Ambulatory Medication Safety in Primary Care: A Systematic Review

Richard A. Young, MD, Kimberly G. Fulda, DrPH, Anna Espinoza, MD, Ayse P. Gurses, PhD, MS, MPH, Zachary N. Hendrix, MS, Timothy Kenny, MLS, and Yan Xiao, PhD

Purpose: To review the literature on medication safety in primary care in the electronic health record era.

Methods: Included studies measured rates and outcomes of medication safety in patients whose prescriptions were written in primary care clinics with electronic prescribing. Four investigators independently reviewed titles and abstracts with dual-reviewer review for eligibility, characteristics, and risk of bias.

Results: Of 1464 articles identified, 56 met the inclusion criteria. Forty-three studies were noninterventional and 13 included an intervention. The majority of the studies (30) used their own definition of error. The most common outcomes were potential inappropriate prescribing/medications (PIPs), adverse drug events (ADEs), and potential prescribing omissions (PPOs). Most of the studies only included high-risk subpopulations (39), usually older adults taking > 4 medications. The rate of PIPs varied widely (0.19% to 98.2%). The rate of ADEs was lower (0.47% to 14.7%). There was poor correlation of PIP and PPO with documented ADEs leading to physical harm.

Conclusions: This literature is limited by its inconsistent and highly variable outcomes. The majority of medication safety studies in primary care were in high-risk populations and measured potential harms rather than actual harms. Applying algorithms to primary care medication lists significantly overestimates rate of actual harms. (J Am Board Fam Med 2022;35:610–628.)

Keywords: Adverse Drug Events, Electronic Prescribing, Family Medicine, Medication Safety, Primary Health Care, Systematic Review

Introduction
Medication-related errors in primary care have been estimated to cause many potentially unnecessary emergency department (ED) visits and hospitalizations. A commonly quoted estimate that appeared shortly after the Crossing the Quality Chasm report was that 27% of all ambulatory patients experienced an adverse medication event. There has always been controversy over how to define medication safety in primary care.

It has been recognized that primary care is a well-connected agent in a complex adaptive system, and therefore it is inappropriate to apply simplistic linear quality measures to this care. High-value primary care could include other goals such as

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From JPS Hospital Family Medicine Residency Program, Fort Worth, TX (RAY); Department of Family Medicine and Osteopathic Manipulative Medicine, North Texas Primary Care Practice-Based Research Network, University of North Texas Health Science Center, Fort Worth, TX (KGF, AE); Armstrong Institute Center for Health Care Human Factors, School of Medicine, Bloomberg School of Public Health, Malone Center for Engineering in Healthcare, Whiting School of Engineering, Johns Hopkins University (APG); University of Texas at Arlington, Arlington, TX (ZNH); Maine Medical Center, Portland, ME (TK); College of Nursing and Health Innovation, University of Texas at Arlington, Arlington, TX (YX).

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Corresponding author: Richard A Young, MD, JPS Hospital Family Medicine Residency Program, 1500 S Main St, Fort Worth, TX 76104, (E-mail: ryoung01@jpshealth.org).
deprescribing in the elderly; patient-centered shared decision-making, where patients accept increased risks in one domain of their life to achieve an important outcome in another domain; and the influence of social determinants and comorbidities in patients with multiple chronic diseases.5–7

Many of the early studies of medication safety in primary care were published before the electronic health record (EHR) era.8 One systematic review recognized the limits of EHRs as a source of actionable data to improve quality and safety.9 Other systematic reviews of safety in primary care list medication outcomes as “incidents” that included studies before the EHR era10 or developed problem-mapping approaches.11 No reviews were identified that explored more deeply the varied ways medication safety in primary care may be defined and measured, the relationship between perceived errors and patient harm, and more recently discussed concepts such as deprescribing and patient shared decision-making that may influence perceptions of medication safety events.

The aim of our study was to systematically review the literature on the definitions of and methodologies for measuring medication safety in primary care and to update estimates of the expected rates of adverse drug events (ADEs) in the EHR era. We were also interested in how considerations of deprescribing and patient shared decision-making that may influence perceptions of medication safety events.

Method

Eligibility Criteria

Studies were included if they were restricted to primary care populations only, measured either potential for harm or actual harm from medications, reflected medications managed by the primary care clinic PCPs, and used EHRs with e-prescribing. Noninterventional and interventional studies were included. Studies were excluded if they included nonprimary care prescribers, medication safety outcomes were not the primary outcome, they only measured part of the medication management plan such as transitions of care from the ED back to the primary care clinic, they only surveyed or interviewed select patients about their definition of harm, they only measured 1 or 2 aspects of medication safety such as medication list accuracy studies or lab monitoring lapses, or if the study was only available as an abstract.

Search Strategy and Study Selection

We searched the published literature from January 1999 to December 2020 using Medline, EMBASE, and SCOPUS for relevant English-language articles examining the rates and outcomes of medication errors in prescriptions written by PCPs for their clinic patients. The complete search strategy with keywords and other detailed methods is available in the supplementary online material.

The titles of the first search were reviewed by 1 investigator (RY) to eliminate studies that clearly did not meet our criteria. The relevant remaining abstracts were reviewed by 2 investigators each, with equivalent numbers between 4 investigators (RY, AE, KF, NH), and agreement was assessed. The remaining disagreements were resolved by consensus of the 4 reviewers.

Data Extraction and Risk of Bias Assessment

Identified studies were evaluated for risk of bias by 2 investigators (RY and KF). For nonintervention studies, risk of bias was based on the JBI Critical Appraisal Checklist for prevalence studies.12 Exposures to medications were based on clear criteria widely used in the literature. The quality of the studies was graded based on the Cochrane methodology.13 Interventional studies measured similar outcomes and were graded by the Cochrane Effective Practice and Organization of Care criteria for nonrandomized and interrupted time series studies.14 Most measured process outcomes, not patient-oriented outcomes, such as whether the PCP altered a prescription based on a pharmacist’s feedback or a drug allergy was not listed in the medical record.

Data Extraction and Synthesis

Preliminary data were abstracted onto an Excel spreadsheet. Four reviewers took different sections of the primary sheet for further extraction and arbitration independently (2 per subsection). Any
The studies were performed all over the world: 31 in Europe,19,21,22,24–32,38,39,41,46,51–54,56–58,67,10 in the US,15,16,20,36,42,48,55,68–71 8 in Asia/the Middle East,17,23,34,35,40,43–45 and 7 other.2,27,31–37,39,40,43,44,46–49,54–56,59–61,63–68,71 The majority of studies (30) used their own definition of error, often including some elements of the Beers or similar list.2,22,27,31–37,39,40,43,44,46–49,54–56,59–61,63–68,71 Others used only the Beers list (14),17,18,23,25,38,41,42,45,50,52,53,56,69,70 screening tool of older persons’ prescriptions (STOPP) (13),21,23,24,28–30,41,50,51,53,56,57,62 screening tool to alert to right treatment (START) (5),21,28,30,31,57 and other definitions (9),15,16,19,20,26,52,56,38,64. The majority of the studies were in high-risk populations (defined by each study somewhat differently), generally patients ≥ age 60 and those taking ≥ 4 chronic medications (39).17–49,21,23–30,33,36–38,40–42,45,46,60–53,56–63,67–71 The most common outcomes were PIPs (45),15–30,33–38,40–42,44,45,50–54,56–58,60–63,65–67,69–71 ADEs (12),20,21,28,30,53,57 and potential prescribing omissions (PPOs) (5).21,28,30,53,57

