

Application of Digital Medicine in Addiction

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Abstract: Digital medicine plays an important role in disease assessment, psychological intervention, and relapse management in mental illnesses. Patients with substance use disorders can be easily affected by the environment and negative emotions, inducing addiction and relapse. However, due to social discrimination, stigma, or economic issues, they are unwilling to go to the hospital for treatment, making it difficult for health workers to track their health changes. Additionally, mental health resources in China are insufficient. Digital medicine aims to solve these problems. This article reviews digital medicine in the field of addiction, hoping to provide a reference for the future exploration of more individualized and effective digital medicine.

Key words: digital medicine, addiction, assessment, intervention, prediction

CLC number: R 749.6 **Document code:** A

0 Introduction

Unhealthy substance use is a broad term that covers hazardous and harmful substance use, and diagnosable substance use disorders (SUDs), i.e., substance abuse and dependence. Based on data from the United Nations Office on Drugs and Crime, over 35 million people suffer from drug use disorders^[1]. A recent cross-sectional epidemiological study in China^[2] found that the weighted lifetime prevalence of any substance use disorder was 4.7%, preceded by anxiety disorder (7.6%) and mood disorder (7.4%), making it the third most common mental illness (excluding dementia). In clinical practice, patients with SUDs are often not referred to addiction specialists on time because of stigma, discrimination, or lack of health resources. Despite having access to treatment services, treatment completion is difficult because of economic and privacy issues. Driven by the third technological revolution, the invention of

computers and mobile phones, and the rapid spread of access to the Internet and smartphones brought initial attempts at digital medicine. Digital medicine refers to the use of digital technology to understand health-related behaviors and provide personalized medical resources to clients. It covers information and communication technology, as well as emerging technologies such as big data and artificial intelligence, and plays an innovative role in the health care system^[3]. Digital medicine can help people to learn skills to deal with daily problems, and clinicians in remote areas can get help from experts through telemedicine, thereby resolving the problem of imbalanced health resources^[4]. Using digital medicine to increase the screening rate of addiction to provide intervention measures and early warning of relapse is effective in reducing the burden of mental health workers, increasing the utilization of medical services, and improving mental health^[5]. According to statistics from the China Internet Network Information Center^[6], as of June 2019, the proportion of clients using mobile phones to access the Internet reached 99.1% of the Chinese netizens. Affected by the COVID-19 epidemic, clients of online medical services have shown an increasing trend, accounting for 21.7% of the total number of netizens. This increasing demand for online medical services has further promoted the development of digital medicine in China. This article reviews the application of digital medicine in the field of SUDs from three perspectives: assessment, psychological intervention, and relapse management.

Received: 2021-03-08 **Accepted:** 2021-07-20

Foundation item: the National Natural Science Foundation of China (No. 81771436/82130041); the Shanghai Municipal Science and Technology Major Project (No. 2018SHZDZX05); the Project of Shanghai Shenkang Hospital Development Center (No. SHDC2020CR3045B); the Project of Shanghai Clinical Research Center for Mental Health (No. 19MC1911100); the Project of Shanghai Engineering Research Center of Intelligent Addiction Treatment and Rehabilitation (No. 19DZ2255200); the Project of Shanghai Key Laboratory of Psychotic Disorders (No. 13DZ2260500)

