Effective Health Care

Technology to Support Medication Adherence

Results of Topic Selection Process & Next Steps

The nominator, Connected Health Initiative (CHI), is interested in a new evidence review on established and emerging medication adherence approaches and believes it would be of great utility to healthcare stakeholders and the U.S. government. CHI is a coalition of industry stakeholders and partners leading efforts to harness the power of technology to improve patient engagement and health outcomes. The topic nomination form and further discussion with the nominator indicated an interest in the benefits of digital pills, associated equipment/software platforms and other novel technology that supports medication adherence. The nominator intends to use the report to provide evidence for greater U.S. government and private sector support of new and innovative tools in preventing and treating painful and expensive diseases. The report would be used in written and spoken advocacy for connected health technologies across public and private systems.

Because limited original research addresses the nomination, a new review is not feasible at this time. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: #0794 Technology to Support Medication Adherence

Nomination Date: 06/22/2018

Topic Brief Date: 09/7/2018

Authors
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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Background

In a 2003 report, the World Health Organization stated that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments." [1] However, the rates of medication non-adherence in the United States have remained relatively stable since then, whereas direct health care costs associated with non-adherence have grown to approximately $100-$300 billion of U.S. health care dollars spent annually.[2] Medication adherence is often low even in the controlled environment of clinical trials where it can lead to complex major implications.[3]

Medication non-adherence can significantly impact clinical outcomes, mortality, and health care costs. Medication adherence is particularly important in patients with chronic medical conditions for whom missing a dose or taking a late dose can result in decreased benefit, increased risk,

and potentially impacting disease progression and quality of life. The average rates of adherence to long-term medications for chronic illness are only about 50%. [4]

Traditionally, a variety of organizational strategies such as pill boxes, blister packages, and other modified medication packaging have been used to simplify medication regimens to support medication adherence. Patient education and behavioral strategies have also been used including prompts (phone calls, texts, timers, reminders, etc.) to remind patients to take medications at the correct time. More recently, a newer, third type of strategy involves self-monitoring of drug administration and/or feedback of drug administration through use of technology. These technologies provide messages or information back to patients and health care providers about the patient's medication use. Technologies such as smartphone, mobile application technologies, digital pills (also known as "smart" pills) or smart pill boxes that record bottle opening or administration are examples of novel technology that fit in this last group.

With the increased availability of technology to patients and health care providers, items such as digital devices, software applications, and smartphones are increasingly being used to support medication adherence through self-monitoring and feedback. These technologies come at much higher cost. The effectiveness, benefits, harms, and costs of all strategies to impact medication adherence are important for patients and providers to consider when choosing a medication and adherence strategy. Demonstration of effectiveness is needed to support use of these newer, higher cost strategies. The nominator for this topic is particularly interested in the benefits of digital pills, associated equipment/software platforms and other novel technology in medication adherence.

In November 2017, the U.S. Food and Drug Administration approved the first drug in the U.S. with a digital ingestion tracking system.[5] Abilify MyCite (ariprazole tablets with sensor) has an ingestible sensor embedded in the tablet that records when the tablet is taken with a smartphone app or web-based portal. Abilify MyCite is approved for treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder, and for use as an add-on treatment for depression in adults. It is important to note that although tracking ingestion of medications for mental illness may be useful for some patients, the FDA states the ability of this product to improve patient medication compliance has not been shown. At the time of this topic brief, this digital pill has not been proven to improve medication adherence.

Nominator and Stakeholder Engagement

The nominator, Connected Health Initative (CHI) is a coalition of industry stakeholders and partners leading efforts to harness the power of technology to improve patient engagement and health outcomes. The topic nomination form and further discussion with the nominator indicated a particular interest in the benefits of digital pills, associated equipment/software platforms, and other novel technology in disease prevention and treatment through medication adherence.

The nominator intends to use the report to provide evidence for greater U.S. government and private sector support of new and innovative tools in preventing and treating painful and expensive diseases. CHI would use the report to support the use of connected health innovations across public and private systems both in the U.S. and outside the U.S. The report would be used in written and spoken advocacy for connected health technologies. The nominator reports that the American Medical Association's Digital Payment Advisory Group would also be very interested in this information.

Key Questions and PICOTS

The key questions for this nomination are:

1. Which technologies (such as digital pills, associated equipment/software platforms, and novel technology) and other strategies have been studied to support medication adherence?

2. What are the benefits and harms of technologies (such as digital pills, associated equipment/software platforms, and novel technology) that support medication adherence, and how do they compare with each other?

