Drug and Alcohol Dependence 229 (2021) 109120

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Short communication

Digital therapeutics for Substance Use Disorders: Research priorities and clinical validation

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ARTICLE INFO

Keywords:
Digital therapeutics
Behavioral interventions
FDA authorization process

1. Introduction

Substance Use Disorders (SUDs) have a substantial adverse impact in the United States, with more than $700 billion annually in health care expenditures and lost earnings (Center for Behavioral Health Statistics and Quality, 2019). The incidence is widespread; approximately 21.6 million individuals over the age of 12 experience substance use or dependence (Center for Behavioral Health Statistics and Quality, 2019). There are safe and effective FDA approved pharmacological treatments for opioid and nicotine use disorders, but long-term SUD treatment remains challenging. Similarly, despite available efficacious behavioral therapies for SUDs delivered in-person by trained professionals, relapse rates are high. As evidenced during the COVID-19 pandemic, traditional methods of delivering treatment have limitations and can be difficult or even impossible to access. Therefore, additional treatments for SUDs are urgently needed. Digital therapeutics (DTx) represent a new opportunity to address this significant public health challenge and were recently identified by the White House Office of National Drug Control Policy (ONDCP) in the priority to expand access to evidence-based treatment including "reimbursement for motivation incentives and digital treatment for addiction."

2. Advantages of DTx to treat SUDs

DTx are mobile, web, or other software-based platforms that deliver effective treatments for medical conditions or diseases. These therapeutic interventions do not include general wellness apps or telehealth that provide remote access to a clinician. Instead, behavioral interventions requiring face-to-face interactions can be delivered whole or in part by DTx. For the treatment of SUDS, DTx can address some of the limitations of current care, such as:

Reproducibility – Behavioral treatment delivery by DTx can be delivered reliably and consistently with limited staff training, following evidence-based guidelines.
Engagement – DTx can encourage patient engagement by having the intervention available 24 h a day, as needed.
Reach – Limited treatment access partly accounts for the reason over 80% of individuals in need of SUD treatment do not receive it (Center for Behavioral Health Statistics and Quality, 2019). DTx have the potential to eliminate or minimize travel to a clinician, increasing treatment options (e.g., rural areas).
Privacy – Stigma is a critical issue for patients when considering treatment (Volkow, 2020). DTx provide enhanced privacy with discreet and confidential care, helping to address the stigma associated with SUDs and its treatment.
Cost – DTx delivery does not require active interaction with a clinician, reducing face-to-face visits and cost. In addition, as clinicians spend less time maintaining treatment fidelity, DTx allow them to spend more effort on evaluation and optimizing treatment effects. A blended care approach is one example of a complete model of care that combines in-person and DTx strategies.
Data Recording – DTx can facilitate the recording of data that clinicians collect during their in-person treatment sessions, and they can also facilitate patient recording of symptoms, feelings, cravings, and other information.

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https://doi.org/10.1016/j.drugalcdep.2021.109120
Received 27 July 2021; Received in revised form 17 September 2021; Accepted 5 October 2021
Available online 9 October 2021

While the potential for increased access to treatment with DTx can address many of the limitations that have led to health disparities, it should be acknowledged there are also digital disparities that DTx have the potential to exacerbate. Issues around treatment access will need continued monitoring as DTx becomes an increasingly larger part of the intervention landscape.

3. Priorities for developing DTx for SUDs

The most extensively studied DTx for SUDs is the Therapeutic Education System (TES). TES is a web-based, interactive, behavior therapy intervention built on the evidence-based Community Reinforcement Approach (CRA) to behavior change. TES was studied in multiple randomized clinical trials with thousands of patients and shown to be effective in reducing relapse to drug use (Budney et al., 2019; Campbell et al., 2014). A commercial version of TES, called reSET®, was tested in a desktop form in combination with outpatient therapy and contingency management. This study demonstrated improvement in abstinence of certain substances of abuse and increased retention in an outpatient program as compared to outpatient therapy alone (Campbell et al., 2014). These data supported the FDA marketing authorization of reSET, launched as a smartphone app, resulting in it becoming the first DTx authorized for patients with SUD through FDA's De Novo classification pathway (De Novo Classification Process Guidance). The De Novo classification pathway can serve to guide other interested parties in developing SUD directed DTx and submitting their premarket submission to the FDA for marketing authorization.

Given the potential benefits of DTx, research on DTx development is an important part of NIDA's portfolio for potential new treatments. To strengthen this effort, NIDA works in partnership with the FDA Center for Devices and Radiological Health (CDRH) under a Memorandum of Understanding for scientific and regulatory collaboration (U.S. Food and Drug Administration, 2020). However, the rapid shift in the digital world over the last decade has resulted in a surge of digital therapeutic developments, many of which have not been clinically studied. NIDA appreciates FDA's role providing independent assessment of risk, safety and effectiveness. DTx developers are encouraged to interact with FDA regarding their product, as appropriate.

