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Mini Review

Software as a Medical Device (Samd) and Optimization of Pharmacological Therapy: The Case of Abilify Mycite® in Monitoring Therapeutic Adherence

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Abstract

In recent years, artificial intelligence has assumed a central role in the transformation of healthcare systems, enabling tools capable of supporting diagnosis, monitoring, and treatment with a level of personalization that was previously difficult to achieve. In this context, the convergence of algorithms, medical devices, and pharmacotherapy has fostered the emergence of digital medicine, a paradigm in which data are no longer merely a byproduct of the care pathway but become an integral part of the therapeutic intervention itself.

Keywords: Artificial Intelligence; Healthcare Systems; Algorithms; Medical Devices; Pharmacotherapy; Samd; Abilify MyCite®

Introduction

Artificial intelligence in medicine

Within this evolution, patient-centered medical devices occupy a distinctive position. These devices are designed to interact directly with patients, assist them in managing their therapy, and encourage a more active role in the care process. This represents a significant shift: patients are no longer simply recipients of prescriptions but active participants in a system that collects information on therapeutic behavior, provides feedback, and enables more continuous monitoring than the traditional model based exclusively on clinical visits.

Among these technologies, digital pills hold a special place. These systems combine a medication with an ingestible sensor capable of confirming drug ingestion and transmitting this information to a digital platform. Interest in these tools stems primarily from the problem of medication non-adherence, which remains one of the leading causes of treatment failure in chronic diseases. Estimates from the World Health Organization indicate that, in developed countries, average adherence to chronic therapies is approximately 50%, with significant consequences for clinical outcomes, hospitalizations, and healthcare costs [1].

This work examines the role of artificial intelligence-based medical devices in pharmacological therapy management, with particular attention to digital medicine systems and the case of Abilify MyCite®, the first example of integration between a medication, an ingestible sensor, a skin patch, a mobile application, and a cloud platform approved by a regulatory authority. The objective is to reconstruct the theoretical and regulatory framework, discuss the problem of medication adherence and its pharmacological implications, describe the functioning of

ingestible sensor systems, and evaluate their potential, clinical limitations, ethical concerns, and future perspectives.

From a methodological perspective, this study is based on a review of the scientific literature, regulatory documents, and major institutional sources. FDA documents related to Abilify MyCite®, IMDRF references on Software as a Medical Device, Regulation (EU) 2017/745 on medical devices, and clinical and observational studies evaluating digital medicine systems in different therapeutic areas were considered.

Artificial intelligence in medicine can be defined as the set of computational methods capable of simulating cognitive processes such as learning, classification, prediction, and decision support. Although its origins date back to the mid-twentieth century, its development in healthcare has accelerated only over the last decade, thanks to the availability of large amounts of data, increased computational power, and the maturation of machine learning and deep learning techniques [2].

Machine learning enables systems to learn from data without being explicitly programmed for each specific task. In medicine, this translates into the ability to classify radiological images, identify at-risk patients, predict clinical events, or detect patterns not immediately visible to human observation. Deep learning, based on deep neural networks, has further expanded these capabilities, particularly in the analysis of images, signals, and clinical texts [3].

Clinical applications are numerous. In diagnostics, advanced algorithms support the identification of pulmonary lesions, breast cancer, diabetic retinopathy, and histological abnormalities. In clinical decision support systems, AI integrates clinical, laboratory, and instrumental data to formulate recommendations regarding risk, prognosis, or potential therapeutic response. In remote monitoring, integration with sensors and wearable devices enables continuous assessment of parameters such as heart rhythm, physical activity, and glycemic trends.

An area of growing interest concerns the integration of AI with clinical pharmacology. Machine learning algorithms are used to predict individual drug responses based on clinical variables and, in some cases, pharmacogenetic factors. For example, variability in CYP2D6 cytochrome activity significantly influences the metabolism of numerous psychotropic drugs, and predictive models can support the identification of patients at risk of altered drug exposure. Similarly, AI-based systems are applied in therapeutic drug monitoring, where they can estimate plasma drug concentrations from dosing data and patient characteristics, as well as in dose optimization through population pharmacokinetic approaches [4].

