receive substance abuse or mental health services treatment [6].

Technology has the potential to address the SUD treatment gap. Over a decade ago, the National Institutes of Health (NIH) issued a call-to-action report that included the goal of digitizing behavioral therapies to allow greater access, standardize treatment protocols, reduce barriers to care, and increase health equity [8]. These new therapies would be evidence-based interventions prescribed and initiated by treating providers and delivered on mobile devices. Today, this vision has been realized in the form of prescription digital therapeutics (PDTs). PDTs are software-based treatments delivered on smartphones or tablets that address the behavioral dimensions of many diseases and conditions [9]. Unlike health and wellness apps, PDTs are rigorously evaluated for safety and effectiveness in randomized controlled trials, are authorized by governmental regulatory bodies such as the US Food and Drug Administration (FDA), and are subject to post-marketing requirements that are similar to regulated pharmaceuticals [10]. PDTs are authorized via the FDA's medical device review pathways (e.g., 510K for de novo devices), are developed following Good Manufacturing Practices (recognized by the World Health Organization, FDA, and other groups), and include stringent security and privacy controls.

PDTs have adapted well-established, evidence-based psychotherapies such as cognitive

behavioral therapy (CBT) for relapse prevention (RPT), CBT for insomnia (CBT-I), cognitive motivational interviewing (MI), the community reinforcement approach (CRA), and contingency management (CM) to digital platforms. Nine PDTs are currently authorized by the FDA to treat the behavioral dimensions of conditions such as substance use disorders, attention-deficit disorder, chronic insomnia, irritable bowel syndrome, and post-traumatic stress disorder [11].

PDT authorizations are based on randomized controlled trials showing significant benefits on key clinical outcomes relevant to the specific indication, such as retention in treatment or abstinence for SUD treatments [12]. The body of evidence supporting PDTs is additionally strengthened by real-world observational studies, i.e., studies taking place in a range of clinic types in patients not restricted by clinical trial inclusion and exclusion criteria, resulting in greater generalizability [13]. This allows for the assessment of outcomes extending beyond retention and treatment to include important data such as patterns of PDT engagement by age, sex, or socioeconomic level. Observational data from healthcare resource utilization (HCRU) research are also critically important for evaluating the overall potential benefits of PDTs because they inform payor decisions that can either limit or expand access to these novel treatments.

Given the ongoing significant unmet needs for behavioral therapies to treat SUDs and the great harms to individuals, families, and society at large inflicted by these disorders, the findings from Shah et al. [14] and Velez et al. [15] in this issue of *Advances in Therapy* are particularly important.

The study by Shah et al. is the first report on real-world health economic outcomes with the reSET® PDT for SUD since the approval of this treatment in 2018. The authors evaluated changes in HCRU and costs-of-care in an early cohort of 101 commercial and Medicaid-eligible patients prescribed the reSET PDT for patients with SUD and compared outcomes pre- and post-PDT-initiation. The study demonstrated that use of the PDT was associated with significant reductions in the use of acute care services including hospital encounters (− 50%), inpatient stays (− 56%), and emergency department visits (− 45%). These reductions drove 6-month per-patient cost reductions of $3591 post-index compared to pre-index. These real-world observations extend the findings of improved treatment retention and abstinence rates seen in the pivotal trials on which FDA authorization of reSET was based [16, 17].

Velez et al. report similar findings with a PDT focused only on opioid use disorder (OUD), reSET-O® but on a longer timescale and in comparison to controls. Previous analyses [18–20] have shown that patients treated with reSET-O had net cost reductions at 6 and 9 months post-treatment vs. control driven by reductions in the use of acute care services. The current study corroborates these results and is the first long-term (12-month) real-world analysis demonstrating a robust durability of response to treatment with PDT-delivered CBT among patients with OUD who are being concurrently treated with buprenorphine pharmacotherapy.

In this retrospective study, the authors evaluated changes in HCRU and buprenorphine adherence up to 12 months after PDT treatment initiation for 901 patients with OUD treated with reSET-O vs. 978 control patients with OUD under standard clinical care. Use of PDT compared to controls was associated with clinically significant reductions in unique hospital encounters (− 14%), inpatient stays (− 28%), emergency department visits (− 7%), intensive care unit stays (− 30%), and hospital readmissions (− 56%), as well as with higher buprenorphine adherence (measured using the medication possession ratio) over 12 months (0.85) vs. controls (0.76) and patients' own 12-month baseline prior to reSET-O (0.63). These changes in HCRU drove per-patient cost differences of − $2791 versus controls with even greater savings in the sub-population of Medicaid-covered patients (− $3832 per patient) over 12 months.

