The First Smart Pill: Digital Revolution or Last Gasp?

Anna K. Swartz, Phoebe Friesen

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ABSTRACT. Abilify MyCite was granted regulatory approval in 2017, becoming the world's first "smart pill" that could digitally track whether patients had taken their medication. The new technology was introduced as one that had gained the support of patients and ethicists alike, and could contribute to solving the widespread and costly problem of patient nonadherence. Here, we offer an in-depth exploration of this narrative, through an examination of the origins and development of Abilify, the drug that would later become MyCite. This history illuminates how an antipsychotic can become a top-selling drug and maintain its blockbuster status for more than a decade. It also provides a detailed case study for how knowledge is constructed within the logic of biomedical capitalism, providing impetus to reexamine claims regarding how MyCite addresses patient nonadherence, engenders patient support, and is ethicist-approved.

1. INTRODUCTION: THE FIRST SMART PILL

In May 2018, HLTH (pronounced "health"), a new industry gathering for senior executives seeking to disrupt the healthcare sector, held its inaugural conference in Las Vegas. The "future of healthcare" event attracted nearly 3,600 attendees over four days and charged an admissions fee of $3,000. Its tagline read: "We are the hottest, newest, largest and most important healthcare event creating a much-needed dialogue focused on disruptive innovation" (HLTH 2018). The speakers included executives and CEOs from major hospitals, insurance firms, pharmaceutical companies, biotech start-ups, policymakers, and venture capitalists. Sponsors included Google, Lyft, and Amazon, and Wyclef Jean performed at the "industry night" (HLTH 2018).

One of the general sessions included a presentation called "The Future of Medicine is Digital." The speakers—Otsuka Pharmaceutical and Proteus

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Digital Health CEOs, Kabir Nath and Andrew Thomson—heralded "the future of digital medicine" by walking onstage to the Van Halen song, "Right Now" (Thompson and Nath 2018). Right then, Nath and Thomson had a lot to celebrate. Less than six months before, in November 2017, Abilify MyCite, a collaboration between their two companies, became the first "digital pill" (also known as a "smart pill") to be approved by the Food and Drug Administration (FDA). Abilify MyCite combines a tiny sensor with the widely used antipsychotic drug Abilify. When ingested, the sensor can be detected by a Bluetooth patch the patient wears on their skin; the data are then transmitted from the patch to the patient and their clinician, creating a record of compliance (Otsuka Pharmaceutical America 2022).

This technology, Nath outlined, is created for "people who fail to take their medicines on a regular basis," letting those in the patient's chosen network "see when a patient has missed a dose and create objective data that allow physicians to determine whether and when to intervene" (Thompson and Nath 2018). As the *New York Times* reported, the approval "marks a significant advance in the growing field of digital devices designed to monitor medicine-taking," a milestone in the fight against "the expensive, long-standing problem that millions of patients do not take their drugs as prescribed" (Belluck 2017). The problem of noncompliance is said to cost between $100 billion and $300 billion annually in the United States, comprising 3%–10% of total healthcare costs (Iuga and McGuire 2014). In patients with a diagnosis of schizophrenia, nonadherence has been recorded in 41% of patients and was found to predict the use of services (e.g., hospitalizations), arrests, being the victim of a crime, and substance misuse (Haddad, Brain, and Scott 2014).[1]

During the presentation, Thompson outlined the role of patients in the development of Abilify MyCite:

> We began working with mental health patients in 2009. We began with a deeply human-centered design process, where we partnered with patients who were bipolar or had schizophrenia. And then we worked with leading physicians who treat these patients, and we designed everything about our system around, first, patient life flow, and then physician workflow. We learned a lot. And what we learned was: that patients liked our solutions so much that they didn't want to go back onto drug therapy after a three-month trial; that the benefits were really, really great. (Thompson and Nath 2018)

Thompson goes on to say that the stress of parents who had kids with a diagnosis of bipolar disorder disappeared along with the ability to monitor

their medications. What's more, Thompson recounts, "without any of our help, patients started going to the National Association for the Mentally Ill [NAMI], putting up a booth and telling doctors about Proteus technology, and telling pharmaceutical companies that they should adopt it and put it inside their drugs" (Thompson and Nath 2018).

Also involved in the development and design of the first smart pill was a team of bioethicists. In a publication in the *American Journal of Bioethics*, these ethicists describe their involvement:

> Over the course of two years, our working group provided substantial input and feedback to the company about numerous aspects of the product, utilizing an approach we have termed Ethics by Design. This approach incorporates bioethicists before, during, and after the product design and launch processes. The goals of Ethics by Design, therefore, are to "ethically pressure test" the products and policies, spot potential ethical pitfalls, and, where possible, design preventive fixes. (Klugman et al. 2018b, W6)

The Ethics by Design framework "encompassed a set of key principles that any effort involving health data should take into consideration," including autonomy, beneficence, non-maleficence, and justice (Beauchamp and Childress 2001; Meldrum 2018). The bioethics experts used these principles to identify relevant and critical issues and weigh ethical considerations from all sides (Meldrum 2018).

1.1 A Revolutionary Pharmaceutical?

By all accounts, this is an impressive feat. The development of a digital medication that can help solve the very expensive problem of patient nonadherence in a condition as complicated as schizophrenia, with the support of patients, families, and ethicists, is a remarkable accomplishment.

Unfortunately, while this story is a rosy one, it is not truth-tracking. Centrally, there is no evidence to suggest that the first digital pill has had any impact on patient adherence. Furthermore, the story of patients pleading for digital pills may be a convenient fiction. And the ethicists involved may represent an unfortunate trend of bioethicists-for-hire, who neglected to consider countless ethical issues related to Abilify MyCite, and instead, offered a deceptively slim analysis of the moral entanglements of smart pills.

To better understand the significance of Abilify MyCite, and in particular, the claims made regarding patient adherence, patient support, and ethicist approval, it is important to comprehend the context in which the first smart pill was developed. Below, we offer an in-depth exploration of how the

first smart pill came into being, tracing its origin back to the development and promotion of Abilify, in order to reexamine the story told above in light of this history and context. In a narrow sense, this history offers a crash course in pharmaceutical industry tactics, illuminating how an antipsychotic can become a top-selling drug and maintain its blockbuster status for more than a decade. In a broader sense, this history reveals the ways in which knowledge is constructed within a realm driven by profit. In light of the story of Abilify, the claims related to adherence, ethicist approval, and patient support of MyCite begin to take on another hue. In questioning these claims, we ask the reader to reconsider the nature of evidence, expertise, and efficacy under biomedical capitalism.

In Section 2, we trace the history and development of Abilify, the blockbuster drug that later became the first digital pill. In Section 3, we describe the introduction of Abilify Maintena, a new formation of Abilify and an initial industry foray into compliance marketing. Next, in Section 4, we explore the development and approval of Abilify MyCite and the parallels between the first smart pill and versions of Abilify that came before. Following this, in Section 5, we reevaluate the claims made above regarding Abilify MyCite as a patient-centered, ethicist-approved technology that supports patient adherence. In section 6, we dig deeper, asking what meaning these claims might have within the logic of capitalism that structures knowledge production in the pharmaceutical industry, and questioning whether adherence is even an appropriate goal to strive for within psychiatry, as well as what harms may result from growing efforts to develop new technologies for mental healthcare. Finally, we conclude with a brief look at what may be coming next.

2. ABILIFY: NOT JUST FOR THE 1%

Aripiprazole, the antipsychotic drug better known by its brand name Abilify, was discovered by scientists Seiji Sato, Yasuo Oshiro, and Nobuyuki Kurahashi at the Japanese pharmaceutical company Otsuka in the late 1970s (Casey and Canal 2017; Otsuka Holdings Co. Ltd. 2013). In 1991, Otsuka obtained a patent on aripiprazole which granted the company a twenty-year monopoly on the compound (Casey and Canal 2017).[2] Since Otsuka was a relatively small pharmaceutical company in Japan, with no recognition in the US, the company sought a strong marketing partner with which to commercialize Abilify, which they found in Bristol-Myers Squibb (BMS). Under the terms of this strategic alliance, BMS agreed to

co-market and co-promote Abilify, as well as to collaborate with Otsuka to complete clinical studies (Bristol-Myers Squibb Company 2003).