However, the value of artificial intelligence in medicine does not depend solely on technical performance. To be truly useful, a system must be generalizable, robust, interpretable, and suitable for real-world clinical settings. Consequently, the contemporary development of healthcare AI is advancing alongside debates on explainable AI, federated learning, bias management, and the use of multimodal data.

In the context of this thesis, AI is considered the infrastructure enabling increasingly personalized, connected, and patient-centered devices, culminating in systems where medication intake monitoring becomes an integral part of the therapeutic pathway itself.

The present work was developed through a narrative review of the scientific and regulatory literature concerning digital medicine systems and Software as a Medical Device (SaMD). The literature search was conducted using international databases such as PubMed, Google Scholar, and institutional documents from the Food and Drug Administration, the International Medical Device Regulators Forum, and the European Commission.

Articles published primarily between 2010 and 2024 were selected using keywords such as *digital medicine*, *ingestible sensors*, *medication adherence*, *SaMD*, and *aripiprazole digital system*.

Observational studies, real-world studies, systematic reviews, and regulatory documents were included, with preference given to those of greater clinical relevance and applicability to practice.

The analysis was supplemented with pharmacological data on aripiprazole and regulatory and ethical considerations to provide a multidimensional perspective consistent with the fields of clinical research and Medical Affairs.

Software as a medical device (SaMD)

The concept of Software as a Medical Device represents a fundamental milestone in the regulatory evolution of digital

healthcare devices. According to the definition provided by the International Medical Device Regulators Forum (IMDRF), SaMD is software intended for one or more medical purposes that performs these functions without being part of a traditional medical hardware device. This distinction is important: SaMD is not software embedded within medical equipment but rather an independent medical function that can operate on smartphones, tablets, computers, or cloud platforms [5].

The relevance of SaMD arises from the fact that an increasing number of clinical functions now depend on software capable of informing, guiding, or supporting diagnosis and treatment. This has compelled regulatory authorities to reconsider categories originally designed for physical devices and to address intangible, updatable, and in some cases adaptive products.

The IMDRF proposes a classification based on both the severity of the clinical condition involved and the type of information provided by the software. This results in a risk-proportionate approach: a system contributing to the treatment of a critical condition cannot be regulated in the same way as a simple wellness application. The classification distinguishes among software that provides information for clinical decisions, software that guides those decisions, and software that determines them more directly.

In the United States, the Food and Drug Administration has established a comprehensive regulatory framework with particular attention to software based on artificial intelligence and machine learning. The focus is not only on initial safety and performance but also on the management of subsequent modifications, especially when algorithms evolve over time. In the European Union, Regulation (EU) 2017/745 introduced more stringent requirements than the previous Directive, mandating stronger clinical evidence, enhanced post-market surveillance, traceability, and extended manufacturer responsibility throughout the product lifecycle [6].

One of the most delicate issues concerns the clinical validation of algorithms. For AI-based SaMD, it is not sufficient to demonstrate that the software functions technically; it must also be shown that the information produced is clinically relevant, reliable, and applicable in the real-world context for which it was designed. This requires careful attention to training datasets, the risk of bias, the representativeness of study populations, and the transferability of results [7].

Alongside these challenges, SaMD offers significant opportunities. It can contribute to the dissemination of specialized expertise, be highly scalable, promote personalized care, and generate valuable data for pharmacovigilance and clinical research. In this thesis, SaMD represents an essential component for understanding how digital medicine systems integrate pharmacological components, software, and data collection into a single regulatory and clinical ecosystem.

Patient-centered medical devices

The evolution of the concept of medical devices reflects the transition from a healthcare model centered primarily on healthcare professionals to one increasingly focused on the patient. In the past, medical devices were instruments intended for hospital or outpatient use, employed by clinicians as extensions of their diagnostic or therapeutic capabilities. Patients had only a marginal and largely passive relationship with these devices.