The rate of PIP varied widely (0.19% to 98.2% PIP rate overall; 4.9% to 98.2% for high-risk patients; 0.19% to 16% for a general patient population). The rate of ADE also varied widely (0.047% to 14.7% overall; 7.4% to 9.4% for high-risk patients; 0.047% to 14.7% for a general patient population). The ADE rate was sensitive to the method of data collection. Studies where physicians voluntarily reported ADEs to a registry had much lower rates (0.047% to 1.7%)2,12,39 than those collected by systematic or computerized record review (2.5% to 74%).20,36,55,56,58,64,68

The rate of PPO also varied widely (22.7% to 84.8%).2,21,28,30,53,57 The methods and results were too heterogeneous to quantitatively analyze (mainly due to different outcome measures used in defining medication errors in terms of PIPs, medication events, DRP, and other types; the outcomes were mainly reported as rates of medications reviewed but also included outcome frequencies per provider or per patient that were not convertible to rates.) In general, higher rates of PIP were found in studies of high-risk populations that incorporated multiple measurements of medication usage for each patient (1 year of clinic records, eg). Smaller PIP rates were seen in studies of general primary care populations over shorter time frames (examining the medication list in the EHR at 1 clinic visit or the prescriptions generated from 1 clinic visit).

Results
In all, 1464 articles appeared in the initial search. After reviewing titles, 154 articles were chosen for further review. Fifty-six articles met the search criteria and were included in the final analysis (PRISMA flowchart shown in Supplementary Figure 1).

Forty-three studies were noninterventional (Table 1),15–58 and 13 included an intervention (Table 2).59–71 The noninterventional studies that measured potentially inappropriate prescribing/medications (PIPs) were all judged to be of low risk of bias because they included defined patient populations with clear process measure outcomes (whether or not a Beers list medication was on a patient’s medication list, eg). The risk of bias assessment of noninterventional studies that measured ADEs or drug-related problems (DRPs) is shown in Supplementary Table 3. One of the 11 studies was judged to be of low risk of bias, 4 with some concern, 6 with a high risk of bias. Among the interventional studies, most also measured process outcomes, such as whether the PCP altered a prescription based on a pharmacist’s feedback or a drug allergy was not listed in the medical record, not patient-oriented outcomes. The risk of bias table for each interventional study is presented in Supplementary Table 4. Only 1 study was judged to be of low risk of bias. The others had a high risk of bias.

discrepancies were further analyzed and discussed by all 4 reviewers (RY, AE, KF, NH), until consensus was reached.

There was significant heterogeneity in the countries of origin, measures of medication safety, and intensity and style of data collection, so it was not appropriate to combine the data using meta-analysis. In addition, this review did not aim to provide a definitive summary statistic for the frequency of medication safety events but rather to show the range in measures and estimates. We also did not attempt to standardize different outcome reporting rates (per prescription, clinic visit, or patient over some longer period of time) to a single measure. Rather, our primary results were expressed in the original units of each study and therefore provide an assessment of broad trends.

We did not predefine concepts such as “high-risk” but reported the descriptions provided by the identified studies. We did not register this study with a database such as PROSPERO.
| Lead Author (Year) | Setting | Number of Patients or Prescriptions | High-Risk Subpopulation? | Definition of Medical Error | Error Rate | Other Outcomes |
|--------------------|---------|------------------------------------|--------------------------|---------------------------|------------|---------------|
| Abramson15 (2011)  | PC in NY | 2432 paper prescriptions at baseline and 2079 electronic at 1 year | No | PIP—IOM definition of prescribing errors | 16.0% |  |
| Abramson16 (2012)  | PC in NY | 1629 prescriptions at 3 months postimplementation, 1738 at 1 year | No | PIP—IOM definition of prescribing errors | 4.5% |  |
| Al-Busadi17 (2020) | Oman PC | 377 patients | Ages 65+ | PIP—Beers, STOPP | 12.7%-17.2% |  |
| Almeida18 (2019)   | Brazilian PC | 227 patients | ≥ 60 years of age | PIP—Beers | 53.7%-63.4% |  |
| Amos19 (2015)      | Italy PC | 865,354 patients | Ages 65+ | PIP—own definition (Mao) | 28% had at least one PIP |  |
| Aspinall20 (2002)  | Pennsylvania Veterans Affairs PC | 198 patient/provider pairs | No, but limited to a VA outpatient population | ADE—provider or patient report | 26% | 83 ADEs reported in active surveillance versus 1 in passive reporting |
| Aubert21 (2016)    | Swiss university PC | 1002 patients | Ages 50-80 | PIP—STOPP PPO—START | PIP 6.7%, PPO 27.5% | > 65 years, 5.6% PIP, 32.2% PPO |
| Avery22 (2013)     | England PC | 6048 prescriptions for 1777 patients | No | PIP—own definition | 4.9% |  |
| Awad23 (2019)      | Kuwait PC | 478 patients, 2645 prescriptions | Ages 65+ | PIP—Beers, STOPP, FORTA, MAI | 44.3%-55.1% |  |
| Barry24 (2016)     | Northern Ireland PC | 6826 patients | Medicine for dementia dispensed | PIP—STOPP | 64.4% |  |
| Blo25 (2015)       | UK PC | 13,900 patients | Ages 65+ | PIP—Beers | 38.4% any, 17.4% long-term |  |
| Bregnhøj26 (2007)  | Danish GP patients | 212 patients, 1621 prescriptions | Age of 65+, taking 5 or medications | PIP—MAI | 94.3% |  |
| Brekke27 (2008)    | Norwegian GP patients | 85,836 patients | Ages 70+ | PIP—own definition | 18.4% |  |
| Bruin-Huisman28    | Dutch GP patients | 4537 patients per year | Ages 65+ | PIP—STOPP PPO—START | 34.7% PIP, 84.8% PPO |  |
| Cahir29 (2014)     | Irish PC | 931 patients | Ages 70+ | PIP—STOPP | 42% PIP |  |