Abilify was introduced in the US in 2002 as an oral tablet for adults with schizophrenia. In its first year alone, sales of Abilify reached nearly $300 million (Bristol-Myers Squibb Company 2003). The following year, Abilify achieved "blockbuster" status on the US market,[3] becoming a top-selling product for both Otsuka and BMS (Bristol-Myers Squibb Company 2004, 4). By the end of its tenth anniversary on the market, the drug was still a cash cow. At its peak between 2013 and 2014, US sales of the atypical antipsychotic drug exceeded $8 billion, making Abilify the best-selling prescription drug in America (Michaelson 2014).[4] As of 2017, Abilify had raked in an estimated $51.34 billion for Otsuka and BMS (Liu 2018).

These numbers are remarkable for a drug developed to treat a psychiatric disorder present in less than 1% of the population.[5] So how does a pill developed for such a small percentage of patients become a multi-billion-dollar wonder drug? According to Otsuka, this growth was "primarily due to the addition of new indications and formulations, and strong promotional efforts" (Otsuka Holdings Co. Ltd. 2009, 30). Otsuka and BMS followed industry standards in promoting Abilify far beyond what it was originally intended to treat—and it paid off. Here, we describe three primary tactics utilized by these companies to turn Abilify into a blockbuster for the masses: expanding indications, developing a good story, and promoting off-label prescriptions. We also describe their costs.

2.1 Tactic #1: Expanding Indications

One simple way to sell more of a product is to find more uses for it. As an author in the trade journal *Pharmaceutical Executive* describes:

> One of the most familiar, and favored, tactics in product lifecycle management is expanding the uses of the product. . . . Indication expansion is tried and tested in the psychotropic field, where diagnostic distinctions can be blurred, and a drug initially promoted as an antidepressant may later find a niche in, for example, bipolar disorders. (Hisley 2004)

From the start, Otsuka and BMS executives understood that the market for Abilify was limited by its indication (the condition it is meant to treat) and that growth would require "exploring additional uses" (Bristol-Myers Squibb Company 2004, 11). By the time BMS issued its annual report in 2004, Abilify had been approved for use in bipolar mania—both as an

acute treatment and as a maintenance treatment for certain patients (FDA 2004). In a 2005 annual report, the company expressed the expanded indication as a strong business decision, succinctly breaking it down by the numbers:

> First approved in late 2002 for schizophrenia, which affects about 3 million people in the US, Abilify was additionally approved in 2004 to treat acute manic or mixed episodes associated with bipolar disorder, which affects up to 12 million. (Bristol-Myers Squibb Company 2005, 21)

Sales of Abilify skyrocketed. A BMS financial report states that sales of Abilify jumped 54% in 2005 from the year before, totaling $912 million; this growth was largely generated from the new bipolar indication (Bristol-Myers Squibb Company 2005, 41). Those numbers rose steadily; by 2007, total revenue from Abilify generated $1.66 billion for BMS (Bristol-Myers Squibb Company 2007, 12). Expanded indications continued (see Table 1 for a list of all indications). In 2007, Abilify was approved for use as an add-on treatment in adult depression, as well as a schizophrenia treatment in adolescent patients, ages 13–17 (FDA 2007). In 2008, it was approved as a maintenance therapy for pediatric bipolar disorder, ages 10–17, and as an add-on to lithium or valproate in both children, ages 10–17, and adults diagnosed with bipolar disorder (FDA 2008b; 2008a). In 2009, indications were further expanded to include the treatment of irritability in autistic children, ages 6–17 (FDA 2009a). In 2014, children with Tourette's syndrome were added, although this was changed to all patients with the diagnosis in 2015.[6]

TABLE 1. ABILIFY'S INDICATIONS AND PATIENT POPULATIONS, BY APPROVAL YEAR

Schizophrenia – Adult	2002
Bipolar disorder – Adult	2004
Major depressive disorder (add-on) – Adult	2007
Schizophrenia – Adolescents	2007
Bipolar disorder – Pediatric	2008
Bipolar disorder (add-on) – Adult and pediatric	2008
Irritability associated with autism – Pediatric	2009
Tourette's syndrome – Pediatric	2014
Tourette's syndrome – Adult	2015

Notably, the expanded indication of Abilify as an add-on treatment for depression expanded the drug's market considerably, from only those diagnosed with a serious mental illness to the enormous population of patients diagnosed with depression, regardless of whether they were already taking an antidepressant. The expansions to pediatric populations here are also noteworthy because of a federal law that authorizes the FDA to grant an additional six months of marketing exclusivity to companies conducting and submitting pediatric clinical data.[7] This incentive was developed in response to concerns that many drugs tested on adults were being prescribed in children without any evidence related to dosage, safety, or efficacy in this population. While collecting such data is essential, the incentive has generated criticism. In particular, it has been noted that it is often abused by companies seeking to secure an extra six months of monopoly on a lucrative brand drug, including drugs intended to treat diseases that are relatively uncommon in children (Simon and Kotler 2003, 191).[8]

Costs: Sales over science?

Significantly less evidence is required to demonstrate the efficacy and safety of new indications for a drug that has already come to market than for a novel drug (Angell 2005; Goldacre 2013). This was well illustrated in the research produced to secure the many additional indications of Abilify. As is common in drug development, the empirical literature documenting the safety and efficacy of Abilify was produced in conjunction with researchers and doctors funded by the drug company. The entanglements of corporate interests and the research process impacted the quality of clinical trials, leading to limited data sets and overzealous conclusions. For example, the approval of Abilify as a treatment in the maintenance of bipolar disorder was based on a single trial with significant design flaws. Tsai and colleagues report that the trial was too short to demonstrate efficacy, that the randomized discontinuation design risked conflating the effects of the drug with the effects of introducing it after discontinuation, and that the sample was far too limited to "draw meaningful conclusions" since the completion rate was only 1.3% and patients who failed to respond to the medication in the stabilization phase were excluded (Tsai et al. 2011, 6).

Similarly, Abilify as an add-on for depression, the most lucrative indication to be added to the drug's profile, lacks solid evidence. A Cochrane review concluded that "there is limited evidence that aripiprazole leads to symptom reduction when added to antidepressants" and that

benefits need to be weighed against significant side effects experienced by those taking the drug (Komossa et al. 2010, 2). Even in the case of schizophrenia, the original indication for Abilify, evidence is limited and research quality has been found to be low; a Cochrane review concluded that:

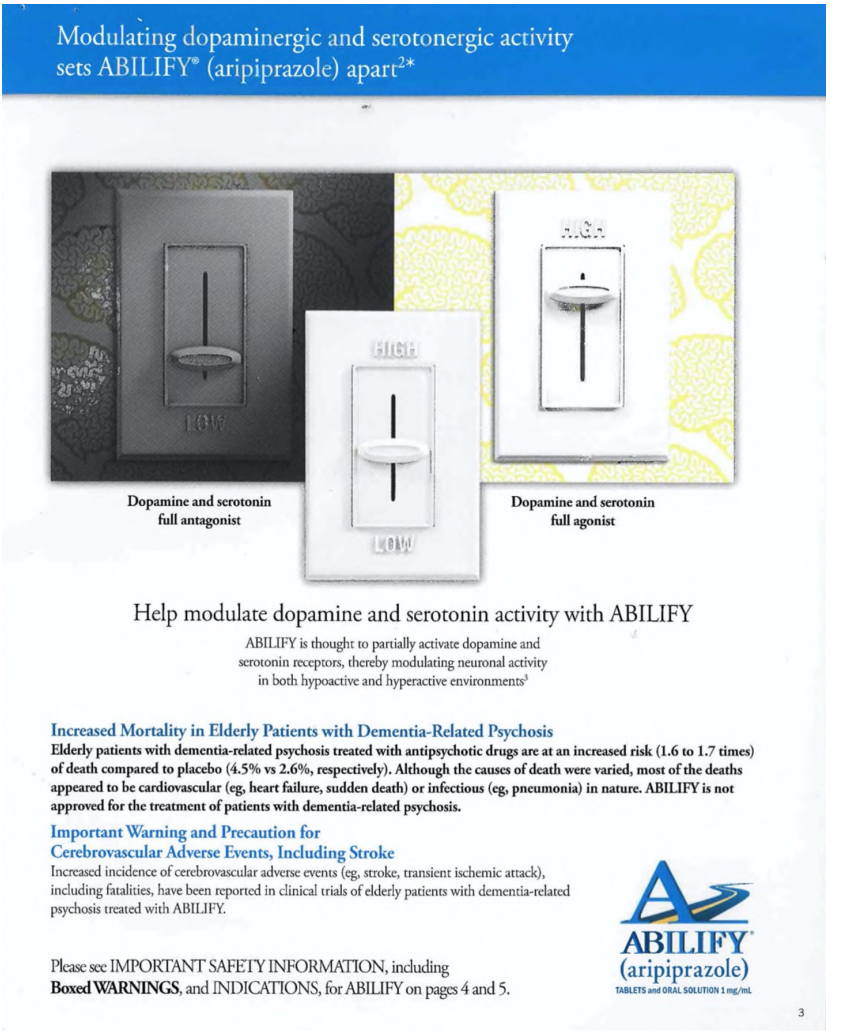
> Despite the fact that 2,585 people participated in nine randomised aripiprazole studies, we were unable to extract any usable data on death, service outcomes, general functioning, behaviour, engagement with services, satisfaction with treatment; economic outcomes or cognitive functioning. (Belgamwar and El-Sayeh 2011, 1)

