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Electronically Tracking Adherence with Antipsychotic Medication: An Analysis of the Legal Framework and Attendant Ethical Concerns

Introduction

In November of 2017, the Food and Drug Administration approved the first drug in the United States that contains a digital ingestion tracking system. Abilify MyCite (MyCite) is a drug-device combination product¹ comprised of an antipsychotic drug tablet embedded with an ingestible sensor that records the fact that the medication was taken.² MyCite is currently in the initial rollout phase of its marketing and use.³ The marketing for MyCite has focused on its ability to help patients track and maintain adherence to their prescribed medication dosage and create communication channels between patients and healthcare practitioners to support the taking of prescribed medication.⁴ The goal of this technology is to address issues of “nonadherence” to medication regimens, which is a phenomenon of patients not following their prescription, and to create better health outcomes by doing so. However, there remain doubts about the evidence-based efficacy of this technology in tackling the very complicated and long-standing problem of nonadherence to medication. These doubts are illustrated by the withdrawal

¹Printed Labeling for Abilify MyCite, CENTER FOR DRUG EVALUATION AND RESEARCH (Nov. 13, 2017), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/207202Orig1s000Lbl.pdf

²FDA approves pill with sensor that digitally tracks if patients have ingested their medication, U.S. FOOD AND DRUG ADMINISTRATION (Nov. 13, 2017), <https://www.fda.gov/news-events/press-announcements/fda-approves-pill-sensor-digitally-tracks-if-patients-have-ingested-their-medication>.

³ Rebecca Robbins, *A ‘digital pill’ for cancer patients is rolled out for the first time, in hopes of improving outcomes*, STAT (Jan. 17, 2019), <https://www.statnews.com/2019/01/17/a-digital-pill-for-cancer-patients-is-rolled-out-for-the-first-time-in-hopes-of-improving-outcomes/>

⁴ Otsuka America Pharmaceutical, Inc., *Is the ABILIFY MYCITE® System right for you?*, ABILIFYMYCITE.COM, <https://www.abilifymycite.com/right-for-you>; Otsuka America Pharmaceutical, Inc., *Meet the ABILIFY MYCITE System Brochure*, ABILIFYMYCITE.COM, <https://www.abilifymycite.com/sites/g/files/qhldwo2381/files/2020-03/Meet%20the%20ABILIFY%20MYCITE%20System%20Brochure.pdf>

of market approval for Abilify MyCite in Europe because of uncertainties about its effectiveness as a combination product.⁵ Furthermore, patients with mental illness often have complex relationships with and reactions to medication, which can have difficult side effects or stigmas attached to them, making it important to evaluate the practical concerns that electronically-tracking adherence brings along with the benefit of accurately reporting drug ingestion.

While the technology underlying Abilify MyCite is novel and potentially promising, there are practical concerns surrounding medication-tracking for patients taking antipsychotic medication that need to be addressed before Abilify MyCite is fully embraced. This paper will examine the technology involved, its intended use, the existing regulations surrounding medical devices, the ethical concerns presented by this data-collecting medical device, and possible policy routes going forward.

What is Abilify MyCite?

The underlying medicine featured in Abilify MyCite is aripiprazole, an “atypical antipsychotic,” which is a class of medicine that works by influencing the behavior of certain neurotransmitters, which are chemicals that transmit signals between neurons (brain cells).⁶ [Atypical antipsychotics are also known as “second generation antipsychotics” as they “are a newer class of antipsychotic medication than first generation ‘typical’ antipsychotics.”]⁷ Specifically, aripiprazole is used to balance levels of dopamine and serotonin to improve

⁵ *Otsuka pulls filing for Abilify MyCite digital medicine after EMA raises reliability concerns*, FIRSTWORD MEDTECH, <https://beta.firstwordmedtech.com/story/5068229>

⁶ National Institutes of Health, *Aripiprazole*, AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS (Apr. 20, 2020), <https://medlineplus.gov/druginfo/meds/a603012.html#why>.

⁷ *Aripiprazole*, NEURA, <https://library.neura.edu.au/schizophrenia/treatments/physical/pharmaceutical/second-generation-antipsychotics/aripiprazole/>

thinking, mood, and behavior.⁸ It is generally prescribed to treat symptoms of schizophrenia in people over the age of thirteen.⁹ Aripiprazole can also be used to treat episodes of mania or mixed episodes associated with bipolar disorder and can be used together with an antidepressant to treat depression when an antidepressant alone is not deemed a sufficient treatment.¹⁰

The other component part of Abilify MyCite is the contribution of Proteus - the technological piece of MyCite. The Proteus ingestible sensor is made up of essential dietary minerals, elements that already exist in a person's diet, such as silicon, magnesium, and copper.¹¹ Proteus co-founder and Chief Medical Officer Dr. George Savage noted that the idea behind this composition "was to try to make it intrinsically safe as a requirement."¹² Proteus works by emitting tiny electric pulses that are picked up by a patch worn by the patient directly on their skin.¹³ The patch - placed on the patient's torso - measures vital signs which reflect information affected by the digested pill.¹⁴ The pill and the patch operate together to create an intelligent system for relaying physiological data, that is then communicated locally to a smart phone app and globally via the internet to servers that process the information.¹⁵ The data

⁸Aripiprazole (Abilify), NATIONAL ALLIANCE ON MENTAL ILLNESS, [https://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Types-of-Medication/Aripiprazole-\(Abilify\)](https://www.nami.org/Learn-More/Treatment/Mental-Health-Medications/Types-of-Medication/Aripiprazole-(Abilify)).