The introduction of self-monitoring tools marked an initial turning point. Glucometers, blood pressure monitors, and other home-use devices made patients more actively involved in managing their conditions. Subsequently, the widespread adoption of smartphones, miniaturized sensors, wireless connectivity, and cloud computing fostered the development of patient-centered medical devices designed to integrate into daily life, continuously collect data, and provide feedback that promotes engagement and adherence.

What primarily distinguishes these devices is their focus on the end user. They are designed not mainly for specialists but for patients and caregivers. Therefore, they must be intuitive, accessible, minimally invasive, and compatible with daily routines. A device that is overly complex, stigmatizing, or has limited battery life may fail despite being technically sound. Consequently, user experience becomes an integral part of clinical quality.

Another distinguishing feature is their ability to influence behavior. Patient-centered devices do not merely measure; they provide reminders, deliver feedback, promote self-awareness, and sometimes incorporate motivational support elements. At the same time, they enable data sharing with healthcare teams, caregivers, or clinical platforms, thereby transforming the traditional information flow within the physician-patient relationship.

This relationship changes significantly. Physicians gain access to continuous, structured data between visits; patients arrive at clinical appointments with greater awareness of their own health trends; and clinical decisions can be more personalized. At the same time, new challenges emerge, including information overload for clinicians, difficulties integrating data into clinical workflows, and questions regarding responsibility when abnormal signals are not addressed promptly.

Overall, patient-centered medical devices fit within more flexible models of care, such as remote patient monitoring and chronic care management programs. Digital medicine systems represent one of the most advanced expressions of this transformation.

Medication adherence: Clinical, pharmacological, and economic impact

Medication adherence is one of the primary determinants of the effectiveness of pharmacological treatments. The World Health Organization defines it as the extent to which a patient's behavior corresponds with recommendations agreed upon with a healthcare professional [1]. A more recent taxonomy proposed by the European ABC project distinguishes three phases: initiation (first dose taken), implementation (the extent to which actual dosing corresponds to the prescribed regimen), and persistence (the overall duration of treatment) [8]. This distinction is useful because it allows different types of non-adherence to be characterized more accurately and interventions to be better targeted.

The magnitude of the problem is substantial. In chronic diseases, average adherence in developed countries is approximately 50%; many prescriptions are never filled, and a significant proportion of patients discontinue treatment within the first year. Non-adherence affects numerous clinical areas, including hypertension, diabetes, HIV, and psychiatry [9].

Its causes are multifactorial. Contributing factors include patient-related aspects such as beliefs about illness, health literacy, and psychological status; disease-related factors such as chronicity and absence of obvious symptoms; treatment-related factors such as the number of medications, adverse effects, and regimen complexity; and healthcare system-related factors such as accessibility and the quality of the physician-patient relationship.

Pharmacological consequences of non-adherence

From a pharmacokinetic perspective, irregular drug intake causes fluctuations in plasma concentrations that may reduce drug levels below the minimum effective concentration or, following resumed treatment, raise them above toxicity thresholds due to accumulation. For drugs with short half-lives, even single missed doses may compromise maintenance of steady-state concentrations. For drugs with narrow therapeutic windows, such as direct oral anticoagulants, immunosuppressants, or antiepileptic drugs, the clinical consequences of these fluctuations may be significant.

Non-adherence may also interfere with enzyme induction or inhibition. Drugs that modulate cytochrome enzyme activity, when taken inconsistently, may unpredictably alter the metabolism of other coadministered medications, with potential consequences for their efficacy and safety.

From a pharmacodynamic perspective, intermittent exposure may promote adaptive receptor phenomena. In the case of antipsychotics, irregular discontinuation and resumption of treatment may contribute to changes in dopamine D2 receptor sensitivity, with possible implications for clinical response and relapse risk. For antimicrobials, subtherapeutic exposure is a recognized factor in the selection of antimicrobial resistance.