Research priorities for DTx include treatments with increased efficacy, defined mechanisms of action, increased efficiency, and are implementable and self-sustaining. Researchers should build on foundational, peer-reviewed studies. DTx research should evaluate clinical findings in appropriately designed randomized clinical trials. Comparators could include a sham control, treatment as usual or a relevant approved treatment. Outcome measures from different domains should confirm one another, especially when novel. Measures obtained directly from a DTx or from a clinician via face-to-face or remote encounters can be used to provide evidence of a clinically meaningful effect on how a patient feels and functions. Independent measures collected from the DTx or by other means, such as assays of biofluids, may serve as independent biomarkers in confirming subjective reports from study participants and clinicians. Clinical trial designs can be developed in coordination with the FDA, as appropriate, to support a DTx's safety and effectiveness.

Dissemination planning of the intervention should also be a high priority for investigators. NIDA's explicit focus on providing new treatments to patients includes both the validation of interventions and the strategies for getting the treatment to those who need it. Investigators should consider distribution platforms and commercialization efforts, perhaps aided by institutional technology transfer offices.

4. Engaging with FDA during development of DTx for SUDs

This section is intended to outline considerations for DTx researchers and developers who may have had limited exposure to FDA in this product space. FDA's Center for Devices and Radiological Health (CDRH) reviews DTx that meet the definition of a medical device for safety and effectiveness. FDA has established mechanisms such as the voluntary Pre-Submission process (The Pre-Submission Guidance Document), which provide opportunities for product developers to engage in discussions with FDA staff about their product. For example, developers can discuss topics such as the regulatory requirements that may apply (if any), the appropriate regulatory pathway for a DTx that meets the definition of a medical device, clinical study design considerations (including the proposed patient population, study endpoints and assessments, the study comparator, statistical analysis plan), appropriate cybersecurity measures to consider, and other questions that may be applicable.

Whether a DTx meets the definition of a medical device that is subject to FDA oversight is determined by the intended use of the product (including the specific intervention and treatment population) and consideration of the risk to the patient. Not all DTx may meet the definition of a medical device (Section 520(o) of the Food, Drug, and Cosmetics Act; Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act). CDRH has outlined policies for low-risk general wellness products (General Wellness: Policy for Low Risk Devices Guidance) and mobile medical applications (Policy for Device Software Functions and Mobile Medical Applications Guidance) that may apply to certain DTx. These policies provide some guidance on the delineation between products that are not subject to FDA's regulatory purview and the products on which FDA intends to focus its regulatory oversight. Products that do not meet the definition of a medical device do not require FDA authorization prior to marketing. CDRH encourages developers of DTx products to reach out to the review divisions via the Pre-Submission program and to points of contact identified in the referenced guidance documents for clarification on the regulatory requirements, if any, that apply to their DTx.

For DTx that meet the definition of a medical device, there are several regulatory pathways to obtaining FDA marketing authorization. The appropriate pathway is dependent, in part, on device risk and risks associated with its use in the intended patient population. For low-to-moderate risk DTx, the "510(k)" and "De Novo" pathways are likely the most relevant for developers interested in marketing their product. Refer to FDA guidance documents for more information (De Novo Classification Process Guidance; 510(k) Program).

Additionally, the Breakthrough Devices Program is a voluntary program for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. This program is intended to help patients have more timely access to these medical devices by expediting their development, assessment, and review, while preserving the relevant statutory standards, consistent with the Agency's mission to protect and promote public health.

FDA premarket review is especially important considering the growing number of marketed digital health solutions with limited or no validation (Rajani et al., 2019). The launch of prescription DTx with FDA marketing authorization provides an important line of demarcation, giving patients and healthcare providers assurance that a DTx that meets the definition of a medical device is safe and effective for its intended use. A prescription DTx receiving FDA marketing authorization is required to comply with the medical device Quality Systems regulations. The Quality Systems regulations cover robust software development and data integrity/security practices, along with software-related pre-market and post-market regulatory documentation and complaint-handling requirements. Additionally, FDA marketing authorization of a DTx does not preclude updates to the DTx based on, for example, user feedback or a developer's wishes to make product improvements. FDA has published guidance (Deciding When to Submit) for industry outlining FDA's thinking on what steps developers should take when they wish to make changes to a device that has been granted marketing authorization.

5. Summary

Together, NIDA and FDA support the development of safe and effective DTx for SUDs, adding to the armamentarium of interventions. DTx offer unique treatment options and can deliver interventions with fidelity and state-of-the-art practices. This federal partnership represents a commitment to help guide academic, private and industry partners to deliver highly efficacious and sustainable clinically-validated DTx to patients.

Funding

None.

Disclosure

P. A. is a pre-market medical device reviewer in the Office of Neurological and Physical Medicine Devices.

Disclaimer

This editorial was prepared or accomplished by the authors. The opinions expressed in this article are the authors' own and do not reflect the view of the National Institutes of Health, the Food and Drug Administration, the Department of Health and Human Services, or the United States government.

Author contributions

All authors contributed to the design of the manuscript. W.M.A. led drafting, and K.M.W, and P.A. provided technical comments and contributed to revisions.

Conflict of interest

There are no conflicts of interest to disclose.

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