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Digital therapeutics in General Medicine

Prior considerations

Italy affords an illustrative example of the potential for the use of digital therapeutics (DTx) in the field of General Medicine. Mean life expectancy for the Italian population is currently 80.6 years for men and 85 years for women, with an expected increase of five years for both men and women by 2065, when the forecast life expectancy will be 86.1 years and 90.2 years respectively[(1)]. In 2017, 35% of Italians were over 65 - 5% more than the main figure for Europe as a whole[(2)]. About one elderly person in two suffers from at least one serious chronic disease or is multi-chronic, more than 60% of them being over the age of 80[(3)]. Chronic diseases, which by definition require long-term treatment and multidisciplinary support, currently account for 70-80% of health resources[(4)]. This results in increasing pressure on the health system, against a background of a shrinking and crisis-ridden national economy. Even before the severe economic fall-out from the CoViD-19 pandemic, in 2018 Italy's debt/GDP ratio was as high as 134.8%, higher even than during the Second World War, when it peaked at 118% in 1943[(5)]. The high mean age of national health service staff, with staff turnover deliberately placed on hold as the principal measure for containing the health budget in recent years, is an additional critical factor[(6)].

Against this background, the way healthcare is delivered raises the

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need for careful thought about the advisability of introducing innovative organizational models, based on measurable and predetermined efficiency and sustainability parameters.

In this perspective, future health policies must of necessity prioritize the focus on patient-centred models, underpinned by the concepts of community care, fragility and multidisciplinary integration. There are few points on the health agenda that find such ready consensus as the need to invest in community care, prioritization of primary care, its integration with hospital care (within the overall development and coordination of social and health services), and the need to ensure availability of the tools best suited to this task (above all, digitalization).

Expectations

Technological innovation, particularly with regard to technologies underpinned by analysis and processing of electronic data, has a greater potential than ever before to make this change materially possible.

In this regard, the introduction of DTx within the Italian health system is a new opportunity to provide broadly accessible therapeutic solutions that offer three main advantages: 1) address therapeutic needs that remain unfulfilled by current traditional treatments; 2) offer therapeutic products with a high safety profile; 3) move beyond the "one fits all" approach that is typical of common drug treatments, thanks to the capacity of DTx to generate masses of extremely valuable health data that are specific to each single patient, and to remodulate treatment on the basis of this information.

Emblematic in this respect is the positive impact on home treatment for cancer patients demonstrated by the US Company Voluntis, with the introduction of the DTx product Oleena. The therapy, comprising an app used by the patients for reporting to the oncology clinic any adverse events that have occurred during treatment, makes it possible to follow the clinical course of the patient's condition and intervene as appropriate in relation to the ongoing treatment. Patients have benefited from significantly higher overall survival than those treated on a standard-of-care regimen[7]. On the basis of these data, the app was given FDA certification and will soon be accessible for clinical use by US patients.

Impact on the General Practitioner's professional practice

The Digital Therapeutics Alliance classifies DTx in the following 4 functional categories:

1. management of a clinical condition;
2. management and prevention of a pathological condition;
3. optimization of treatment;
4. treatment of a pathological condition.

The various DTx products that have been approved to date or are currently in advanced clinical development are indicated for many different chronic pathological conditions, such as depression, substance dependency, insomnia, hypertension, obesity, schizophrenia, generalized anxiety disorder, asthma, chronic obstructive pulmonary disease and type 2 diabetes.

Clinical management of these new therapeutic tools is therefore bound to depend first and foremost on primary care, meaning General Practitioners (GPs), paediatricians, clinical specialists, nurses, community healthcare providers and the health authority staff who are the linchpin of care for chronic conditions.

The use of DTx based on input from the GP broadens the armamentarium available to all community healthcare staff, ushering in a new concept of treatment that is proving able to address important clinical needs not fulfilled by traditional care models. Above all, this new approach makes it possible to generate huge quantities of clinical data that enhance knowledge of disease and improve outcomes.

From Big Health Data generated by DTx, artificial intelligence-based systems can offer the GP a dashboard with a comprehensive view of the patient's clinical condition. This further advantage is not an end in itself, but allows the GP to have constantly updated real-life clinical data for the individual patient, leading in turn to personalized decision-making on the basis of predictive outcomes automatically generated by the machine learning software. Important challenges of General Medicine, like clinical monitoring, patient compliance and community care, can thus be addressed. In addition, managing clinical parameters in this way makes it possible to integrate them with data in the electronic patient medical record, today still essentially a bureaucratic concept, thus giving scope for horizontal flows of knowledge and information in General Medicine research. This aspect is also particularly important in relation to the very topical subject of telemedicine, for which many potential clinical ap-

proaches are applicable in actual practice only if the doctor can have an overall view of the patient's health data. In this respect, the customary diagnostic step of asking patients for details of their pharmacological and clinical history becomes particularly complicated in the setting of a teleconsultation with elderly, polypathological and fragile subjects.

All health technologies, before and during use, require regulatory surveillance of their ethical, clinical and social impact on the healthcare system. Digital products are no exception in this respect. The GP can play a leading role in the paradigm shift that we are now experiencing, and need not be seen simply as the user of new tools. In the last 40 years, drug classes that have come to play a fundamental role in primary care (antihypertensives, anti-inflammatories and bronchodilators being just a few examples) have been developed in academic research contexts, coming into contact with community medicine only after they have entered clinical use. This means that the GP has until now been essentially a consumer of new therapeutic products, developing the evidence-based dimension of professional practice in an observational setting. To date, as an example, analysis of Italian General Medicine publications shows a majority of observational studies, almost always centred on organizational aspects of the profession, with very few experimental clinical studies. This means that there is little if any precedent in Italian general medicine for fully fledged, autonomous experimental investigation, able to address GPs' clinical, professional or management issues.