Patients with ≥ 2 PIP indicators were twice as likely to have an ADE (adjusted OR 2.21), have a significantly lower mean HRQoL utility (adjusted coefficient − 0.09), and nearly a 2-fold increased risk in the expected rate of A&E visits (adjusted IRR 1.85).
| Lead Author (Year) | Setting                      | Number of Patients or Prescriptions | High-Risk Subpopulation? | Definition of Medical Error | Error Rate | Other Outcomes                                                                 |
|--------------------|------------------------------|-------------------------------------|--------------------------|------------------------------|------------|--------------------------------------------------------------------------------|
| Castillo-Paramo30 (2014) | Spanish PC                     | 272 patients                        | Ages 65+                  | PIP—STOPP PPO—START          | 37.5%-50.7% | Two thirds of PIP medications on PC medication list were started by hospital doctors |
| Chen31 (2005)       | England PC                     | 37,940 patients                     | No                       | PIP—own definition           | 0.19% drug-drug, 0.49% drug-disease |                                                            |
| Clark32 (2007)      | Scotland PC                    | 2513 ADR reports in year 2000 and 1455 ADR reports in 2001 | No                       | ADE—own definition           | The “top 10” medications accounted for 1715 of 2817 (60.9%, 95% CI 59.1, 62.7) ADE reports but only 2.2 million out of a total of 128 million primary care prescriptions (1.7%). |
| Corona-Rojo33 (2009) | Mexico public health centers   | 1400 patients                       | Ages 70+                  | PIP—own definition           | 53%        |                                                                                   |
| Dhabali34 (2011)    | Malaysia University PC         | 17,288 patients                     | No                       | PIP—own definition           | 5.3%       |                                                                                   |
| Dhabali35 (2012)    | Malaysia University PC         | 23,733 patients                     | No                       | PIP—own definition           | 0.87%      |                                                                                   |
| Diaz Hernandez36 (2018) | US federally funded PC           | 2218 patients                       | Ages 65+ with at least one chronic condition who received pharmacy services with 2 or more medications and experienced a medication error or an ADE | PIP—own definition, several sources | Medication errors 12.5/100, potential ADE 9.4/100, ADE 5.0/100 |                                                                                   |
| Doubova Dubova37 (2007) | Mexico PC                          | 624 patients                        | Ages 50+ with nonmalignant pain syndrome who received prescriptions of nonopioid analgesics | PIP—own definition | 80%        |                                                                                   |
| Fix38 (2011)        | German PC                      | 744 patients                        | Ages 50+ who regularly took one or more drugs, rural areas of Germany, GP home visits | PIP—Beers | 18%        |                                                                                   |

Continued
| Lead Author (Year)    | Setting                  | Number of Patients or Prescriptions | High-Risk Subpopulation? | Definition of Medical Error | Error Rate | Other Outcomes                                                                 |
|----------------------|--------------------------|-------------------------------------|--------------------------|------------------------------|------------|--------------------------------------------------------------------------------|
| Gnadinger39 (2017)   | Switzerland PC           | 197 cases of medication incidents   | No                       | “Medication incidents” self-described | 2.07 per GP per year = 46.5 per 100,000 contacts. |                                                      |
|                      |                          | 180 physicians (GP and pediatricians) at 144 practices |                          |                              |            |                                                                                 |
| Goren40 (2017)       | Turkish PC               | 1206 patients                       | Ages 65 +                | PIP—own definition           | 33%        | They detected 29 (0.9%) A, 380 (11.8%) B, 2494 (77.7%) C, 289 (9%) D, and 18 (0.6%) X risk rating category PIPs |
| Guthrie41 (2011)     | UK PC                    | 139,404 patients                    | “Particularly vulnerable” defined by age, pre-existing disease, or pre-existing coprescription. | PIP—STOPPPO—START | 13.9%      |                                                                                 |
| Jayaweera42 (2020)   | US PC                    | 111,461 PCPs who specialized in family medicine, internal medicine, general practice, and geriatric medicine | Medicare Part D patients | PIP—Beers                    | 4.9%       | PIP varied widely across PCPs with the bottom quartile at 1.2% and the top quartile at 10.1% |
| Kheir43 (2014)       | Qatar PC                 | 52 patients, 175 DRPs were identified with an average of 3.4 DRPs per patient | No                       | DRP—own definition           | 3.4 DRPs per patient | The most commonly reported DRPs were nonadherence to drug therapy (31%), need for education and counseling (23%), and ADRs (21%) |
| Khoja44 (2011)       | Saudi Arabia PC          | 463 prescriptions from public clinics and 2836 from private clinics | No                       | “Prescription errors”—own definition | 18.7%      | Type B errors were detected in 8.0% versus 6.0% of drugs prescribed by public and private clinics, respectively and type C errors were found in 2.2% versus 1.1% drugs prescribed by public and private clinics, respectively |
| Komagamine45 (2018)  | Japan hospital PC        | 671 patients                        | 65+                      | PIP—Beers                    | 54.8% in patients exempt from payment, 36.0% for others |                                                      |
| Kovacevic46 (2017)   | Serbian PC               | 388 prescriptions                   | “Elderly” with polypharmacy | DRP—own definition           | 98.2% with at least one DRP |                                                      |
| Lead Author (Year) | Setting | Number of Patients or Prescriptions | High-Risk Subpopulation? | Definition of Medical Error | Error Rate | Other Outcomes |
|--------------------|---------|------------------------------------|--------------------------|-----------------------------|------------|---------------|
| Kunac47 (2014)     | New Zealand PC | 376 voluntary reports | No | Medication errors—own definition | 14.7% of reports listed a patient harm |               |
| Miller49 (2006)    | Australian PC | 8215 patients Each GP was asked to record whether or not each of 30 patients had experienced an ADE in the preceding 6 months | No | ADE—own definition; frequency of hospitalization | 852 patients (10.4%) had experienced ADE | A GP severity rating for the most recent ADE was provided for 551 patients. Over half (53.9%) were rated as having a “mild” event(s), with a third rated as “moderate.” A “severe” rating was given for 55 patients (10.0% of those with an ADE or 6.7 per 1000 patients sampled). Responses to the question on hospitalization were received for 223 patients in survey 2. Of these, 7.6% (95% CI, 3.6 to 11.6) had been hospitalized as a result of the most recent ADE (9.7 per 1000 patients in the total sample). Preventability was judged for 327 patients in survey 3. GPs classified the ADE as preventable for 23.2% (95% CI, 17.4 to 29.1), made up of 19.9% of “mild” events, 25% of “moderate” and 32% of “severe” events |
| Oliveira50 (2015)   | Brazilian family health units | 142 patients Ages 60+ | PIP—Beers, STOPP | 33.8%-51.8% |               |
| Perez51 (2018)     | Ireland PC | 38,229 patients Ages 65+ | PIP—STOPP | 45.3%-51.0% |               |
| Ryan52 (2009)      | Ireland PC | 500 patients Ages 65+ and at least 1 medication | PIP—Beers and IPET | 13% |               |
| Ryan53 (2009)      | Ireland PC | 1329 patients Ages 65+ and at least 1 medication | PIP—Beers, STOPP PPO—START | 18.3%-21.4% 22.7% | 177 (61.8%) of the potential PIPs identified were of “high severity” |
| Stocks54 (2015)    | UK PC | 949,552 patients No | PIP—own definition | 5.26% |               |
| Trinkle55 (2017)   | Ohio University PC | 1160 patients A pharmacist performed a comprehensive EHR review and conducted a telephone interview with each of the respective participants at 7-21 days (first screen) and 30-60 days (second screen) following a medication change | ADE—own definition | Of the 701 participants and 1568 unique medication changes, 226 (32%) suspected ADEs were identified; 30% of the suspected ADEs were deemed to be “definite” or “probable” following causality assessment, 21% of the 68 ADEs were preventable, and 40% were ameliorable | All ADEs were considered significant; however, only 2 were serious or life-threatening |
Table 1. Continued