2.2 Tactic # 2: Marketing a Good Story

Another central technique used by Otsuka and BMS to expand the sales of Abilify was to tell a compelling story of how the drug works, and how it is unlike any drug that had come before. Here's how it went: Before Abilify, available antipsychotics consisted primarily of first-generation antipsychotics (FGAs), which operate as dopamine receptor antagonists (blocking dopamine D_2 receptors), and second-generation antipsychotics (SGAs), which are dopamine and serotonin receptor antagonists (blocking both D_2 and serotonin 5-HT2A receptors). Like SGAs, aripiprazole modulates both dopamine and serotonin. However, in contrast to previous antipsychotics, which acted as antagonists, aripiprazole acts as a "partial agonist," "raising levels of certain neurotransmitters when they are low and reducing levels when they are too high" (Bristol-Myers Squibb Company 2004, 11; The Imperial Invention Prize 2013).[9] Ads for Abilify described the drug as working "like a thermostat to restore balance" (Lacasse and Leo 2006, 1192). What's more, FGAs are associated with extrapyramidal side effects, including muscle spasms, tremors, rigidity, and restlessness, as well as hyperprolactinemia (which impacts sex hormones and lactation) and decreases in bone density, while SGAs frequently lead to type II diabetes, obesity, and metabolic syndrome (Casey and Canal 2017). In contrast, Abilify improves symptoms "with less side effects," allowing patients to take the drug "without discontinuation" and to "reintegrate into society" (Otsuka Holdings Co. Ltd. 2012, 16; The Imperial Invention Prize 2013).

Costs: A compelling fiction?

Unfortunately, the story wasn't entirely true. In 2015, the FDA wrote a letter to Otsuka indicating that Abilify's promotional material was found to make "misleading claims" about the drug, violating federal law (FDA 2015). The letter was written in reference to a pharmacology ad for Abilify, which included images of three dimmer light switches (Figure 1), representing full agonists (with the dimmer set to high), full antagonists (with the dimmer set to low), and Abilify as a partial agonist (with the dimmer in the middle). In response, the FDA noted that these materials "suggest a definitive understanding of Abilify's ability to modulate



dopaminergic and serotonergic activity in humans," when in fact the mechanism of action is unknown (FDA 2015). Furthermore, the letter points out that the materials "misleadingly imply that Abilify has a clinical advantage due to its pharmacology," but that the "FDA is not aware of any evidence to support the implication that Abilify offers significant advantages over other prescription drugs" (FDA 2015).

The second component of the story, in which Abilify leads to fewer side effects than other antipsychotics, also appears tenuous when one looks closer. While there is evidence that suggests that some side effects are less likely with Abilify, additional side effects are more likely. A particularly impactful one is compulsive behaviors (e.g., gambling, eating, sex, shopping). One patient "incurred gambling losses of more than $65,000" after being prescribed Abilify, but stopped gambling once she stopped taking the drug (Silverstrini 2020). As of June 2019, more than 2,600 lawsuits had been filed in US federal courts related to compulsive behaviors and Abilify, and hundreds more have been filed in Canada (Silverstrini 2020). Since 2016, the FDA has required Abilify labels to include a warning statement regarding the risk of pathological gambling and other compulsive behaviors (FDA 2016b). Abilify prescribed for the treatment of irritability in autism also appears to be associated with significant weight gain (FDA 2009b, 50).

Furthermore, Otsuka seems to have oversold the disassociation between Abilify and extrapyramidal side effects. Two whistleblowers who worked as drug reps for BMS revealed a clever way of selling the story about Abilify and extrapyramidal side effects, which are often abbreviated to EPS. In this case, EPS didn't stand for the usual extrapyramidal side effects, but for extrapyramidal syndrome, a much rarer condition, making the rates of EPS correlating with Abilify look even more impressive (Hrodey 2015). One extrapyramidal symptom, akathisia, which involves an inner restlessness and an inability to stay still, appears to be very common in patients taking Abilify, with 42% of patients experiencing it in one study (Yoshimura et al. 2019); another publication reported that the NNH (number needed to harm) for akathisia was only four (Spielmans et al. 2013). This tactic of downplaying side effects is especially worrisome in the case of patients taking Abilify as an add-on for depression. As an article in *Consumer Reports* explains, "because of their harsher side effects, antipsychotics are usually considered an option of last resort for depression, to be tried only after exhausting other options" (Hirsh 2009). Despite this, advertisements for Abilify's "antidepressant enhancing"

potential did not inform viewers that the drug is a powerful antipsychotic originally approved for schizophrenia.

2.3 Tactic # 3: Off-Label Prescriptions

In cases in which additional indications for a drug cannot be secured, or before such indications have been granted, off-label prescriptions (when a drug is prescribed for a condition that it has not been approved to treat) can generate significant sales. According to Sam Halabi, the "off-label market presents a key channel of many drugs' revenue streams" (2018, 41). While promoting off-label prescriptions is illegal, it is a common and rewarding practice in the pharmaceutical industry because legal fees are usually offset by sales revenues (Van Norman 2023). In the case of Abilify, efforts to increase off-label prescriptions were aimed at two particularly vulnerable groups: children and older people. According to the US Department of Justice, from 2002 through the end of 2005:

> BMS directed its sales force to call on child psychiatrists and other pediatric specialists, and the sales force also urged physicians and other providers to prescribe Abilify for pediatric patients. BMS also created a specialized long-term care sales force that called almost exclusively on nursing homes, where dementia-related psychosis is far more prevalent than schizophrenia or bipolar disorder. (2007)

Like expanded indications, off-label prescriptions can expand the market for a drug considerably, without the labor and expense of gaining regulatory approval, and can be especially lucrative in the case of populations and conditions for which few treatments exist. Antipsychotics, in particular, are often used off-label to treat aggression or other "behavioral symptoms" in children with developmental disorders or older patients with dementia, perhaps because they tend to sedate patients who may be thought of as "difficult" (Kamble et al. 2010; Carton et al. 2015).[10]

Costs: Never quite settling?