DTx, given their intrinsic characteristics, are developed by digitalized clinical trials with a decentralized set-up, taking place outside the clinical investigation centre. In this type of arrangement, recruitment, data collection and analysis take place close to the patient's natural care setting, so that s/he does not have to go constantly from home to an investigation centre. This arrangement is a significant opportunity for giving new impetus to clinical research in General Medicine. The GP, together with community care providers, is a privileged observer of real-life clinical dynamics, and thus steps naturally into the role of investigator in this innovative form of clinical trials. In addition, the digitalization of clinical research makes it possible to negotiate some of the barriers that have so far slowed down clinical research in General Medicine, particularly in relation to the type of premises required – e.g., mandatory facilities for storage of pharmaceuticals, equipment and instrumentation (refrigerator units, etc.), study data archives (with related data protection requirements).

However, before DTx research and its application in clinical practice can be managed in the community care setting, the GP must acquire full mastery of new treatment concepts such as online consultation and recruitment, digital patient-reported outcomes and biomarkers, wearable medical devices, data protection, machine learning and artificial intelligence. This means that the GP needs to undergo specific training, devised to complement development of clinical expertise with acquisition of skills from other disciplines such as data science. The aim is to prepare doctors and healthcare providers for ongoing or future changes to the healthcare sector, as a result of new technologies coming into use. DTx offer a significant example of this, but not the only one.

Mastery of DTx certainly requires the will to address broad-spectrum scientific challenges, typical of frontier research. As an example, investigation of DTx presupposes definition of digital endpoints without ready availability of a gold standard in the literature. The same is true of assessing the dose-response curve for treatments whose active principle is an algorithm. Even understanding this active principle (algorithm) is technically challenging in the case of machine learning-based algorithms, whose performance can shift in response to acquisition of new training data while the study is still in progress. Though DTx do not exert their main action through metabolic processes, the occurrence of adverse events cannot be ruled out. On the one hand, prolonged exposure to DTx software enables interaction with the subject and positive changes (efficacy) in terms of human behaviour; on the other hand, however, it is important not to overlook the risk that this can induce negative behavioural changes such as dependencies, sleep disorders or postural problems. In the same way, one cannot rule out the possibility of interaction between several DTx products administered at the same time, just as occurs with pharmaceuticals.

Strictly technical considerations of this kind still have to be addressed. They offer the GP who acquires experience in DTx R&D the opportunity to build up technical expertise on a par with that of academic researchers, and to break new ground. This creates scope for high-profile professional recognition of community medicine, with combined experience of clinical practice and research finally becoming a *sine qua non* of primary care. The GP, as a clinician and researcher, thus comes to be seen not as a mere prescriber of drug treatments, but as a major therapeutic asset.

The challenge for Scientific Societies and healthcare institutions is to welcome the advent of DTx in the Italian healthcare system and maximize its potential benefits. The rationale for this is based not only on the related health advantages, as discussed above, but also on the resulting strategic added value for the country's economy. In 2018, the global DTx market was estimated at 1.8 billion dollars, with an expected rise to 7.1 billion dollars by 2025[8], the main areas of development being treatment of obesity, chronic respiratory disease and psychiatric disorders[9]. This indicates the scale on which DTx could bring new opportunities for the country's R&D and manufacturing systems, while also ushering in innovative treatment pathways that could enable significant savings for the health system through a more sustainable approach to today's prohibitive levels of expenditure on chronic medical treatments.

In conclusion, DTX are a valuable treatment tool in the complex scenario of healthcare digitalization, offering a real possibility of enhanced efficacy, safety and effectiveness for biomedical research and for delivery of healthcare services. In this respect, DTx can be seen as an indispensable opportunity - not only, as we have seen above, with a view to addressing major challenges of sustainability for the health system, but also for attracting and boosting investments in national research and manufacturing systems.

What is known

- Increased life expectancy and the growing weight of multiple chronic diseases create ever-increasing pressure on the health system, indicating the need for efficient and sustainable organizational models
- Future health policies must necessarily pay close attention to patient-centred models, underpinned by the concepts of non-hospital treatment, fragility and multidisciplinarity
- In the definition of health investment policies, there is now widespread consensus on the need to promote community care, with a major role for primary care side by side with hospital care, prioritizing development and coordination of health and social services accordingly
- Application of digital technologies to healthcare, including the use of DTx, is a significant opportunity for a boost to the system's efficiency, with the GP taking on a particularly important role in managing progress towards the objectives that this entails.

What is uncertain

- Taking up the opportunities offered by digital health medicine treatment presupposes a major update in terms of technological know-how and cultural approach, still not adequately or uniformly achieved in many countries
- Traditionally, pharmacological treatments for chronic diseases are developed in an academic research setting, but are then mostly used in community care. DTx are predominantly developed by digitalized clinical trials that provide an opportunity for closer involvement of the GP in scientific investigation. To reinforce this, an appropriate regulatory framework and the related infrastructure must be developed accordingly
- DTx can be an option of great interest not only for achievement of healthcare objectives, but also with a view to the health system's sustainability. In some countries (including Italy), it is not yet clear what course will be adopted regarding the place in therapy of DTx.

What we recommend

- For correct and efficient governance of DTx in the community care setting, the GP must be able to understand and manage new concepts of a technological nature, for which adequate training must be organized so the clinical skills can be appropriately complemented
- At institutional level, concrete measures should be taken as soon as possible in terms of regulatory and infrastructure-related needs, so that community medicine and the national health systems as a whole can benefit from the significant potential advantages offered by DTx.

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