Clinical and economic consequences

Clinically, non-adherence reduces the expected effectiveness of treatments and increases the risk of disease exacerbations, hospitalizations, disease progression, and, in some conditions, mortality. Economically, it generates direct and indirect costs associated with preventable complications, medication waste, and productivity losses [10].

Methods for measuring adherence

Measuring adherence also presents challenges. Indirect methods, such as questionnaires, pill counts, dispensing records, and devices that record container opening, provide useful information but do not confirm actual ingestion. Direct methods, such as plasma drug concentration measurements, are more objective but expensive, invasive, and often impractical in routine clinical practice.

It is in this context that ingestible sensors offer a different approach: documenting medication intake objectively, continuously, and in a manner compatible with patients' daily lives. Digital medicine systems should therefore be viewed not merely as technological innovations but as attempts to address a structural problem in chronic pharmacotherapy.

Digital medicine and ingestible devices

Digital medicine represents an evolution of digital health in which medications, devices, and data are integrated into a single therapeutic architecture. Unlike the broader concept of digital health, digital medicine implies a direct relationship between technology and the therapeutic act itself. Ingestible sensor systems constitute one of its most characteristic applications because they incorporate into the pharmacological pathway a component capable of recording medication intake and converting it into usable data.

System architecture

These systems are based on four main elements: an ingestible sensor embedded in the tablet, a skin patch that receives the signal, a mobile application that collects and displays the data, and a cloud platform that stores the information and makes it available to the patient or healthcare team.

The sensor measures approximately 1 mm^2 and is made of biocompatible materials: silicon, magnesium, and copper. Upon contact with gastric fluids, the acidic environment of the stomach activates an electrochemical reaction between the two metals, generating a small electric current that powers the device. This mechanism, analogous to a galvanic cell, enables the sensor to emit a low-frequency identifying signal that is detected by the adhesive patch placed on the patient's abdomen [11].

The patch incorporates a receiving antenna, a microprocessor, memory, an accelerometer, and Bluetooth connectivity. In addition to detecting the sensor signal, it can record simple parameters such as physical activity and posture. Through Bluetooth, it transfers the information to the patient's smartphone. The mobile application displays the medication history and trend data, while the cloud platform enables alert configuration and data sharing with the authorized clinician.

Biopharmaceutical aspects

Embedding the sensor within the tablet raises issues concerning bioequivalence. Specific studies must demonstrate that the pharmacokinetic profile of the active ingredient is not altered by the presence of the sensor. In the case of Abilify MyCite®, studies confirmed that absorption parameters are comparable to those of the conventional formulation [12].

The functioning of the sensor depends on activation in the acidic gastric environment. Factors that alter gastric pH, such as the concomitant use of proton pump inhibitors or antacids, or conditions such as gastroparesis, could theoretically influence activation time [11].

Regulatory classification

From a regulatory perspective, these systems are complex because they combine a pharmaceutical component with a medical device component. The FDA classifies them as combination products, and the software component must also be evaluated according to SaMD criteria. This entails specific requirements for validation, cybersecurity, software updates, and post-market surveillance.

The Abilify MyCite® case

The case of Abilify MyCite® is the primary reference for understanding a digital medicine system in practical terms. The product was developed through a collaboration between Otsuka Pharmaceutical, the owner of aripiprazole, and Proteus Digital Health, the creator of the ingestible sensor technology. FDA approval in November 2017 marked the first regulatory recognition of an integrated drug-sensor-digital platform system [12].

Why aripiprazole

The choice of the psychiatric field addresses a specific clinical need. In schizophrenia and bipolar disorder, non-adherence is particularly common and is associated with relapse, functional deterioration, and increased hospitalizations. Estimates indicate that more than 50% of patients with schizophrenia do not take their prescribed therapy regularly, with a significant impact on the course of the disease [13].

