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Digital Therapeutics in Perspective: From Regulatory Challenges to Post-Marketing Surveillance

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Digital therapeutics (DTx) are innovative therapeutic interventions, in which the therapeutic activity is carried out by algorithms and software. They represent a new opportunity especially for the treatment of chronic pathologies associated with dysfunctional lifestyles and behaviors, where conventional drug therapy is not fully effective. DTx are highly customizable therapeutic tools, allowing a better involvement of the patient in the management of the disease. To date, the clinical use of DTx in Europe is still generally limited. One of the main issues related to DTx is the general lack of education of healthcare professionals in this sector that leads to a knowledge gap between data scientists, and physicians, who should identify all those clinical needs that could be better addressed through the use of DTx. From a regulatory perspective, DTx are classified as Medical Devices. However, their research and development process is similar to that of conventional drugs, since they are tested in clinical trials and their approval refers to specific therapeutic indications. For this reason, precise criteria for marketing approval, for the health technology assessment and for the reimbursement of these therapies need to be defined. Moreover, as for conventional drugs, it is also fundamental to conduct post-marketing studies on DTx, aiming at re-evaluating the benefit-risk profile and collecting information related to large-scale use in real world setting. The aim of this review is to describe the main challenges for DTx development, regulation and widespread clinical use.

Keywords: digital therapeutics, regulation, pharmacovigilance, digital health, post-marketing surveillance

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INTRODUCTION

Over the last decade, digital revolution has been radically transforming all sectors of society and it has recently begun to produce an impact in the healthcare sector especially, mainly due to the increasing amount of health data generated by each individual patient and the increased computational capacity both in terms of data archiving and analysis. COVID-19 pandemic has significantly boosted the digital transition in healthcare and many digital health solutions became key components in keeping non-COVID-19 pathways running. Consumer-grade digital tools for routine monitoring and diagnosis in multiple diseases are increasingly used by physicians (Dang et al., 2021). According to the IQVIA Report on Digital Health Trends, published in July 2021, investments on digital health has increased, reaching a record $24 billion of investments 2020, mainly driven by continued acceleration of mergers and acquisitions and a growing impact of private equity investors (The IQVIA Institute., 2021).

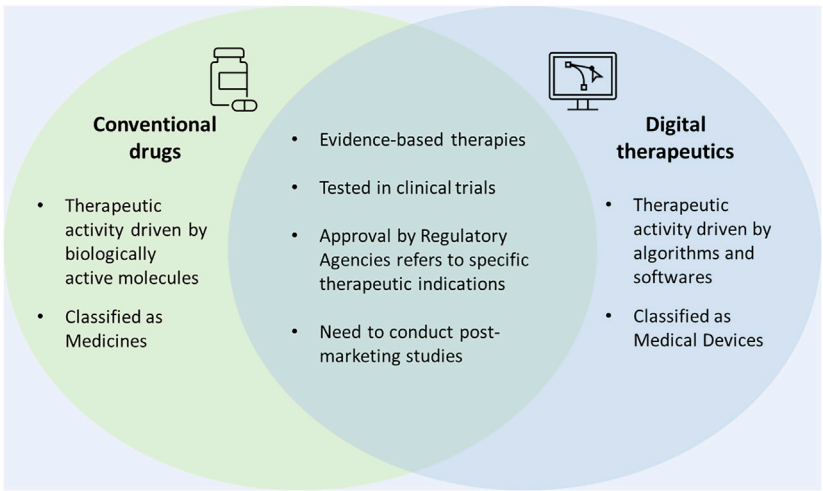

FIGURE 1 | Comparison of conventional drugs and Digital Therapeutics: common characteristics and differences.

By the term "digital health" is meant "the field of knowledge and practice associated with the development and use of digital technologies to improve health. Digital health expands the concept of eHealth to include digital consumers, with a wider range of smart-devices and connected equipment. It also encompasses other uses of digital technologies for health such as the Internet of things, artificial intelligence, big data and robotics" (World Health Organization., 2021). Many technologies, including telemedicine, wearable devices, smartphones and digital therapeutics (DTx) are included within this broad definition (Recchia et al., 2020). The main difference between DTx and the other digital health technologies is that, while the latter are aimed at supporting users in changing their lifestyle and pursuing goals related to their well-being, DTx are technological tools offering evidence-based therapeutic interventions aiming at preventing, managing or treating medical problems or diseases. Unlike conventional drugs, the therapeutic activity of DTx is driven by algorithms and high-quality software programs (Digital Therapeutic Alliance., 2019) (**Figure 1**). DTx can be prescribed either independently (stand-alone therapies) or in association or in combination with conventional drugs, devices or other therapies (Sverdlov et al., 2018).