| Lead Author (Year) | Setting | Number of Patients or Prescriptions | High-Risk Subpopulation? | Definition of Medical Error | Error Rate | Other Outcomes |
|--------------------|---------|-------------------------------------|--------------------------|-----------------------------|------------|----------------|
| Wallace56 (2017)   | Ireland PC | 605 patients for ADE interview; 662 patients for EQ-5 Days-3L questionnaire; 806 patients for chart review | Ages 70+ | PIP—Beers, STOPP ADE—own definition HRQoL—Euro Qual-5 Dimensions (EQ-5 Days)-3L | 40% STOPP 26% Beers 74% ≥ 1 ADE | In multivariable analysis ≥2 Beers 2012 PIP was not associated with ADE’s (adjusted incidence rate ratio 1.00 [95% CI 0.78, 1.29]), poorer HRQoL (adjusted coefficient −0.05 [95% CI −0.11, 0.003]), A&E visits (adjusted OR 1.54 [95% CI 0.88, 2.71]), or emergency admission (adjusted OR 0.72 [95% CI 0.41, 1.28]). At baseline, the prevalence of ≥ 1 PIP was 40% (n = 243), with 362 (60%) participants prescribed no PIP, 142 (24%) 1 PIP, and 101 (16%) ≥ 2 PIPs |
| Wauters57 (2016)   | Belgium PC | 503 patients in the Belfrail-Med cohort | Ages 80+ | PIP—STOPP PPO—START | PIP 56% PPO 67% | Increase risk of hospitalization (HR 1.26) and mortality (HR 1.39) for underuse but not overuse |
| Wucherer58 (2017)  | Germany PC | 446 patients | Ages 70+ with positive screening for dementia | DRP—PIE-Doc®-System | 92.8% | Problems related to administration and compliance were the most common group of DRPs (59.9% of registered DRPs; n = 645), followed by problems with drug interactions (16.7%; n = 180), problems with inappropriate drug choice (14.7%; n = 158), problems with the dosage (6.2%; n = 67), and problems with ADEs (2.5%; n = 27) |

Abbreviations: A&E, accident & emergency; ADE, adverse drug event; ADR, adverse drug reaction; Beers, Beer’s criteria; DRP, drug-related problem; EHR, electronic health record; FORTA, fit for the aged; GP, general practitioner; HRQoL, health-related quality of life; IOM, Institute of Medicine; MAI, medication appropriateness index; PC, primary care; PCP, primary care physician; PIP, potentially inappropriate prescribing; PPO, potential prescribing omission; START, screening tool to alert to right treatment; STOPP, screening tool of old people’s prescriptions.
| Lead Author (Year) | Setting | Number of Patients or Prescriptions | High-Risk Subpopulation                                                                 | Definition of Medical Error | Intervention | Error Rate | Other Outcomes |
|-------------------|---------|-------------------------------------|-----------------------------------------------------------------------------------------|-----------------------------|--------------|------------|----------------|
| Benson59 (2018)   | Australian GP patients | 493 patients | Polypharmacy (5+ medications), diabetes, adherence concerns, asthma/chronic obstructive pulmonary disease, inadequate response to therapy, suspected adverse reaction, patient request, pain management, recent hospital discharge, and medication with a narrow therapeutic index | DRP—own definition | Feedback by pharmacist to GP | 1124 DRPs in 493 consultations, 685/984 (70%) recs accepted. 94% of patients had at least 1 DRP | Pharmacists made a total of 984 recommendations in relation to the 1140 DRPs identified, of which 685 (70%) were recorded as acted on by the GP. Harms not measured |
| Clyne60 (2015)     | Ireland PC | 196 patients | Ages 70+ | PIP—own definition | Intervention GP participants received a complex, multifaceted intervention | Completion PIP: 100% to 52% in the intervention group, 100% to 77% in the control group (P = .02) | 0.7 PIP per patient intervention, 1.18 control (P = .02) | Harms not measured |
| Clyne61 (2016)     | Ireland PC | 196 patients—follow-up of primary study | Ages 70+ | PIP—own definition | Pharmacist feedback as above. | 51% patients with PIP in the intervention group, 76% in the control group (P = .01). The mean number of PIP drugs in the intervention group was 0.61, 1.03 in the control group (P = .01) | Harms not measured |
| Gibert62 (2018)    | France PC | 172 patients | Ages 75+ who were taking at least 5 drugs | PIP—STIPP | GPs taught to use STOPP criteria on their own patients | GP’s intervention decreased the number of PIMs according to STOPP criteria to 106 and was beneficial for 44.9% of the patients (n = 44). The mean MAI score of all medications and PIMs decreased by 14.3% (P < .001) and 39.1% (P < .001) respectively | Harms not measured |
| Lead Author | Setting | Number of Patients or Prescriptions | High-Risk Subpopulation | Definition of Medical Error | Intervention | Error Rate | Other Outcomes |
|-------------|---------|-------------------------------------|--------------------------|-----------------------------|--------------|------------|---------------|
| Howard<sup>63</sup> (2014) | UK PC | 2038 patient records reviewed | Taking one of 8 classes of potentially hazardous medications | Potentially hazardous prescribing—own definition | Intervention practices received simple feedback plus a pharmacist-led information technology complex intervention (PINCER) lasting 12 weeks | Pharmacists recommended 2105 interventions in 74% (95% CI 73, 76; 1516/2038) of cases and 1685 actions were taken in 61% (95% CI 59, 63; 1246/2038) of cases; control group not reported | Harms not measured |
| Leendertse<sup>64</sup> (2013) | Netherlands PC | 364 intervention and 310 control patients | Patients with a high risk on medication-related hospitalizations based on old age, use of 5 or more medicines, nonadherence and type of medication used | Medication-related hospital admissions, ADE, survival, quality of life (EQ5D/Visual Analog scale) | The intervention consisted of a patient interview and evaluation of a pharmaceutical care plan. The patient’s own pharmacist and GP carried out the intervention. The control group received usual care and was cared for by a GP other than the intervention GP | 6 (1.6%) admissions in intervention group, 10 in control group (3.2%), p = NS | The secondary outcomes were not statistically significantly different either |
| Lenander<sup>65</sup> (2014) | Sweden PC | 209 patients | Ages 65+ and 5+ medications | DRP—own definition | The pharmacist reviewed all medications (prescription, nonprescription, and herbal) regarding recommendations and renal impairment, giving advice to patients and GPs. Each patient met the pharmacist before seeing their GP. Control patients received their usual care | No significant difference was seen when comparing change in DRPs between the groups | Groups not balanced at beginning of trial. Harms not measured |
| Lead Author | Year | Setting | Number of Patients or Prescriptions | High-Risk Subpopulation | Definition of Medical Error | Intervention | Error Rate | Other Outcomes |
|-------------|------|---------|-------------------------------------|-------------------------|----------------------------|--------------|------------|---------------|
| Lopez-Picazo | 2011 | Spain PC | 81,805 patients of 265 family physicians | No | Potentially serious drug interactions—own definition | Specially designed software analyzed EHR data and generated reports. Physicians and their patients randomized into 4 groups: control, report, sessions, and face-to-face personal interviews | Overall, a baseline mean of 6.7 interactions per 100 patients, which was reduced to 5.3 interactions after follow-up | Harms not measured |
| Peek | 2020 | UK PC | 47,413 patients in 43 general practices | Have 1 or more risk factors for any of the 12 medication safety indicators at the start of the intervention | 12 medication safety indicators (10 relating to potentially hazardous prescribing and 2 to inadequate blood-test monitoring) developed for SMASH | SMASH comprised (1) training of clinical pharmacists to deliver the intervention; (2) a web-based dashboard providing actionable, patient-level feedback; and (3) pharmacists reviewing individual at-risk patients and initiating remedial actions or advising general practitioners doing so. | At baseline, 95% of practices had rates of potentially hazardous prescribing (composite of 10 indicators) between 0.88% and 6.19%. The prevalence of potentially hazardous prescribing reduced by 27.9% (95% CI 20.3% to 36.8%, \( P < .001 \)) at 24 weeks and by 40.7% (95% CI 29.1% to 54.2%, \( P < .001 \)) at 12 months | Harms not measured |
| Singh | 2012 | New York PC | 1125 patients preintervention; 1050 patients postintervention | Ages 65+ | ADE—own definition | This was a cluster randomized trial in which 12 practices were each randomized to one of 3 states (4 practices each): (1) team resource management intervention; (2) team resource management intervention with PEA; (3) no intervention (comparison group). | In the "Intervention with PEA" group there was a statistically significant decrease in the overall rate of preventable ADEs after the intervention compared to before (7.4 per 100 patient-years vs 12.6, \( P = .018 \)) and in the rate of moderate or severe (combined) preventable ADEs (1.6 vs 6.4, \( P = .035 \)). Examples of preventable errors include missed allergy, wrong dosage, errors of dispensing, administration errors, and failure to order or complete laboratory monitoring. Harms not measured. Groups were not balanced at baseline. | |
| Vanderman | 2017 | Veterans Affairs PC in North Carolina | 1539 patients preintervention; 1490 patients postintervention | Ages 65+ | PIP—Beers | Computerized physician order entry in Epic EHR | PIP rate 12.6% preintervention, 12.0% post (\( P = .NS \)) | Top 10 PIPs 9.0% to 8.3%, (\( P = .016 \)) Harms not measured |
A small subset of the studies (6/56 [10.7%]) reported actual harms (Clark et al.\(^32\) reported adverse drug reactions but provided no further detail on harms.).\(^{20,29,49,55,56,64}\) In a study that may have included events not originating from the primary care clinic, 55/8171 (0.67%) of patients reported a severe ADE in the past 6 months and were hospitalized as a result (the hospitalization estimate was calculated from numbers in the article that only included 1 of 3 study periods).\(^{49}\) General practitioners judged 23.2% of the ADEs to be preventable. Another study, using its own definition of ADE, concluded that all ADEs were significant, and 0.2% of patients suffered a “serious or life-threatening” ADE (this is a good example of the subjectivity of these ADE measurements—in 1 of the 2 cases, the patient passed out and fell after a medication dose was reduced; in the other, a patient with a history of falls fell, went to the ED, and the X-rays were normal).\(^{55}\) A study using its own definition of ADE calculated that 1.7% of prescriptions had any level of ADE, with no further reporting of actual harm.\(^{32}\) Another study using its own definition of a medication incident reported an ADE rate of 0.047% of physician-patient contacts over 1 year.\(^{39}\)