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1 Assessment

1.1 Digital Assessment Tools

Symptom descriptions and psychological measurements are commonly used assessment methods in psychiatry; however, the traditional assessment scales and structured interviews are complicated, as health workers need systematic training before utilizing them. Researchers have adapted the traditional assessment tools to digital versions for SUD screening and severity measurement to resolve the problem of inadequate training and lack of workforce in primary health care settings. The common design principle of digital assessment tools is called computerized adaptive testing (CAT), which uses computer algorithms and logical skips to match subsequent questions based on the results of the subjects' answers to each question with no need to manually calculate scores, thus saving time. CAT can be rapidly used for disease screening, diagnosis, symptom severity assessment, and telemedicine assistance in the form of standardized questions^[7]. The Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) is a widely used structured interview developed by the World Health Organization (WHO) to screen and stratify the risk of specific drugs. When health workers conduct face-to-face interviews with patients, it takes about 5–15 min to complete ASSIST, including complex question skip patterns and score calculations. A digital version of ASSIST^[8] and a shortened similar digital screening tool, which is named tobacco, alcohol, prescription medication, and other substance use (TAPS)^[9], are both completed on tablet computers with audio-assisted systems, making it more humanized and rapid to perform screening in health care settings. However, as these tools are primarily used for screening, they are often characterized by high sensitivity for detecting unhealthy substance use but low sensitivity for identifying SUDs, especially for addictive substances that are not commonly seen in primary health care settings. Gibbons et al.^[10] developed a digital assessment tool that comprehensively measured addictive symptoms or participants' propensity to SUDs and other symptoms, such as depression, anxiety, trauma, social isolation, functional impairment, and risk-taking behaviors. Ho et al.^[11] reported that adolescents are more likely to receive digital assessments than semi-structured interviews, and that digital assessments have higher disclosure rates on sensitive topics, such as mood disorders, drug use, and sex. If people are more willing and honest on digital assessment tools than on face-to-face interviews, we could consider using digital assessment tools to help workers complete automated screening, thereby reducing the burden on health workers.

1.2 Ecological Momentary Assessment

The real condition of a person often fluctuates with changes in the environment and time. Common dig-

ital assessment tools are currently used in healthcare settings to measure the average substance use during a period that cannot capture the dynamic daily changes in the natural environment. Ecological Momentary Assessment (EMA) is a method used to analyze emotional and behavioral changes by requiring patients to report real-time records to researchers. EMA studies of addiction focus on related indicators of substance use behaviors, such as motivations, mood, cravings, self-efficacy, and sleeping. The traditional EMA form is completed on paper sheets; however, with the development of digital technologies, EMA has become more diversified. Nowadays, EMA usually involves electronic devices such as mobile phones for receiving and sending text messages^[12], smart phones with electronic diary apps or with links to web-based survey programs^[13], and electronic bracelets with reporting buttons, which can avoid the possibility of incorrect reports or omission of data from patients' failure to recall when filling in paper-based EMA^[14]. By collecting real-time data on substance use, emotions, and cravings, EMA studies have found an association between substance use and negative emotions^[15] and craving intensity^[16]. The time point of the EMA survey was based on the needs of the researchers. It can be set at random, based on an event, at several fixed times or with daily diaries^[17]. A complete EMA design must consider assessment indicators, research period, record frequency, signal algorithm, event reporting, device type, and data storage^[13]. It is necessary when designing EMA studies to emphasize whether the assessment period is momentary (focus on the present) or retrospective, with clarity on the range of retrospection (e.g., past 15 min)^[18], as well as on the time of assessment of various indicators in correlation with substance use behavior.

1.3 Digital Phenotyping

Self-reporting data in EMA are subjective, while passively collected objective data will not be easily disturbed by the individual's educational level, cognitive dysfunction, or language barriers. The combination of mobile/wearable electronic technology and EMA allows the collection of subjective and objective information of clients in daily life^[19-20]. It helps to determine the instantaneous background of changes in behavior and emotions, and verify the authenticity of clients' self-reports. Digital phenotyping^[21] is a general term for data collected through digital technologies, such as physiological activity, body movement, GPS, and mobile phone content (e.g., social activity, text messaging, and typing patterns). Digital phenotyping reflects a person's behavior, mood, and cognition. GPS data from a mobile phone can be used to understand the patient's location changes and the time spent in high-risk places, such as bars. Communication records can convey information from social networks. Bergman et al.^[22] found that compared with people not using

addictive substances, anyone who is at risk of drinking or taking drugs (e.g., marijuana, cocaine, and heroin) are more likely to post on Instagram. Wearable devices, such as watches, wristbands, chest straps, and transdermal patches, facilitate real-time collection of various types of data, such as biological samples, location, and physiological changes, to help researchers understand the causes and consequences of substance use^[19]. These small portable biosensors can continuously monitor the client's body parameters, such as sympathetic nervous system activity (e.g., heart rate, skin electrical activity, and skin temperature) or the biochemical content of addictive substances, to predict whether the client has used addictive substances. Physical activity measurement is particularly useful for monitoring drug use. Increased heart rate, increased skin electrical activity, decreased skin temperature, or characteristic changes in ECG indicate cocaine use or relapse^[23], while decreased activity and increased skin temperature are associated with opioid use^[24]. Transdermal alcohol detection technology uses an ankle or wrist band to monitor alcohol levels in sweat that are roughly linear to blood alcohol levels^[25]. The transdermal alcohol concentration (TAC) can reliably detect at least two standard drinks. The challenge of digital phenotyping is how to analyze and model the collected data and translate it into clinically meaningful results.