⁹National Institutes of Health, *Aripiprazole*, AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS (Apr. 20, 2020) <https://medlineplus.gov/druginfo/meds/a603012.html#why>

¹⁰*Id.*

¹¹Dave Muoio, *Proteus CMO talks regulation hurdles, future plans for digital pill*, MOBIHEALTHNEWS (Mar. 8, 2018), <https://www.mobihealthnews.com/content/proteus-cmo-talks-regulation-hurdles-future-plans-digital-pill>

¹²*Id.*

¹³Alexis Madrigal, *Someday Soon You May Swallow A Computer With Your Pill*, NPR.COM, (June 18, 2014), <https://www.npr.org/sections/health-shots/2014/06/18/323243085/someday-soon-you-may-swallow-a-computer-with-your-pill>

¹⁴*Id.*

¹⁵*Id.*

collected by the smartphone app can be shared with select family, caregivers, and healthcare providers.¹⁶ See the following image for an illustration of the whole system.¹⁷



The ingestible sensor relays information reflecting the identity of the drug, who prescribed it, which pharmacy dispensed it, and the fact that the pill was taken by the patient,¹⁸ but it is capable of detecting other meta-data like location, heart rate, and stress levels.¹⁹ Taken together, and when placed in the context of larger structures of data-collecting done in today's digital world, these collections can amount to a lot of sensitive data and protected health information about people, identifying aspects of their health and being, all located in one place.

As noted in the “About” section on the website for Abilify, while users of the app can record and view more than the documentation of ingestion, “only functions related to tracking

¹⁶Laurel Wamsley, *FDA Approves First Digital Pill That Can Track Whether You've Taken It*, NPR.COM (Nov. 14, 2017), <https://www.npr.org/sections/thetwo-way/2017/11/14/564112345/fda-approves-first-digital-pill-that-can-track-if-youve-taken-it>.

¹⁷ Center For Drug Evaluation and Research, *Summary Review of Abilify MyCite*, FDA.GOV (Oct. 20, 2017), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/207202Orig1s000SumR.pdf.

¹⁸ Alexis Madrigal, *Someday Soon You May Swallow A Computer With Your Pill*, NPR.COM, (June 18, 2014), <https://www.npr.org/sections/health-shots/2014/06/18/323243085/someday-soon-you-may-swallow-a-computer-with-your-pill>

¹⁹ Wim Van Biesen, et al., *Remote digital monitoring of medication intake: methodological, medical, ethical and legal reflections*, INTERNATIONAL JOURNAL OF CLINICAL AND LABORATORY MEDICINE (Dec 23, 2019).

drug ingestion have been evaluated or approved by FDA.”²⁰ This reference to tracking ingestion relates to a larger issue in the medical field, referred to as nonadherence, which will be explored further in the following sections of this paper, as there have been concerns raised about the technology’s efficacy in attaining greater patient adherence to medications as it claims.

Currently, Otsuka Pharmaceutical Co., Ltd., the pharmaceutical company that owns and licenses Abilify MyCite, is making MyCite available in collaboration with a limited number of regional health plans and their affiliated doctors through this initial launch period. Doctors in these partner networks can prescribe MyCite to patients and the MyCite Kit is obtainable at specialty pharmacies.²¹

The Path to FDA Approval

Abilify MyCite is a combination drug-device product and is regulated as such under FDA laws, including the Federal Food, Drug, and Cosmetic Act (FD&C Act), which defines and sets the regulatory scheme for combination products. This section of the paper examines the regulatory approval of both parts of Abilify MyCite – the aripiprazole drug and the Proteus sensor – to provide a complete picture of the product.

The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services.²² The FDA’s goal is to ensure public health and safety by regulating the safety, efficacy, and security of drugs, medical devices, biological products,

²⁰ *What is the ABILIFY MYCITE® System?*, OTSUKA AMERICA PHARMACEUTICAL, INC., <https://www.abilifymycite.com/about>

²¹ *How to get the ABILIFY MYCITE® System*, OTSUKA AMERICA PHARMACEUTICAL, INC., <https://www.abilifymycite.com/getting-started>

²² *Definition: FDA (U.S. Food and Drug Administration)*, TECHTARGET, <https://searchhealthit.techtarget.com/definition/FDA-US-Food-and-Drug-Administration>

veterinary products, tobacco products, as well as monitoring the country's food supply, cosmetics, and products that emit radiation.²³ On the whole, the FDA has broad regulatory authority. The laws contributing to the system of public health number in the hundreds.²⁴ Among them is the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Section 503(g) of the FD&C Act sets forth regulation for “combination products,” which refers to any “product composed of two or more different types of medical products (i.e., a combination of a drug, device, and/or biological product with one another). The drugs, devices, and biological products included in combination products are referred to as ‘constituent parts’ of the combination product.”²⁵ This section of the FD&C requires that the combination product's “primary mode of action” (PMOA) be determined, which is the “single mode of action of a combination product expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.”²⁶ The PMOA might be the drug, the device, or a medical product.²⁷ The PMOA for Abilify MyCite is the drug,²⁸ aripiprazole, meaning that the “agency center charged with premarket review of drugs”²⁹ has *primary* jurisdiction. However, FDA draft guidance notes:

“The regulatory requirements for combination products arise from the statutory and regulatory requirements applicable to drugs, devices, and biological products, *which do*

²³ *What We Do*, U.S. FOOD AND DRUG ADMINISTRATION, <https://www.fda.gov/about-fda/what-we-do#approval>

²⁴ *Laws Enforced by FDA*, U.S. FOOD AND DRUG ADMINISTRATION (Mar. 29, 2018), <https://www.fda.gov/regulatory-information/laws-enforced-fda>

²⁵ *Principles of Premarket Pathways for Combination Products Guidance for Industry and FDA Staff*, U.S. FOOD AND DRUG ADMINISTRATION (Feb 2019), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-premarket-pathways-combination-products>.

²⁶ 21 U.S.C. § 253(g)(1)(C) (2016)

²⁷ 21 U.S.C. § 253(g)(1)(D) (2016)

²⁸ Iñigo de Miguel Beriain and Marina Morla González, ‘*Digital pills*’ for mental diseases: an ethical and social analysis of the issues behind the concept, *Journal of Law and the Biosciences* (Jul 27, 2020), <https://academic.oup.com/jlb/advance-article/doi/10.1093/jlb/ljaa040/5857113>

²⁹ 21 U.S.C. § 253(g)(1)(D) (2016)

*not lose their distinct regulatory identity when they become part of a combination product. Therefore, the premarket requirements for demonstrating the safety and effectiveness of a combination product as a whole derive from the statutory and regulatory requirements applicable to its constituent parts.”*³⁰

The premarket requirements for demonstrating a combination product’s safety and effectiveness are sourced from the statutes and regulations governing its constituent parts.³¹ Therefore, this paper will examine the classification and approval of Abilify MyCite’s device component, Proteus, as well as the drug, to present the full picture of how this combination product works and how it was evaluated.