Three noninterventional studies correlated PIP findings with actual harm. One found no association between patients with \(\geq 2\) PIPs and harms such as ADEs, reduced quality of life, ED visits, or hospital admissions.\(^{56}\) One found an association between \(\geq 2\) PIP and a lower mean health-related quality of life utility (adjusted coefficient \(-0.09, SE 0.02, P < .001\)) and an increased risk in the expected rate of ED visits (adjusted IRR 1.85; 95% CI 1.32, 2.58, \(P < .001\)) but no difference in hospitalizations or other outcomes.\(^{29}\) One study in frail elderly greater than 80 years of age found an adjusted increased risk of hospitalization (HR 1.26) and mortality (HR 1.39) for underuse of medications but not overuse.\(^{57}\)

One intervention study measured patient harms and found that the intervention had no impact on hospitalizations.\(^{64}\) Most intervention studies involved pharmacists reviewing patient charts or pharmacy data and making recommendations to the physicians, which were accepted to varying degrees (25% to 70%).\(^{29,39,61,63\text{-}65,67,68}\) less so with automated EHR reminders (5% to 21%).\(^{66,69}\) These recommendations were mostly process changes such as adding indications for the medications or ordering lab tests for routine monitoring.

| Table 2. Continued |
|-------------------|

| Lead Author | Setting | Number of Patients or Prescriptions | High-Risk Subpopulation | Description of Medical Error | Error Rate | Other Outcomes |
|-------------|---------|------------------------------------|-------------------------|-----------------------------|------------|----------------|
|            |         |                                    |                         |                             |            |                |
| Wessell \(^32\) (2008) | South Carolina PC | 124,802 patients | Ages 65+ | High-risk medication use based on 44 indicators | Always inappropriate 0.41%, rarely appropriate medication decreased from 1.48% to 1.30% | Harms not measured |
| Wessell \(^71\) (2013) | 20 PC sites in 14 US states | 49,047 patients | High-risk medication use based on 44 indicators | Always inappropriate 0.41%, rarely appropriate medication decreased from 1.48% to 1.30% | Improved 3/5 measures by 2.9% to 4.0%; 2/5 measures unchanged over 2 years | Harms not measured |

Abbreviations: ADE, adverse drug event; Beers, Beer’s criteria; DRP, drug-related problem; EHR, electronic health record; GP, general practitioner; MAI, medication appropriateness index; PC, primary care; PEA, practice enhancement associate; PIM, potentially inappropriate medication; PIP, potentially inappropriate prescribing; PREP, practice enhancementassociate; STOPP, screening tool of old people’s prescriptions.
No studies in our review considered patient shared decision-making processes or cases where patients accepted a degree of risk from a medication to achieve another goal more important to the patient. No studies measured other aspects of harms reported by patients in other studies to be important such as emotional discomfort; wasted time for patients, physicians, and the health care system; loss of relationship and trust in the clinician; and financial costs to patients, clinicians, and the health care system.

Discussion
We found that actual harm from medication errors in primary care, versus potential for harm, is much lower than is commonly quoted (or projected) and rarely results in ED visits or hospital admissions. The existing literature does not take into account shared patient decision-making, accepted risk-benefit trade-offs, or deprescribing goals in the elderly, nor does it measure other patient-centered outcomes such as patient and caregiver hassles, cost, and loss of trust with the primary care team. The ranges of reported ADE and medication error rates illustrate the inadequacies of current evidence to suggest both the scope of medication error-related harms as well as how medication errors should be defined.

Limitations
There are limitations to the literature and our analysis. Most identified studies only measured PIPs and not patient harms. Medication lists were obtained from available clinic or national pharmacy records. There may have been discrepancies between the electronic reports and the medications that PCPs and patients considered to be the active list. In other studies, as many as 90% of the patients at home were found to have inaccurate medication information in their chart, and nearly half of patients experienced medication discrepancies during care transitions. We attempted to limit studies to only those where the chronic and acute medications were prescribed by PCPs. In studies using national pharmacy databases, it is possible that some of the prescriptions were written by non-PCPs. The studies also did not make distinctions between medications that were on the patients’ medication lists that were heavily influenced by non-PCP physicians versus medications originally prescribed by the PCPs. The majority of studies self-described their patient populations as “high-risk,” though there were many variations of that definition.

Our study was limited to only the medication list and prescribing in the primary care center. We did not include other sources of medication safety concerns in primary care such as transitions from hospital or rehabilitation facilities. Therefore, our review might have missed important sources of medication safety concerns related to primary care. We limited our searches to our definition of studies in the EHR era. It is possible that relevant studies were missed using this strategy. We limited our searches to primary care terms. It is possible that relevant studies were conducted in primary care settings that did not use that keyword or a similar keyword such as family medicine. Our review did not include studies that defined a medication error as a chronic disease goal not achieved (such as a hemoglobin A1c for a diabetic patient) or where laboratory monitoring for adverse drug effects did not occur.

