



Topic Brief: Medication Adherence Measures

Date: 02/09/2020

Nomination Number: 0876

Purpose: This document summarizes the information addressing a nomination submitted on 5/6/2019 through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue:

Medication nonadherence is common and associated with higher rates of hospital admissions, suboptimal health outcomes, increased morbidity and mortality, and increased health care costs. Improving medication adherence is a public health priority and could reduce the economic and health burdens of many diseases and chronic conditions. Multiple interventions have been attempted to address nonadherence, but it is not clear which interventions are most effective.

Program Decision:

The EPC Program will not develop a new Medication Adherence Measures because we found systematic reviews addressing the concerns of this nomination.

Key findings

- A systematic review of systematic reviews (SR) on medication adherence by Anderson et al was published in Am H Health Systems Pharmacy in 2020. The literature search went thru Feb 2017. They reviewed 390 SRs and included 25 covering 50 medication adherence interventions conclusions. We find it to be a high quality SR and largely duplicative of the topic nomination.
- In addition there were 85 systematic review that addressed key question one covering 14 different medical conditions and 4 systematic reviews that addressed key question two covering 5 different medical conditions that covered a variety of medication adherence interventions.

Background

Adherence to prescribed medications is associated with improved clinical outcomes for chronic disease management and reduced mortality from chronic conditions.¹ Conversely, nonadherence is associated with higher rates of hospital admissions, suboptimal health outcomes, increased morbidity and mortality, and increased health care costs.² In the United States, 3.8 billion prescriptions are written annually.³ Approximately one in five new prescriptions are never filled, and among those filled, approximately 50% are taken incorrectly, particularly with regard to timing, dosage, frequency, and duration.⁴ Whereas rates of nonadherence across the United

States have remained relatively stable, direct health care costs associated with nonadherence have grown to approximately \$100–\$300 billion of U.S. health care dollars spent annually.^{5,6} Improving medication adherence is a public health priority and could reduce the economic and health burdens of many diseases and chronic conditions.⁷

Medication adherence is a complex behavior influenced by factors along the continuum of care, relating to the patient, providers, and health systems.⁸ Successful efforts to improve rates of adherence often incorporate multiple strategies across the continuum of care. Although a range of interventions have demonstrated improved medication adherence and health outcomes during the study period, few studies have shown that these benefits were maintained over time.⁹ Interventions that can sustain patient medication adherence are needed. Understanding root causes of medication nonadherence and cost-effective approaches that are applicable in diverse patient populations is essential to increasing adherence and improving long-term health impact.¹⁰

Nomination Summary

The nominator is the Chief Quality Officer at the Palo Alto Medical Foundation and is interested in medication adherence measures and specifically, what are the best practices to improve outcomes for these measures and help patients. He believes that health systems can benefit from learning what interventions are most successful to improve medication adherence and do the approaches vary by disease condition. They have an existing team of quality improvement specialists who are ready to implement best practices into their population health programs to optimize outcomes for these measures. The key questions and PICOTS were based on the 2012 Comparative Effectiveness Review on Medication Adherence Interventions.¹¹ The only change from the 2012 review was in the population of interest from secondary or tertiary prevention of chronic diseases to primary or secondary prevention and management of chronic diseases.

Scope

1. Among patients with chronic diseases with self-administered medication prescribed by a provider, what is the comparative effectiveness of intervention **measures** aimed at patients, providers, systems, and combinations of audiences in improving medication adherence?
 - a. Does the effectiveness vary by the target of the intervention including patients, providers, health system?
 - b. What combinations of interventions are most effective and for patient type(s) and clinical conditions?
 - c. What patient characteristics (e.g. age, gender, race/ethnicity, SES, insurance status, clinical conditions, including and not limited to multiple co-morbidities, patients experiencing polypharmacy) identify subpopulations where specific interventions are most effective?
 - d. Is improved medication adherence associated with improvement in patient-centered outcomes such as morbidity, quality of life, patient satisfaction, health utilization, and cost of care?