The choice of aripiprazole also offers practical advantages: once-daily oral administration, a relatively favorable tolerability profile compared with other antipsychotics, and the availability

of long-acting injectable formulations as an alternative, allowing indirect clinical comparisons.

Pharmacological profile of aripiprazole

Aripiprazole belongs to the class of second-generation antipsychotics but has a distinctive mechanism of action. It is a partial agonist of dopamine D2 and D3 receptors and serotonin 5-HT1A receptors, as well as an antagonist of 5-HT2A receptors. Its intrinsic activity at D2 receptors is estimated to be around 25–30% compared with endogenous dopamine. This partial agonist behavior enables the drug to modulate dopaminergic transmission according to baseline tone: under conditions of dopaminergic excess, it acts as a functional antagonist, whereas under conditions of deficiency, it may exert an agonist effect. For this reason, it is sometimes referred to as a dopamine stabilizer [12,14].

From a pharmacokinetic perspective, aripiprazole has an oral bioavailability of approximately 87%, with peak plasma concentrations reached within 3 - 5 hours. Plasma protein binding, mainly to albumin, exceeds 99%. The volume of distribution is large, about 4.9 L/kg, indicating extensive tissue distribution [12].

Metabolism occurs primarily in the liver through the CYP2D6 and CYP3A4 cytochrome enzymes. The main metabolite, dehydroaripiprazole, is pharmacologically active and contributes approximately 40% of the total exposure. The elimination half-life is long: about 75 hours for the parent compound and 94 hours for the active metabolite. Consequently, steady state is reached in approximately 14 days [12].

Genetic variability of CYP2D6 has clinical relevance. Poor metabolizers exhibit 60 - 80% higher exposure than extensive metabolizers, and clinical guidelines recommend dose reductions in these patients.

Similarly, concomitant use of strong CYP2D6 or CYP3A4 inhibitors requires dose adjustments [4,12].

Pharmacological implications for adherence

The long half-life of aripiprazole gives the drug some ability to tolerate occasional missed doses without immediate loss of therapeutic effect: after a missed dose, plasma concentrations decline slowly and may remain within a potentially effective range for several days. However, prolonged interruption results in complete elimination of the drug and loss of steady state, requiring approximately two weeks to restore it [12].

This characteristic makes aripiprazole relatively "forgiving" compared with drugs that have short halflives, but it does not eliminate the consequences of sustained non-adherence. Furthermore, intermittent exposure could theoretically contribute to receptor adaptation phenomena, although direct evidence is limited.

Components of the Abilify MyCite® system

The system includes four elements:

- **Tablet with sensor**: Aripiprazole in standard doses (2, 5, 10, 15, 20, 30 mg) with an embedded ingestible sensor.
- **Skin patch (MyCite Patch):** Applied to the left side of the abdomen, detects the sensor signal and records additional data; replaced weekly.
- **Mobile application (MyCite App):** Displays medication-taking history, provides trends, and allows optional data sharing.
- **Web portal:** Accessible to healthcare professionals and caregivers authorized by the patient.

The system is designed to confirm medication ingestion, not to modify therapy or send automatic alerts to healthcare providers without the patient's consent.

Detection accuracy

The FDA review reported that 90% of aripiprazole-plus-sensor ingestions were detected within 30 minutes and 97% within two hours. Detection may be delayed or may not occur, and no serious sensor-related safety issues were identified [12].

Limitations identified

Several limitations have emerged. From a practical perspective, the system requires patients to correctly manage the patch, smartphone, and application: paradoxically, a device designed to improve medication adherence itself requires technological adherence. From a clinical perspective, it remains unclear whether the patients at greatest risk of non-adherence are also those most likely to accept and use such a complex system [15].

From an economic perspective, high costs and insufficient demonstration of the value proposition have limited payer coverage and adoption in clinical practice. Available evidence has not convincingly demonstrated an impact on robust clinical outcomes such as relapse or hospitalization in randomized trials.