A. Aripiprazole

The Kefauver-Harris Amendments to the FD&C Act require that drug manufacturers provide proof of the effectiveness of their drugs prior to approval in addition to the pre-existing requirements that the drugs be demonstrated as safe.³² The Amendments also require drug manufacturers to disclose accurate information pertaining to any drug side effects.³³ The Amendments require also that evidence of efficacy be based on “adequate and well-controlled clinical studies conducted by qualified experts” in which study subjects had given their informed consent.³⁴

³⁰ *Principles of Premarket Pathways for Combination Products Guidance for Industry and FDA Staff*, U.S. FOOD AND DRUG ADMINISTRATION (Feb 2019), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-premarket-pathways-combination-products>.

³¹ *Id.*

³² Shawn Kennedy, *FDA Kefauver-Harris Amendment (1962)*, IMARC RESEARCH, INC. (Feb. 20, 2015), <https://www.imarcresearch.com/blog/bid/361199/FDA-Kefauver-Harris-Amendment-1962>

³³ *Id.*

³⁴ *Kefauver-Harris Amendments Revolutionized Drug Development*, U.S. FOOD AND DRUG ADMINISTRATION, (Sep. 10, 2012), <https://www.fda.gov/consumers/consumer-updates/kefauever-harris-amendments-revolutionized-drug-development>

Following the required studies, medical and clinical reviews, Abilify (Aripiprazole) Tablets were approved by the FDA in 2002 for use in treating schizophrenia.³⁵ It was later approved for treatment of other illnesses as well, including bipolar disorder and depression.³⁶

B. Proteus

As a medical device, the Abilify component, Proteus, was also subject to certain requirements under FDA law in order to gain market approval. Proteus was categorized as a class II device, which set the pathway for its approval.

The 1976 Medical Device Amendments (MDA) authorized the FDA to categorize all medical devices into three classes, Class I, II, or III.³⁷ The Class to which a device belongs determines its regulatory path towards market approval.³⁸ The devices labeled as Class I are thought of as presenting a minimal potential for harm to the user and often have a simpler design than Class II or Class III devices.³⁹

Class II devices must meet applicable special controls in addition to general controls in order to ensure the safety and effectiveness of the device.⁴⁰ Class I and class II devices are subject to reporting requirements and Good Manufacturing Practices (GMP) regulations, which are regulations requiring manufacturers, processors, and packagers of drugs and medical devices

³⁵ Drug Package for Abilify (Aripiprazole) Tablets, U.S. FOOD AND DRUG ADMINISTRATION, (March 07, 2003), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-436_Abilify.cfm

³⁶ Approval Date(s) and History, Letters, Labels, Reviews for NDA 021436, U.S. FOOD AND DRUG ADMINISTRATION, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varAppNo=021436>

³⁷ *History of Federal Regulation: 1902–Present*, INDEPENDENT INSTITUTE, <https://www.fda.gov/oc/issuances/history-of-federal-regulation-1902-present/>

³⁸ David G. Adams, et al., *Food and Drug Law and Regulation*, FOOD AND DRUG LAW INSTITUTE (2015).

³⁹ *Learn if a Medical Device Has Been Cleared by FDA for Marketing*, U.S. FOOD AND DRUG ADMINISTRATION (Dec. 28, 2017), <https://www.fda.gov/medical-devices/consumers-medical-devices/learn-if-medical-device-has-been-cleared-fda-marketing>

⁴⁰ David G. Adams, et al., *Food and Drug Law and Regulation*, FOOD AND DRUG LAW INSTITUTE (2015).

to take steps ensuring the safety and efficacy of their products.⁴¹ The Current Good Manufacturing Practice (CGMP) regulations were established to be flexible and allow a manufacturer to decide individually how to best implement the required systems to assure proper design, monitoring, and control of manufacturing processes and facilities.⁴² For combination products, the CGMP requirements which apply to each of the constituent parts also apply to the combination product they make up.

Lastly, Class III devices sustain or support life, are implanted, or present potential unreasonable risk of illness or injury.⁴³ These devices must be proven safe and effective in clinical trials, and must pass an FDA premarket approval process, unless they are substantially equivalent to a device already on the market.⁴⁴

The Abilify MyCite component Proteus - which is an “ingestible event marker” - was classified and approved as a Class II device.⁴⁵ An ingestible event marker “is a prescription device used to record time-stamped, patient-logged events” and “links wirelessly through intrabody communication to an external recorder which records the date and time of ingestion as well as the unique serial number of the ingestible device.”⁴⁶

⁴¹*What is GMP?*, INTERNATIONAL SOCIETY FOR PHARMACEUTICAL ENGINEERING, <https://ispe.org/initiatives/regulatory-resources/gmp/what-is-gmp>

⁴²*Facts About the Current Good Manufacturing Practices (CGMPs)*, U.S. FOOD AND DRUG ADMINISTRATION (June 25, 2018), <https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmpps>

⁴³*Id.*

⁴⁴*History of Federal Regulation: 1902–Present*, INDEPENDENT INSTITUTE, <https://www.fdareview.org/issues/history-of-federal-regulation-1902-present/#p10>

⁴⁵ *Evaluation of Automatic Class III Designation (De Novo) For Proteus Personal Monitor Including Ingestion Event Marker*, FDA.GOV (May 14, 2012), https://www.accessdata.fda.gov/cdrh_docs/reviews/K113070.pdf

⁴⁶ *CFR - Code of Federal Regulations Title 21*, FDA.GOV (Apr. 1, 2019), <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=880.6305>

