CLINICAL REVIEW

Ambulatory Medication Safety in Primary Care: A Systematic Review

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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 analyzed 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 potentially 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.[1] 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.[2] There has always been controversy over how to define medication safety in primary care.[3]

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.[4] High-value primary care could include other goals such as

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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 era[10] 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 impacted definitions and measurements of medication safety. For studies with interventions to improve medication safety, we evaluated ambulatory patients cared for by primary care physicians (PCPs) who prescribed medications from their clinics. Interventions could include any aimed to affect PCP prescribing. Outcomes could include any measure of medication safety or patient harm.

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

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.

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.

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.[18,33,37,47,49,50,59] The majority of studies (30) used their own definition of error, often including some elements of the Beers or similar list.[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),[21,28,30,41,57] and other definitions (9).[15,16,19,20,26,52,56,58,64] 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).[17–19,21,23–30,33,36–38,40–42,45,46,50–53,56–65,67-71] 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),[20,32,36,39,44,47,49,55,56,58,64,68] 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%)[32,39] 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%).[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).

Table 1. Noninterventional Studies

Lead Author (Year)	Setting	Number of Patients or Prescriptions	High-Risk Subpopulation?	Definition of Medical Error	Error Rate	Other Outcomes
Abramson[15] (2011)	PC in NY	2432 paper prescriptions at baseline and 2079 electronic at 1 year	No	PIP—IOM definition of prescribing errors	16.0%	
Abramson[16] (2012)	PC in NY	1629 prescriptions at 3 months postimplementation, 1738 at 1 year	No	PIP—IOM definition of prescribing errors	4.5%	
Al-Busadi[17](2020)	Oman PC	377 patients	Ages 65+	PIP—Beers, STOPP	12.7%-17.2%	
Almeida[18] (2019)	Brazilian PC	227 patients	≥ 60 years of age	PIP—Beers	53.7%-63.4%	
Amos[19] (2015)	Italy PC	865,354 patients	Ages 65+	PIP—own definition (Maio)	28% had at least one PIP	8%, 10%, and 14% of individuals were prescribed at least one medication that "should always be avoided," is "rarely appropriate," and has "some indications but [is] often misused," respectively.
Aspinall[20] (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
Aubert[21] (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
Avery[22] (2013)	England PC	6048 prescriptions for 1777 patients	No	PIP—own definition	4.9%	
Awad[23] (2019)	Kuwait PC	478 patients, 2645 prescriptions	Ages 65+	PIP—Beers, STOPP, FORTA, MAI	44.3%-53.1%	
Barry[24] (2016)	Northern Ireland PC	6826 patients	Medicine for dementia dispensed	PIP—STOPP	64.4%	
Ble[25] (2015)	UK PC	13,900 patients	Ages 65+	PIP—Beers	38.4% any, 17.4% long-term	
Bregnhoj[26] (2007)	Danish GP patients	212 patients, 1621 prescriptions	Age of 65+, taking 5 or medications	PIP—MAI	94.3%	
Brekke[27] (2008)	Norwegian GP patients	85,836 patients	Ages 70+	PIP—own definition	18.4%	
Bruin-Huisman[28] (2017)	Dutch GP patients	4537 patients per year	Ages 65+	PIP—STOPP PPO—START	34.7% PIP, 84.8% PPO	
Cahir[29] (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).

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Table 1. Continued

Lead Author (Year)	Setting	Number of Patients or Prescriptions	High-Risk Subpopulation?	Definition of Medical Error	Error Rate	Other Outcomes
Castillo-Paramo[30] (2014)	Spanish PC	272 patients	Ages 65+	PIP—STOPP PPO—START	37.5%-50.7%	
Chen[31] (2005)	England PC	37,940 patients	No	PIP—own definition	0.19% drug-drug, 0.49% drug-disease	Two thirds of PIP medications on PC medication list were started by hospital doctors
Clark[32] (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-Rojo[33] (2009)	Mexico public health centers	1400 patients	Ages 70+	PIP—own definition	53%	
Dhabali[34] (2011)	Malaysia University PC	17,288 patients	No	PIP—own definition	5.3%	
Dhabali[35] (2012)	Malaysia University PC	23,733 patients	No	PIP—own definition	0.87%	
Diaz Hernandez[36] (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	Potential ADE and ADE—own definition, several sources	Medication errors 12.5/100, potential ADE 9.4/100, ADE 5.0/100	
Doubova Dubova[37] (2007)	Mexico PC	624 patients	Ages 50+ with nonmalignant pain syndrome who received prescriptions of nonopioid analgesics	PIP—own definition	80%	
Fiss[38] (2011)	German PC	744 patients	Ages 50+ who regularly took one or more drugs, rural areas of Germany, GP home visits	PIP—Beers	18%	