2. Among patients with chronic diseases with self-administered medication prescribed by a provider, what is the comparative effectiveness of policy intervention **measures** in improving medication adherence?
 - a. Does the effectiveness vary by the target of the intervention including patients, providers, health system?
 - b. What combinations of interventions are most effective?
 - c. What patient characteristics (e.g. age, gender, race/ethnicity, SES, insurance

status, clinical conditions, including and not limited to multiple co-morbidities, patients experiencing polypharmacy) identify subpopulations where specific interventions are most effective?

- d. Is improved medication adherence associated with improvement in patient-centered outcomes such as morbidity, quality of life, patient satisfaction, health utilization, and cost of care?

Table 1. Questions and PICOTS (population, intervention, comparator, outcome, timing and setting)

Question	1. Comparative effectiveness of intervention measures in improving medication adherence?	2. Comparative effectiveness of policy intervention measures in improving medication adherence?
Population	Adults prescribed self-administered medication for primary or secondary prevention and management of chronic diseases	Adults prescribed self-administered medication for primary or secondary prevention and management of chronic diseases
Interventions	Any intervention for included clinical conditions intended to improve adherence with prescribed self-administered medications	Any policy intervention for included clinical conditions intended to improve adherence with prescribed self-administered medications
Comparators	Any other intervention or no intervention, standard care	Any other intervention or no intervention, standard care
Outcomes	<ul style="list-style-type: none"> • Medication adherence • Biomarkers, mortality, morbidity, quality of life, patient satisfaction, health utilization, cost of care, quality of care for studies with a statistically significant improvement in medication adherence, provider care team experience 	<ul style="list-style-type: none"> • Medication adherence • Biomarkers, mortality, morbidity, quality of life, patient satisfaction, health utilization, cost of care, quality of care for studies with a statistically significant improvement in medication adherence, provider care team experience
Setting	<ul style="list-style-type: none"> • Outpatient primary and specialty care settings • Community-based settings • Home-based settings 	<ul style="list-style-type: none"> • Outpatient primary and specialty care settings • Community-based settings • Home-based settings

Assessment Methods

See Appendix A.

Summary of Literature Findings

There were 85 systematic reviews out of 214 reviewed relevant to key question one covering 14 different medical conditions plus 7 found in other databases and 35 protocols registered in PROSPERO. Interventions covered in the systematic reviews included education, persuasion, training, environmental restructuring and enablement. Four systematic reviews out of 40 relevant to key question two plus one protocol registered in PROSPERO. The systematic reviews covered 5 different medical conditions and included a variety of medication adherence interventions including communication and marketing, guidelines, regulations, service provision and environmental and social planning. A systematic review of systematic reviews (SR) on medication adherence by Anderson et al was published in Am H Health Systems Pharmacy in January 2020, which covered the nomination and met the needs of the nominator. The literature search went through Feb 2017, and included 25 systematic reviews covering 50 medication adherence interventions conclusions.

Table 2. Literature identified for each Question

Question	Systematic reviews (1/2017-12/2019)
Question 1: Comparative effectiveness of intervention measures in improving medication adherence?	Total: 85 <ul style="list-style-type: none"> • Cochrane: 1¹² • AHRQ: 0 • PUBMED: 84¹³⁻⁹⁶ • Other: 10^{19, 97-105} • PROSPERO: 35*
Question 2: Comparative effectiveness of policy intervention measures in improving medication adherence?	Total: 4 <ul style="list-style-type: none"> • Cochrane: 0 • AHRQ: 0 • PUBMED: 4^{47, 65, 106, 107} • Other: 0 • PROSPERO: 1*

*See Appendix C for PROSPERO citations

See Appendix B for detailed assessments of all EPC selection criteria

Summary of Selection Criteria Assessment

Medication adherence is an important and affects health outcomes across many conditions. We found one review of reviews that covers the entire nomination. In addition we found 85 systematic review that addressed key question one covering 14 different medical conditions and 4 systematic reviews that addressed key question two covering 5 different medical conditions that covered a variety of medication adherence interventions.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

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Author

David W. Niebuhr

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Robyn A. Paynter, Research Librarian at Evidence-based Synthesis Program (ESP), VA Portland Health Care System, Portland, Oregon