The failure of Proteus Digital Health in 2020, despite considerable investment, highlighted these challenges. Contributing factors included system complexity, limited clinical evidence, resistance from clinicians and patients, and competition from simpler solutions.

For these reasons, Abilify MyCite® represents both a significant innovation and a case study of the limitations of technology when it is not accompanied by clearly demonstrated clinical benefits and a sustainable business model.

Clinical evidence for digital medicine systems

The available literature on digital medicine systems is growing but remains characterized by methodological heterogeneity and important limitations. Most evidence comes from observational studies, retrospective analyses, or pilot studies conducted on small samples with short follow-up periods.

Studies on Abilify MyCite®

Studies conducted on the aripiprazole system have documented technical feasibility, safety, and usability [12,15]. In a phase 3b mirror-image trial, use of the system was associated with improved confirmed medication ingestion and reduced psychiatric hospitalizations compared with the retrospective standardof-care period [16].

In the phase 3b study involving adults with schizophrenia, psychiatric hospitalizations decreased by 9.7 percentage points during prospective months 1 - 3 and by 21.3 percentage points during months 1 - 6 compared with the corresponding retrospective standard-of-care periods [16].

In patients with uncontrolled hypertension and type 2 diabetes, use of a digital medicine offering was associated with medication adherence of at least 80% and improvements in clinical parameters including blood pressure and glycated hemoglobin [17].

However, these findings should be interpreted cautiously, as they are derived mainly from observational, non-randomized studies in which selection bias and patient engagement effects may significantly influence the observed outcomes.

A real-world study published in 2023 compared patients treated with the digital system with patients receiving standard aripiprazole formulations, observing a reduction in psychiatric hospitalizations in the digital medicine group. However, the observational design and potential selection bias limit the strength of these conclusions [18].

Studies in other therapeutic areas

Ingestible sensor technology has also been studied outside psychiatry. Studies involving patients with uncontrolled hypertension and type 2 diabetes have shown improvements in measured adherence and, in some cases, in clinical parameters such as blood pressure and glycated hemoglobin. However, even in these studies, translating improved adherence into sustained clinical benefits has not always been evident [17].

Limitations of the evidence

The critical issue is that, to date, there is no robust demonstration of the impact of digital medicine systems on clinical outcomes in adequately powered randomized controlled trials. The system's ability to document medication ingestion does not automatically translate into improved health outcomes. Monitoring alone may not be sufficient unless integrated with educational interventions, clinical support, or behavioral strategies.

Systematic reviews converge on a cautious conclusion: ingestible sensors represent a mature technology in terms of safety and feasibility, but their comparative clinical effectiveness remains unclear. Gaps remain regarding identification of patients who may benefit most, cost-effectiveness, and added value compared with less invasive approaches [19].

Lack of pharmacokinetic data

Another limitation concerns the absence of studies correlating sensor-recorded ingestion data with pharmacokinetic measurements, such as plasma concentrations of aripiprazole. Such a correlation could strengthen the validity of the system as a tool for verifying actual drug exposure and would allow

exploration of relationships between documented adherence and clinical response [4,19,20].

Regulatory aspects: FDA and the European MDR

The regulatory framework for digital medicine systems is complex because these products combine a medicinal product, a medical device, and software.

FDA approval

FDA approval of Abilify MyCite® in 2017 represented a major milestone. The system was evaluated as a combination product: the drug component followed the standard evaluation pathway, while the sensor, patch, and software required specific assessments of biocompatibility, performance, cybersecurity, and usability [12].

The FDA clarified that approval concerned the system's ability to track medication ingestion, not demonstration of improved adherence or clinical outcomes. The labeling explicitly states that the product's ability to improve adherence or clinical outcomes has not been established [12].

In subsequent years, the FDA developed a more structured framework for Software as a Medical Device (SaMD) and AI/ML-based systems, including considerations for post-approval modifications and predetermined change control plans for adaptive algorithms.