2 Digital Intervention

Digital intervention refers to interactive and self-guided interventions available on digital devices. When clients have treatment needs, they can receive treatment support through digital medicine at any time and anywhere, which will overcome the imbalance of medical institutions at the geographical location and service level.

2.1 Digital Psychotherapeutic Lessons

The core principles of digital psychological interventions are guided by evidence-based psychological therapies, such as cognitive behavioral therapy (CBT), motivational interview (MI), and contingency management (CM), to provide psychotherapy to patients, including psychoeducation, desire management, and coping strategies^[26], on digital devices. The National Drug Abuse Treatment Clinical Trials Network, launched by the U.S. National Institute on Drug Abuse, has proved the safety and effectiveness of the web-based therapeutic education system (TES) by conducting rigorous nationwide, multi-site trials^[27]. TES showed effectiveness among alcohol, cannabis, and stimulant users, but had little or no effect on opioid users. It included a series of self-guided CBT lessons and an incentive program with the theory of CM for clients if they completed lessons and kept drug or alcohol abstinence. Computer/web-based interventions have shown better efficacy than

clinician-delivered psychotherapy^[28], with a higher rate of treatment retention and satisfaction, and lower rates of drug use. However, computer/web-based interventions appear to be difficult to operate for some participants, and the study found that usability scores for web-based interventions were lower than those for mobile applications^[29]. The web-based TES was modified into mobile app versions called reSET and reSET-O (especially for opioid users). The U.S. Food and Drug Administration has approved reSET and reSET-O as digital prescriptions for SUDs^[4]. Clinicians can view clients' substance use and learning progress at the administrative interface of reSET/reSET-O^[30]. A study of reSET-O^[31] found that patients who simultaneously received buprenorphine therapy and used reSET-O had a higher illegal opioid abstinence rate and treatment retention. MI is a widely used brief intervention to enhance the client's motivation and determination to change addictive substance use habits. Artificial intelligence, such as Chatbot, can mimic how psychotherapists provide MI on websites or smartphone apps. The presentation mode of chatbots can be text, verbal, or images of virtual characters^[32]. Chatbots typically use natural language processing to automatically understand the meaning of basic words in unstructured texts and conversations, and to process and analyze human language^[33]. The feedback from participants using chatbot showed that more than one-third of the participants liked to have a conversation with it^[34]. Woebot is a chatbot designed to deliver CBT through conversations and mood tracking to resolve daily mental health problems. A 2-week randomized controlled trial (RCT)^[35] showed that Woebot reduced depressive symptoms, as measured by the 9-item Patient Health Questionnaire (PHQ-9). In addition to mood tracking, Woebot customized for SUDs (W-SUDs) also had the function of craving and pain tracking, CBT lessons, and MI. Clients using W-SUDs for an 8-week treatment period showed significant improvements in substance use, craving levels, confidence to resist cravings to use substances, and depressive and anxiety symptoms^[36].

2.2 Digital Intervention for Cognitive Deficits

People with SUDs are still prone to relapse after receiving evidence-based psychotherapy. This phenomenon can be partially explained by impairments in cognitive functions, which consist of the classical cognitive (memory, attention, and executive function), substance-bias (cognitive bias, which refers to preferential processing substance-related stimuli), and social cognition (effective perception and response to interpersonal signals sent by other people) systems^[37]. Training for impaired neuropsychological function may improve treatment outcomes, better social function, and quality of life for SUD patients. People with SUDs typically have two types of cognitive bias: attentional bias (paying more attention to substance-related cues) and