Before it was approved for marketing, the device manufacturers were required to study and demonstrate that Proteus was biocompatible and non-toxic. In measuring the biocompatibility of the device, the makers sought to demonstrate that the components which users would be in contact with would perform its intended use appropriately, which is to enable unattended data collection of physiological and behavioral metrics for clinical and research applications.⁴⁷ Proteus also underwent in-vivo studies conducted with rodents, canines, and porcine, to determine the device's performance and safety.⁴⁸ Then there were electromagnetic capability and electrical safety tests, which showed accordance with FDA standards.⁴⁹ Finally, in clinical studies, the device's system performance was measured based on its "positive detection accuracy" (97.2%) and "negative detection accuracy" (100%) in order to state the system's ability to properly detect and record ingestions.⁵⁰

C. Abilify MyCite as a Combination Product

Because of the PMOA determination, the studies conducted for Abilify MyCite itself were composed of research and clinical evaluations of the aripiprazole tablet,⁵¹ its efficacy and effects, rather than on how the tablet and the sensor work together to effectively fulfill the underlying purpose of their union, which as Proteus states, is to "enhance collaboration with healthcare providers who treat patients with certain serious mental illnesses"⁵² and increase

⁴⁷*Evaluation of Automatic Class III Designation (De Novo) For Proteus Personal Monitor Including Ingestion Event Marker*, FDA.GOV (May 14, 2012), https://www.accessdata.fda.gov/cdrh_docs/reviews/K113070.pdf

⁴⁸ *Id.*

⁴⁹ *Id.*

⁵⁰ *Id.*

⁵¹ *Abilify MyCite Medication Guide*, FDA.GOV (Feb. 2020), https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207202s002s004lbl.pdf#page=48

⁵² *Otsuka and Proteus® Announce the First U.S. FDA Approval of a Digital Medicine System: Abilify MyCite® (aripiprazole tablets with sensor)*, PROTEUS DIGITAL HEALTH (Nov. 14, 2017), <https://www.proteus.com/press-releases/otsuka-and-proteus-announce-the-first-us-fda-approval-of-a-digital-medicine-system-abilify-mycite/>

patient adherence with medication. So, as the device’s clinical review itself puts it: “the most accurate statement regarding Abilify Mycite’s capabilities is that ‘Abilify Mycite successfully tracks ingestion of aripiprazole with embedded sensor,’”⁵³ *but*, “The ability of the ABILIFY MYCITE to improve patient compliance or modify aripiprazole dosage has not been established.”⁵⁴ This makes it odd that the clinical reviews of Abilify MyCite still refer to poor patient adherence to pharmacological treatment for mental illness and go further to invoke the possibility that Abilify MyCite can add to existing treatments and increase patient adherence “by allowing clinicians and caregivers another way to track aripiprazole ingestion” in its “Benefit-Risk Summary and Assessment.”⁵⁵

While both component parts of the Abilify MyCite system have been studied and approved separately, the efficacy of their combination has not been proven to increase or aid greater adherence to the medication.

Patient Nonadherence and Abilify MyCite’s “Potential”

The clinical review of Abilify MyCite as well as the media attention to it have both highlighted the potential use of the device to address a larger problem in the area of mental healthcare: patient nonadherence. So, what exactly is that problem, and is it practical or prudent to place hopes of mitigating nonadherence on technology such as this?

⁵³ Daniel J. Lee, Center For Drug Evaluation and Research, *Clinical Review of Abilify MyCite*, FDA.GOV (Oct. 20, 2017), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/207202Orig1s000MedR.pdf

⁵⁴ *Abilify MyCite Medication Guide*, FDA.GOV (Feb. 2020), https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207202s002s004lbl.pdf#page=48

⁵⁵ Daniel J. Lee, Center For Drug Evaluation and Research, *Clinical Review of Abilify MyCite*, FDA.GOV (Oct. 20, 2017), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/207202Orig1s000MedR.pdf

Adherence to medication is the extent to which a patient's medication-taking conforms to their prescription.⁵⁶ Medication adherence lies on a spectrum between a patient never taking their prescribed medication to always taking it on time, as agreed between the patient and the doctor.⁵⁷ Issues with nonadherence can include taking excess medication, which is less common, or taking less medication than prescribed.⁵⁸ Nonadherence with medication is an issue impacting patients with all kinds of chronic medical disorders. The World Health Organization notes that of 3.8 billion prescriptions written each year, 20% are never filled, and of those that are filled, up to 50% of patients receiving medication for chronic conditions are nonadherent, resulting in almost \$300 billion a year in added healthcare costs.⁵⁹ Nonadherence also specifically impacts more than one third of patients with schizophrenia annually, as most people with schizophrenia experience it as a chronic condition, although the long term prognosis for most is stable or positive.⁶⁰

There are several factors that make nonadherence a particularly challenging issue to address in relation to patients with schizophrenia, which include: “a lack of illness awareness, the direct impact of symptoms, social isolation, comorbid substance misuse, stigma, and the increasing fragmentation of mental health services in many countries.”⁶¹ The adverse symptoms of antipsychotics can often be debilitating, including weight gain, sexual dysfunctions, nausea, and vomiting, making it so that nonadherence comes to represent a rational decision on the part

⁵⁶ Peter Haddad, Cecilia Brain, and Jan Scott, *Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies*, NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION (Jun. 23, 2017), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4085309/>

⁵⁷ *Id.*

⁵⁸ *Id.*

⁵⁹ Tina Caliendo and Olga Hilas, *The Promise and Pitfalls of Digital Medication*, U.S. PHARMACIST (Jul 2019).

⁶⁰ Peter Haddad, Cecilia Brain, and Jan Scott, *Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies*, NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION (Jun. 23, 2017), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4085309/>.