European MDR regulation

In Europe, Regulation (EU) 2017/745 made the regulation of medical devices more stringent. Requirements include stronger clinical evidence, structured post-market surveillance systems, traceability through Unique Device Identification (UDI), and extended manufacturer responsibility [6].

As a short-term invasive device, the ingestible sensor falls within Class IIa under the MDR classification. However, some fragmentation remains in the management of products combining drugs and devices compared with the more integrated U.S. combination product model.

Regulatory challenges

The main challenges concern validation of potentially adaptive algorithms, management of software updates, interoperability with healthcare information systems, and defining the balance between rapid innovation and safety guarantees. A digital device cannot be treated as a static product when its software evolves.

International debate, promoted by IMDRF and WHO, is moving toward greater harmonization, with the aim of supporting innovative technologies while preserving the principles of safety, effectiveness, and transparency.

Implications for pharmacovigilance and medical affairs

Digital medicine systems have important implications for pharmacovigilance and medical affairs activities.

Enhanced pharmacovigilance

Traditional pharmacovigilance relies on spontaneous reporting, observational studies, and analyses of administrative databases. These sources have limitations in terms of completeness, time delays, and difficulty in accurately correlating exposure with adverse events, especially when actual adherence is unknown.

Digital systems create the possibility of obtaining more granular and prospective data. If medication intake is documented with a precise timestamp, it becomes possible to correlate actual exposure with the onset of adverse reactions over time. This could improve the quality of signal detection and facilitate identification of temporal patterns in adverse drug reactions (ADRs).

Furthermore, integrating adherence data with pharmacogenetic information, when available, could enable more refined analyses of patient subgroups at greater risk.

Real-world evidence

Digital medicine systems generate longitudinal, temporally defined, and potentially multidimensional data. These datasets may be valuable in post-marketing research, Post-Authorization Safety Studies (PASS) required by regulatory authorities, evaluations of effectiveness in real-world settings, and submissions for indication extensions or renegotiations with payers.

Medical affairs

For medical affairs, it becomes necessary to design appropriate observational studies, train clinicians in the use of new technologies, communicate evidence transparently, and contribute to defining clinical and economic value. There are also opportunities for technologically assisted patient support programs and access models based on measurable outcomes.

However, these opportunities do not eliminate existing challenges: data quality must be validated, systems must be interoperable, governance must be transparent, and there is a risk of information overload for clinicians.

In this context, the pharmacist assumes a strategic role, particularly in hospital and community settings. Pharmacists can contribute to implementing digital medicine systems through therapeutic education, adherence support, and interpretation of data generated by the devices. In addition, the availability of objective information on medication intake can improve the quality of pharmacovigilance reports by strengthening the temporal relationship between drug exposure and adverse events.

From the medical affairs perspective, these systems represent an innovative tool for generating highgranularity real-world evidence, useful both for post-marketing studies (PASS) and for market access strategies based on value-based models. The involvement of medical affairs therefore becomes crucial in designing observational studies, training clinicians, and communicating the clinical and economic value of these technologies.

Ethical and privacy concerns

Ethical and privacy issues represent one of the most sensitive aspects of digital medicine systems.

Data protection

These tools collect information about therapeutic behavior, daily routines, and intimate aspects of patients' lives. Information on whether and when a person has taken a medication constitutes sensitive health data requiring robust encryption measures, access controls, and transparent governance. There is also a risk of secondary uses or re-identification even when information has been formally anonymized [21].

Informed consent

Consent cannot be limited to prescribing the medication but must extend to understanding how the system works, how data flow, and who can access them. This is particularly delicate in psychiatry, where decisionmaking capacity may fluctuate and where the risk of perceiving the system as an instrument of external control is greater.

Risk of coercion

The most widely discussed issue concerns potential coercion. In institutional or asymmetric contexts, a medication monitoring system could be used as a tool of pressure by family members, institutions, insurers, or judicial systems. Even without explicit coercion, patients may perceive the device as an expression of mistrust or an intrusion on their autonomy.