In 2007, BMS paid out more than $515 million to settle federal and state investigations into "a wide assortment of illegal marketing and pricing practices," including off-label marketing of Abilify as a prescription for children and older people (US Department of Justice 2007). The following year, Otsuka agreed to settle the same off-label marketing allegations for around $4 million (US Department of Justice 2008). These settlements required the companies to sign corporate integrity agreements, which

involved, among other things, the creation of programs to ensure their drug reps would stop promoting off-label uses (Hrodey 2015; Staton 2015). It is not clear that these settlements were effective deterrents, however. While, according to their corporate integrity agreement, BMS was required to remove the names of pediatric and geriatric physicians from their sales representatives' call lists, many these names remained (Hrodey 2015). This was reported by two whistleblowers, who provided evidence in 2011 that the company encouraged them to promote Abilify to pediatricians before it was approved for kids, and that "the companies paid doctors to speak about Abilify, handed out samples, offered free meals, and used other incentives to persuade physicians to prescribe the drug" (Staton 2015). However, because the former employees could not demonstrate that these actions were performed in terms of both the writing and filling of off-label prescriptions, the claims were dismissed (Staton 2015). Still, in December 2016, BMS agreed to pay another $19.5 million settlement to the federal government and a group of states over claims that the company "pushed Abilify as a treatment for kids and for elderly patients with dementia" (New York State Office of the Attorney General 2016).

3. PREPARING FOR PATENT LOSS: THE INTRODUCTION OF ABILIFY MAINTENA

Over time, Otsuka developed a global reputation for Abilify. Anticipating the loss of its Abilify patent in 2015, however, the company was facing a significant challenge. For Otsuka, the Abilify patent—described in their 2014 annual report as "our top selling pharmaceutical product"—was the heart of their earnings, creating "risks related to our reliance on a specific product for a significant portion of our total net sales" (Otsuka Holdings Co. Ltd. 2014). In the midst of such desperation, Otsuka invested a great deal of time and money into preparing for patent loss. While many tactics were utilized during this transition, we focus here on the case of Abilify Maintena, illuminating two strategies that Otsuka later took up in the case of Abilify MyCite: product hopping and compliance marketing.

3.1 Product Hopping: Shifting the Market

Product hopping can be an effective technique for companies seeking to retain a dominant market position in the face of an impending patent expiration on a popular brand-name drug. The basic idea is to transfer "the consumers themselves into the product loyalty sphere of the next patented drug" over the course of two stages (Applbaum 2009b, 200).

First, "evergreening" must take place, in which "slight modifications to a drug's delivery system, dosage, or other characteristics" make the new drug eligible for additional exclusivity and patents (Feldman and Frondorf 2017, 69).[11] Second, intense marketing must follow the approval of the "new" drug, touting the benefits of the new product in the hopes of shifting the market. A company may offer rebates or discounts to encourage doctors, insurers, and patients to switch to the new product. In some cases, the company will complete the product hop by pulling the original product off the market, leaving consumers with little choice but to shift to the new product (Feldman and Frondorf 2017). It has been estimated that, between 2008 and 2016, evergreened reformulations cost Medicaid $9.35 billion (Dickson 2019).

Several years before the Abilify patent expired, Otsuka began preparing for the loss by switching patients onto a new and more expensive formulation, Abilify Maintena. This new version of Abilify came in the form of a once-monthly, long-acting, intramuscular injection, "designed for patients who struggle to take medications regularly, making them prone to relapse" (Otsuka Holdings Co. Ltd. 2013, 16).[12] Maintena's new drug application (NDA) was approved in February 2013, securing Otsuka three years of exclusive marketing rights for the formulation under the Hatch–Waxman Act (FDA 2013a). Otsuka aggressively targeted physicians and teaching hospitals in the promotion of Abilify Maintena, paying them $5 million and $4.77 million, respectively, to promote Abilify Maintena and Abilify in the last half of 2013 (Ornstein and Grochowski Jones 2015; Ornstein, Weber, and Grochowski Jones 2019). According to ProPublica's Docs for Dollars project, during this same period, Abilify Maintena and Abilify ranked tenth and eleventh, respectively, in the top twenty drugs that companies paid the most to promote (Groeger et al. 2015; Ornstein and Grochowski Jones 2015). Within a year of losing its Abilify patent, Otsuka withdrew three other formulations from the market. The oral solution was discontinued in 2015, and in 2016, Otsuka also stopped marketing its oral disintegrating tablets and short-acting, intramuscular injectable (Beall, Darrow, and Kesselheim 2019).[13]

The introduction of Abilify Maintena was another success for Otsuka, with the company reporting a sales growth of 41.4% between 2015 and 2016 for the drug (Otsuka Holdings Co. Ltd. 2016). For patients, of course, these increased earnings translated to increased costs. While a monthly supply of Abilify Maintena retails at around $3,070 (or $36,840 for a year's supply), a thirty-day supply of generic Abilify oral 5 mg tablets

can be purchased for as little as $11 (GoodRx 2022a; 2022b).[14] It has been estimated that, if evergreened versions of Abilify hadn't delayed the marketentry of generics, nearly $124 million could have been saved by Medicaid between 2008 and 2016 (Dickson 2019). As Carrier and Shadowen have pointed out, product hopping "can significantly decrease consumer welfare, impairing competition from generic drugs to an extent that greatly exceeds any gains from the 'improved' branded product" (2017, 168).

3.2 Noncompliance as a Business Opportunity

Beyond its success in shifting the market to a new drug with a secure patent, Abilify Maintena was significant in that it demonstrated to Otsuka the potential of "treatment noncompliance as a business opportunity," a strategy that would later be reintroduced with the first smart pill (Applbaum 2009a). From a public health perspective, long-acting injectables seem to promise a solution to the enormous issue of nonadherence in psychiatry, as patients no longer have the option to stop taking their medication. From an industry perspective, such "maintenance treatments" can be an enormous boon, as they are designed to be taken regularly, from diagnosis until death (or until untenable side effects prevent continued use), and thus, to bring in maximum profits from each consumer. As Simon and Kolter put it, such "compliance improvement" treatments are "one of the most underutilized approaches" for pharmaceutical companies because "it completes a continuum of consumer loyalty that starts from awareness and diagnosis and ends with the monitoring of treatment outcomes" (2003, 172–173). They are also among the most expensive drugs on the market (Howard 2019).

FDA documents surrounding the approval of Abilify Maintena demonstrate how the narrative of compliance was considered a compelling one, even without evidence to support it. Maintena was approved on the basis of a fifty-two-week randomized placebo-controlled trial, commissioned by Otsuka, which took place across 108 trial centers around the world (FDA 2013b, 17). The manuscript reporting the results of the trial opens with a discussion of the issue of patient adherence and the way intramuscular injections can potentially help with this issue, but no outcomes related to adherence are reported (Kane et al. 2012).[15] In a clinical review of the trial, FDA medical officer Gregory Dubitsky noted that the design of the trial had quality issues, "because it included only patients who had tolerated and experienced a response to several weeks

of treatment with both oral and IM [intramuscular] depot" Abilify—which presented issues in assessing the drug's safety due to "a substantial difference in follow-up times between the drug and placebo treatment groups"—and numerous protocol violations (FDA 2013b, 13–14). Despite these issues, Dubitsky voted to approve the drug, noting that the "assured delivery of the drug" makes it an appealing, improved option, "especially for patients with poor compliance" (FDA 2013b, 5).[16]

4. ABILIFY MYCITE: HOW A DIGITAL PILL GOES TO MARKET

It was within this same context—of desperation and preparation for patent loss—that the first smart pill was introduced. In 2012, Otsuka announced plans to develop and market a digital form of Abilify, in partnership with Proteus Digital Health (Otsuka Holdings Co. Ltd. 2013, 16). Proteus was in the business of creating "ingestible event markers" (IEM) intended to track when a person took their medication. Abilify MyCite is one such marker, involving a tiny sensor attached to the Abilify drug that can be detected from a Bluetooth patch the patient wears when ingested. Capitalizing on cultural trends toward digitalization and personalized medicine, Otsuka signed an agreement with Proteus to license their IEM technology for this "smart pill" version of Abilify.[17]

Abilify MyCite also provided another example of product hopping, called "digital evergreening" (Cosgrove et al. 2019), since it was developed with the aim of transferring patients with schizophrenia, bipolar disorder, and depression to this new, patent-protected product to prevent losing them to the unpatented, and much more affordable, generics. Like Abilify, the evidence base for MyCite was thin. But fortunately for the company, this did not pose a significant challenge. Like Maintena, a compelling compliance narrative helped seal the deal with the FDA. Below, we briefly describe how the first digital pill came to market, highlighting the synergy between the history of Abilify detailed above and the advent of Abilify MyCite.