3. What patient outcomes are associated with the use of these technologies and strategies that support medication adherence?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, outcomes, timing, and setting (PICOTS) of interest (Table 1).

Table 1. Key Questions and PICOTS

Key Questions	**1. Which technologies (such as digital pills and associated equipment/software platforms) and other strategies have been studied to support medication adherence?**	**2. What are the benefits and harms of technologies (such as digital pills and associated equipment/software platforms) that support medication adherence, and how do they compare with each other?**	**3. What patient outcomes are associated with the use of these technologies and strategies that support medication adherence?**
Population	Patients with chronic conditions for whom medication adherence is important, particularly adults and vulnerable populations	Patients with chronic conditions for whom medication adherence is important, particularly adults and vulnerable populations	Patients with chronic conditions for whom medication adherence is important, particularly adults and vulnerable populations
Interventions	Strategies to improve medication adherence	Technologies (such as smartpills) to improve medication adherence	Strategies to improve medication adherence
Comparators	Placebo, no intervention, other intervention	Placebo, no intervention, other intervention aimed at medication adherence, other technology to improve medication adherence	Placebo, no intervention, other intervention
Outcomes	Primary: medication adherence statistics Secondary: patient satisfaction, quality of life, improved care, reduced hospitalization, assessments of usability, costs, clinical outcomes, harms and adverse events.	Primary: medication adherence statistics Secondary: patient satisfaction, quality of life, improved care, reduced hospitalization, assessments of usability, costs, clinical outcomes, harms and adverse events.	Primary: medication adherence statistics Secondary: patient satisfaction, quality of life, improved care, reduced hospitalization, assessments of usability, costs, clinical outcomes, harms and adverse events.
Timing/Setting	All	All	All

Methods

We assessed the nomination "Technology to Support Medication Adherence" for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix A for detailed description of the criteria.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature search in PubMed from September 2013 through September 2018. See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

We reviewed all identified titles and abstracts for inclusion and classified identified studies by study design to assess the size and scope of a potential evidence review.

Results

See Appendix A for detailed assessments of all EPC selection criteria.

Appropriateness and Importance

This topic is both appropriate and important. This review potentially affects all patients with chronic diseases, a very large proportion of the population. The WHO has stated that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments."[1] However, the rates of medication non-adherence in the United States have remained relatively stable. New technology that supports medication adherence can be costly, and patients, prescribers, and payers want to know the risks and harms. Further assessment of key questions 1 and 3 led to the conclusion that the questions map existing technology, and the main interest lies in assessing the risk, benefits and comparing the technologies to support medication adherence. Thus only key question 2 was assessed further.

Desirability of New Review/Duplication

A new evidence review would not be duplicative of an existing evidence review. We found two in-process systematic reviews that potentially address the nomination scope and key question 2, however, we do not know if and when these systematic reviews will be published. These systematic reviews focused on studies of smartphone or mobile application technologies and smart pill technology (2017-2018).

- An in-process systematic review was identified in PROSPERO. This review "Effect of electronic adherence monitoring devices on adherence and outcomes in chronic disease: a systematic review" is being done at University College London with the University of Auckland.[14] The authors confirmed that their review "included any electronic/digital monitors that were used as part of an adherence intervention, and included a control group as part of a RCT comparison. Both Proteus and Abilify MyCite would fit that criteria, however as far as we are aware it does not seem to have been used as part of a RCT." The author also replied they have just completed the analyses of the review, are writing up for publication, and anticipate another literature search prior to publication. This in-process review could potentially address all three of our key questions.

- Another in-process systematic review from PROSPERO "Digital aripiprazole (Abilify MyCite): a systematic review and meta-analysis of the evidence, and a review of its dissemination into the scientific literature, its press releases and its coverage in newspapers" from the Clinical Investigation Center of Rennes (http://cic.chu-rennes.net).[15] The authors will review the evidence supporting its use from randomized controlled trials and examining how evidence of effectiveness has been represented and disseminated in the scientific literature and newspapers/press releases. Preliminary searches have begun so the review is just starting. This in-process review could potentially address all three of our key questions in part as it centers around the digital aripiprazole product. It does not appear this review will evaluate medication adherence of the Abilify MyCite product against other adherence technologies.

See Table 2, Duplication column for additional information.