DTx represent a new therapeutic opportunity especially for the treatment of chronic diseases associated to dysfunctional lifestyles and behaviors, where conventional drug therapy is only partially effective. In fact, DTx have the potential to correct these dysfunctional behaviors, by stimulating the patient's involvement in the management of the disease (Kvedar et al., 2016).

From a regulatory perspective, both in United States and in Europe, DTx are classified as Medical Devices. However, since they are actually tested in clinical trials and their approval by regulatory agencies refers to specific therapeutic indications, their research and development process is similar to that of conventional drugs (Recchia et al., 2020).

Several DTx have been already authorized in some countries, where they are prescribed by physicians and reimbursed by public health services or reimbursed by insurance systems (**Table 1**). However, to date, the clinical use of DTx in Europe is still generally limited. Nevertheless, DTx have a great potential and several advantages.

In this review, the main challenges for DTx development, regulation and widespread clinical use are described.

REGULATORY ASPECTS OF THE MARKETING OF DIGITAL THERAPEUTICS

Although in some European countries several procedures have been set up for the marketing authorization and reimbursement of DTx, these are just individual and uncoordinated initiatives. The European regulatory system concerning DTx is still immature and specific regulations aimed at evaluating these tools and ensuring the safety of the devices and the integrity of the data collected are lacking. In Europe, the regulatory legislation for DTx is represented by the European Regulation on Medical Devices 2017/745 (MDR), implemented in Europe in May 2021, even if it does not explicitly mention them (Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EE). Since the development and delivery features of DTx are similar to those of conventional drugs, evidence on efficacy and safety must be provided before they can obtain a CE mark and be authorized for marketing. Therefore, it is necessary to harmonize the development and marketing approval procedures for DTx on a global scale. In Germany, a specific fast-track regulatory process for digital health applications (DiGA, *Digitale Gesundheitsanwendungen*) was launched in December 2019 to allow physicians to prescribe digital health applications (including several DTx) that can then be reimbursed by health insurance companies (German Federal Institute for Drugs and Medical Devices., 2020). To date, globally 24 DTx received

TABLE 1 | Digital Therapeutics approved up to December 2021 and market authorization pathways.

Digital therapeutic	Indication of use	Medical prescription required	FDA Approval	CE mark via MDD/MDR (Europe)	CE mark and DiGA (Germany)
EndeavorRx®	ADHD	✓	✓	✓	--
Parallel®	Irritable bowel syndrome	✓	✓	✓	--
NightWare®	PTSD	✓	✓	--	--
reSET®	Substance use disorder	✓	✓	--	--
reSET-O®	Opioid use disorder	✓	✓	--	--
Somryst®	Chronic insomnia	✓	✓	--	--
EasyVR®	Chronic lower back pain	✓	✓	--	--
Vivira®	Pain (back, hip, knee)	✓	--	--	✓
Selfapys®	Depression, anxiety, eating disorders, burnout	✓	--	--	✓
Mika®	QoL and psychological issues	✓	--	--	✓
Rehappy®	Stroke or intracerebral bleeding/haemorrhagic stroke	✓	--	--	✓
Kalmeda Tinnitus®	Tinnitus	✓	--	--	✓
Zanadio®	Obesity	✓	--	--	✓
Mindable®	Panic and agoraphobia	✓	--	--	✓
M-sense Migräne®	Migraine	✓	--	--	✓
Somnio®	Insomnia	✓	--	--	✓
Elevida®	Multiple sclerosis-related fatigue	✓	--	--	✓
Velibra®	Anxiety disorder, panic, agoraphobia	✓	--	--	✓
Deprexis®	Depression	✓	--	--	✓
Vorvida®	Alcohol use disorder	✓	--	--	✓
Space from Depression®	Mental health, behavioural disorders	--	--	✓	--
Kaia Health®	Musculoskeletal pain	--	--	✓	--
Pivot Program®	Smoking cessation	--	✓	✓	--
MindMotion GO®	Neuro-rehabilitation	--	✓	✓	--
Freespira®	Panic attack symptoms, PTSD	--	✓	--	--

ADHD, attention deficit hyperactivity disorder; DiGA, digitale gesundheitsanwendungen; FDA, food and drug administration; MDR, medical device regulation; MDD, medical device direction; PTSD, post-traumatic stress disorder; QoL, quality of life.

market authorization in at least one country (**Table 1**). Their therapeutic indications mainly concern mental illnesses (e.g., attention deficit and hyperactivity disorder–ADHD, sleep disorders, depression), but also chronic diseases (e.g. diabetes mellitus, chronic obstructive pulmonary disease, hypertension) and addictions (Recchia et al., 2020). A recent systematic review on 136 studies registered on ClinicalTrials.gov about DTx found that 35%, 19%, 13%, and 9% of them were indicated for mental health, chronic diseases, addiction, and sleep conditions, respectively (Santoro et al., 2021). The same systematic review also found that DTx are based on several digital health tools including app (42%), web-based interventions (26%), videogames (9%), and virtual reality (4%) (Santoro et al., 2021).