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Table 1. Continued

Lead Author (Year)	Setting	Number of Patients or Prescriptions	High-Risk Subpopulation?	Definition of Medical Error	Error Rate	Other Outcomes
Gnadinger[39] (2017)	Switzerland PC	197 cases of medication incidents 180 physicians (GP and pediatricians) at 144 practices	No	"Medication incidents" self-described	2.07 per GP per year = 46.5 per 100,000 contacts.	
Goren[40] (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
Guthrie[41] (2011)	UK PC	139,404 patients	"Particularly vulnerable" defined by age, pre-existing disease, or pre-existing coprescription.	PIP—STOPPPPO—START	13.9%	
Jayaweera[42] (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%
Kheir[43] (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%)
Khoja[44] (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
Komagamine[45] (2018)	Japan hospital PC	671 patients	65+	PIP—Beers	54.8% in patients exempt from payment, 36.0% for others	
Kovacevic[46] (2017)	Serbian PC	388 prescriptions	"Elderly" with polypharmacy	DRP—own definition	98.2% with at least one DRP	

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Table 1. Continued

Lead Author (Year)	Setting	Number of Patients or Prescriptions	High-Risk Subpopulation?	Definition of Medical Error	Error Rate	Other Outcomes
Kunac[47] (2014)	New Zealand PC	376 voluntary reports	No	Medication errors—own definition	14.7% of reports listed a patient harm	
Miller[49] (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
Oliveira[50] (2015)	Brazilian family health units	142 patients	Ages 60+	PIP—Beers, STOPP	33.8%-51.8%	
Perez[51] (2018)	Ireland PC	38,229 patients	Ages 65+	PIP—STOPP	45.3%-51.0%	
Ryan[52] (2009)	Ireland PC	500 patients	Ages 65+ and at least 1 medication	PIP—Beers and IPET	13%	
Ryan[53] (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"
Stocks[54] (2015)	UK PC	949,552 patients	No	PIP—own definition	5.26%	
Trinkley[55] (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	No	ADE—own definition	Of the 701 participants and 1368 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

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Table 1. Continued

Lead Author (Year)	Setting	Number of Patients or Prescriptions	High-Risk Subpopulation?	Definition of Medical Error	Error Rate	Other Outcomes
Wallace[56] (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 Quol-5 Dimensions (EQ-5 Days)-3L	40% STOPP 26% Beers 74% ≥ 1 ADE	In multivariable analysis ≥2 Beers 2012 PIP was not associated with ADEs (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
Wauters[57] (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
Wucherer[58] (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.

Table 2. Interventional Studies

Lead Author (Year)	Setting	Number of Patients or Prescriptions	High-Risk Subpopulation	Definition of Medical Error	Intervention	Error Rate	Other Outcomes
Benson[59] (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 actioned by the GP Harms not measured
Clyne[60] (2015)	Ireland PC	196 patients	Ages 70+	PIP—own definition	Intervention GP participants received a complex, multifaceted intervention Control practices received simple, patient-level PIP feedback	Baseline PIP: 1.31 drugs/patient intervention group, 1.39 in control group 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
Clyne[61] (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
Gibert[62] (2018)	France PC	172 patients	Ages 75+ who were taking at least 5 drugs	PIP—STOPP	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

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Table 2. Continued

Lead Author (Year)	Setting	Number of Patients or Prescriptions	High-Risk Subpopulation	Definition of Medical Error	Intervention	Error Rate	Other Outcomes
Howard[63] (2014)	UK PC	72 general practices 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[64] (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[65] (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

