

# Digital medicine systems: an evergreening strategy or an advance in medication management?

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Poor adherence to prescribed medications is a major public health problem in the USA and worldwide, leading to substandard management of diseases and their associated symptoms, as well as increasing healthcare costs.<sup>1</sup> The development of innovative technologies to improve medication adherence is important and may hold promise, but any new technologies need to be supported by robust evidence of patient benefit and safety prior to regulatory approval, clinical uptake and payer reimbursement.

Most technologies developed to improve medication adherence are ancillary or supportive: automated pill dispensers, mobile phone applications that remind patients to take their pills, or smart pill bottles that track when a pill is removed.<sup>2</sup> Proteus Digital Health's ingestible sensor reimagines the way technology is used in medicine. The sensor is embedded within an oral tablet and transmits a signal to a wearable patch after exposure to stomach acid, providing patients and their clinicians with trackable ingestion data on medication use. The intent of the product is to improve medication adherence, but it may also have additional benefits, such as mitigating the risks of overdose and abuse.<sup>3</sup> Since the sensor was cleared by the Food and Drug Administration (FDA) as a stand-alone device through the 510(k)-premarket notification process in 2012, Proteus has collaborated with several manufacturers to embed the sensor directly into FDA-approved drugs.<sup>4</sup> In November 2017, Abilify MyCite, which combines the atypical antipsychotic, aripiprazole, with Proteus' digital sensor, became the first FDA-approved digital medicine system, a drug-device combination that measures and reports medication ingestion.<sup>5</sup>

In this issue of *BMJ Evidence-Based Medicine*, Cosgrove *et al* systematically reviewed the evidence supporting FDA's approval of the precedent setting Abilify MyCite, as well as any additional evidence supporting use of the drug-device combination product.<sup>6</sup> The authors conclude that regulatory approval was based on weak evidence, with no clinical studies demonstrating that Abilify MyCite was associated with better, or even non-inferior, medication adherence than the older, readily available, Abilify tablet.

In total, the authors identified three clinical studies supporting FDA's approval, all non-comparative uncontrolled cohorts, which primarily examined the usability of the product among patients with disease, demonstrating that Abilify MyCite successfully tracks ingestion of aripiprazole. However, lacking comparator arms, these studies cannot provide evidence that Abilify

MyCite improved medication adherence, nor evidence of its effect on quality of life, psychiatric symptoms or remission. Additionally, the three trials provide limited safety data, particularly considering that Abilify MyCite is intended for chronic use. The longest trial was 16 weeks in duration and all the trials in aggregate included fewer than 200 participants, with no comparative data on gastrointestinal, skin or other adverse events.

The authors then reviewed the scientific literature, including all papers citing these trials, as well as news reports, finding that both the published literature and media conveyed an impression that Abilify MyCite was associated with important benefits, even though no such evidence had been demonstrated. Over half failed to acknowledge the lack of efficacy data from clinical trials and three-fourths claimed benefits that were unsupported by the evidence.

These findings raise several concerns. First, FDA approval of Abilify MyCite without comparative efficacy data raises the concern that digital medicine systems may represent a new strategy to 'evergreen' drugs approaching the end of their market exclusivity periods. Evergreening involves a range of practices pharmaceutical manufacturers pursue to extend monopoly protection, most often by making minor changes to the dosing or formulation of older, readily available drugs, the newer versions of which offer marginal or no additional benefit to patients.<sup>7</sup> These slightly modified drugs are often priced expensively relative to generic versions of the older drug. For example, a month's supply of Abilify MyCite in the US costs approximately 85 times that of generic aripiprazole. Because of these higher prescription drug costs, evergreening may also worsen patient outcomes, as the inability to afford drugs has been shown to be a major cause of non-adherence.<sup>8</sup> Thus, any potential gains in adherence from digital medicine systems may be offset by their increased costs.

Additionally, digital medicine systems present unique ethical and safety concerns. For example, Cosgrove *et al*<sup>6</sup> and other experts have raised concerns about the potential negative effects of giving ingestible drugs with sensors to patients with serious psychiatric illnesses, including some of whom may suffer from paranoia and delusions.<sup>9</sup> Finally, further evaluation of the accuracy medication ingestion tracking is needed. One FDA reviewer of the Abilify MyCite New Drug Application noted that one study of healthy adults suggested the digital medicine system had a roughly 20% false negative rate,<sup>10</sup> which could



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lead to an increased risk of overuse and overdose. Despite such concerns, limited preapproval safety data were collected, and FDA did not require any postmarketing studies at the time of approval that could generate reliable safety, or efficacy, data.

Several steps are needed to promote more rigorous evaluation of digital medicine systems to ensure that older drug products being brought to market as part of innovative delivery systems are improving outcomes for patients and not simply increasing profits for manufacturers through another evergreening strategy. First, the FDA should raise the evidentiary standards required for these products, ideally requiring clinical evidence of superiority as compared with the older drug products. In addition to examining patient adherence to medications, studies should measure additional patient-important outcomes such as quality of life, symptom burden and functional status. At a minimum, studies should use a non-inferiority design, as placebo control studies in this context would be unethical.

Second, clinicians should defer prescribing these products and payers should not provide coverage until rigorous evidence is generated demonstrating that digital medicine systems improve outcomes for patients and are worth the added costs. Finally, the FDA and the US government should consider measures to better incentivize manufacturers to develop and market generic versions of the non-digital products, even after market entry of the digital medicine system. Continued availability of the generic, non-digital versions will help prevent 'forced switches' that often accompany evergreening strategies,<sup>11 12</sup> and help ensure patient access to more affordable therapies, which may be a better option, particularly for those at lower risk for medication non-adherence.

Digital medicine systems have the potential to provide several benefits to patient care, including increasing medication adherence, providing real-time tracking of drug use and mitigating risks of overdose and abuse.<sup>13</sup> However, until robust evidence of patient benefit and safety is generated, clinicians ought to be hesitant to prescribe Abilify MyCite and any future FDA-approved digital medicine systems.

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