These two studies add important real-world data to the already existing evidence base provided by randomized controlled trials (RCTs) and extend those results to longer time frames of 6 or 12 months. The studies also have some

limitations. First, the results are based on claims data, hence conclusions can only provide an association between treatment and measured outcomes, as opposed to causation (for which full medical history and a controlled environment would be necessary to minimize external biases).

Another potential limitation is the lack of detailed information about the nature and intensity of engagement with the PDT. The study methodologies required patients to have engaged with the PDT for at least 1 week, but this provides little visibility into how patients who engaged for a short period or who completed only a few learning modules responded compared to those who spent more time with the PDT or completed the full course of training modules. A prior paper reporting on these types of real-world engagement outcomes in patients treated with reSET-O found that in the 12-week study duration, 66% of patients completed at least half of all core treatment modules and 74% of patients were still engaging in PDT treatment during the last 4 weeks of their prescription [21]. Nevertheless, these studies show that the use and economic impact of the these PDTs in a naturalistic setting is not trivial (i.e., the PDT use was not driven by participation in a study but rather by the unsupervised interaction between clinicians and patients resulting in patients engaging with the PDTs on their own free will). A final limitation applies to the study by Shah et al., which included a relatively small number of patients in the analysis of reSET data, which may limit generalizability of the conclusions. Future analyses of larger data sets, however, are expected to address this issue.

The use of PDTs by patients and their adoption by clinicians are not without some challenges. For example, despite 85% of the US population owning smartphones, older and lower-income adults disproportionately may not have access to a device, or a device with a PDT-compatible operating system [22]. In addition, the FDA authorization processes that differentiate PDTs from other health and wellness applications may raise some barriers to the rapid implementation of software updates and content enhancements desired by manufacturers, but fortunately PDTs conform to a "standard of care" requirement when cleared or authorized by the FDA, reducing the need for frequent updates.

Getting PDTs into the hands of the patients who need them also requires that prescribers be familiar, comfortable, and competent in deploying these therapeutics. Prescribing a non-medication treatment to a patient with an SUD may be novel for many clinicians since it is operationally distinct from referring a patient for psychotherapy. A non-medication therapy may also face challenges when clinicians use e-prescribing through electronic medical systems that are not yet set up to accept such transactions. Likewise, as payers adapt their benefit designs to accommodate PDTs, this coverage information needs to also be integrated into the patients' medical record. Most clinicians were not taught about, or exposed to, PDTs during their training, which may slow adoption of this new treatment modality and subsequent uptake by patients. Medical, nurse practitioner, and physician assistant graduate schools should add training in digital technologies to their curriculums in order to facilitate wider patient use of these potentially valuable treatments.

As effective as PDTs can be for easing the burden on clinicians, there may be patients with such complex clinical profiles or comorbid medical or psychiatric conditions that they need additional direct clinical guidance and support to facilitate the digital intervention. Additional research is needed to determine the extent to which PDTs can be effective for these types of patients.

In summary, the increasing use of PDTs to expand access to vital behavioral treatments is built on a foundation of data generated from studies spanning the spectrum of RCT, observational, and HCRU evidence. The two papers published in this issue of *Advances in Therapy* add to the body of evidence suggesting that the clinical benefits and cost savings related to use of PDTs are robust over periods of time longer than typical RCTs, i.e., 6–12 months. Importantly, the 12-month OUD study provides further evidence that these benefits are achieved even among patients with relatively high levels of buprenorphine adherence, i.e., use of the

PDT provides an additive benefit above, or supportive of, the benefits resulting from the use of buprenorphine.

PDTs are just one way that medicine is evolving to incorporate digital technologies of all kinds—technologies with the potential to improve health outcomes for patients, reduce clinician workload and attendant burnout, lower costs of care, reduce current health disparities based on geography or socioeconomic levels, and expand access to vitally needed behavioral treatments for a range of conditions and disorders. Much work remains to facilitate full integration of PDTs into clinician and organizational workflows, to ensure coverage of these treatments for patients, and to streamline all of the steps required to prescribe and implement PDTs for the patients who need them. But we believe the adoption of digital technologies in medicine is inevitable and that such adoption will ultimately improve the lives of both clinicians and patients.

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