⁶¹ *Id.*

of patients.⁶² Other influencing factors may be patients' views on medication-taking, life circumstances, available resources, or opposing priorities.⁶³

These factors contribute to the prevalence of nonadherence with antipsychotics, and although studies of the issue by way of electronic monitoring have shown that nonadherence is both underestimated and difficult to pin down, “there is a clear consensus that [nonadherence] is a major problem”⁶⁴ This acknowledgement has led to great interest in exploring methods of increasing adherence, in part because “nonadherence with antipsychotic medication can lead to relapse for patients in remission,” which can spell hospitalization or incorrect diagnosis of treatment resistance.⁶⁵ It can also lead to persistent symptoms for those with existing symptoms, which includes impaired functioning, self-harm, and substance misuse.⁶⁶

Because nonadherence to medication is not a new phenomenon, attempts at improving patient adherence have a long and varied history. Among the techniques of increasing adherence are “psychoeducation and other psychosocial interventions, antipsychotic long-acting injections, electronic reminders, service-based interventions, and financial incentives.”⁶⁷ These forms of intervention tend to overlap, and all have shown some evidence of effectiveness.⁶⁸ Long-acting injectable antipsychotics (LAIs) were developed in part to help address the issues of

⁶² Jacinthe Flore, *Ingestible sensors, data, and pharmaceuticals: Subjectivity in the era of digital mental health*, NEW MEDIA & SOCIETY (Jun 2020).

⁶³ Wim Van Biesen, et al., *Remote digital monitoring of medication intake: methodological, medical, ethical and legal reflections*, INTERNATIONAL JOURNAL OF CLINICAL AND LABORATORY MEDICINE (Dec 23, 2019).

⁶⁴ Peter Haddad, Cecilia Brain, and Jan Scott, *Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies*, NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION (Jun. 23, 2017), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4085309/>.

⁶⁵ *Id.*

⁶⁶ *Id.*

⁶⁷ *Id.*

⁶⁸ *Id.*

nonadherence in patients with schizophrenia or bipolar disorder.⁶⁹ There are eight LAI agents that are FDA approved for the treatment of schizophrenia and “current treatment guidelines for schizophrenia recommend that clinicians consider LAIs, not only in patients who are inadequately adherent to pharmacological therapy, but also in patients who prefer such treatment.”⁷⁰ LAI antipsychotics have been established to be among the most effective treatments in psychiatry, contributing to significant reductions in health care utilization and overall costs, but are said to be underutilized in clinical practice.⁷¹

With the problem of nonadherence being a larger challenge within the field of medicine - particularly psychiatric medicine - it is expected that there be ambitious and innovative approaches at providing a solution. But the question of whether Abilify MyCite is that solution remains somewhat doubtful and unsupported. The idea that Abilify MyCite represents is not yet matched with its documented reality. That is not to say that there is no research that could lend support to MyCite’s intended goals, as related research has demonstrated that patients with schizophrenia have found text message reminders about medication adherence useful and accessible.⁷² But that is to be taken with a grain of salt, as a 2015 review of smartphone apps designed for patients with schizophrenia noted generally high rates of feasibility and acceptability of use among patients, but also showed a lack of data related to efficacy.⁷³

⁶⁹ Tingjian Yan, et al., *Medication Adherence and Discontinuation of Aripiprazole Once-Monthly 400 mg (AOM 400) Versus Oral Antipsychotics in Patients with Schizophrenia or Bipolar I Disorder: A Real-World Study Using US Claims Data*, NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION (Sep. 11, 2018), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6182631/>

⁷⁰ *Id.*

⁷¹ Christoph Correll, et al., *The Use of Long-Acting Injectable Antipsychotics in Schizophrenia: Evaluating the Evidence*, NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION (2016), <https://www.ncbi.nlm.nih.gov/pubmed/27732772/>

⁷² John Torous et al., *Methodology and Reporting of Mobile Health and Smartphone Application Studies for Schizophrenia*, NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION (June 2017), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5419869/>

⁷³ *Id.*

The lack of relevant data and research to back up usefulness claims is worrisome and may prove hasty, as critics have pointed out. The presumption surrounding the presentation and design of Abilify MyCite is that it will improve adherence by helping track ingestion, but the FDA didn't receive or evaluate any evidence on whether it does actually affect adherence.⁷⁴ And in 2019, a team of researchers reviewed the evidence supporting the FDA's approval of Abilify MyCite as well as how that evidence was disseminated in scientific literature and news reports. That report concluded that,

“regulatory approval for this first-ever digital drug was based on weak evidence, and there was no evidence of better adherence with the digital version of aripiprazole compared with the non-digital version...both the scientific literature and news reports conveyed an unsupported impression of benefit.”⁷⁵

Ethical Concerns Surrounding Abilify MyCite

In addition to the general lack of supporting data for Abilify MyCite's efficacy, as reported on within the FDA and by media outlets, there are also other concerns surrounding the digital drug. The literature and commentary surrounding Abilify MyCite has prompted some worries about the implications of drug-tracking on patient privacy, autonomy, and coercion as it relates to promoting adherence.

A. Patient Autonomy: Privacy and Coercion

⁷⁴ Tara Haelle, *FDA Approval of Medication With a Digital Monitoring System: Major Breakthrough or “Brave New World”?*, HAYMARKET MEDIA, INC. (July 23, 2018), <https://www.psychiatryadvisor.com/home/topics/mood-disorders/bipolar-disorder/fda-approval-of-medication-with-a-digital-monitoring-system-major-breakthrough-or-brave-new-world/>

⁷⁵ Lisa Cosgrove et al., *Digital aripiprazole or digital evergreening? A systematic review of the evidence and its dissemination in the scientific literature and in the media*, BMJ (Nov. 21, 2019), <https://ebm.bmj.com/content/24/6/231.abstract>

Tracking and communicating adherence requires patients to be open with their healthcare information and could create undue pressure for them to comply with medication regimens rather than creating two-sided dialogue about their treatment with medical practitioners. This creates overlapping concerns of intruding upon the privacy of patients by tracking their ingestion and making it so that they must passively comply with prescriptions.

