Journal of Pharmacy Technology
2017, Vol. 33(4) 137–139

DOI: 10.1177/8755122517704212
journals.sagepub.com/home/pmt
SAGE

Digital Medicine: Innovative Drug-Device Combination as New Measure of Medication Adherence

Ximena Vallejos, PharmD, BCPS[1] and Christine Wu, PharmD, BCPS[1]

Abstract

In September 2015, the Food and Drug Administration accepted the first digital medicine new drug application for a drug-device combination of Otsuka's Abilify® (aripiprazole) and an ingestible sensor embedded in the tablet that digitally records ingestion. When this digital medicine is taken, it sends a signal to a patch worn by the patient. The information is recorded, time-stamped, and relayed to any Bluetooth-enabled device and, with patients' consent, to their physicians and/or their caregivers. An encapsulation model in which a tablet is co-encapsulated with the ingestible sensor has been successfully used in the setting of renal transplant, diabetes, hypertension, and hypercholesterolemia.

Keywords

medication adherence, aripiprazole, technology, electronic monitoring

Introduction

Medication nonadherence can have a significant impact on patients' health and overall health care costs, as it is associated with poor health outcomes and increased health care utilization. Up to 50% of patients do not adhere to prescribed medications, which is estimated to cost $290 billion in excess health care utilization.[1,2] The reasons for medication nonadherence are multifactorial and there is no single solution. The first step in addressing the issue is gaining a better understanding in medication-taking patterns to identify individual challenges and improve communication.

Monitoring of medication adherence is complex and consists of direct and indirect methods.[2] Examples of direct methods include directly observed therapy (DOT) and laboratory monitoring tests. Indirect methods to measure adherence include patient self-reports, pill counts, rates of prescription refills, and electronic pill caps.[2] Despite the variety of methods available, medication adherence remains a challenge. It is difficult to recognize it and intervene given none of the aforementioned methods are considered to be the "Gold Standard."

In September 2015, the Food and Drug Administration (FDA) accepted for revision the first digital medicine new drug application consisting of Otsuka's Abilify® (aripiprazole) and an ingestible sensor embedded in the tablet that digitally records ingestion.[3] Otsuka Pharmaceutical (Rockville, MD), the manufacturer of the branded aripiprazole, partnered with Proteus Digital Health, Inc (Redwood City, CA) to develop this innovative formulation called digital medicine. Proteus Digital Health, Inc, is a company that develops and commercializes the ingestible sensor and wearable sensor patch that obtained FDA approval in 2012. Through their partnership with Otsuka Pharmaceutical, they developed the Abilify® (aripiprazole) digital medicine. This is the first time a new drug application for a digital medicine is accepted for revision by the FDA. If approved, it would provide a unique way to measure medication adherence and physiologic response in patients with schizophrenia, bipolar disorder, or major depressive disorder. This technology can serve as a tool to measure and identify nonadherence. Having this information in real time and sharing it with health care providers can play a role in developing better communication and counseling interventions.

When the Abilify® (aripiprazole) digital medicine is taken, the sensor sends a signal to the wearable sensor patch after it reaches the stomach. This information is recorded and relayed to patients on a mobile phone or other Bluetooth-enabled device and, only with their consent, to their physicians and/or their caregivers.[3]

This commentary discusses this innovative method to measure medication adherence and the potential use for

[1]Miami VA Healthcare System, Miami, FL, USA

Corresponding Author:
Ximena Vallejos, Miami VA Healthcare System, 1201 NW 16th St (119), Miami, FL 33125, USA.
Email: ximena.vallejos@va.gov

this technology if applied to other medications that manage chronic diseases.

The Technology of the Digital Medicine

The digital medicine consists of an ingestible sensor of 1 mm^2 in size that is embedded in an oral solid formulation such as a tablet, a wearable sensor patch, and a mobile computing device. The sensor is coated with digestible metals such as copper and magnesium. Once ingested and activated by gastric fluid, the sensor generates a signal that is perceived by the patch.[4,5] The amount of copper and magnesium that can be absorbed by the intestine from the ingestible sensor is very small compared with their daily allowable amounts for human consumption of 0.3% (7.7 ng) and 0.003% (9.8 ng), respectively.[6]

The wearable sensor patch is a body-worn sensor of approximately 10 cm in length that detects and records the date and time of medication ingestion. A foam surface holds the adhesive and provides a waterproof enclosure for the device's electronics. It should be applied on the torso, and it can be worn throughout most activities, including exercise and bathing. High levels of activity and water may cause the patch to peel off, so the adhesive should be replaced weekly.[4] The patch also records physiological metrics such as heart rate, physical activity (ie, steps recognized from an accelerometer), body position, and skin temperature.[4]