approach bias (impulsively engaging with these substance-related cues). Cognitive bias can be corrected through cognitive bias modification (CBM), which includes a variety of computerized training programs to evaluate attention, behavior, or cognitive processes triggered by substance-related cues^[38]. Computerized cognitive training can be performed by patients through repeated training, thus facilitating behavioral changes in their own homes, saving healthcare professionals' time, and reducing the cost of treatment. A web-based approach bias modification (ApBM)^[39] was designed to use different colors to mark related (blue) and non-related (yellow) pictures to smoking, and participants were asked to use a computer mouse to push blue pictures or pull yellow pictures to change automatic behavioral tendencies. This RCT found that the 4-week ApBM training reduced daily cigarette consumption with a short-term effect (directly evaluated after training), while long-term effects were not observed at the 6-month follow-up. Another RCT^[40] attempted to combine two kinds of web-based CBM interventions: attentional bias modification (AtBM) and ApBM. AtBM was delivered by asking participants to respond to a visual probe pointing to the stimuli (e.g., a smoking-related picture and a neutral picture), then training them to shift their attention from smoking-related pictures to neutral pictures. However, the researchers failed to find evidence for the effectiveness of single and combined interventions in improving abstinence rates, daily cigarette use, and targeted bias when compared with their sham version. As found in other studies, cognitive bias modification (CBM) is controversial, with unclear effectiveness^[38]. This may be due to individual differences in neuropsychological impairments, and the current cognitive interventions only focus on the deficit of one cognitive system. Moreover, the drop-out rates for web-based interventions were generally high^[39-40], and mobile phone apps for individuals with alcohol use disorders or SUDs were well-accepted and considered to be easy to use; interactive, motivational, and positive effects were observed after intervention^[41]. To simultaneously help methamphetamine users overcome their cognitive deficits, enhance their control of impulse problems, and enable them to better control cognitive biases, Zhu et al.^[42] designed a phone app called computerized cognitive addiction therapy (CCAT) that combined cognitive training and CBM, including two working memory training tasks (N-back task and memory matrix task) and two methamphetamine-related attention-bias control tasks, and found that the CCAT improved cognitive impairments and impulse control, but did not significantly change attention biases and social cognition. Despite limited evidence on the effectiveness of neurocognitive training programs in the treatment of addiction, it is recommended that patients with SUDs should receive

an early and comprehensive assessment of their neuropsychological function (both after withdrawal and relapse) to customize personalized neurocognitive training programs^[37].

2.3 Digital Intervention with Other New Technologies

Patients with SUDs are particularly affected by substance-related social and environmental cues that trigger cravings and lead to relapse. Cue exposure therapy (CET) is a behavioral psychotherapy for SUDs. It aims to repeatedly expose patients to relevant substance cues, making them realize the negative consequences of using substances, and to improve self-efficacy through self-talk in high-risk situations, thereby reducing their cue reactivity and cue-induced cravings^[43]. Virtual reality (VR) CET (VET) allows clinicians to control the intensity of exposure. It provides a more immersive feeling than the traditional CET. VR is delivered to participants through a head-mounted display, presenting the VR scene of computer-generated images, and creating an atmosphere of immersion in the VR environment by simulating the visual and auditory cues in the real world through visual and auditory stimuli^[44]. Segawa et al.^[45] concluded that VR was effective in inducing cravings in patients with SUDs, with increased physiological responses and attentional bias. For alcohol- and nicotine-dependent participants^[46], various virtual cues (proximal [related items], contextual [places of purchase], and complex [parties]) may induce craving. For cocaine-dependent participants^[47], contextual and complex environmental cues can induce cravings, with interaction with cocaine sellers causing the highest craving rates. Pericot-Valverde et al.^[48] found that VET was related to the reduction of nicotine cravings in a 5-week intervention with an 8–20 min weekly sessions, and prolonging the duration of exposure to cues may be more helpful in reducing cravings induced by smoking-related cues. Metcalf et al.^[49] developed a recovery support game called Take Control on Windows, which combined CBT and VET to allow clients to fight against substance-clues through actions (beating, kicking, etc.), thereby practicing rejection skills. During the intervention period, participants reported reduced substance use, and alcohol patients had better efficacy than tobacco patients.

