Digital Therapeutics for Substance Use Disorders: Clinically Validated New Treatment Options

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Advances in Technology, Part I
Goals and Learning Objectives

- This workshop will highlight research to support the development of safe and effective Digital Therapeutics (DTx), discuss strategies to accelerate their delivery to patients, and improve SUD treatment outcomes
- Illuminate NIH-supported and FDA-authorized DTx options for patients
  - Discern which technologies constitute DTx
  - Gain an understanding of DTx as stand-alone treatments or integrated with FDA-approved SUD treatments
  - Learn about the FDA authorization process for DTx

Why the Need for New Treatment Options?

- As evidenced during the COVID pandemic:
  - Traditional methods of delivering health care are limited and can be difficult to access
  - Rural and urban healthcare “deserts” highlight the need to expand options to increase access
- One of the most promising methods is the use of digital therapeutics (DTx) to address this public health challenge
- April 1, 2001—White House Office of National Drug Control Policy (ONDCP) announced its priority to expand access to evidence-based treatments which includes...“reimbursement for motivational incentives and digital treatment for addiction, especially stimulant use disorder.”

NIDA Views on Digital Therapeutics

What are DTx and What are they not?
- DTx are clinical-grade software programs that can deliver behavioral interventions previously only available via direct, face-to-face interactions with a clinician
- DTx are designed to prevent, manage or treat a medical disorder or disease
- DTx are available via mobile, web or other related platforms
- DTx are not wellness apps or telehealth – remote access to a clinician
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NIDA Priorities on Digital Therapeutics

- Improve treatment efficacy
- Integrate behavioral treatments having defined mechanisms of action with a standardized therapeutic delivery
- Boost effects and increase efficiency of interventions
- Produce technology-enhanced treatments that are implementable and self-sustaining
- Increase options for remote treatment delivery

Notable Advantages of Digital Therapeutics

- Reproducibility - Reliably delivered treatment with limited staff training, following evidence-based guidelines (quality control)
- Engagement - DTx can encourage patient engagement by having the intervention available 24 hours 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
  - DTx 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
  - DTx provide enhanced privacy with discreet and confidential care, helping to address stigma
- Cost - DTx delivery does not require active interaction with a clinician, reducing face-to-face cost (less time maintaining treatment fidelity, and more time on evaluation and optimizing treatment effect)

Unanswered Questions re: Digital Therapeutics?

- Are there ways to establish or maintain rapport? What is the balance between digital health and interpersonal contact?
- How will digital therapeutics intersect with health disparities populations in the area of addiction research?
- Health-care system requirements including HIPPA compliance?

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Overall DTx Landscape

- Across health conditions, there are over 300K “touted” digital health solutions in the marketplace (e.g., hundreds of smoking cessation apps available through the Apple Store and Google Play, yet very few have any clinical validation)
- Research efforts on development of DTx have far outpaced validation studies
- As such, there is a need to bring order to the “Wild West” with a trusted entity responsible for:
  - Review of clinical effectiveness and usability of DTx
  - Authorize DTx that are worthy of patient consideration

Less Chaff, More Wheat...

To Validate or Not to Validate—That is the Question!

- The importance of validation in the target population is as important for DTx as more traditional medications
- Yet the pathway leading to treatment in the clinic is much more varied for DTx
- All medications in the US need to be approved by the FDA prior to being prescribed by physicians
  - Digital interventions, on the other hand, can be given to patients without FDA review and authorization
  - Whether FDA review is required depends on several aspects, including the level of risk associated with the treatment population or the intervention
  - While several products available on the market were tested in clinical studies and shown to be effective, there is no standard that patients can rely on to be assured of their efficacy

NIDA and FDA Partnership MOU

NIDA/FDA (Center for Devices and Radiological Health) MOU was established in 2019 and allows regular interaction and sharing of information about DTx

Three major actions items were prioritized:
- NIDA Guide Notice for information on FDA authorization DTx
- FDA/NIDA collaboration on presentations to applicants on authorization process
- Development of a joint commentary on NIDA/FDA priorities and regulatory pathways for DTx

Focus on opportunities to:
- Provide guidance to grant applicants to help navigate the FDA submission and authorization process
- Accelerate the progression of these technologies through the regulatory pathway

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### FDA Regulatory Pathways for DTx

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wellness</td>
<td>Low risk devices, do not make diagnostic or therapeutic claims (do not need clearance)</td>
</tr>
<tr>
<td>PMA Pathway</td>
<td>High risk/class III medical devices, FDA inspection required, not relevant to DTx</td>
</tr>
<tr>
<td>510(k) Pathway</td>
<td>Low to moderate risk devices, must demonstrate equivalence to predicate device, FDA decreasing 510(k) submissions in favor of de novo</td>
</tr>
<tr>
<td>De Novo Pathway</td>
<td>Novel, low to moderate risk devices, new product classification</td>
</tr>
<tr>
<td>Breakthrough Devices Program</td>
<td>Program to give priority review—for medical devices and device-led combination products; goal is to give patients timely access to breakthrough technologies (De Novo, 510(k), or PMA placed towards top of queue)</td>
</tr>
</tbody>
</table>