Regardless of the nature of the active ingredient and the regulatory procedure, the clinical evidence required for the approval of DTx must be the same as for conventional drugs, both in terms of quantity and methodology applied for their generation (Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EE). The evaluation of the efficacy and the safety of DTx should be based on high-quality controlled clinical trials carried out according to the standards required by regulatory agencies. For each DTx, the cost-effectiveness profile, the additional therapeutic value and the impact on patient's health and on the budget should be also established.

The need of a global and systematic multidisciplinary assessment of the economic, social and ethical consequences of the use of DTx in clinical practice is critical. From a regulatory point of view, it is necessary to define specific indications for DTx approval, taking into account their peculiar characteristics, such as the rapidity of digital evolution and the issues concerning patients' privacy and data security (Gopal et al., 2019). Harmonizing regulatory processes is essential, since the lack of specific regulations to guarantee safety and quality of these devices is a further obstacle for the development of DTx (Rassi-Cruz et al., 2022). The experiences conducted so far in Europe are quite limited, and essentially concern the assessments of the National Institute for Health and Care Excellence (NICE) that has outlined an evidence standards framework for DTx aiming at the standards of evidence health innovators will be expected to produce for different types of digital health technologies. Concerning psychological DTx, such as Deprexis for the treatment of depression and Sleepio for the treatment of insomnia (National Institute of Health, 2017; National Institute for Health and Care Excellence., 2018), NICE provides a summary of clinical effectiveness, technical standards assessment, content assessment and cost and resource impact that is evaluated by an expert panel. Sharing best practices, learning from each other and building structures to allow for mutual recognition of evidence or even complete certification is essential for European Countries (Ahlqvist and Kalliola., 2021).

POST-MARKETING SURVEILLANCE OF DIGITAL THERAPEUTICS

The post-marketing surveillance of the efficacy and safety of DTx has to be carefully implemented, as for conventional medicines, to integrate evidence on benefit-risk profile of DTx with data gathered from real world setting. With the increasing uptake of DTx into clinical practice, setting up a proper pharmacovigilance monitoring of DTx will become of paramount importance also for rapidly identifying potential safety signals and in general establishing the safety profile of these technologies. Although the side effects associated with DTx may be generally less severe and easier to be managed than those caused by conventional drugs, based on pivotal trials, adverse effects of DTx may still occur to a greater extent than in respective control arms. For example, in the clinical trials that provided the scientific evidence used by the Food and Drug Administration (FDA) to approve EndeavorRx, a DTx for the treatment of ADHD in patients aged between 8 and 12 years, 7% of treated patients experienced non-serious adverse events associated with the digital treatment, including frustration, headache, dizziness, emotional reactions, nausea or aggressiveness, as compared to 2% of children treated with active control (Kollins et al., 2020). As for conventional therapies, conducting post-marketing studies will provide information about larger and more heterogeneous populations, and about the long-term safety of DTx. In particular, post-marketing studies are helpful to identify new and/or less common adverse effects that may not be observed in clinical trials and to provide relevant information concerning patients' adherence and user experience in the real-world setting.

The main purposes of post-marketing studies are to re-evaluate the benefit-risk ratio of DTx and to collect information about their large-scale use. The Medical Devices Regulation encourages the use of the results of real-world studies to generate new evidence, to improve and update the software.

DTx also allow to collect patient-level data that can be used to re-evaluate their safety and effectiveness in real-world setting and to study patients' quality of life through the collection of patient-reported outcomes. On the other hand, the exponential increase in data related to individual patients raises concerns about the quality and security of collected data (Gopal et al., 2019). Moreover, the growing implementation of data sharing technologies implies the need to define a legal framework, able to safeguarding individual privacy, while allowing transparent data sharing for research purposes.

It is therefore important that manufacturers set up systems for collecting real-world data, assuring data quality and respecting patients' data protection. An example of data collection is Natural Cycles, a DTx used for birth control. Using this device, data was collected in several retrospective observational studies to estimate the effectiveness of the device in both the experimental and the real-world setting. In addition, starting from these data, the manufacturer had the opportunity to obtain further evidence related to activities directly connected with the use of the device, allowing the dissemination of important scientific content (Bull et al., 2019).

Recently, it has been published an observational study aimed at evaluating the use and effectiveness of reSET-O, a DTx indicated for the treatment of opioid addiction, through the use of real-world data. The study included a geographically and clinically heterogeneous cohort, more than 30 times larger than the population enrolled in the pivotal trial on which the FDA authorization was based. The study results showed that reSET-O was widely used by opioid-addicted patients (80% of patients completed 8 or more core modules, 66% completed half of all core modules, and 49% completed all major modules) and that the therapy was effective for quitting opioid consumption (the proportion of patients with at least 4 weeks-long opioid abstinence ranged from 66% to 91%, compared to 77% in the pivotal trial) (Maricich et al., 2021).