Biofeedback/neurofeedback, a new category of digital medicine, refers to a painless, non-invasive procedure that can measure characteristic data of the autonomic nervous system and brain activity (e.g., electroencephalography, electrocardiography, electrical skin activity, skin temperature, and functional magnetic resonance imaging (fMRI)) and provide real-time feedback to patients, and CBT or relaxation training techniques are adopted on the basis of feedback results, which can help patients achieve treatment goals through positive reinforcement^[50]. A study that

combined the imaging of non-drug-related rewards with fMRI neurofeedback found that dopaminergic activity in the midbrain and other reward areas in cocaine users were activated, indicating that feedback could change the imbalance in reward sensitivity of people with cocaine use disorders and restore the reward response to non-drugs^[50]. A study of VR intervention combined with biofeedback/neurofeedback successfully explored the mechanism of processing drug-related cues by measuring brain electrophysiological responses and autonomic nervous responses when stimulating cravings of methamphetamine users^[51], and found that drug-related cues were associated with changes in gamma activity in the meso-cortico-limbic reward and executive control circuits, as well as skin conductance level.

3 Relapse Management

Addiction diseases require long-term treatment. A challenge in the treatment process is understanding, predicting, recognizing, and coping with relapse. For patients with SUDs, once they leave the treatment environment, they rarely return for regular follow-up, making it difficult to track changes in their condition. EMA studies support addiction theory in a natural setting where decreased self-control ability and higher levels of craving are potentially associated with the likelihood of substance use^[52]. The key to preventing relapse is self-control. By monitoring internal (feelings or desires) and external (people, places, activities) factors related to relapse, EMA enables self-monitoring and conscious control in a variety of everyday situations. Self-reporting can make people aware of risky behaviors associated with relapse of SUDs, enhancing their ability to recognize and respond to stress and cravings. When pressing the button on the EMA device, clients felt the release of stress and became more immersed in thinking about coping with the situation and getting rid of cravings^[53]. The utilization of EMA and providing real-time intervention is helpful in achieving the goal of relapse management. A community-based addiction rehabilitation electronic system^[54] was designed to help social workers monitor the drug use behaviors of patients with SUDs who were receiving community detoxification treatment programs. It has been proved that Ecological Momentary Intervention (EMI) such as teaching coping strategies on days when clients reported more negative emotions could reduce alcohol use^[55]. The combination of EMA and EMI is recommended because the usage of EMA is associated with continued EMI usage, indirectly affecting abstinence^[56]. Trigger Health is a commercial application^[57] that utilizes machine learning to predict the risk of relapse of SUDs; if the client's risk of relapse is at the highest level, members of the treatment team will be notified, but so far, there is little evidence to support that the trigger health

app can prevent or reduce drug use.

The number of EMA and digital phenotyping data is often too large to be analyzed by common statistical methods, so machine learning is necessary to analyze valuable data corresponding to relevant activities and behaviors to achieve relapse prediction and prevention. Machine learning can quickly extract information from large data sets and information sources, calculate and analyze patients' behavior patterns, develop risk models, and determine an individual's susceptibility to disease. Commonly used machine learning methods include supervised, unsupervised, and deep learning^[33]. Supervised machine learning (SML) learns from large amounts of labeled training data, such as diagnoses of major depression and non-depression, and then tests the algorithm against unlabeled data to determine whether it can correctly classify target variables. Unsupervised machine learning (UML) algorithms learn unlabeled data and classify the data by identifying similarities between input data, such as identifying rare psychiatric subtypes from neuroimaging biomarkers, to provide prognostic predictions and optimal treatment. Both SML and UML data inputs require the guidance of a clinician or researcher, while deep learning can learn directly from raw data without human guidance to process a variety of complex unclassified raw data artificially, often predicting the risk of opioid use disorder in a specific population using electronic health records^[58].

4 Discussion

Qualitative research shows that patients do not have much resistance to digital medicine except for data security concerns, but from the perspective of health workers, it is controversial^[3]. Although the original intention of the development of digital assessment is to make the work of health workers more convenient, the feasibility in the clinical work environment should be seriously considered, including the willingness of health workers to use it and the consumption of workforce and financial resources. As the development of digital assessment tools is expensive, it takes a certain amount of time to accumulate to obtain economic benefits. At the beginning of use, health workers are often required to use both paper versions and digital assessment tools, which may bring them twice the workload. Therefore, before the implementation of digital evaluation tools, we must carefully investigate the willingness of the target population, consider the various problems in the promotion process, and formulate how to provide follow-up technical support.