In patients with psychotic disorders, monitoring may also be interpreted through paranoid ideation, with potentially negative effects on the therapeutic relationship.

Guiding principles

The ethical literature emphasizes several principles: the benefit must be real and proportionate to the level of invasiveness; psychological and social risks must not be underestimated; refusal to use the system must always remain possible without consequences for the quality of care; and access to such technologies must not create new forms of discrimination [19].

The success of digital medicine systems will also depend on the ability to ensure ethically sustainable use. Without a clear framework, technologies designed to promote care risk undermining the trust that forms the foundation of the therapeutic relationship.

Future perspectives

The future of digital medicine systems depends on the convergence of several factors.

Extension to other molecules

Ingestible sensor technology is potentially applicable to any solid oral medication. Areas of interest include oral oncology, where adherence is critical for the effectiveness of tyrosine kinase inhibitors such as imatinib or ibrutinib; antiretroviral therapy, where suboptimal exposure promotes resistance; post-transplant immunosuppressants, where variability in tacrolimus concentrations is associated with rejection risk; and oral anticoagulant therapy, where even single missed doses may have thromboembolic consequences.

Predictive systems

Advances in artificial intelligence make it plausible to develop systems capable not only of recording what has happened but also

of anticipating the risk of non-adherence or clinical deterioration. Combining medication intake data, behavioral parameters, and predictive models could enable personalized proactive interventions.

Decentralized clinical trials

Objective documentation of adherence could improve the methodological quality of clinical trials, particularly Phase IV studies and post-marketing programs. The possibility of collecting data remotely would reduce the need for in-person visits and allow inclusion of populations located far from research centers.

Value-based models

In healthcare systems increasingly oriented toward rewarding outcomes rather than service volumes, having objective data on adherence and treatment response may become strategic for outcome-based contracts, disease management programs, and negotiations with payers.

Conditions for success

The future of these technologies will not, however, be determined solely by engineering sophistication. Comparative clinical evidence, sustainable economic models, simpler user experiences, and a strong ethical foundation will be required. Only under these conditions can digital medicine systems evolve from experimental technologies into integrated tools in clinical practice.

Conclusion

Patient-centered medical devices based on digital technologies represent one of the most significant innovations in the management of chronic pharmacotherapy. Their potential value lies in their ability to connect the prescription with what actually happens in patients' daily lives, reducing the gap between theoretical therapy and treatment actually followed.

The analysis presented here reveals a multifaceted picture. On the one hand, digital medicine systems introduce new possibilities: objectively measuring medication intake, generating high-granularity realworld data, supporting patients, and providing clinicians with information that was previously difficult to obtain. On the other hand, the case of Abilify MyCite® demonstrates that technological innovation does not automatically translate into clinical, economic, or adoption success.

The challenges are clear: evidence of effectiveness on clinical outcomes remains limited; the technological burden may be excessive for some patients; costs are high; the advantage over simpler solutions is not always demonstrated; and the risk of transforming support into surveillance cannot be ignored.

From a pharmacological perspective, these systems address a real problem: non-adherence compromises drug exposure, causes fluctuations in plasma concentrations, and may contribute to therapeutic failure, development of resistance, or receptor adaptive phenomena. The choice of aripiprazole, with its long halflife and partial agonist profile, represents a relatively favorable case but does not eliminate the need to demonstrate concrete clinical benefits.

At present, perhaps the greatest contribution of digital medicine systems is not that they have solved the problem of adherence, but that they have highlighted how central this problem is and how necessary it is to address it with new tools. Their future will depend on their ability to demonstrate measurable benefits, maintain ease of use, integrate into care pathways, and respect patient autonomy.

In this scenario, the contribution of clinical research and Medical Affairs will be crucial in bridging the gap between technological potential and real value, guiding development toward solutions that are not only innovative but also clinically relevant, ethically sustainable, and economically justified. Only under these conditions can digital medicine systems establish themselves as foundational tools in the medicine of the future.

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