Implied Yet Unproven: The Digital Pill – Present and Future

MATTHEW J. HAGAN, BS; PAUL GEORGE, MD, MHPE; ELI Y. ADASHI, MD, MS

KEYWORDS: digital medicine, medical device, medical ethics, health policy, patient medication adherence

On November 13, 2017, Otsuka Pharmaceutical received approval of a New Drug Application (NDA) for the use of its antipsychotic medication, aripiprazole (Abilify), with Proteus Digital Health's ingestible sensor technology. This sensor, composed of copper, magnesium, and silicon (ingredients found in food), is embedded within Abilify and sends an electrical signal to an adhesive patch on the abdomen once the sensor mixes with stomach acid. The medication provides real time data on patient medication adherence to both patient and provider with most ingestions detected within 30 minutes, while 97% of ingestions are detected within 2 hours.[1] The goal of this technology is to improve patient medication adherence. Proteus' sensor technology has now been paired with over 40 different medications for a variety of diseases like hepatitis C, diabetes, hypertension, and cancer. While Proteus does not outwardly claim improved adherence rates, scientific articles and lay reviews alike tout the medical benefits of the digital pill.[2] Before Abilify MyCite can be widely adopted though, the path to its approval and its effects on treatment adherence must be better understood. It is the purpose of this article to analyze the regulatory approval process for the technology and to review the current body of literature of the device.

It is essential to fully understand the approval process of Proteus' technology before the efficacy and safety data of the combination therapy can be discussed. On February 7, 2014, the Food and Drug Administration (FDA) approved Proteus Digital Health's sensor as a medical device via the 510(k) premarket notification route (this route assures that a Class I, II, or III medical device intended for human use is at least as safe and effective as a legally marketed medical device). The approval enabled Proteus to market the patch, including an ingestible sensor (also included was a mobile application). Proteus, Otsuka and the Center for Drug Evaluation and Research then discussed using the technology with Abilify. After communications between the parties, the FDA provided the applicant (Otsuka) with parameters for the NDA for the combined product: a human validation study would need to be performed with 36 patients from three different diagnostic groups (schizophrenia, major depressive disorder, and bipolar 1 disorder). The FDA agreed that the applicant would not need to submit any new safety data as the combination of Abilify and Proteus' sensor, named Abilify MyCite, was presumed to have similar adverse side effects compared to Abilify without the sensor technology.[4]

Since the safety and efficacy profile of Abilify Mycite was already presumed to be comparable to traditional Abilify, no controlled clinical trials or integrated summary of safety were required.[1] The company's original review, performed with placebo, was rejected as the technology was unreliably able to detect ingestion at 30 minutes and there was an overall variability in transmission times. The FDA then instructed the applicant to design a trial that tested the Abilify MyCite combination in real-world conditions. The company submitted clinical trials that showed that the technology was able to sense medication ingestion. As stated in the FDA clinical review, "the most accurate statement regarding Abilify MyCite's capabilities is that 'Abilify MyCite successfully tracks ingestion of Abilify with embedded sensor.'"[4] However, there was no difference in rates of adherence in the submitted trials. Furthermore, scant safety data was submitted on the drug device combination as the FDA relied upon previous safety data from when the drug Abilify itself was first approved.[2] Cosgrove and colleagues reviewed the clinical trials submitted to the FDA, finding that there was no evidence of improved quality of life, reduction of symptoms, nor improved adherence over the non-digital version of Abilify. Additionally, the group found that there are no prospective, double-blind randomized clinical trials that have compared the non-digital formulation of Abilify against the digital Abilify MyCite or a placebo.[3] The trials submitted to the FDA were comprised of open label, single arm studies that contained 20–60 patients focused on usability, adverse reactions from the adhesive patch and the latency period between ingestion and tracking the devices ingestion.