4.1 Seeking Approval for Digital Evergreening

The first NDA for Abilify MyCite, submitted to the FDA in 2015, was unsuccessful (FDA 2016). The evidence base for this drug-device system—the first of its kind—was limited: it consisted of two open-label, single-arm studies with psychiatric patients, two one-day studies with healthy subjects to evaluate whether the sensor could be detected, one twenty-eight-day trial testing the patch on healthy subjects, and a human usability

trial (FDA 2017a). Additionally, a laundry list of concerns were aired in clinical reviews of this research, including "multiple failures and difficulties observed with critical tasks" that might render the "system ineffective," "deficiencies" during an inspection of Otsuka's manufacturing plant, and insufficient evidence, noting that twenty-five of twenty-six trained and untrained patient users "failed one or more critical steps in using the product" under simulated "real-world" conditions (FDA 2016, 3; 2015b, 20; 2017a, 16, 23). Based on these data, one reviewer concluded that the application did "not provide adequate evidence that Abilify-MyCite could be used as intended" and did "not support safe and effective use in the intended population" (FDA 2015b, 23-24).

In 2017, a new application was submitted, consisting of two additional trials: one in which 66% of participants (N = 35) were able to demonstrate correct use at the end of two days, and another that evaluated the functionality of a call center providing support to those taking Abilify MyCite over eight weeks (FDA 2017a, 23). In the second study, the primary outcome measure was the number of calls to the center during the trial, which was taken to represent functionality, but claims were also made about patient adherence, which was said to be higher than usual for similar patients (Kopelowicz et al. 2017, 2648).[18] As with the previous study, approximately half of the sample experienced adverse events (Kopelowicz et al. 2017).

Based on the new data, Daniel Lee, who evaluated the application on behalf of the FDA, noted that the 66% success rate in the usability study "represents an improvement from the first review cycle where participants demonstrated 52% correct use after eight weeks" (FDA 2017a, 23). He observed that the number of adverse effects was high—"9–18 times the predicted percentage of total adverse effects" based on trials with oral Abilify—but suggested that post-marketing studies could explore these results further (FDA 2017b). Lee also noted that the simulated-use study conducted for resubmission offered "no additional data regarding adherence," and observed that rates of adherence with regards to Abilify MyCite were "no different than rates of adherence noted in real-world adherence trails for daily oral antipsychotics" (FDA 2017a, 10).

Despite very little change in demonstrations of efficacy or safety since the first application and no data related to adherence, Lee voted to approve Abilify, stating that "approval will likely spur future innovation of similar technology" (FDA 2017b, 12–13). In November 2017, Abilify MyCite was approved. As it happens, Lee is now employed at Otsuka, a fact that should not be underappreciated (Lee 2022; 2019).[19]

4.2 A Good, and Familiar, Story

Given their previous experience with Abilify, Otsuka knew that the success of Abilify MyCite depended on a good story. And through the launch of Abilify Maintena, they had learned that there was a big market in psychiatry for technologies promising to solve the problem of patient noncompliance. Heavily-redacted meeting minutes—from meetings, as far back as August 2013, between Otsuka and Proteus executives and officials from the FDA—reveal the sponsors' intention to receive a "FastTrack" designation for Ability MyCite on the basis that it addressed an "unmet medical need" by promoting patient compliance (FDA 2013c). In a May 2014 financial presentation, Otsuka executives told investors that—along with Maintena, the injectable form of Abilify—smart pills are another solution for "patients with a lower comprehension of the importance of adherence" (Otsuka Holdings Co. Ltd. 2014). The strategy was a promising one.

Despite a press release from the FDA, which clearly stated that "the product's ability to improve patient compliance with their treatment regimen has not been shown," the story of MyCite as a solution to issues of compliance was heavily promoted (FDA 2017c). In an analysis of literature covering the release of Abilify MyCite, Cosgrove and colleagues found that, out of seventy news stories and reports about the first smart pill, sixty-five did not acknowledge the lack of safety data, forty failed to report on the lack of efficacy data, fifty-two suggested a benefit that was unsupported by research (e.g., compliance), and twenty-one cited experts with financial ties to Otsuka or Proteus. They found similar results in the scientific data: of fourteen articles, ten gave an "unsupported impression of benefit," and eight included at least one author with financial ties to Otsuka or Proteus (Cosgrove et al. 2019).

Bearing this out, an article in *WIRED* quotes Otsuka's chief strategic officer, who observed that "the adherence issue is particularly relevant to serious mental illness," and cites a clinician, who stated that "this is as good as any high-tech method" when it comes to adherence; the lack of evidence for Abilify MyCite improving adherence is not mentioned (Zhang 2017). An op-ed, written by Dawn Velligan (a pharmaceutical consultant who has received honoraria from Otsuka) and Saher Kamil, is boldly titled "Enhancing Patient Adherence: Introducing Smart Pill Devices," and contains a pull-quote stating:

> The promise is that better adherence as well as better information about the adherence of a particular patient will ultimately improve outcomes for multiple longstanding medical and psychiatric conditions. (2014)

5. SMART PILL, SMART TACTICS: SEEKING USER AND ETHICIST APPROVAL

In two important respects, the launch of Abilify MyCite went above and beyond any version of Abilify that had come before. Perhaps in response to early negative press that the "snitch pill" (Caplan 2015) was already getting, Otsuka and Proteus worked hard to promote a positive story of Abilify MyCite. As mentioned above, they recruited two crucial stakeholder groups whose approval they attached to the new product: patients and ethicists. Here, we look a bit closer at the involvement of each of these groups.

5.1 Patient Empowerment?

Crucially, Otsuka and Proteus sought to generate patient support, or at least, an *impression* of patient support, for Abilify MyCite. This tactic, of engaging consumers and emphasizing the alignment between patient goals and corporate interests, fits well with Otsuka's "Declaration of Customer-Centric Commitment," in which the company speaks of "aiming to maintain the trust of our customers and society . . . fulfill[ing] our social responsibilities through honest and trustworthy dialogue . . . always put[ting] patients and consumers first" (Otsuka Holdings Co. Ltd. 2018, 69). After the Van Halen introduction to their session at HLTH, Thompson and Nath, the CEOs of these companies, touted their businesses' success in "enabling the creation of products and services that can be exquisitely tailored to the needs of individual consumers" in ways that not only "reduce costs, eliminate waste, and improve satisfaction," but also "expand access, improve outcomes, enhance physician and care-team productivity, and make innovation much more sustainable" (HLTH 2018). What's more, Thompson and Nath spoke of how patients enthusiastically, and without any prompting, brought this new technology to share with others at NAMI (Thompson and Nath 2018).

Despite our best efforts, we were unable to find any additional information or evidence regarding Thompson and Nath's claim that patients, of their own accord, attended NAMI, "telling doctors about Proteus technology, and telling pharmaceutical companies that they should adopt it and put it inside their drugs" (Thompson and Nath

2018). However, this kind of claim is becoming more popular among pharmaceutical companies that strive to look like they are patient-centered and driven by consumer demand. Kalman Applbaum refers to what are sometimes described as "value co-creation" efforts, which aim to involve consumers in designing and marketing new products (2009c, 15). These efforts often involved the strategic use of shared language, cashing in on the fact that:

> Many words that connote what might be called "communal" meanings, such as "good," "share," "or value(s)," also happen to be key terms in the business world carrying financially oriented meanings, *viz*., goods, shares and value. (Applbaum 2009a, 114)

While these terms can be appealing to patients, Applbaum notes, such language may "conceal or camouflage divergent purposes, permitting partial truths to stand in for whole ones" (2009a, 114). Such "relationship marketing" is presented as morally inviolable, due to an emphasis on foundational values of choice, self-determination, and empowerment, making it "able to draw in the energy, willingness and participation of those who would be both the instruments and the victims of that power" (Applbaum 2009b, 189).