Data originating from the ingestible sensor is communicated conductively through the body to the patch and uploaded to a paired Bluetooth-enabled computing device. The data is stored locally in the device but it can be uploaded to a cloud-based personal health record (PHR). PHR data are encrypted to decrease the likelihood of unintentional or intentional disclosure of identifiable patient information. The patient has the ability to enable sharing of PHR data with health care providers or disable it at any time.[4]

Clinical Studies

There have been observational studies assessing the performance, safety, and cost of the digital medicine. One study evaluated the potential cost savings of wirelessly observed therapy (WOT) versus 3-day and 7-day DOT in patients undergoing the 4-month continuation phase of tuberculosis treatment. WOT provided cost savings in comparison to 3-day and 7-day DOT. The total cost of treatment of 3-day DOT was US$1772 and of 7-day DOT was US$3472. Personnel and retreatment costs were the leading cost drivers of tuberculosis treatment. However, with WOT, the less frequent labor-intensive personnel interactions yielded a lower cost of US$1273. Based on this difference in treatment cost, the model demonstrated that WOT would allow providers to treat 1.4 times and 2.7 times more patients compared to 3-day and 7-day DOT, respectively.[5]

An early prototype of the ingestible sensor and wearable sensor patch has been evaluated in a study with tuberculosis patients to determine accuracy and safety. Thirty patients completed 10 DOT visits and over 1000 ingestion events. The prototype showed 95.0% (95% confidence interval [CI] = 93.5% to 96.2%) positive detection accuracy, defined as the number of detected sensors divided by the number of sensors administered. The specificity was 99.7% (95% CI = 99.2% to 99.9%) based on 3 false signals recorded. The prototype's identification accuracy, defined as the number of correctly identified ingestible sensors divided by the number of sensors detected, was 100%.[7] Of 11 adverse events, 4 were deemed possibly related to the device: 3 mild skin rashes and 1 complaint of nausea.[7]

An open-label multicenter study evaluated the usability of the aripiprazole digital medicine over 8 weeks in schizophrenia patients. Sixty-seven patients were enrolled, and 49 patients completed the study. The majority of patients were rated mildly ill on the Clinical Global Impression–Severity scale. By the end of week 8, 82.1% of the patients had completed the task of pairing/applying the wearable sensor independently or with minimal assistance.[8]

Possible Future Directions

The blockbuster drug Abilify® (aripiprazole) with the embedded ingestible sensor appeared to be a reasonable first choice to submit for FDA review. Patients suffering from mental illnesses are nonadherent due to unique challenges such as lack of awareness of the illness itself, psychosis-related cognitive impairment, and perceived lack of medication efficacy.[9]

However, medication nonadherence is a significant problem across chronic diseases and there may be other clinical applications beyond mental health for the digital medicine. For instance, nonadherence to immunosuppressive drugs is a risk factor for organ rejection and allograft loss. In renal transplant patients, nonadherence is estimated to occur in 22% of patients and may be a component of allograft loss in approximately 36% of patients.[10] Current methods of quantifying nonadherence are not reliable due to inconsistency. Electronic pill caps record the date and time of each bottle opening but they are limited by the lack of certainty that the medication was actually ingested or that the correct dose was taken. Pill counts and prescription refill rates are difficult to monitor and reveal nothing about timing of ingestion. In addition, monitoring drug levels in blood or urine can be confounded by white-coat compliance in which adherence increases 5 days before a medical visit and wanes thereafter.[10]

The ingestible sensor and patch were tested in 20 renal transplant patients in an open-label, single-arm exploratory study. In this study, the sensor was encapsulated with enteric-coated mycophenolate sodium tablets. Over 12 weeks, the positive detection accuracy was 100% (95% CI

= 89.7% to 100%). No serious adverse events were reported, but 2 patients discontinued the study due to gastrointestinal symptoms and adhesive-related rash. However, the study was not designed to address the acceptance of the ingestible sensor across different transplant patient populations or to modify patient behavior using any interventions.[11]

More recently, the digital medicine has been tested in patients with hypertension, diabetes, and hypercholesterolemia. Ninety-six patients with uncontrolled hypertension who had failed at least 2 antihypertensives plus metformin and/or a sulfonylurea were enrolled in a 12-week study.