Implications for Practice, Policy, and Future Research
When viewing harms from a patient’s perspective, Kuzel et al found that 70% of reported harms were psychological, including anger, frustration, belittlement, and loss of relationship and trust in one’s clinician, which are in contrast with physical harms such as pain, bruising, worsening medical condition, emergency visits, and hospitalizations. Such psychological harms were not reported in the studies in our review. Kuzel et al concluded that errors reported by interviewed patients suggest that breakdowns in access to and relationships with clinicians may be more prominent medical errors than technical errors in diagnosis and treatment.

Perhaps medication safety should not even be conceptualized as complying with recommendations from medication lists such as Beers, STOPP, or START. Lai et al interviewed frontline clinicians and patients and found in both groups that safety was conceptualized more in terms of work functions involving grouping of tasks or responsibilities, rather than domains such as medications, diagnoses, care transitions, referrals, and testing. In addition not considered in the literature is the critical roles of patients and families beyond the prescribing actions by family physician. Review of hypoglycemic events resulting in ED visits showed that the most common...
precipitants were reduced food intake and administration of the wrong insulin product.82

A commonly used definition of an ADE was that there was at least a 50% chance that the symptom was related to the medication in question. However, most of the reported ADEs were mild, such as bruising when taking warfarin or constipation when taking a calcium channel blocker. Similar to our study focused on the primary care clinic, a recent randomized trial of care transitions from hospital to primary care found that in-home assessments by pharmacists with communication to the primary care team made no impact on ADEs or medication errors.83

In the intervention studies, we found that the impact on a prescriber to change medications is greater if there is personal communication by the pharmacist and the change requested by the pharmacist is relatively minor (such as adding the indication to the prescription or updating the medication list in the EHR) and uncommonly impacts major prescribing decisions such as whether the patient should take a drug at all. Perhaps shared decision-making processes help explain why PCPs ignore most computerized drug alerts84–86 and why the intervention studies identified in this review made little to no impact on PIP rates. Even high-risk medications such as benzodiazepines are helpful in selective elderly patients, where the benefits likely outweigh the risks.87

Other studies of ambulatory care outside of primary care have measured actual harms. For example, Gandhi et al estimated that rates of life-threatening ADEs in a multispecialty group were 138/1000 person-years, but that only 11% were preventable.88 Most of the root causes of the preventable cases were patients that did not take their medications as prescribed, not PIP by prescribers.

Our findings share some conclusions with other reviews on medication safety in primary care, including most medication errors are “not clinically important”;89 ADEs are not usually preventable;90 computer decision support inconsistently affects PIP rates with no evidence it reduces patient harms91 and actually creates new sources of error such as alarm fatigue;92 and the variance of reported “medication errors” is large and a function of patient populations, methods, definitions, and the parts of the system studied—and interventions make little difference.93 Medication safety is not measured well with ADEs, because many are expected side effects of the medications and are not preventable. Safety is better conceptualized as a series of actions to perform, which is more analogous to aviation safety, and is consistent with how frontline primary care teams conceptualize safety.81 Our review confirms other observations that potential medication errors do not usually result in injuries or fatal outcomes,94 and conversely, just because a patient experienced an ADE does not mean that a medication error occurred. The Agency for Healthcare Research and Quality (AHRQ) first highlighted these distinctions in 2019, adding subcategories to ADEs such as preventable, potential, ameliorable, and nonpreventable.95 The vast majority of studies in our sample do not make these distinctions.

EHR-focused studies have found that alerts are ignored by physicians 90% of the time in adult ambulatory care,84 and acceptance rates of alternative recommendations to potentially inappropriate medications followed only 11.1% of the time.86 EHR alerts for coprescribing high-risk medication combinations such as benzodiazepines and opioids did not change prescribing practices.85 EHRs were found to be the root cause of medical errors at high risk for an adverse event in 14% of reported cases in an embedded practice-based anonymous reporting system.96 In summary, our review and other evidence concludes that alerts from computers suggesting medication changes to clinicians are most often ignored, implying that there are likely good reasons for patients to be on medications that computerized algorithms flag as high risk.97

**Future for Primary Care Medication Safety Research**

We make the following recommendations for future research and practice of medication safety in primary care.

1. All studies purporting to measure preventable ADEs (to use the AHRQ definitions) in the future should:
   a. Include chart reviews of flagged cases. Potentially inappropriate prescribing rarely leads to actual physical harm.
   b. Take into consideration patient shared decision-making, acceptance of risk-benefit trade-offs, and deprescribing goals in elderly patients and do not count these decisions as medical errors. Deprescribing is complex. Few studies have examined the success rate and safety of deprescribing, and there is a
risk of relapse of symptoms. Deeper consideration should also be given to the critical roles of patients and families beyond the prescribing actions by PCP.

c. Include patient harms such as psychological injury, wasted time, unnecessary trips to health care facilities, and increased costs. To adjudicate and measure these outcomes, individual chart reviews will likely be necessary with judgement calls made by clinicians for each potential case. Also, patients can be asked directly if they believe their medications may be causing illness.

2. For primary care practices trying to improve the quality of their care, voluntary reporting systems for clinicians, staff, and patients are feasible to guide understanding of potential quality improvement themes, though they are unreliable for absolute measures of errors or harms. Confidential reports appear to be superior to anonymous reports and may be more useful in understanding errors and designing interventions to improve patient safety.

3. Primary care offices could possibly be made safer by changing work flows, improving the hectic environment, and allowing the primary care teams to have more time to review medication concerns. For example, a study examining how receptionists and general practitioners interact found potential sources of error that could be reduced with improved communication.

4. Future studies designed to measure the effects of interventions on more serious physical harms caused by preventable ADEs will require thousands of high-risk patients, as rates are expected to be less than 1% of the study population per year.

5. There may be a role for a core outcome set to be developed for primary care medication safety (www.comet-initiative.org). The complexity of primary care and multifaceted nature of primary care prescribing outcomes make this a difficult task.

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Appendix

Appendix Figure 1. PRISMA Flow Chart

Potential titles identified through database searching (Medline, EMBASE, SCOPUS) (n=1,464)

Additional records identified through other sources. (n=0)

Titles remaining after duplicates and non-relevant studies removed. (n=154)

Abstracts screened (n=154)

Studies excluded
- Paper prescriptions (n=19)
- Did not measure errors (n=19)
- Not clinic-based (n=15)
- Data not just primary care (n=14)
- Abstract/poster only (n=11)
- Not focused on medication errors (n=9)
- Limited to < 5 drugs or diseases (n=4)
- Other (n=5)

Full-text articles assessed for eligibility and quality (n=58)

Studies excluded
- Not focused on medication errors (n=4)
- Did not measure errors or potential errors (n=1)

Studies included
- Studies in references not identified in original literature search (n=3)

Studies included in review (n=56)

Additional records identified through other sources. (n=0)