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years on Dec 30, 2019 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
 - AHRQ Evidence Reports <https://www.ahrq.gov/research/findings/evidence-based-reports/index.html>
 - EHC Program <https://effectivehealthcare.ahrq.gov/>
- US Department of Veterans Affairs Products publications
 - Evidence Synthesis Program <https://www.hsrd.research.va.gov/publications/esp/>
 - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program <https://www.healthquality.va.gov/>
- Cochrane Systematic Reviews <https://www.cochranelibrary.com/>
- University of York Centre for Reviews and Dissemination database <https://www.crd.york.ac.uk/CRDWeb/>
- PROSPERO Database (international prospective register of systematic reviews and protocols) <http://www.crd.york.ac.uk/prospero/>
- PubMed <https://www.ncbi.nlm.nih.gov/pubmed/>
- Epistemonikos <https://www.epistemonikos.org/>
- Health Systems Evidence <https://www.healthsystemsevidence.org/>

Duplication Search strategy

MEDLINE ALL (Ovid) 1946 to December 26, 2019

Date searched: December 27, 2019

Searched by: Robin Paynter, MLIS

1 Medication Adherence/ (17981)

2 ((medication* or pharmaceutical* or drug* or pharmacotherap* or psychopharmac* or pharmacolog*) adj2 (adheren* or non-adheren* or nonadheren* or complian* or non-complian* or noncomplian* or persist* or non-persist* or nonpersist*)).ti. (5538)

3 or/1-2 (20786)

4 Hypertension/ or exp Hypertension, Renal/ or (hypertens* or "high blood pressure").ti,ab,kf. (486198)

5 Diabetes Mellitus/ or exp Diabetes Mellitus, Type 1/ or exp Diabetes Mellitus, Type 2/ or diabet*.ti,ab,kf. (652622)

6 Cardiovascular Diseases/ or exp Heart Diseases/ or exp Vascular Diseases/ or ((cardiovascular or cardio-vascular or vascular) adj2 (disease* or disorder*)).ti,ab,kf. (2418931)

7 Depression/ or depress*.ti,ab,kf. (470184)

8 exp Asthma/ or asthma*.ti,ab,kf. (174660)

9 Pulmonary Disease, Chronic Obstructive/ or Bronchitis, Chronic/ or Pulmonary Emphysema/ or ("chronic obstructive pulmonary" or COPD).ti,ab,kf. (81947)

10 Opiate Substitution Treatment/ or Buprenorphine/ or Buprenorphine, Naloxone Drug Combination/ or Methadone/ or Naloxone/ or Naltrexone/ or (("opioid agonist" or "opioid antagonist" or buprenorphine or "medication assisted" or methadone or opiate* or opioid* or naloxone or naltrexone) adj2 (maintenance or pharmacotherap* or pharmaco-therap* or substitution or therap* or treat*)).ti,ab,kf. or (Belbuca or Buprenex or Butrans or Diskets or Dolophine or Evzio or Methadose or Narcan or Revia or Suboxone).ti,ab,kf. (48909)

11 Comorbidity/ or Multimorbidity/ or (comorbid* or co-morbid* or "chronic disease" or "chronic diseases" or multimorbid* or multi-morbid* or polypharmac* or poly-pharmac*).ti,kf. (300613)

12 or/4-11 (3860912)

13 (intervention or interventions or program* or reduce or reduction or patient-level* or strateg* or enhanc* or improv* or increas* or device* or pill* or remind* or refill* or re-fill* or inject* or depot* or LAI or dosing or tele* or email* or text* or virtual* or computer* or electronic* or internet or ehealth or online or interactive* or technolog* or monitor* or record* or counsel* or therap* or alliance or communicat* or cognitive or interview* or psychosocial or psycho-social or multicomponent or multi-component or diary or diaries or behavioral or behavioural or family* or families* or peer or peers or communit* or decision* or educat* or psychoeducation* or psycho-education* or train* or incentiv* or facilitat* or ((reduc* or remov*) adj2 barrier*)).ti,ab. (14093822)

14 and/3,12-13 (7837)

15 limit 14 to english language (7425)

16 (meta-analysis or systematic review).pt. (180411)

17 (meta-analy* or metaanaly* or ((evidence or systematic) adj3 (review or synthesis))).ti,ab,kf. (284613)

18 or/16-17 (306344)

19 and/15,18 (471)