The primary outcome was change in systolic blood pressure, and the secondary outcome was change in diastolic blood pressure. Interim results showed that the digital medicine arm had a greater reduction in systolic blood pressure than standard care (digital medicine: −23 ± 2 mm Hg; standard care: −14 ± 4 mm Hg). The digital medicine arm also had a greater reduction in diastolic blood pressure (digital medicine: −9 ± 2 mm Hg; standard care: −5 ± 2 mm Hg). Furthermore, the digital medicine arm had a greater reduction in low-density lipoprotein (LDL) cholesterol. The baseline LDL level for the digital medicine arm was 110 ± 4 mg/dL compared with 97 ± 5 mg/dL for the standard care arm. The digital medicine reduced LDL by 18 ± 7 mg/dL versus 1 ± 2 mg/dL for patients on standard care.[12]

Conclusion

The Abilify® (aripiprazole) digital medicine introduces a novel technological method for measuring medication adherence that provides real-time feedback to patients and health care providers allowing for timely interventions.

This new technology is not without barriers to implementation, as this new formulation will likely cost significantly more than the generic version, making it inaccessible for many patients or limited to clinical trials. Another big concern is patients' privacy. Patients have to grant consent in order for the information to be shared with health care providers. Data sharing and privacy issues may emerge as the information is transmitted via Bluetooth and misuse of the information still may occur even if retrieved from a secure web portal.

On April 2016, the FDA issued a complete response letter requesting additional data regarding the performance of the digital medicine to ensure safe and effective use in patients.[13] While its approval is uncertain, Otsuka Pharmaceutical and Proteus Digital Health, Inc, will determine the appropriate path to address the FDA's comments. The previously described co-encapsulation model is currently being used with satisfactory results, and the potential for an integrated model of the sensor inside the tablet could be an important achievement for the new era of pharmaceutical innovation.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. CVS Caremark Pharmacy Care Research Institute. 2013 State of the states: adherence report. https://cvshealth.com/sites/default/files/SOS-Adherence-Report-2013_Final_2.pdf. Accessed April 3, 2016.
2. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487-497.
3. Otsuka Pharmaceuticals. U.S. FDA accepts first digital medicine new drug application for Otsuka and Proteus Digital Health. http://www.otsuka-us.com/newsroom/Pages/NewsArticle.aspx?ItemId=18. Published September 10, 2015. Accessed April 3, 2016.
4. Proteus Digital Health. Instructional material. http://www.proteus.com/instructions/. Accessed April 3, 2016.
5. Au-Yeung KY, DiCarlo L. Cost comparison of wirelessly vs. directly observed therapy for adherence confirmation in antituberculosis treatment. *Int J Tuberc Lung Dis*. 2012;16:1498-1504.
6. European Medicines Agency. Qualification opinion on ingestible sensor system for medication adherence as biomarker for measuring patient adherence to medication in clinical trials. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/02/WC500201943.pdf. Published February 15, 2016. Accessed March 17, 2017.
7. Belknap R, Weis S, Brookens A, et al. Feasibility of an ingestible sensor-based system for monitoring adherence to tuberculosis therapy. *PLoS One*. 2013;8:e53373.
8. Peters-Strickland T, Pestreich L, Hatch A, et al. Usability of a novel digital medicine system in adults with schizophrenia treated with sensor-embedded tablets of aripiprazole. *Neuropsychiatr Dis Treat*. 2016;12:2587-2594.
9. Kane JM, Kishimoto T, Correll CU. Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies. *World Psychiatry*. 2013;12:216-226.
10. Prendergast MB, Gaston RS. Optimizing medication adherence: an ongoing opportunity to improve outcomes after kidney transplantation. *Clin J Am Soc Nephrol*. 2010;5:1305-1311.
11. Eisenberger U, Wüthrich RP, Bock A, et al. Medication adherence assessment: high accuracy of the new ingestible sensor system in kidney transplants. *Transplantation*. 2013;96:245-250.
12. Proteus Digital Health. Proteus Digital Health presents interim results at ACC from a randomized controlled clinical study of Proteus Discover. http://www.proteus.com/press-releases/proteus-digital-health-presents-interim-results-at-acc-from-a-randomized-controlled-clinical-study-of-proteus-discover/. Published April 4, 2016. Accessed May 9, 2016.
13. Business Wire. FDA issues complete response letter for digital medicine new drug application. http://www.businesswire.com/news/home/20160426006993/en/FDA-Issues-Complete-Response-Letter-Digital-Medicine. Published April 26, 2016. Accessed April 26, 2016.