### Interacting with FDA and considerations for Digital Therapeutics

**Mechanism:** Pre-submission Program
- **Sample Early Interaction Progression:**
  - **Pre-Submission(s):** Provides an opportunity to obtain FDA feedback prior to IDE or marketing submission
  - FDA provides written feedback and an optional meeting
  - Pre-submissions are NOT intended for “pre-review” of data
  - The purpose of any discussion during the meeting is to clarify feedback, not to respond in real-time to new information or proposals

**Pre-Submission (Q-Submission):**
- Provides an opportunity to obtain FDA feedback prior to IDE or marketing submission
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**Guidance Document:**
“Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff”
### Medical Device Definition

- Definition of a medical device is specified in section 201(h) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321) *
- Section 201(h) states in part:
  - The term "device"...means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is...
  - "...intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease..." or
  - "...intended to affect the structure or any function of the body... and which does not achieve any of its primary intended purposes through chemical action... and which is not dependent upon being metabolized for the achievement of its primary intended purposes."
Developing a Digital Therapeutic for SUD: Points to Consider

### Design considerations:
- Type of behavioral therapy
- How does device implement the principles of this behavioral therapy
- Indicated for use as an adjunct to usual best medical care or
- indicated for use as a standalone DTx?

### Non-clinical testing considerations:
- Software validation

### Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices

### Clinical testing considerations:
- Human factors/Usability testing
- Applying Human Factors and Usability Engineering to Medical Devices
- Clinical trial - to evaluate safety and effectiveness of the DTx

### Medical device trials differ from drug studies
- Device studies are designed to support a “reasonable assurance of safety and effectiveness”
- Endpoints of interest can be highly diverse between studies
  - Dependent on indication for use being sought
- Clinical trial should be designed to support your indication for use and target population
Developing a Digital Therapeutic for SUD: Points to Consider

- Recommend evaluating the safety and effectiveness of the device in the population for which it is to be indicated
- Specific use vs. general use (Guidance for Industry: General/Specific Intended Use (https://www.fda.gov/media/71966/download)
- Time frames for evaluating the primary endpoint should be defined
  - Consider time course of the specific SUD
  - Do patients have an initial immediate response and then tend to relapse?
- Endpoints should be prespecified
  - 1 or more “safety” endpoints
  - 1 or more “effectiveness” endpoints

Well-controlled study
- Sham control vs. usual care (or treatment as usual)
- Considerations:
  - Need to account for the placebo effect and treatment groups having equivalent “time on task”

Adjunctive use vs. standalone
- If used as adjunct:
  - Patients should be on usual care
  - Protocol should delineate what usual care constitutes
  - If patients are allowed to be on medications, protocol should include a plan for how medications will be managed and monitored
- If used as a standalone:
  - Protocol should have specific plan for patient safety if patients will not be on medication or other usual care
  - Protocol should have a plan for how patients will be “washed” from medications or other usual care

Inclusion/exclusion criteria should meet the target population for indication for use

Some statistical considerations:
- Pre-specified plan for handling missing data
- Pre-specified success criteria for secondary endpoints if you plan to make labeling claims based on secondary endpoints and to further support device safety and effectiveness

Randomization
Blinding
- Patients, investigators, and study staff blinded along with a plan for blinding assessment

Generalizability to the US population

Insights into FDA Views on DTx

- FDA regulation – while a DTx can collect endpoint measures, the FDA may not accept measures collected by the DTx to validate the treatment
  - May require independent collection of the data, such as by a study physician
  - Concerned the DTx could give biased assessments
- Currently, FDA only has the ability to authorize non-medications, which is distinct from the approval given to medications
  - DTx industry wants to have the same level of validation for these interventions as medications
  - DTx organizations are lobbying congress to pass a law to give FDA that authority
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Changing Landscape: Key Breakthroughs

- 2017: FDA Approves 1st Digital Therapeutic for SUD Treatment from Pear Therapeutics
  - NIDA-funded efficacy trial
  - reSET provides CBT as an adjunct to treat stimulant, cannabis, cocaine and alcohol use
  - reSET-O approved in 2018 for OUD as adjunct to medication treatment