Edward Walker has shown that we often think of grassroots tactics, like patients setting up a booth at NAMI, as "weapons of the weak, in that those who are kept out of the government organizations decision-making processes are forced to adopt strategies that fall outside of traditional avenues of influence," but in fact, companies are increasingly adopting such strategies (2010, 47). In doing so, these tactics "not only build public support for certain approaches, they help companies 'put a human face' on issues, personalizing matters for elite decision-makers" (Walker 2010, 47).[20]

NAMI is also an interesting site for patient promotion of MyCite to take place. While it calls itself the "largest grassroots mental health organization" in the US, NAMI's ties with the pharmaceutical industry have provoked critiques from service users and clinicians alike (Davidow 2017; Jaffe 2010; McCarthy 2019 National Alliance on Mental Health 2022b).

The organization is primarily funded by pharmaceutical companies, including Otsuka, and is well known for lobbying alongside the pharmaceutical industry in favor of legislation that promotes industry profits and restricts the liberty of service users (Davidow 2017; Harris 2009; 2019). In every one of its available annual reports, from 2010 to

2020, Otsuka is named as a corporate sponsor (National Alliance on Mental Health 2022a). In 2009, a whistleblower, who had previously worked as a drug rep for Pfizer, claimed that the company funded NAMI to promote the use of an antipsychotic in children, for which it had not been approved. Apparently, even the president of NAMI at the time, James McNulty, had received personal grants for talks he gave in support of such prescriptions, although he failed to disclose these (Edwards 2009).

5.2 Bioethicist Endorsement?

According to the bioethicists hired by Otsuka, when Abilify MyCite started getting bad press as a potential "snitch pill," Otsuka had to choose to either "ignore the criticism as a distraction from the goal of FDA approval, or bring in bioethicists to carefully examine the product while still in its development phase,"and fortunately, the bioethicists write, "the company chose the latter path" (Klugman et al. 2018b, W6). These bioethicists—including two lawyers, a physician,[21] and a medical anthropologist—introduced the Ethics by Design framework, highlighting the four principles of biomedical ethics: autonomy, beneficence, non-maleficence, and justice (Beauchamp and Childress 2001; Klugman et al. 2018b; Meldrum 2018).[22] They also published a target article in the high-ranking *American Journal of Bioethics (AJOB)*, offering an ethical analysis of smart pills utilizing the Ethics by Design framework.

The article offers a remarkably cheerful ethical analysis of smart pills. Avoiding any discussion of psychiatry—the actual context within which Abilify MyCite was developed and implemented—the paper discusses difficulties in adherence for those with diabetes and how effective smart pills could be in that context (Klugman et al. 2018a, 42). As a target article, the manuscript was circulated in advance of publication, and commentaries were elicited from other bioethicists. While several of these commentaries raised the significant concerns—related to risks of coercion, targeting marginalized populations, and surveillance and monitoring requirements from courts or the state—in their response, the authors of the original article state that they chose not to engage with these "complex" contexts (Guta et al. 2018; Martinez-Martin and Char 2018; Terrasse and Sisti 2018; Swartz 2018; Carter et al. 2018; Klugman et al. 2018a, 42). Klugman et al. 2018a). Instead, the authors spend a significant amount of time motivating the problem of patient adherence, only mentioning once that another author had noted a lack of evidence that smart pills improve adherence. This mention also occurs in conjunction with the consideration

of a case in which "a patient wants the digital solution because she or he feels this will really help and the clinician does not agree with the use of such devices or with the specifics of the user agreement" (Klugman et al. 2018a, 42).[23] The context of pharmaceutical development in which the drug is introduced, and the tactics commonly utilized in this context, are never mentioned.

The authors' silence on crucial contextual aspects of digital pills strikes us as a significant failure, but one that is not atypical within the discipline of bioethics. As Hedgecoe has pointed out, bioethicists tend to "accept unquestioningly scientists' expectations" regarding new technologies, engaging in a bioethical debate, "the boundaries of which have been laid down and defined by academic and industry scientists" (2010, 163). This may be an innocent mistake. As Hedgecoe suggests, because bioethicists may be inclined to accept scientists' expertise when it comes to claims about the technology, which may lead to a "chance of 'slippage' when bioethicists also accept scientists claims about the ethical future" (2010, 172). Furthermore, all too often, bioethicists utilize abstract frameworks, such as principlism or consequentialism, as a way to survey the ethical issues at hand, but in doing so, distract themselves from the larger contexts of politics, marketing, and economics they are working within.

Bioethicists are increasingly hired by pharmaceutical companies as the new "thought leaders" of the moral realm [24] (Sharp et al. 2008; Van Campen et al. 2014). As Carl Elliot has pointed out:

> Bioethicists help write the policies that govern the ethics of medical research, and they sit on the institutional review boards and research ethics committees that decide which research protocols can go forward. It should be no surprise that the pharmaceutical industry is eager to influence them. (2005, 422)

Indeed, bioethicists have been hired to examine ethical issues related to recruiting those without homes for phase-1 research, biotechnology in the developing world, stem-cell research, and placebo-controlled trials for mood-altering drugs (Elliott 2005). Google's DeepMind and other companies, like Facebook, now have ethics teams devoted to exploring emerging moral issues related to their developing technologies. As bioethicists-for-hire become increasingly popular, the question of what these experts offer becomes increasingly important. While you might hear more or less the same assessment when you hire different scientific or technological experts to provide guidance, this is not the case with ethics, since disagreements among professional ethicists are widespread and often

irresolvable. Noting the lack of ground rules in ethics, De Vries and Keirns ask whether bioethics can "find a way to live with this tension, to serve two masters—truth and money" (2008). Yet, as Elliot warns, "Embracing the role of trusted adviser means foregoing other potential roles, such as that of critic" (2010, 147).

The bioethicists hired by Otsuka are, unsurprisingly, supportive of the shift toward bioethicists as corporate consultants, arguing that "Ethics by Design for novel products ought to become an integral part of pharma and medical technology development" (Klugman et al. 2018b, W7). They further suggest that, by "examining the traditional bioethical principles and issues" and "looking at concerns of social justice and patient participation," bioethicists can mitigate the risks of their financial relationships with the pharmaceutical industry and "assist the producers, prescribers, and users of this technology with an interdisciplinary approach to understanding and application" (Klugman et al. 2018b, W7). However, they do warn that, in working with industry:

> It is essential to define role expectations, tasks to be accomplished, and how the bioethical analysis will be used by the company . . . bioethicists should retain independence… without the company's review or editing. (Klugman et al. 2018b, W6–W7)

They also suggest that multiple bioethicists should be consulted (Klugman et al. 2018b). Despite these recommendations, the authors do not mention their involvement with Otsuka within their target article on smart pills, although it was declared in a mandatory disclosure statement alongside the article.[25]

6. MAKING MEANING UNDER BIOMEDICAL CAPITALISM

6.1 The Logic of Industry

What does it mean for Otsuka and Proteus to claim support from patients and ethicists? As has been made abundantly clear from the story of Abilify told above, the companies responsible for Abilify's many indications and iterations are driven by financial goals. Given their status as profit-driven enterprises, they are responsible to their shareholders and must continue to make gains in order to keep them invested. The importance of continuing to make profits is what drives the development of products, the research invested, the narratives constructed, the applications filed, the drugs added to and removed from circulation, the marketing strategies, and so on. As Joseph Dumit points out, this motivation toward profit is not wrong or

malicious; it is simply the logic of the system of biomedical capitalism, which fundamentally shapes knowledge produced by the pharmaceutical industry (2012, 23).

Are patient goals compatible with this logic? Are ethical analyses? For drug companies, the goal is to satisfy company requirements at all costs. This means that goals put forward by patients and ethicists must be subordinated to the goal of selling medication. To pretend that the values of patients and ethicists can neatly fit into the logic of industry, driven by profit, is to embrace an illusion. While there may well be some moments in which these goals are in harmony, these instances are likely to be few and far between. Costs and profits, for example, are always likely to be at odds. A monthly prescription for Abilify MyCite is currently listed at a hefty $1,988 for the drug alone, without the required smartphone and service plan (GoodRx 2022c). Given that no benefit of MyCite has been demonstrated beyond that of generic aripiprazole, which costs under $11 per month, it's not clear what the introduction of this new technology is offering (GoodRx 2022d). Additionally, the goal of health is not a shared one either. As Dumit observes:

> A healthy person who is not on or not likely to be on medicine is, from the perspective of this economy, not valuable. In other words, from the perspective of value, healthiness is antithetical to biomedicine. (2012, 94)

The story of Abilify shines a spotlight on the logic of drug development. Unfortunately, this story is not unique; versions of it have been told time and again, particularly in the context of psychiatric research (Brill 2015; Elliott 2010). Examining the details of how a drug like Abilify comes to be, dominates the market, and strives to hang on to profits for as long as possible, while not unusual, should lead us to question the compatibility of this industry with patient well-being and ethical analysis.