Studies in references not identified in original literature search (n=3)
## Appendix Table 1. PRISMA Checklist

| Section and Topic | Item # | Checklist Item | Location where item is reported |
|-------------------|--------|----------------|---------------------------------|
| **TITLE**         |        |                |                                 |
| Title             | 1      | Identify the report as a systematic review. | 1                             |
| **ABSTRACT**      |        |                |                                 |
| Abstract          | 2      | See the PRISMA 2020 for Abstracts checklist. | 2                             |
| **INTRODUCTION**  |        |                |                                 |
| Rationale         | 3      | Describe the rationale for the review in the context of existing knowledge. | 3                             |
| Objectives        | 4      | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 3-4                           |
| **METHODS**       |        |                |                                 |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 4                             |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | 4                             |
| Search strategy   | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Appendix                       |
| Selection process | 8      | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | 5                             |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 5                             |
| Data items        | 10a    | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | 5-6                           |
|                   | 10b    | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | 5-6                           |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | 5                             |
| Effect measures   | 12     | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | n/a                           |
| Synthesis methods | 13a    | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | n/a                           |
|                   | 13b    | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | n/a                           |
|                   | 13c    | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | 5-6                           |
|                   | 13d    | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | 5-6                           |
|                   | 13e    | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | n/a                           |
|                   | 13f    | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | n/a                           |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | n/a                           |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | n/a                           |
| Section and Topic      | Item # | Checklist Item                                                                 | Location where item is reported |
|-----------------------|--------|---------------------------------------------------------------------------------|---------------------------------|
| RESULTS               |        |                                                                                 |                                 |
| Study selection       | 16a    | Describe the results of the search and selection process, from the number of     | Appendix                        |
|                       |        | records identified in the search to the number of studies included in the review,|                                 |
|                       |        | ideally using a flow diagram.                                                  |                                 |
|                       | 16b    | Cite studies that might appear to meet the inclusion criteria, but which were    | 18-19                           |
|                       |        | excluded, and explain why they were excluded.                                  |                                 |
| Study characteristics  | 17     | Cite each included study and present its characteristics.                      | Tables 1 and 2                  |
| Risk of bias in studies | 18    | Present assessments of risk of bias for each included study.                    | Appendix                        |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | 7-15                           |
| Results of syntheses   | 20a    | For each synthesis, briefly summarise the characteristics and risk of bias      | n/a                             |
|                       | 20b    | Present results of all statistical syntheses conducted. If meta-analysis was    | n/a                             |
|                       |        | done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. |                                 |
|                       | 20c    | Present results of all investigations of possible causes of heterogeneity      | n/a                             |
|                       |        | among study results.                                                           |                                 |
|                       | 20d    | Present results of all sensitivity analyses conducted to assess the robustness    | n/a                             |
|                       |        | of the synthesized results.                                                    |                                 |
| Reporting biases      | 21     | Present assessments of risk of bias due to missing results (arising from        | n/a                             |
|                       |        | reporting biases) for each synthesis assessed.                                 |                                 |
| Certainty of evidence | 22     | Present assessments of certainty (or confidence) in the body of evidence        | n/a                             |
|                       |        | for each outcome assessed.                                                     |                                 |
| DISCUSSION            |        |                                                                                 |                                 |
| Discussion            | 23a    | Provide a general interpretation of the results in the context of other         | 17-19                           |
|                       |        | evidence.                                                                       |                                 |
|                       | 23b    | Discuss any limitations of the evidence included in the review.                 | 18-19                           |
|                       | 23c    | Discuss any limitations of the review processes used.                           | 18                              |
|                       | 23d    | Discuss implications of the results for practice, policy, and future research.  | 19-22                           |
| OTHER INFORMATION     |        |                                                                                 |                                 |
| Registration and      | 24a    | Provide registration information for the review, including register name and     | 6                               |
| protocol              |        | registration number, or state that the review was not registered.               |                                 |
|                       | 24b    | Indicate where the review protocol can be accessed, or state that a protocol    | 6                               |
|                       |        | was not prepared.                                                              |                                 |
|                       | 24c    | Describe and explain any amendments to information provided at registration or in the protocol. | n/a                             |
| Support               | 25     | Describe sources of financial or non-financial support for the review, and the | Appendix                        |
|                       |        | role of the funders or sponsors in the review.                                |                                 |
| Competing interests   | 26     | Declare any competing interests of review authors.                             | Cover letter                    |
| Availability of data, | 27     | Report which of the following are publicly available and where they can be       | Cover letter                    |
| code and other        |        | found: template data collection forms; data extracted from included studies;     |                                 |
| materials             |        | data used for all analyses; analytic code; any other materials used in the     |                                 |
|                       |        | review.                                                                        |                                 |
Detailed Methods

Study Selection

Studies were included if they were restricted to primary care only, measured either potential for harm or actual harm from medications, reflected medications managed by the primary care clinic, and used EHRs with e-prescribing. Different forms of data collection were allowed, e.g. data culled from EHRs in the clinic or reports of possible harms from clinic personnel or patients. Observational and interventional studies were included. Studies were excluded if they included non-primary care prescribers; medication safety outcomes were not the primary outcome; only measured part of the medication management plan such as transitions of care from the ED back to the primary care clinic; only surveyed or interviewed select patients about their definition of harm; only measured one or two aspects of medication safety such as medication list accuracy studies or lab monitoring lapses, or if the study was only available as an abstract. We also excluded studies that limited the patient population to those with less than 4 symptoms, diagnoses, or drug classes, for example, a study only looking at benzodiazepine prescribing in an elderly population.

The titles of the first search were reviewed by 1 investigator (RY) to eliminate studies that clearly did not meet our criteria. The relevant remaining abstracts were reviewed by 2 investigators each, with equivalent numbers between 4 investigators (RY, AE, KF, NH), and agreement was assessed. The initial agreement rate was 65%, so the investigators met to further clarify inclusion/exclusion criteria. The most important type of study without initial agreement was one where a national pharmacy database was used to analyze for potentially inappropriate prescribing (PIP) as opposed to records housed in the primary care EHR. The team agreed that if the report provided a statement that all or nearly all of the reviewed prescriptions were controlled by primary care then the study was included.
repeat review of the literature review showed 88% agreement. The remaining disagreements were resolved by consensus of the 4 reviewers.

Data Extraction and Quality Assessment

Identified studies were evaluated for risk of bias by 2 investigators (RY and KF). All identified observational studies were deemed to have a low risk of bias. Exposures to medications were based on clear criteria widely used in the literature. The studies that used their own definition of PIP were mostly based on existing criteria such as Beers lists. For similar reasons, confounding was deemed to be a minimal concern. Most studies did not measure patient outcomes – such as hospitalizations or deaths – merely the exposure to certain medications. Studies enrolled subjects with widely varying underlying risks for ADEs, but each were clear on their criteria and were based on the totality of the primary care clinic populations.

Intervention studies measured similar outcomes. Most measured process outcomes, not patient-oriented outcomes, such as whether the primary care physician altered a prescription based on a pharmacist’s feedback or a drug allergy was not listed in the medical record. One intervention study measured patient harms with little chance for misclassification bias: hospital admission. Another used multiple reviewers to assess an ADE, then determine the probability that a certain medication caused it.

