**Evidence Beyond The Digital Medication Pill**

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# First in the market

The digital revolution that has so profoundly transformed the first decades of the 21st century has yet to impact medicine fundamentally. (1) In November 2017, the Food and Drug Administration (FDA) issued a first-of-its-kind approval of a digital version of the second-generation antipsychotic aripiprazole that includes an ingestible digital tracker. (2) The digital version of the drug, which costs almost $1700 per month, might improve the patient’s compliance. In comparison, the cost of the generic oral version of the drug costs less than $20 per month. This first approval of a drug/device combination sets a precedent for how technology-enhanced medical drug delivery systems will be evaluated before marketing. (3) This technology is designed to track drug ingestion, which can provide objective data about patient medication-taking behaviours. That data can enable clinicians to remotely make more information-based therapeutic interventions. Furthermore, it can allow patients to have an active role in their therapeutic plans.

# How robust is the evidence beyond this digital dosage form?

There is a question about the availability and strength of evidence reporting on this digital medication pill. Recently, a systematic review aimed to examine the evidence supporting the FDA's approval of digital aripiprazole found that the data submitted to the FDA were limited to trials that only assessed whether patients could use the digital medication pill as indicated.(4) None of the studies provided data on remission, quality of life, or any clinical outcome. (4) There were no prospective, double-blind, randomised controlled trials comparing digital aripiprazole with non-digital formulations of the second-generation antipsychotics, or other active comparators or placebo.(4, 5) Also, the review did not show evidence of better compliance rates with the digital aripiprazole in comparison to the non-digital version. (4)

# Applicability in Cardiovascular Medicine

Patients with uncontrolled hypertension, diabetes, and hypercholesterolemia are usually at high-risk for cardiovascular events and costly interventions. (6, 7) Controlling these diseases has been shown to reduce the risk of these complications. (8-10)

Recently, a pilot randomised clinical trial has used the digital sensor to track patient compliance with cardiovascular medications for conditions like hypertension and type 2 diabetes. (11, 12) The purpose of this trial was to evaluate the ability of a new digital pill to lower arterial blood pressure and glycated haemoglobin in patients with uncontrolled hypertension and type 2 diabetes, respectively (11, 12) The study enrolled subjects with uncontrolled hypertension and type 2 diabetes that have already failed at least two different antihypertensive medications and metformin and/or a sulfonylurea. Subjects were randomised to one of three arms: use of the digital pill for four weeks, use of the digital pill for 12 weeks, or usual care. Subjects randomized to the two intervention arms, used the study digital pill in order to (i) provide automatic and passive electronic documentation of medication compliance and patterns of medication-taking behaviour, (ii) assist healthcare providers in distinguishing inadequate medication compliance or pharmacologic unresponsiveness as the root cause for uncontrolled hypertension and type 2 diabetes; and (iii) inform therapeutic interventions such as dose adjustment, medication initiation or change, patient education, or referral to a specialist physician. Subjects randomised to usual care received usual medical care such as medication changes, patient education, and lifestyle coaching. The healthcare providers are also able to schedule additional visits without restrictions. (11) The study included 109 participants from 12 geographical sites (mean age, 58.7±1.4 years; female gender, 49.5%) The characteristics of the participants were: 49.5% Hispanic; 56.9% were of income ≤ US $20,000; 52.3% of ≤ high school education. The digital pill arms included 80 participants from seven geographical sites, and the usual care had 29 participants from five sites. The preliminary results of the study revealed that the arms of patients with uncontrolled hypertension and diabetes who used the digital pill achieved a statistically significant reduction in blood pressure (BP) and low-density lipoprotein-cholesterol (LDL), and were more likely to achieve their target BP than the patients of the usual care arm. (11) By week 4, 85% of the digital pill arms (n=72) and 33% of the usual care arm (n=24) achieved the BP target. The digital pill patients had a greater reduction in Systolic BP than usual care (-23 ± 2 mmHg vs -14±4 mm Hg, respectively). The digital pill arms also had a greater significant reduction in Diastolic BP compared to usual care (-9 ± 2 mmHg vs -5 ± 2 mmHg respectively). Patients receiving the digital pill had a significantly greater reduction of LDLc -18 ± 7 mg/dL compared to patients under usual care 1 ± 2 mg/dL.(11)

Noble and colleagues reported on the satisfaction of a cohort of community pharmacists in the United Kingdom with the digital pill utilisation. (13) The system helped pharmacists to identify specific factors contributing to uncontrolled hypertension, to make evidence-based prescribing and lifestyle recommendations for achieving treatment goals, and to create a collaborative experience for patients in the management of their self-care. (13)

# Clinical Perspective

Patient’s compliance can be challenging, and a new "digital pill" may allow healthcare providers to monitor their patients remotely but closely. Given the strong belief in the potential ability of digital medicine to provide valuable insights into patient medication-taking behaviours and overcome health disparities in the most vulnerable patient populations, including those with mental health disorders, cardiovascular, cancer, or other disabilities, there are still many questions in terms of the clinical studies sample size and robustness in addition to the cost-effectiveness of the digital pills’ incremental cost. (3) That will depend on what the evidence ultimately shows in terms of improving compliance rates and reducing the consequences of patients’ poor compliance. The aforementioned studies were limited by their small sample size and short-term follow-up. Also, the effectiveness and safety of the digital pill will remain controversial due to a lack of strong evidence.

Digital medicines can represent a future for cardiovascular healthcare helping to identify barriers in implementation of preventative and therapeutic interventions. They can also be used to track drug administration and, in future, send automatic alerts in case of missed administration. This latter point can be of specific importance for patients taking antiplatelets and anticoagulants and heart failure medications. Furthermore, these drug monitoring systems can be implemented in clinical trials for monitoring purposes and to identify non responders from non-adherent patients.

# Word count = 1016

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