Firstly, doctors have pointed out that it may be concerning or counterintuitive to use a digital pill to track ingestion for patients with psychiatric disorders such as schizophrenia, which causes symptoms like paranoia, with fears over the drug increasing both paranoia and delusions.⁷⁶ And many have discussed how the complex realities of nonadherence, which can be purposeful on part of patients who are discontented and frustrated with negative side-effects of their medication, raise ethical queries over whether patients should be able to refuse treatment or confidently engage in conversation about alternatives with their doctors.⁷⁷

Here, a distinction between adherence and compliance becomes material. Medical literature describes adherence as “a therapeutic agreement between the patient and the physician after ample explanation,” while compliance assumes a “paternalistic conceptualization of medication-taking behavior, disregarding patients’ expectations and experiences” and suggesting that the patient is passively following the doctor’s orders.⁷⁸ A third term, “concordance,” has also been introduced. Concordance emphasizes the existence of an agreement between the clinician and the patient, taking into account the perspective of each regarding medication-

⁷⁶ John Torous and Matcheri Keshavan, *Digitally Tracking Patients With Schizophrenia: The Future Is Here*, PSYCHIATRIC TIMES (Nov. 22. 2017), <https://www.psychiatristimes.com/schizophrenia/digitally-tracking-patients-schizophrenia-future-here>

⁷⁷ Sierra Lear, *Abilify MyCite: The Ethically Hard Pill to Swallow*, BERKELEY SCIENCE REVIEW (May 24, 2019), <https://berkeleysciencereview.com/2019/05/abilify-mycite/>

⁷⁸ Wim Van Biesen, et al., *Remote digital monitoring of medication intake: methodological, medical, ethical and legal reflections*, INTERNATIONAL JOURNAL OF CLINICAL AND LABORATORY MEDICINE (Dec 23, 2019).

taking, and referring to a broader process of open discussions, communicating information, and supporting patients on long-term medication.⁷⁹ It is a process that acknowledges and respects patients' views, even if they may reflect choices which appear to be in conflict with the clinician's views.

Because of the distinctions between these three concepts which frame patients' medication-taking habits, different technological systems designed to improve adherence, concordance, or compliance will behave differently, and have different outcomes. For instance, "a system which simply assists the patient by reminding [them] that a pill is due to be taken may improve adherence," which requires shared decision making by the patient and practitioner, and the patient's willingness to take the medication.⁸⁰ Given those elements, a simple alerting system would be sufficient to remind the patient to take their medication.⁸¹ In contrast, "a system which involves any form of coercion or undue inducement is instead one for increasing compliance."⁸²

If a competent, informed patient refuses medication, forcing or unduly inducing them to track their intake would be disproportionate and intrusive, and would violate patient autonomy through paternalistic decision making.⁸³ The principle of proportionality necessitates that the purpose for taking the drug be sufficiently important to justify breaching patient autonomy.⁸⁴ And when there is doubt over whether the patient can be involved in the decision making because of incompetence or legal constraints, monitoring intake is not per se violative of patient

⁷⁹ Subho Chakrabarti, *What's in a name? Compliance, adherence and concordance in chronic psychiatric disorders*, WORLD J PSYCHIATRY (Jun 22, 2014).

⁸⁰ Wim Van Biesen, et al., *Remote digital monitoring of medication intake: methodological, medical, ethical and legal reflections*, INTERNATIONAL JOURNAL OF CLINICAL AND LABORATORY MEDICINE (Dec 23, 2019).

⁸¹ *Id.*

⁸² *Id.*

⁸³ *Id.*

⁸⁴ *Id.*

autonomy, but the concept of proportionality requires that the reason for taking the drug be sufficiently important to justify breaching patient autonomy.⁸⁵ Going beyond reminders to take medication towards tracking intake when that medication is not life-saving can be disproportionate, if there is no overriding benefit to breaching patient autonomy.⁸⁶

The Abilify MyCite development team did take these issues into account in developing its patient authorization and consent form, which empowers patients to choose who accesses their digital records of adherence, and provides that they may choose to terminate the agreement to use the digital pill at any time and prevent others from viewing their information.⁸⁷

Although the pill would theoretically be voluntarily taken and would, ideally, foster greater communication between physicians and patients, the nature of the digital drug raises ethical quandaries about it potentially being used to monitor patients, or by insurance companies in coercive ways, or by law enforcement as a condition of parole or for releasing patients who've been committed to psychiatric facilities.⁸⁸ These concerns are somewhat speculative at this point, but at least nine health systems in six states in the US have already begun prescribing pills containing a Proteus sensor, and the company has stated that the use “has been found to improve adherence in patients with uncontrolled hypertension” and other conditions.⁸⁹

Moreover, as critics point out, the conjectural nature of these patient autonomy worries are grounded within the context of America's history of coercive exercises of psychiatric

⁸⁵ *Id.*

⁸⁶ *Id.*

⁸⁷ Sierra Lear, *Abilify MyCite: The Ethically Hard Pill to Swallow*, BERKELEY SCIENCE REVIEW (May 24, 2019), <https://berkeleysciencereview.com/2019/05/abilify-mycite/>

⁸⁸ Pam Belluck, *First Digital Pill Approved to Worries About Biomedical 'Big Brother'*, THE NEW YORK TIMES (Nov. 13, 2017), <https://www.nytimes.com/2017/11/13/health/digital-pill-fda.html>

⁸⁹ *Id.*

illness.⁹⁰ Some critics argue that the mere existence and designed purpose of these tech-backed systems “deprives the patient of the ability to not take the pill without others knowing, thus harming patient autonomy.”⁹¹ The tracking and sharing of medication-intake potentially denies patients free choice by removing the option to stop taking medication.

With Otsuka Pharmaceuticals’ emphasis on generally improving patient adherence, and continued attention on the financial costs⁹² of nonadherence, commentary has also homed in on the capitalist-driven motivation behind Abilify MyCite.⁹³ It also raises concerns of broader financial implications, with fears that insurers might withdraw healthcare coverage unless a patient uses the Abilify system:

“Within the framework of value-based healthcare, quality standards for adherence to different medications...have been introduced. To achieve the standard, more than 75% of patients of a healthcare provider need to obtain at least 80% of the medication prescribed to them. The calculations are currently done on the basis of prescription refill records, but digital tracking could be a more efficient system.”⁹⁴

These value-based insurance systems could end up using patient-profiling based on collected data to “ban patients before they enter an insurance program, or increase insurance fees, based on their presumed risk of incorrect medication intake.”⁹⁵ Furthermore, other patient-related data

⁹⁰ David M. Perry, *Your Pills Are Spying On You*, PACIFIC STANDARD (Feb. 1, 2018), <https://psmag.com/social-justice/the-pills-have-eyes>

⁹¹ Wim Van Biesen, et al., *Remote digital monitoring of medication intake: methodological, medical, ethical and legal reflections*, INTERNATIONAL JOURNAL of CLINICAL AND LABORATORY MEDICINE (Dec 23, 2019).