Impact of a New Evidence Review

A new systematic review may have high impact. Costs are higher for new technology, and patients, prescribers, and payers want to know if the strategies to improve medication adherence work. This is especially important since some medication adherence strategies cost much less than others. The effectiveness, benefits, harms, and costs of all strategies to impact medication adherence are important for patients and providers to consider when choosing a medication and adherence strategy.

It is important to note that FDA did not find sufficient evidence to approve a medication adherence claim for the Abilify MyCite product when it approved. Thus this product has not demonstrated in clinical trials to improve medication adherence.

Feasibility of a New Evidence Review

A new evidence review is not feasible. Our literature search identified two feasibility studies and two safety, tolerability or useability studies incorporating novel technologies such as digital pills and associated equipment/hardware. A variety of other non-RCT study types incorporating novel technologies were also identified including observational, controlled, and ancilliary studies. However, we found a lack of published randomized clinical trials comparing medication adherence technologies such as digital pills and associated equipment/hardware with other adherence strategies. Therefore, a new evidence review comparing new technologies such as digital pills and associated platforms is not feasible.

FDA approved the Abilify MyCite product in November 2017 so it has been on the market for less than one year. A systematic review with original research studies on this product might be more feasible in a few years when the digital pill technologies and novel applications to support medication adherence have been on the market for a longer time and any studies in the pipeline have been published.

See Table 2, Feasibility column.

Table 2. Key Questions and Results for Duplication

Key Question	Duplication (9/2013-9/2018)	Feasibility (9/2013-9/2018)
KQ #2	Total number of identified systematic reviews: #2 Completed SR • General strategies-0 • Includes technology-0 In-process SR • Includes technology-2 [6 7]	Size/scope of review Relevant Studies Identified: #9 o RCT-2 [8] o Observational-1 [9] o Controlled Trial-1 [10] o Ancillary Study-1 [11] o Feasiblity Study-2[12 13] o Safety, Tolerability, Usability-2[14, 15] Clinicaltrials.gov • Recruiting:2 [16 17] • Complete: 2 [18 19]

Abbreviations: KQ=Key Question;

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would not be duplicative of an existing product.
- Impact: A new systematic review has high potential.
- Feasibility: A new review is not feasible as there is limited primary research comparing medication adherence technologies such as digital pills and associated equipment/hardware with other adherence strategies. A systematic review with original research studies on this product might be more feasible in a few years when the digital pill technologies and novel applications to support medication adherence have been on the market for a longer time and any studies in the pipeline have been published.

Appendix A. Selection Criteria Summary

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for a systematic review?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Potentially affects all patients with chronic diseases, a very large proportion of the population.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, costs are high for new technology and patients, prescribers, and payers want to know if they work. This is especially important since some medication adherence strategies cost much less. The effectiveness, benefits, harms, and costs of all strategies to impact medication adherence are important for patients and providers to consider when choosing a medication and adherence strategy.
2c. Represents important uncertainty for decision makers	Yes
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	No, it would not be redundant. The nomination scope is covered by two in-process systematic reviews, however, we do not know if and when these systematic reviews will be published.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes, FDA did not approve a medication adherence claim for smart pills. It remains unclear if the benefits and risks justify the higher cost when comparing medication adherence strategies.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	N/A
5. Primary Research	

Selection Criteria	Assessment
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	A systematic review is not feasible due to a lack of primary research studies. FDA approved the Abilify MyCite product in November 2017 so it has been on the market for less than one year. A systematic review with original research studies on this product might be more feasible in a few years when the digital pill technologies and novel applications to support medication adherence have been on the market for a longer time and any studies in the pipeline have been published.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question

Appendix B. Search for Evidence Reviews (Duplication)

Listed are the sources searched.

AHRQ: Evidence reports and technology assessments, USPSTF recommendations
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/
PubMed
PubMed Health http://www.ncbi.nlm.nih.gov/pubmedhealth/
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
CADTH (Canadian Agency for Drugs and Technologies in Health) https://www.cadth.ca/
DoPHER (Database of promoting health effectiveness reviews) http://eppi.ioe.ac.uk/webdatabases4/Intro.aspx?ID=9
ECRI institute https://www.ecri.org/Pages/default.aspx
Secondary Sources checked on an as needed basis
Campbell Collaboration http://www.campbellcollaboration.org/
McMaster Health System Evidence https://www.healthsystemsevidence.org/
Robert Wood Johnson http://www.rwjf.org/
Systematic Reviews (Journal) : protocols and reviews http://systematicreviewsjournal.biomedcentral.com/
UBC Centre for Health Services and Policy Research http://chspr.ubc.ca/
WHO Health Evidence Network http://www.euro.who.int/en/data-and-evidence/evidence-informed-policy-making/health-evidence-network-hen
CINAHL (EBSCO)