Since approval, limited evidence suggests that the

technology actually accomplishes what it set out to do – improve medication adherence. Researchers reviewed the current literature on the device published subsequent to the 501(k) approval in 2014 and noted that medication adherence was infrequently the primary objective of the completed studies.[5] Instead, the primary objectives were health outcomes and potential health savings the technology might provide. However, adherence was usually tracked, and while studies showed increased adherence rates, they were conducted on small sample sizes, took place over a short period of time, and were largely funded by Proteus. Heretofore, the current research that addresses the digital pill is limited to only a handful of peer-reviewed studies, and there is a need for large scale, investigator initiated, rigorous clinical trials that focus on safety, adherence, and patient outcomes.

Despite a majority of scientific articles demonstrating benefit of the Abilify MyCite formulation, the FDA received no evidence that Abilify MyCite is better than traditional Abilify. Additionally, Otsuka and Proteus supplied limited safety information about the combination therapy. Subsequent to Abilify Mycite's approval, few clinical trials have been published that suggest the new technology is an improvement over the non-digital Abilify.[2] However, this did not stop Virginia Medicaid authorities from approving coverage for Abilify MyCite at a price almost 30 times higher than generic Abilify.[6] Nonetheless, the Abilify MyCite, and Proteus' digital pill technology is a novel approach to improve medication adherence rates. In March of 2019, the Durham VA Medical Center and Otsuka began a study looking at the difference between adherence and all cause healthcare use between traditional Abilify and Abilify MyCite. The trial is currently enrolling patients and is expected to have 300 enrollees. Additionally, a recent trial looked at the Proteus sensor used as a replacement for directly observed therapy (DOT) finding that the patients preferred the technology over DOT and had adherence rates comparable to that of DOT.[7]

Trials like these could provide insight into the potential for more honest communication between patient and provider, increased patient engagement in their own healthcare, and improved adherence rates. These factors, coupled with a conceivable improvement in patient outcomes is promising as healthcare looks for ways to make patients healthier and lower healthcare spending. Despite Proteus' financial difficulties and recent Chapter 11 Bankruptcy filing, this technology could improve on already existing, low-tech mechanisms of enhancing medication adherence such as self- reported medication diaries, and weekly pillbox.[8] However, more safety and efficacy evidence in the form of robust, blinded clinical trials need to be addressed before the technology can be ubiquitously adopted.

References

1. Lee D. Clinical Review. In: Research CFDEa, ed. Vol NDA 2072022017.
2. Cosgrove L, Cristea I, Shaughnessy A, Mintzes B, Naudet F. Digital aripiprazole or digital evergreening? A systematic review of the evidence and its dissemination in the scientific literature and in the media. *BMJ Evid Based Med.* 2019.
3. Klugman C, Dunn L, Schwartz J, Cohen I. The Ethics of Smart Pills and Self-Acting Devices: Autonomy, Truth-Telling, and Trust at the Dawn of Digital Medicine. *Am J Bioeth.* 2018;18(9):38-47.
4. Andreason P. Clinical Review. In: Research CFDEa, ed. Vol NDA 2072022016.
5. Bittner B, Schmit Chiesi C, Kharawala S, Kaur G, Schmidt J. Connected drug delivery devices to complement drug treatments: potential to facilitate disease management in home setting. *Med Devices (Auckl).* 2019;12:101-127.
6. Rowland C. This $1,650 pill will tell your doctors whether you've taken it. Is it the future of medicine? The Washington Post. 2019 April 28.
7. Browne S, Umlauf A, Tucker A, et al. Wirelessly observed therapy compared to directly observed therapy to confirm and support tuberculosis treatment adherence: A randomized controlled trial. *PLoS Med.* 2019;16(10):e1002891.
8. Hale C. Digital pill developer Proteus files for bankruptcy. *Fierce Biotech* 2020.

Authors

Matth ew J. Hagan, BS, Alpert Medical School of Brown University, Providence, RI.

Paul George, MD, MHPE, Professor of Family Medicine and Medical Science, Alpert Medical School of Brown University, Providence, RI.

Eli Y. Adashi, MD, MS, Professor of Medical Science, Alpert Medical School of Brown University, Providence, RI.

Disclosures

Interest: The authors report no conflict of interest.
Funding/Support: None.

Correspondence

Matthew J. Hagan
Matthew_hagan@brown.edu