⁹² Andrew Rebhan, *Medication nonadherence is a \$300 billion problem—here's how 3 IT vendors want to solve it*, ADVISORY BOARD (Feb. 15, 2018), <https://www.advisory.com/research/health-care-it-advisor/it-forefront/2018/02/medication-nonadherence>

⁹³ Nick Scott, *Abilify MyCite: the wrong implementation of a promising piece of technology*, EMERGENCY DIGITAL HEALTH INNOVATION (June 20, 2018), (<http://www.brownedhi.org/abilify-mycite-wrong-implementation-promising-piece-technology/>)

⁹⁴ Wim Van Biesen, et al., *Remote digital monitoring of medication intake: methodological, medical, ethical and legal reflections*, INTERNATIONAL JOURNAL of CLINICAL AND LABORATORY MEDICINE (Dec 23, 2019).

⁹⁵ *Id.*

from the system may be collected and processed with no benefit reaching the patient, raising more privacy concerns.

B. Data Use: Benefits Versus Harms and Security Questions

Using a digital sensor to physically track ingestion can conceptually provide greater assurance and peace of mind for patients and practitioners that a medication was taken when it was meant to be taken, preventing double-dosage or missed dosages, and doing so with more surety than a patient's manual tracking. The new technology featured in Abilify MyCite has the potential to provide instantaneous feedback, and because it can be shared with healthcare providers, ideally, it could advance more immediate communication with patients.⁹⁶

But there are several concerns surrounding the technology's collection and storage of this healthcare data. Firstly, medical devices, like other computer systems, can be vulnerable to hacking and other security breaches, impacting the safety and effectiveness of the device.⁹⁷ And "this vulnerability increases as more medical devices are connected to the internet, hospital networks, and to other medical devices."⁹⁸ While medical device manufacturers must comply with federal regulations, including quality system regulations (QSRs) which require that medical device manufacturers address all risks, including cybersecurity risk, the FDA itself does not test medical devices for cybersecurity: "Testing is the responsibility of the medical product manufacturer."⁹⁹ However, the FDA does issue guidance to manufacturers on maintaining

⁹⁶ Tina Caliendo and Olga Hilas, *The Promise and Pitfalls of Digital Medication*, U.S. PHARMACIST (Jul 2019).

⁹⁷ *Cybersecurity*, U.S. FOOD AND DRUG ADMINISTRATION, <https://www.fda.gov/medical-devices/digital-health-center-excellence/cybersecurity>

⁹⁸ Mike Stankiewicz, *Is FDA Doing Enough for Device Cybersecurity?*, PRIVACY & SECURITY LAW REPORT (BNA) (Dec. 26, 2017), <https://news.bloomberglaw.com/health-law-and-business/is-fda-doing-enough-for-device-cybersecurity>.

⁹⁹ *The FDA's Role in Medical Device Cybersecurity: Dispelling Myths and Understanding Facts*, U.S. FOOD AND DRUG ADMINISTRATION, <https://www.fda.gov/media/123052/download>

secure medical devices and monitoring any threats. Additionally, if a risk is identified, the FDA may issue a “safety communication,” which contains information about the vulnerability and recommended actions for patients, providers and manufacturers.¹⁰⁰

As a general trend, security concerns over hacking of private health information have been increasing, with the FDA recalling Internet-connected pacemakers over data breach worries¹⁰¹ in 2017 and Johnson & Johnson warning consumers that its insulin pumps could be hacked in 2016.¹⁰² With devices that collect healthcare data, concerns over security of data are heightened because of the sensitive nature of the information: “Breaches can reveal very sensitive information about medical conditions and produce other harms, even employment discrimination...identity theft and exploitation of financial information...and criminals armed with stolen information might even use it to submit fraudulent health insurance claims.”¹⁰³ And because the data transmissions within Abilify MyCite “make several stops along the way to authorized users—from the sensor to the patch to a phone and to a web portal,” this creates multiple points of vulnerability and potential exposure.¹⁰⁴

Another facet of patient data collection is the obligations and responsibilities it creates for physicians and other health care practitioners. The tracking of patient intake of medication potentially creates an obligation for physicians to monitor and respond if the patient is not

¹⁰⁰ *Medical Device Cybersecurity: What You Need to Know*, U.S. FOOD AND DRUG ADMINISTRATION, <https://www.fda.gov/consumers/consumer-updates/medical-device-cybersecurity-what-you-need-know>

¹⁰¹ Nicholas Shields, *The FDA has recalled about 500,000 internet-connected pacemakers over hacking fears*, BUSINESS INSIDER (Sep. 1, 2017), <https://www.businessinsider.com/fda-recalls-500000-internet-pacemakers-hacking-fears-2017-9>

¹⁰² Jim Finkle, *J&J warns diabetic patients: Insulin pump vulnerable to hacking*, REUTERS (Oct. 4, 2016), <https://www.reuters.com/article/us-johnson-johnson-cyber-insulin-pumps-e/jj-warns-diabetic-patients-insulin-pump-vulnerable-to-hacking-idUSKCN12411L>

¹⁰³ Greg Langlois, *Otsuka's Digital Drug: A Privacy Poison Pill?*, PRIVACY & SECURITY LAW REPORT (BNA) (Jan 8, 2018), <https://www.bloomberglaw.com/product/blaw/document/XE0VLDQG000000>

¹⁰⁴ *Id.*

cohering to the prescription.¹⁰⁵ The resulting duty could then lead to issues of liability for physicians if they fail to check up on patients based on the data they receive. Some have pointed out that this could lead to “data overload” for physicians, and potential lead to the tracking of physician performance and prescribing practices, which may “result in undesirable pressures being put on the physician to prescribe the more profitable digital pill.”¹⁰⁶

Recommendations

The fears clouding Abilify MyCite’s novel approach to tracking adherence can be mitigated by providing due consideration and respect for patient rights, employing best practices in the area of device/data security, and continuing to research the device’s effectiveness in order to demonstrate it more clearly.