Appendix C. Search Strategy & Results (Feasibility)

PubMed.gov (September 10, 2018)

(("drug therapy"[MeSH Terms]) AND "patient compliance"[MeSH Terms] OR "medication adherence"[MeSH Terms]) AND "electronic monitoring"[Title/Abstract] OR "monitoring device"[Title/Abstract] OR "sensor"[Title/Abstract] OR "digital device"[Title/Abstract] OR "adherence strategies"[Title/Abstract]) OR "technology mediated"[Title/Abstract]) AND ("2013/09/12"[PDAT] : "2018/09/10"[PDAT]) AND "clinical trial"[Filter])))))))))))))

540 studies found. All 540 were reviewed.

Clinicaltrials.gov (September 10, 2018)

https://clinicaltrials.gov/ct2/results?cond=medication+adherence&term=technology&cntry=&state=&city=&dist=&Search=Search

67 Studies found for: technology | Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies | Interventional Studies | medication adherence

Appendix D: Nomination

Topic Suggestion Description

Date submitted: June 25, 2018

Describe your topic.

The benefits of digital pills and associated equipment/software platforms in disease prevention and treatment through medication adherence. Americans suffering from mental illnesses for which medication adherence is important, particularly non-pediatric and vulnerable populations. CHI urges AHRQ to focus the evidence review on strategies to prevent and treat diseases through ensuring medication adherence. Digital pills and associated equipment/software platforms would be compared to other existing means for medication adherence (e.g., physician office calls to remind, voluntary patient reporting, etc.). Primarily medication adherence statistics; secondarily, cost savings, improved care, reduced hospitalizations, avoidance of complications, and improved patient satisfaction.

Describe why this topic is important.

Medication adherence is foundational to disease prevention and treatment. Study after study has demonstrated how, as medication adherence slips, the disease(s) being treated may progress or a complication may develop that worsens over time. As digital health tools continue to proliferate in the prevention of disease and the delivery of treatments, medication adherence is no exception. Traditionally, methods as simple as pill boxes have served as reminders for medication adherence, but new cutting edge digital health innovations, such as “digital pills” that contain wireless transmitters and associated hardware/software systems to provide real-time insights to caregivers and other authorized parties regarding medication adherence. CHI believes that an AHRQ evidence report on established and emerging medication adherence approaches would be of great utility to healthcare stakeholders and the U.S. government.

Tell us why you are suggesting this topic.

New sensor- and internet connectivity-enabled innovations offer incredible opportunity to prevent diseases and aid in treatment. Evidence provided by AHRQ should help policymakers and private sector stakeholders support policy changes that will unlock this potential. We believe that medication adherence, a foundational aspect of prevention and treatment, is a powerful use case to demonstrate the potential of digital health innovations and to support their use.

Target Date.

2019-06-01

Describe what you are doing currently and what you are hoping will change because of a new evidence report.

CHI actively advocates for the use of connected health technologies to be used in preventing and treating diseases. We believe that existing evidence supports the use of connected health tech offers a critical means to prevent and treat this suffering, but continue to hear from some U.S. policymakers that they need to understand, on a granular and statistics basis, how digital health tools transform healthcare. Through exploration of approaches to medication adherence, the evidence report CHI proposes would provide a crucial basis for greater U.S. government for, and private support of, new and innovative tools in preventing and treating painful and expensive diseases.

How will you or your group use the information from a new evidence report?

CHI would use this report to support the use of connected health innovations across public and private systems, both in the U.S. and elsewhere. This evidence report's impact, coming from AHRQ, would be extremely impactful.

How would you or your group plan to disseminate information from the report? Who would you plan to disseminate it to?

We would share public links to the report and cite it in our own written and spoken advocacy across any appropriate fora.

Do you know of organizations that could use an evidence report to change clinical practice? Are you a part of, or have you been in contact with, any organizations that might implement the research findings of an evidence report?

CHI has been in contact with a wide range of organizations that would benefit from the evidence report that we propose. These include a wide range of providers, from the largest and most distributed in America to small and rural providers. Some of these organizations are members of the CHI's Steering Committee.

Information About You: (optional)

Provide a description of your role or perspective.

If you are you making a suggestion on behalf of an organization, please state the name of the organization.

CHI

Please tell us how you heard about the Effective Health Care Program.

AHRQ email announcements/AHRQ website

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