6.2 "The Problem of Adherence"

Although Otsuka has worked hard to control the narrative surrounding MyCite, promoting the story of a medical miracle that can solve the problem of patient noncompliance, an essential question underlying this narrative remains unasked: Is adherence the problem we should be addressing? At this moment, patients and practitioners alike are increasingly questioning the efficacy and safety of antipsychotics as a treatment for individuals diagnosed with schizophrenia (Correll, Rubio, and Kane 2018; Harrow and Jobe 2018). Despite the fanfare surrounding the introduction of SGAs

in the 1990s, recovery rates—measured in terms of functional outcomes—have not improved, resting at around 13% for decades (Jääskeläinen et al. 2013). While psychotic symptoms do often subside after the administration of antipsychotics, a small body of long-term research suggests that the use of antipsychotics may lead to an increase in psychotic symptoms over time (Harrow, Jobe, and Faull 2014; Wunderink, Nieboer, and Wiersma 2013). This possibility—in combination with the debilitating side effects that often accompany antipsychotic use—has led experts in the field to ask whether antipsychotics are doing more harm than good (Harrow and Jobe 2013; Sohler et al. 2015). Others are working to develop tools for tapering off and discontinuing their use (Murray et al. 2016; Suzuki et al. 2003). While the evidence in this area is not conclusive, these data should certainly give us pause in our pursuit of compliance.

Furthermore, a focus on adherence can be harmful, reinforcing negative stereotypes of "difficult" patients and distracting from more important issues (Roe and Davidson 2017). Crucially, a focus on adherence often leads to a focus on blame, since noncompliance is often taken as indicative of a failure or lack of willingness on the part of the patient (Applbaum 2009a). The terms "noncompliant" and "nonadherent" are frequently used pejoratively in the context of medicine to describe a patient's refusal to partake in treatment, no matter the reason for their decision. However, as mentioned above, patients may have very good reasons for refraining from complying with the medication regimen prescribed to them. As we've seen, the side effects of antipsychotics can be wide-ranging and severe, involving weight gain, tremors, drowsiness, and a shorter life expectancy. In the comment section under Nath and Thompson's HLTH presentation on YouTube, someone wrote that "its [sic] a defective product alright—people opt out using them because they are awful things to take with massive side effects and really bad long time [sic] outcomes" (Thompson and Nath 2018). Such experiences are not accounted for in marketing strategies that point to patient adherence as a singular goal.

6.3 Is a Digital Fix What We Need?

Advocates portray digital tools as major drivers of change in healthcare, making medicine more personal, more precise, and more advanced. But technologies by themselves do not disrupt, reinvent, or empower; indeed, some create the opposite effect. In 2017, the same year that Abilify MyCite was approved, the National Institutes of Health (NIH) reported that research dollars spent on schizophrenia averaged just $243 per

affected individual (NIH 2023). The mental healthcare that the American "consumer" receives is, in most cases, barely adequate, and has a long way to go before reaching parity with healthcare for other conditions. Concentrating an enormous amount of time and resources toward creating costly biotechnology that fails to offer any novel benefit for patients, as in the case of Abilify MyCite, stands in stark contrast to small investments elsewhere. More broadly, while problems such as the widening of health disparities in our societies remain unsolved, large sums of public and private money are invested in creating digital infrastructures for medical practice and research (Skorburg and Friesen 2021). Focusing funding and research around cost-prohibitive technology, rather than community-specific barriers to both access and adherence, guarantees that we will (re)produce a fundamentally unjust and unequal world.

The push to digitize healthcare is increasingly framed in terms of empowering patients through more choice, convenience, and information. The taken-for-granted narrative when it comes to (mental) healthcare is that anything we can do to give patient "consumers" more access, control, and information to manage their medical conditions is a step in the right direction and should be embraced. We talk of making things "smarter" and "easier" by adding a technical dimension, but these rhetorical tics seem to be one more way of bypassing much larger and more pressing issues. Such claims of revolution, transformation, and empowerment are rhetorical devices that must be critically assessed with respect to their plausibility and unflinching commitment to tech solutionism.

7. CONCLUSION: A LAST GASP?

During the HLTH session, Nath spoke to the challenges facing pharmaceutical companies in this day and age:

> In technology, there's been five decades of getting cheaper, more successful, more reliable, and quicker—a phenomenon driven by Moore's law. In R&D [research and development] discovery and development, we've had five decades of getting slower, less successful, and more expensive. A phenomenon that some have dubbed Eroom's law, for Moore's law spelled backward. (Thompson and Nath 2018)

This is certainly the case for Abilify MyCite, which perfectly represents a new product that has demonstrated nothing in terms of success for patients, but is much more expensive than previous versions of Abilify.

Abilify MyCite has always been about the future. Now, the future is here, and unfortunately, while painted as a revolution in technology and

medicine, one that might solve the enormous problem of adherence, it proved to be neither of these. Instead, as this story reveals, Abilify MyCite was merely another move made to capitalize on the enormous success of Abilify that was slipping away from an increasingly desperate company.

In a last gasp, with the approval of Abilify MyCite, Otsuka invested $88 million in the new product, hoping to move patients onto a new, expensive, patented version of Abilify, to make up for the losses they would experience at the end of Abilify's patent. But since then, Otsuka has refused to invest any additional money into Proteus (Farr 2019). In early 2020, Proteus and Otsuka ended their "partnership," and Proteus has moved away from developing products for mental health conditions (Muoio 2020). An article discussing the break reports, "the issue involved a lack of traction among patients" (Iskowitz 2019). In 2020, Proteus filed for bankruptcy (Farr 2020).

Given the stellar rise of Abilify, perhaps Otsuka was due for a fall. However, new collaborations may be on the horizon. Not long ago, Otsuka announced an initiative with a nonprofit organization in Florida called Thriving Mind South Florida, which is building a mental health center that will offer support to individuals diverted from the criminal justice system (Harris 2019). As Harris points out, this collaboration could "provide Otsuka with an opportunity to demonstrate Abilify MyCite's use in a captive population" (2019). It has also been reported that free samples of Abilify Maintena were requested by and given to a correctional system in Maricopa County, Arizona (Blau 2019).

NOTES

1. We use the terms noncompliance and nonadherence interchangeably within this manuscript, but we acknowledge that there is disagreement about whether they refer to the same phenomenon.
2. The patent on Abilify (US Patent No. 5,006,528) was originally scheduled to expire on October 20th, 2009. This was extended to October 2014 after the United States Patent and Trade Office ruled in favor of Otsuka's request for reexamination in 2009 (Bristol-Myers Squibb Company 2009; *Otsuka Pharmaceutical Co. v. Sandoz, Inc.* 2010).
3. According to Marcia Angell (2005), a blockbuster drug is commonly defined as a drug that nets $1 billion in annual sales.
4. Ahead of Nexium, Humira, and Crestor.
5. According to the American Psychiatric Association (2022), schizophrenia affects less than 1% of the US population, while the National Institute of

Mental Health (2022) reports that the prevalence of schizophrenia is between 0.25% and 0.64% in the US and between 0.33% and 0.75% internationally.