Role of the Funding Source

This review was funded by the Agency for Healthcare Research and Quality (AHRQ), which had no role in the conception, design, and implementation of this study. The authors are solely responsible for the content of this article.
### Appendix Table 1. Search Strategies for Online Databases, Coverage 1999-2020

| Database | Strategies                                                                 | Results |
|----------|-----------------------------------------------------------------------------|---------|
| PubMed   | (((((((Drug-Related Side Effects and Adverse Reactions)[Mesh] OR adverse drug event OR drug event)[Title]) OR [Medication Errors][Mesh] AND medication error OR medication error*[Title] OR medication safety)[Title] OR prescription error*[Title] OR [Medical Errors][Mesh]) OR [Medical error*[Title]]) AND [1999/01/01[PDAT] : ”2020/12/31”[PDAT]) AND English[lang]) AND (Primary Health Care)[Mesh] OR [”Physicians, Primary Care”[Mesh]] OR [”Internal Medicine”[Mesh]] OR [internal medicine OR [internal medicine][Title]] OR [”Ambulatory Care Facilities”[Mesh]] OR [primary care OR (primary care)[Title]] OR [ambulatory care OR [ambulatory care][Title]] OR [”Family Practice”[Mesh]] OR (family practice)[Title] OR [family medicine OR (family medicine)[Title]]) AND [1999/01/01[PDAT] : ”2020/12/31”[PDAT]) AND English[lang]) AND (primary OR family OR internal OR patient OR [patient safety][Title]) AND ([”1999/01/01”[PDAT] : ”2020/12/31”[PDAT]) AND English[lang]) AND (prospective OR multicenter OR observational OR cross-sectional OR cross-sectional OR cohort OR chart review) Filters: from 1999/1/1 - 2020/12/31 | 926     |
| EMBASE   | ("adverse drug reaction":ti OR "adverse drug reactions":ti OR "medication error":ti OR "medication safety":ti OR "medical errors":ti OR "drug safety":ti OR [prescribing error]*ti OR [prescribing errors]*ti) AND ["internal medicine":ti OR "family practice":ti OR "family medicine":ti OR "primary care":ti OR "general practice":ti OR "ambulatory care":ti OR "family":ti OR "primary":ti OR "internal":ti OR "ambulatory":ti OR ["patient safety":ti]) AND [1999-2020]/py | 354     |
| SCOPUS   | TITLE-ABS-KEY (”drug related side effects” OR "adverse drug event” OR "drug-event” OR "medication error” OR "medication safety” AND TITLE-ABS-KEY (”internal medicine” OR "general internal medicine” OR "ambulatory care” OR "family practice” OR "family medicine” OR "general practice” AND TITLE [internal OR primary OR "family” OR "general” OR "ambulatory” OR "patient safety”] ) AND TITLE-ABS-KEY (prospective OR multicenter OR observational OR ["cross-sectional” OR cross-sectional OR cohort] ) | 184     |
| Total    |                                                                             | 1464    |
|          | After Duplicates Removed                                                    | 1178    |
## Appendix Table 3. Risk of Bias of Identified Studies

Non-Intervention Studies with Adverse Drug Event or Drug Related Problems Outcomes.

| Paper     | Sample frame | Study participants | Sample size | Subject described | Analysis is complete | Valid methods to ID condition | Measured standard reliable | Appropriate statistics | Response rate adequate | Bias/Quality Assessment |
|-----------|--------------|---------------------|-------------|-------------------|----------------------|-----------------------------|--------------------------|------------------------|------------------------|-------------------------|
| Aspinall  | +            | -                   | +           | -                 | +                    | -                           | +                        | +                      | -                      | High risk               |
| Clark     | +            | +                   | -           | +                 | -                    | -                           | +                        | +                      | -                      | High risk               |
| Diaz-Hernandez-Carrillo | -        | +                   | +           | +                 | -                    | +                           | -                        | +                      | -                      | High risk               |
| Gunasinghe | +            | +                   | +           | +                 | +                    | -                           | +                        | +                      | +                      | High risk               |
| Kheir     | -            | +                   | -           | +                 | +                    | +                           | +                        | +                      | -                      | High risk               |
| Kovacevic | -            | -                   | +           | +                 | -                    | +                           | +                        | +                      | +                      | High risk               |
| Kunac     | +            | +                   | +           | +                 | -                    | +                           | +                        | +                      | +                      | Some concern            |
| Miller    | +            | +                   | +           | +                 | -                    | +                           | +                        | +                      | +                      | Some concern            |
| Trinkley  | -            | +                   | +           | +                 | -                    | +                           | +                        | +                      | -                      | Some concern            |
| Wallace   | +            | +                   | +           | +                 | -                    | +                           | +                        | +                      | +                      | Some concern            |
| Wucherer  | +            | +                   | +           | +                 | +                    | -                           | +                        | +                      | +                      | Some concern            |
### Appendix Table 3. Risk of Bias for Intervention Studies

#### Risk of Bias for Quasi-Experimental Intervention Studies

| Study             | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Baseline characteristics similar | Baseline outcome measurement (detection bias) | Baseline outcome assessment (detection bias) | Reporting against contamination | Selective reporting (reporting bias) | Other bias |
|-------------------|--------------------------------------------|----------------------------------------|---------------------------------|-----------------------------------------------|---------------------------------------------|-----------------------------------|-------------------------------------|-----------|
| Bannow 2018       | ✗                                          | ✗                                      | ✗                              | ✗                                             | ✗                                           | ✗                                 | ✗                                   | ✗         |
| Clyne 2015        | ✗                                          | ✗                                      | ✗                              | ✗                                             | ✗                                           | ✗                                 | ✗                                   | ✗         |
| Clyne 2016        | ✗                                          | ✗                                      | ✗                              | ✗                                             | ✗                                           | ✗                                 | ✗                                   | ✗         |
| Gilbert 2018      | ✗                                          | ✗                                      | ✗                              | ✗                                             | ✗                                           | ✗                                 | ✗                                   | ✗         |
| Leendertse 2013   | ✗                                          | ✗                                      | ✗                              | ✗                                             | ✗                                           | ✗                                 | ✗                                   | ✗         |
| Lenander 2014     | ✗                                          | ✗                                      | ✗                              | ✗                                             | ✗                                           | ✗                                 | ✗                                   | ✗         |
| Lopez-Perez 2011  | ✗                                          | ✗                                      | ✗                              | ✗                                             | ✗                                           | ✗                                 | ✗                                   | ✗         |
| Singh 2012        | ✗                                          | ✗                                      | ✗                              | ✗                                             | ✗                                           | ✗                                 | ✗                                   | ✗         |
| Vandermar 2017    | ✗                                          | ✗                                      | ✗                              | ✗                                             | ✗                                           | ✗                                 | ✗                                   | ✗         |
| Wessell 2008      | ✗                                          | ✗                                      | ✗                              | ✗                                             | ✗                                           | ✗                                 | ✗                                   | ✗         |

#### Risk of Bias for interrupted time series studies

| Study             | Interven on independent of other changes | Shape of the intervention on effect data collection | Binding of outcome assessment (detection bias) | Incomplete outcome data (detection bias) | Reporting against contamination | Selective reporting (reporting bias) | Other bias |
|-------------------|-----------------------------------------|----------------------------------------------------|-----------------------------------------------|-----------------------------------------|-----------------------------------|-------------------------------------|-----------|
| Peak 2020         | ✗                                      | ✗                                                  | ✗                                             | ✗                                      | ✗                                 | ✗                                   | ✗         |
| Wessell 2013      | ✗                                      | ✗                                                  | ✗                                             | ✗                                      | ✗                                 | ✗                                   | ✗         |