THE IMPORTANCE OF TRAINING EXPERTS IN THE FIELD OF DIGITAL THERAPEUTICS

The use of artificial intelligence in healthcare has created new possibilities and continues to evolve in terms of its capabilities, scope, and scale. For DTx industry specifically, artificial intelligence may play in the future a key role in providing more customized algorithms and interventions and driving engagement to help patients achieve better health (Palanica et al., 2020).

The increasing evidence on DTx in clinical setting makes it necessary to educate healthcare professionals in the field of artificial intelligence and machine learning technologies.

More important is the lack of training in this sector leading to a knowledge gap between data scientists, who create the digital technologies, and physicians, who should be able to identify all those clinical needs that could be better addressed through the use of DTx. In turn, this gap leads to a possible confusion regarding the use of the term "DTx." For example, in a systematic review of studies registered on ClinicalTrials.gov about DTx found that 424 studies (3 out 4 retrieved by a specific search string) were incorrectly associated with DTx because they were not based on randomized clinical trials (specifically they were based on observational studies or single arm trials) or involved digital health tools with aims not related to a "therapy" (Santoro et al., 2021). Training on DTx among physicians and on clinical research methodology and evidence based medicine among developers could help reducing this knowledge gap and avoiding confusion when using digital health terms. In addition, the involvement of physicians and other healthcare professionals in projecting DTx, could be useful to both ensure safe and effective applications of these therapies and to entice patients to use them (Rassi-Cruz et al., 2022).

Furthermore, since the end user of DTx is the patient, who uses the devices directly, the role of the Expert Patient in DTx research and development teams is crucial and it is necessary to promote training programmes for the development of this new patient role. Filling this gap is therefore necessary to optimize and consolidate the use of DTx in clinical practice (Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/

EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EE). In this regard, for DTx to gain a broader acceptance by patients, it is also important that DTx developers endeavor to align innovation with a user-friendly experience (Wiederhold., 2021). Moreover, educating physicians in statistics and information technology may also significantly contribute to the development and evaluation process of such DTx. In particular, physicians should also be familiar with how patient data is collected and processed by DTx and should also be up-to-date on current Regulations on patients' privacy and data security. The need to improve the digital skills of healthcare professionals, patients, and software/hardware developers however, is not limited to DTx only, but it concerns the entire spectrum of digital health. Performing systematic reviews and meta-analyses on DTx studies could also help in identifying medical areas, conditions, and patients where they are shown to be effective.

The World Health Organization (WHO) has recently announced the Global strategy on digital health 2020–2025, whose aim is to accelerate the implementation and optimize the use of digital technologies in the area of health in a fair and sustainable way, allowing all patients to better manage their health (World Health Organization., 2021). The WHO Global strategy highlighted the need to develop a cross-sector coordination for the integration of financial, organizational, human and technological resources, with the objective of making the best use of digital services in the health sector (Dhingra and Dabas., 2020). Because of the intrinsic multidisciplinary nature of digital health, there is the need to promote the interaction between the world of information technology and healthcare, i.e., creating a concrete interdisciplinary collaboration between computer scientists/engineers, patients, healthcare professionals, and clinical research experts. It is indeed essential to address real-world clinical challenges and medical or public health issues and to recognize unmet clinical needs.

CONCLUSION

Digital health provides new tools to address some of the main issues of the health system, and DTx represent a new therapeutic opportunity especially for the treatment of patients suffering from chronic diseases associated with incorrect lifestyles and dysfunctional behaviors. Since these therapies are similar to traditional drugs in terms of research, development and marketing, an international harmonization of assessments and regulatory processes concerning DTx is fundamental. Moreover, the growing evidence of Digital health in the clinical setting makes it crucial to educate healthcare professionals and software developers in the fields of DTx and of clinical research methodology, and to support the development of Expert Patients in digital health technologies. Lastly, as for conventional therapies, conducting post-marketing studies is essential to provide information on larger and more heterogeneous populations and on the long-term safety of DTx.

Take-Home Messages

- As with traditional drugs, DTx marketing approval should be followed by close reassessment of their risk-benefit profile in the real-world setting;
- To ensure DTx safety and quality, it is essential to globally harmonize their development and market approval procedures;
- Training healthcare professionals and patients in the field of digital health is crucial to optimize and consolidate the use of DTx in clinical practice.

AUTHOR CONTRIBUTIONS

GT conceived the study. SC wrote the first draft of the article. ES and GR critically revised the manuscript.

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