20 limit 19 to yr="2016 -Current" (214)

21 (controlled clinical trial or randomized controlled trial).pt. (587401)

22 trial.ti,ab. or random*.ab. (1347045)

23 or/21-22 (1526448)

24 and/15,23 (1829)

25 limit 24 to yr="2014 -Current" (1051)

26 Cohort Studies/ or Comparative Study/ or Controlled Before-After Studies/ or Follow-Up Studies/ or Interrupted Time Series Analysis/ or Longitudinal Studies/ or Prospective Studies/ or Retrospective Studies/ or (evaluation studies or observational study).pt. (3655123)

27 (before-after or "interrupted time" or ((observational or cohort or evaluation or follow-up or longitudinal or prospective or retrospective) adj2 (study or design))).ti,ab,kf. (763043)

28 or/26-27 (3866616)

29 and/15,28 (2805)

30 limit 29 to yr="2014 -Current" (1536)

31 Policy Making/ or Public Policy/ or "State Health Planning and Development Agencies"/ or Insurance Claim Review/ or "Medicare Part D"/ or Medicaid/ or Health Services Accessibility/ or Health Policy/ or "Formularies as Topic"/ or Community Pharmacy Services/ or Cost-sharing/ or "Health Benefit Plans, Employee"/ or "Insurance, Pharmaceutical Services"/ or Managed Care

Programs/ or "Health Maintenance Organizations"/og or Drug Costs/ or Drug Packaging/
(251156)

32 (CMS or HMO or HMOs or coach* or claim or claims or clinic or clinics or coordinat* or co-
ordinat* or doctor* or healthcare or (health adj3 (care or maintenance or service* or system*)) or
guidance or insurance or interdisciplinary or inter-disciplinary or Medicaid or Medicare or
"managed care" or manager* or manag?ment or "medical home" or packag* or pharmacy* or
pharmacies* or pharmacist* or pharmacologist* or physician* or provider* or policy or policies
or support* or state or tailor* or team or teams).ti. (1245376)

33 or/31-32 (1396849)

34 and/3,12,33 (2148)

35 limit 34 to english language (2073)

36 and/18,35 (86)

37 limit 36 to yr="2016 -Current" (40)

38 and/23,35 (514)

39 limit 38 to yr="2014 -Current" (298)

40 and/28,35 (844)

41 limit 40 to yr="2014 -Current" (441)

EBM Reviews (Ovid) Cochrane Central Register of Controlled Trials November 2019

Date searched: December 27, 2019

1 ((medication* or pharmaceutical* or drug* or pharmacotherap* or psychopharmac* or
pharmacolog*) adj2 (adheren* or non-adheren* or nonadheren* or complian* or non-complian*
or noncomplian* or persist* or non-persist* or nonpersist*).ti. (1505)

2 (hypertens* or "high blood pressure").ti,ab. (54570)

3 diabet*.ti,ab. (82826)

4 ((cardiovascular or cardio-vascular or vascular) adj2 (disease* or disorder*).ti,ab. (24346)

5 depress*.ti,ab. (72492)

6 asthma*.ti,ab. (31054)

7 ("chronic obstructive pulmonary" or COPD).ti,ab. (17771)

8 (((("opioid agonist" or "opioid antagonist" or buprenorphine or "medication assisted" or
methadone or opiate* or opioid* or naloxone or naltrexone) adj2 (maintenance or
pharmacotherap* or pharmaco-therap* or substitution or therap* or treat*)) or (Belbuca or
Buprenex or Butrans or Diskets or Dolophine or Evzio or Methadose or Narcan or Revia or
Suboxone)).ti,ab. (5416)

9 (comorbid* or co-morbid* or "chronic disease" or "chronic diseases" or multimorbid* or multi-
morbid* or polypharmac* or poly-pharmac*).ti. (2913)

10 or/2-9 (260293)