A. Patient Rights

One important part of the solution to the overlapping issues that medication-tracking presents for patient privacy and autonomy is that of informed consent. Prior to use of Abilify MyCite as a treatment, patients must demonstrate full willingness and capability to use all the components of the system. This should include providing patients with technological training and assistance, help with digital literacy, and an evaluation that the technology is compatible with their specific smartphone device, as well as information about what’s being tracked and the patient’s power to withdraw access to their data, and alternative treatment plans. For patients

¹⁰⁵ Wim Van Biesen, et al., *Remote digital monitoring of medication intake: methodological, medical, ethical and legal reflections*, INTERNATIONAL JOURNAL of CLINICAL AND LABORATORY MEDICINE (Dec 23, 2019).

¹⁰⁶ *Id.*

who are deemed unable to consent, the technology should not be employed, as it removes the elements of patient-clinician agreement and open communication.

B. Cybersecurity

Regarding cybersecurity, the FDA recommends that manufacturers establish “design inputs” related to cybersecurity and develop a cybersecurity vulnerability and management method as part of the software validation and risk analysis.¹⁰⁷ The agency also suggests that medical device manufacturers “provide justification in the premarket submission for the security functions chosen for their medical devices” and provides examples of the kinds of security functions that should be considered for device protection.¹⁰⁸ It is understandable that the FDA treats cybersecurity protections as a “shared responsibility among stakeholders including the medical device manufacturer, the user, the Information Technology (IT) system integrator, Health IT developers, and an array of IT vendors.”¹⁰⁹ However, the issues surrounding the security of data are quickly being acknowledged as being equally as important as issues of device safety. The FDA should consider making it a requirement that device manufacturers not only assess the cybersecurity risks, but to provide proof of the security protocols in place for the device as part of their application for FDA approval.

C. Need for Further Study and Evidence of Efficacy

¹⁰⁷ *Postmarket Management of Cybersecurity in Medical Devices Guidance for Industry and Food and Drug Administration Staff*, U.S. FOOD AND DRUG ADMINISTRATION (Dec. 28, 2016), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarket-management-cybersecurity-medical-devices>

¹⁰⁸ *Content of Premarket Submissions for Management of Cybersecurity in Medical Devices Guidance for Industry and Food and Drug Administration Staff*, U.S. FOOD AND DRUG ADMINISTRATION (Oct. 2, 2014), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-management-cybersecurity-medical-devices-0>

¹⁰⁹ *Postmarket Management of Cybersecurity in Medical Devices Guidance for Industry and Food and Drug Administration Staff*, U.S. FOOD AND DRUG ADMINISTRATION (Dec. 28, 2016), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarket-management-cybersecurity-medical-devices>

The fact that Otsuka Pharmaceutical's affiliate in the Netherlands withdrew its application for a marketing authorization of Abilify MyCite in the European Union underscores the worries that exist specifically around it and similar technologies. The Committee for Medicinal Products for Human Use (CHMP), which is the European Medicines Agency's (EMA) committee responsible for human medicines, announced that the company withdrew its application for approval to market Abilify MyCite in one, several, or all European Union Member States.¹¹⁰

Based on the data that Otsuka Pharmaceutical provided, the EMA could not assess how well the tablet, integrated sensor, patch, and the app work together since “only limited aspects of usability and technical performance were investigated.”¹¹¹ Additionally, they found that “there was not sufficient evidence that Abilify MyCite is able to reliably measure intake of the medicine in the target population,” which created a risk a patient could take too many doses.¹¹² The lack of reliability of the system as a whole speaks to the lack of evidence showing that the device would improve adherence and calls into question the benefits to patients, which is why the EMA believed that the benefits of Abilify MyCite did not outweigh its risks.¹¹³ And in the company's withdrawal letter, Otsuka stated that “certain major objections [of the agency] cannot be fully addressed at this point in time.”¹¹⁴

This lack of demonstrated reliability of the device creates an urgent need to continue evaluations of its effectiveness in tracking ingestion. Patients and practitioners alike must be able

¹¹⁰ *Abilify MyCite: Withdrawal of the marketing authorisation application*, EUROPEAN MEDICINES AGENCY, <https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/abilify-mycite>.

¹¹¹ *Id.*

¹¹² *Id.*

¹¹³ *Id.*

¹¹⁴ *Withdrawal Letter for Abilify MyCite*, OTSUKA PHARMACEUTICAL NETHERLANDS B.V. (Jul 17, 2020), https://www.ema.europa.eu/en/documents/withdrawal-letter/withdrawal-letter-abilify-mycite_en.pdf.

to trust that the MyCite Kit relays accurate information about drug intake. Otherwise, there's a risk that it will contribute to the harms associated with nonadherence rather than promoting solutions that create better healthcare outcomes.

Conclusion

All these coalescing concerns – over patient privacy, autonomy, and data security – highlight the need for clear federal regulations to govern medical applications and information sharing, as medical practitioners have previously raised warning flags about the sharing of health information over smartphone apps in other contexts.¹¹⁵ Moreover, while there is still the potential for the uncertainties circling Abilify MyCite to be mitigated through the gathering of more data showing its effectiveness, the current lack of robust evidence demonstrating its efficacy is concerning. There remains a need to prioritize patient autonomy and confidence in using the device, which requires evidence that the sensor and drug featured in Abilify MyCite are effective at working together to achieve what they propose in the marketing.

¹¹⁵ Sarah R. Blenner et al., *Privacy Policies of Android Diabetes Apps and Sharing of Health Information*, AMERICAN MEDICAL ASSOCIATION (Mar. 8, 2016), <https://jamanetwork.com/journals/jama/fullarticle/2499265>