The EMA method is time-consuming and laborious. Repeating answers will increase the burden on clients and may make them feel troublesome^[13]. A meta-analysis found that the pooled EMA compliance rate

(75.06%) was lower than the recommended rate (80%), indicating that it may not be convincing enough to represent the clients' daily lives^[59]. To improve compliance with EMA, researchers have tried to use monetary incentives or client preference or convenience regarding time of treatment. However, these cannot solve the essential problems of the EMA. To avoid clients receiving a large number of notifications at inconvenient or unnecessary moments, the EMA notification system needs to comply with the individual's behavioral habits and detect the right time to provide information and questions. Aminikhanghahi et al.^[20] designed SEP-EMA, an EMA combined with machine learning. First, SEP-EMA asked clients if they were convenient at each EMA, assessed the client's current mental and physical state, and asked clients to mark their recent activities. Then, it analyzed the clients' most suitable EMA response time through machine learning. Compared with EMA sending by random time, the response rate of SEP-EMA increased by 7.1%.

Digital phenotyping is an objective data, but the sensitivity, specificity, and accuracy of biosensors will be an important issue in clinical research. It is valuable and challenging for clinicians and technology developers to find a set of digital phenotyping that reflects the patient's current use of an addictive substance. Because EMA and digital phenotyping data come from patients' personal devices or hospital electronic medical record systems, it inevitably involves the issue of data security, especially if commercial partners are involved, and the method of data storage is also an important issue that cannot be avoided and must be resolved.

The majority of current digital medicine only supports one psychotherapy or one digital technology; if all kinds of digital technologies and digital interventions can be integrated, such as combining digital intervention (digital psychotherapy such as mobile phone app, and chatbot) with VR technology or wearable devices in order to improve the interaction and enjoyment of intervention, it may solve the problem of insufficient efficacy and high dropout rate of monotherapy. VR technology needs to be further optimized for portability to make the application of VR intervention more routine; for example, it will be more acceptable if it can be commonly used at home. The application of VR technology in the field of addiction has considerable space for development, such as exploring more diverse VR simulation scenarios, targeting different addictive substances, and combining different psychotherapies.

WHO has pointed out that digital medicine must show long-term progress compared with traditional medical services to allow continuous application and integration into medical systems^[3]. Despite a high enthusiasm for the development of digital medicine worldwide, the actual clinical use rate of digital medicine is relatively low. Most existing apps are independent com-

mercial products that are not admitted by the public healthcare system. There are a large number of apps currently available in app stores with similar intervention functions that have not been scientifically verified^[60]. Only with evidence of validity can the app be qualified for clinical use. Even for some digital medical products that had evidence of effectiveness, the quality of their evidence was poor and not convincing, because many existing RCTs relied only on self-reported data, without physiological data and biological specimens for verification, with short intervention duration, short or no follow-up, high drop-out rates, and low utilization, and underrepresentation of the sample. Few assessment indicators were selected for the study outcomes, and confounding factors, such as the presence of multi-drug use, anxiety, and depression symptoms, were not considered during analysis. Fu et al.^[61] found that the heterogeneity of these types of research results was large. Future multi-site and unified researches should be conducted through international and regional cooperation to achieve repeatability of the research results.

5 Conclusion

The application of digital medicine in the field of addiction is embodied in digital assessment tools, the use of EMA and digital phenotyping, digital interventions such as psychological interventions on digital devices, cognitive function training, and new technologies such as VR and biofeedback/neurofeedback, and the integration of various digital technologies for relapse management. The most important feature of digital medicine is its convenience, and with the continuous maturity and popularization of new technologies, digital medicine will present advantages over traditional medical services in terms of cost. The realization of the clinical application of digital medicine in the field of addiction requires the cooperation of multiple disciplines and departments, such as psychiatry, computer science, engineering, and public health systems.

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