11 (intervention or interventions or program* or reduce or reduction or patient-level* or strateg*
or enhanc* or improv* or increas* or device* or pill* or remind* or refill* or re-fill* or inject*
or depot* or LAI or dosing or tele* or email* or text* or virtual* or computer* or electronic* or
internet or ehealth or online or interactive* or technolog* or monitor* or record* or counsel* or
therap* or alliance or communicat* or cognitive or interview* or psychosocial or psycho-social
or multicomponent or multi-component or diary or diaries or behavioral or behavioural or
family* or families* or peer or peers or communit* or decision* or educat* or psychoeducation*
or psycho-education* or train* or incentiv* or facilitat* or ((reduc* or remov*) adj2
barrier*).ti,ab. (1177194)

12 and/1,10-11 (538)

13 limit 12 to english language (393)

14 limit 13 to yr="2014 -Current" (232)

15 (CMS or HMO or HMOs or coach* or claim or claims or clinic or clinics or coordinat* or co-ordinat* or doctor* or healthcare or (health adj3 (care or maintenance or service* or system*)) or guidance or insurance or interdisciplinary or inter-disciplinary or Medicaid or Medicare or "managed care" or manager* or manag?ment or "medical home" or packag* or pharmacy* or pharmacies* or pharmacist* or pharmacologist* or physician* or provider* or policy or policies or support* or state or tailor* or team or teams).ti. (72242)

16 and/1,10,15 (132)

17 limit 16 to english language (107)

18 limit 17 to yr="2014 -Current" (77)

Appendix B. Selection Criteria Assessment

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, medication adherence measures are available in the U.S.
1b. Is the nomination a request for an evidence report?	Yes, the request is for an evidence report.
1c. Is the focus on effectiveness or comparative effectiveness?	The nomination focus is on comparative effectiveness.
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, the nomination focus is supported by biological plausibility and consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Medication nonadherence is associated with higher rates of hospital admissions, suboptimal health outcomes, increased morbidity and mortality, and increased health care costs.
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	Approximately one in five new prescriptions are never filled, and among those filled, approximately 50% are taken incorrectly, particularly with regard to timing, dosage, frequency, and duration.
2c. Incorporates issues around both clinical benefits and potential clinical harms	Medication adherence is critical to improving chronic disease outcomes and reducing health care costs.
2d. 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	Direct health care costs associated with nonadherence have grown to approximately \$100–\$300 billion of U.S. health care dollars spent annually.
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	<p>No. There were 87 systematic review that addressed key question one covering 14 different medical conditions and 4 systematic reviews that addressed key question two covering 5 different medical conditions that covered a variety of medication adherence interventions.</p> <p>The review that best addressed the nomination was a systematic review of systematic reviews (SR) on medication adherence by Anderson et al was published in Am H Health Systems Pharmacy in January 2020. The literature search went through Feb 2017, reviewed 390 systematic reviews and included 25 covering 50 medication adherence interventions conclusions.</p>

Abbreviations: AHRQ=Agency for Healthcare Research and Quality;

Appendix C. Prospero Citations

Key Question One

Catherine Goetzinger, Guglielmo Bruni Roccia. *Ehealth technologies to improve medication adherence in patients with chronic diseases: a systematic review*. PROSPERO 2019 CRD42019142725 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019142725

Xiaona Jia, Shuang Zhou, Daohuang Luo, Xia Zhao, Ying Zhou, Yimin Cui. *Effect of pharmacist-led interventions on medication adherence and inhalation technique in patients with asthma or COPD: a systematic review and meta-analysis*. PROSPERO 2019 CRD42019144793 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019144793

Ran Li, Therese Hesketh, Ning Liang, Fanlong Bu. *Effectiveness of self-management of hypertension using mHealth: a systematic review*. PROSPERO 2019 CRD42019152062 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019152062

Yihang Peng, Han Wang, Liling Xie, Qin Fang, Lingzhi Shu, Wenjing Sun. *Effectiveness of mobile applications (app) on medication adherence in adults with chronic diseases: a systematic review and meta-analysis*. PROSPERO 2019 CRD42019139941 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019139941

Rebecca Normansell, Amy Chan, Caroline Brigitte Katzer, Kayleigh Kew, Marissa Mes, Chris Newby, Anoop Chauhan, Stephanie Taylor, Hilary Pinnock, Aziz Sheikh, Vari Wileman. *Health psychology interventions to improve adherence to maintenance therapies in asthma* [Cochrane protocol]. PROSPERO 2019 CRD42019146052 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019146052

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