NIDA Supported DTx Studies

Loyalty and Reward-Based Technologies to Increase Adherence to Substance Use Disorder Pharmacotherapies (R43/R44—RFA-DA-19-014; 015)
  - DTx as an adjunct to increase medication adherence
  - Primary endpoint: adherence to FDA-approved medications for SUD (e.g., buprenorphine, naltrexone, NRT)
  - Rewards and contingencies delivered in a self-sustaining manner

Developing Digital Therapeutics for Substance Use Disorders (UG3/UH3—PAR-21-183)
  - Research to develop and test DTx for stand-alone treatments or integrated with FDA-approved SUD treatments
  - DTx indications: prevention of SUD initiation, medication adherence, treatment retention, treatment of withdrawal, abstinence or reduction of relapse

Examples of Research Activities Funded through NIDA During UG3

- Development of a finalized version of the DTx and validation in the study population;
- Evidence that the intervention affects efficacy related endpoints:
  - For example: craving, dependence, days of abstinence, etc;
- Evidence the intervention affects behavioral endpoints as they relate to SUD:
  - For example: measures of working memory, impulsivity, risk-taking propensity, distress tolerance, self-regulation, stress reactivity, etc;
- Evidence an adequate dose range/treatment duration for the DTx intervention(s) can be applied with acceptable safety, tolerability, adherence, etc;
- Evidence when integrated with an FDA-approved treatment, there is enhanced adherence, retention, efficacy or effects on other measures relevant to the approved treatment;
- Completion of a proof-of-concept, feasibility clinical trial;
- Q-submission to obtain FDA feedback on the regulatory pathway; Filing an IDE;
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**Smartphone-based financial incentives to promote smoking cessation during pregnancy**

- **Primary endpoint**: biochemically confirmed smoking abstinence
- **Best practices**: brief smoking cessation counseling at start and at two assessments
- **Incentives**: best practices and remote financial incentives intervention
- **Assessments**: breath and saliva tests were submitted remotely in the form of videos of participants completing the tests

(Kurti et al., 2020)

**Digital Therapeutic is as Effective as “Gold Standard” Clinician-Delivered Treatment in Medication Treatment for OUD (n=135)**

(Bickel, Marsch et al., 2008)

**RCT of a Novel Smoking Cessation Application for Individuals with Serious Mental Illness**

- **Grant funded to test Learn to Quit, a smoking cessation app tailored to individuals with SMI**
- **Combines Acceptance and Commitment Therapy with nicotine replacement therapy**
- **Data from pilot study, pivotal trial funded**

(Vilardaga et al, 2020)
Closing Remarks

• FDA regulatory authorization is important considering the growing number of marketed digital health solutions with limited or no validation
• FDA authorization provides an important line of demarcation, giving patients and healthcare providers assurance about safety and effectiveness of the DTx
• A prescription DTx receiving FDA regulatory authorization is required to demonstrate
  o Good manufacturing practices including robust software development
  o Data integrity/security practices
  o Compliance to applicable medical device Quality Systems regulations

Closing Remarks

• NIDA is committed to treatment of substance use disorders investing in scientific and theory-informed DTx with a focus on clinical validation studies
• Technology helps treatments to: (1) maintain potency, (2) become more easily implementable and sustainable
• NIDA/FDA MOU goals focus on improving design, development, and methods for delivering regulated and clinically-validated DTx to patients
  o Guidance to investigators to help navigate the FDA submission and authorization process
  o Accelerate the progression of these technologies through the regulatory pathway
  o Add exponentially to the armamentarium of SUD treatment options

FDA Guidance Documents

• General Wellness Guidance Document
• Policy for Device Software Functions and Mobile Medical Applications
  https://www.fda.gov/media/80958/download
• Significant Risk/Non-Significant Risk Guidance Document
• FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act
• “Software as a Medical Device (SAMD): Clinical Evaluation”
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/software-medical-device-samd-clinical-evaluation
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FDA Guidance Documents

- Benefit Risk Guidance for IDE Submissions

- Benefit-Risk Guidance for Medical Device Premarket Approval and De Novo Classifications

- Benefit-Risk Guidance for 510(k) Submissions

FDA Guidance Documents

- IDE Submission Information
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046706.htm

- Design Considerations for Pivotal Clinical Investigations Guidance

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• Engagement in the Black Community: Keeping Focus

OCTOBER 15, 2021, 11:00 AM – 6:00 PM ET
• Adicción, Salud mental, e inmigración: adhesión al tratamiento ambulatorio (Spanish)
  or
• Nicotine Use Disorders and Effective Treatment

OCTOBER 22, 2021, 11:00 AM – 6:00 PM ET
• Clearing the Smoke: Cannabis Update for Addictions Professionals
  or
• The Criminal Justice System and Recovery

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  Zoom Webinar

Part III: Working with LGBTQQ+ Native American Elders
  Friday, August 27, 2021 12:00-3:00 PM ET
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