6. This story is an interesting one in itself. The Orphan Drug Act—which grants seven years of market exclusivity to drugs that treat rare diseases (defined as any disease or condition that affects fewer than 200,000 persons in the US)—is an incentive developed to promote research and development of drugs that are unlikely to generate significant profits (Seoane-Vazquez et al. 2008). This incentive is frequently exploited by pharmaceutical companies to retain market exclusivity, and Otsuka planned to do so as well. Just before the patent for Abilify was set to expire, the company submitted an application for a new indication. On the basis of two short-term trials, Otsuka won approval for Abilify in treating pediatric Tourette's in April 2014 (FDA 2014). However, in February 2015, the FDA sent a "corrected" letter to Otsuka, informing them that the approval was "for the treatment of Tourette's syndrome," in general, and was not specific to pediatric populations (*Otsuka Pharmaceutical Co. Ltd. v. Burwell* 2015a, 3-4). This quickly led to a lawsuit in which Otsuka sued the FDA for illegally expanding the indication of Tourette's syndrome to include the population at large, as the clinical data submitted demonstrated the safety and effectiveness of the drug in pediatric patients only (*Otsuka Pharmaceutical Co. Ltd. v. Burwell* 2015a). In response, the FDA reversed their decision and limited the drug to pediatric patients diagnosed with Tourette's syndrome. This case reveals the perversity of how both companies and regulators are required to operate within the regulatory constraints and economic pursuits that dominate this realm. Otsuka, seeking to keep their shareholders happy, took the FDA to court for expanding their market, since they had been planning to take advantage of an incentive meant to motivate research and development for rare diseases, but which has primarily led to increased profits for blockbuster drugs; in 2015, seven of the ten bestselling drugs were orphan drugs (Tribble and Lupkin 2017). On the other hand, in an equally bizarre move, seeking to block Otsuka's manipulation of the Orphan Drug incentive, and thereby to increase the accessibility and affordability of Abilify, the FDA was required to expand an indication, from pediatric populations with a diagnosis of Tourette's to all populations, without an evidence base.
7. 21 US Code § 355a.
8. In practice, many trials conducted to obtain pediatric exclusivity are limited, not published in peer-reviewed journals, and take place in low-income countries (Gaifulinay 2011).

9. It was also sometimes called a "dopamine system stabilizer." Despite the prominence of dopamine antagonists in antipsychotics, the dopamine hypothesis of schizophrenia is not well supported (Kendler and Schaffner 2011) and several other mechanisms that appear to be causally linked to symptoms of psychosis are currently under investigation (Howes, McCutcheon, and Stone 2015; Khandaker et al. 2015; Young and Geyer 2013).
10. Research has found that nearly a quarter of nursing home residents in the US are prescribed SGAs (including Abilify) and the vast majority of these prescriptions (86%) are off-label (Kamble et al. 2010).
11. There is some disagreement about how to define evergreening. Here, we adopt the definition offered by Feldman and Frondorf (2017). In contrast, Beall et al. (2016) have suggested that evergreening only applies in cases where a secondary patent (regulatory exclusivity) extends a drug's monopoly without providing proportionate therapeutic benefit.
12. Maintena was developed in partnership with the Danish company Lundbeck, who paid Otsuka $1.8 billion upfront, followed by several clinical milestone payments of around $270 million (Global News Wire 2011).
13. According to the FDA's "Orange Book," these discontinuations were done voluntarily by the company and were not due to safety or efficacy.
14. In 2015, the average cost per prescription of Abilify Maintena was $1,664 (AccessRx Impacts 2017, 23).
15. The study did find, however, that both symptoms and relapse rates were lower in patients taking the study drug (Kane et al. 2012). As many have pointed out, comparing a new drug or formulation with a placebo is much more likely to lead to clinically significant results than comparing it with another available medication (Angell 2005).
16. It is possible that Dubitsky merely had in mind the obvious sense in which one cannot remove an injectable depot from one's system once it has been injected and so is therefore guaranteed that patients will be "adherent" for a month after injection.
17. The device–drug combination is referred to as a "smart tablet" in the FDA documents, but is more popularly known as a "smart pill" or "digital pill."
18. Adherence was calculated by dividing the number of transmissions to the server reporting ingestion by the number of treatment days with "good patch coverage" (having either 80% patch data for a day or detecting an injection transmission within a twenty-four-hour period). Days without good patch coverage were not included in the calculation of adherence, inflating the percentage representing adherence, which was 88.6%. The authors concluded that there was a "high rate of ingestion adherence" compared to the usual rate of less than 60% among similar patients (Kopelowicz et al. 2017).

19. In a feature article in *Science*, Charles Pillar details possible financial conflicts of interest among FDA advisors, examining publicly available data concerning 107 physician advisors and finding that forty of them have received benefits, including payment for hotels and research grants, from pharmaceutical companies. More than half of them, he notes, received over $100,000 in such "gifts," and seven of them received gifts worth more than $1 million. Importantly, none of the payments were reported to the FDA. One doctor in particular, he notes, received $1.9 million from a pharmaceutical company after one of its drugs was approved by a panel on which that doctor had been an advisor. The FDA does not make stipulations in its guidelines concerning post-advisory financial relationships between pharmaceutical companies and advisors (Piller 2018). So Lee may not be an exceptional case.
20. Another interesting example of Otsuka engaging in such "grassroots" tactics comes from their response to an NDA for aripiprazole lauroxil (trade name: Aristada), filed by competitor Alkermes in 2014, soon after Maintena came on the market. Aristada was a "a novel, once-monthly, long-acting injectable atypical antipsychotic for the treatment of schizophrenia" (Alkermes 2014). In response to Alkermes' NDA, Otsuka filed two citizen petitions with the FDA in 2014 and 2015, arguing that the evidence submitted for Aristada was insufficient, since only one novel trial had been submitted, rather than the two required. For the second trial, Alkermes relied on data submitted years before by Otsuka in support of Abilify, arguing that since the main ingredient, aripiprazole, was the same, the data could support Aristada as well. When the citizen petitions were unsuccessful, Otsuka sued the FDA, alleging that the Alkermes drug is merely a "chemical trick" designed by "a follow-on copycat company" trying to get a free ride on the innovation efforts of Otsuka (*Otsuka Pharmaceutical Co. Ltd. v. Burwell* 2015b, 3). This case reveals the bizarre logics underlying the legal, economic, and regulatory terrain surrounding pharmaceutical development in the US. Within this system, Otsuka pretends to represent the public by filing multiple citizen petitions to block a competitor's entry into the market. A citizen petition is a channel developed in the 1970s to allow ordinary people to raise concerns over drug safety with the agency in the hopes of delaying, appealing, or withholding approval. They are now regularly utilized as a tactic by pharmaceutical companies, as in this case. The FDA is also not immune to these perverse logics. In this case, the FDA maintains both that Aristada is identical to Abilify, in that they both consist of aripiprazole, and therefore can rely on the same clinical data for regulatory approval, but also that they are distinct enough that Aristada can be approved as a "new chemical entity."

21. According to Open Payments, the physician has received nearly $60,000 from Otsuka and Lundbeck (Otsuka's partner in Abilify Maintena) since 2016 (US Centers for Medicare & Medicaid Services 2022). Some of these payments came in the form of lunches, dinners, and travel, but most were compensation for "consulting." Since the other authors are not physicians, information on their payments is not available online.
22. These also happen to be the four ethical principles that are outlined in the most commonly used bioethics textbook (Beauchamp and Childress 2001). In terms of Abilify MyCite, this meant considering the product in terms of: 1) ensuring informed consent in the form of a user agreement; 2) using clear language to enhance patient understanding of monitoring; 3) providing clarity around data management (storage, usage, etc.); and 4) making sure the technology is accessible to those from different income levels so distribution is fair (Meldrum 2018).
23. One of the bioethicists, Glenn Cohen, also published an opinion piece in *New Scientist* with colleague Alex Pearlman on the topic. They promote the notion of adherence technologies for the benefit of patients, writing: "some people undergo directly observed treatment for tuberculosis, for example, which involves a doctor watching them take their medication. Is a digital medicine an encroachment on freedom, or a welcome, less intrusive option? Digital medicine products have the potential to improve healthcare for all involved" (Cohen and Pearlman 2018).
24. While some have suggested that "worries about the cooption of bioethics research by a few interested stakeholders are greatly overstated" (Sharp et al. 2008), representatives from Eli Lilly report an increase in their bioethical consultations from five per year in 2008 to one per week in 2013 (Van Campen et al. 2014).
25. Their disclosure statement did make clear that, while the authors served as consultants for Otsuka, "The company neither funded the preparation of this article nor played a role in its drafting or review" (Klugman et al. 2018a).

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