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Table 2. Continued

Lead Author (Year)	Setting	Number of Patients or Prescriptions	High-Risk Subpopulation	Definition of Medical Error	Intervention	Error Rate	Other Outcomes
Lopez-Picazo[66] (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 No difference between the control and report groups	Harms not measured
Peek[67] (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 PINCER	SMASH comprised (1) training of clinical pharmacists to deliver the intervention; (2) a web-based dashboard providing actionable, patient-level feedb ack; and (3) pharmacists reviewing individual at-risk patients and initiating remedial actions or advising general practitionerson doing so	At baseline, 95% of practices had rates of potentially hazardousprescribing (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[68] (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[69] (2017)	Veterans Affairs PC in North Carolina	1539 patients preinterv ention; 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

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Table 2. Continued

Lead Author (Year)	Setting	Number of Patients or Prescriptions	High-Risk Subpopulation	Definition of Medical Error	Intervention	Error Rate	Other Outcomes
Wessell[70] (2008)	South Carolina PC	124,802 patients	Ages 65+	PIP—Beers	Quarterly performance reports, on-site visits, and annual meetings for 4 years	Always inappropriate 0.41% to 0.33%, 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	PIP—own definition	Local performance review, quarterly reports, and academic detailing	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; STOPP, screening tool of old people's prescriptions.

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 ≥ 2 PIPs and harms such as ADEs, reduced quality of life, ED visits, or hospital admissions.[56] One found an association between ≥ 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%),[59–61,63–65,67,68] 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.

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;[72,73] wasted time for patients, physicians, and the health care system;[72,74,75] loss of relationship and trust in the clinician;[73] and financial costs to patients, clinicians, and the health care system.[74,75]

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,[76] and nearly half of patients experienced medication discrepancies during care transitions.[77,78] 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)[79] or where laboratory monitoring for adverse drug effects did not occur.[80]

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.[73] 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.[73]

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.[81] 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 alerts[84–86] 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 harms[91] 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.[98] 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.[99]

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.[100]
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.[101] For example, a study examining how receptionists and general practitioners interact found potential sources of error that could be reduced with improved communication.[102]
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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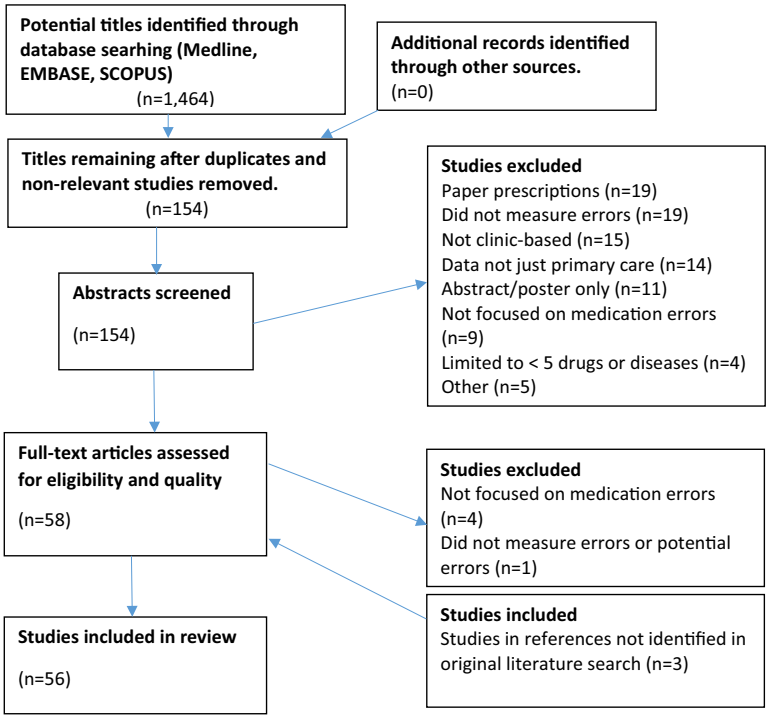
Appendix

Appendix Figure 1. PRISMA Flow Chart



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 records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Appendix
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	18-19
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), ideally using structured tables or plots.	7-15
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	n/a
	20b	Present results of all statistical syntheses conducted. If meta-analysis was 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.	n/a
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	n/a
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	n/a
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	n/a
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	17-19
	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 protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6
	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 role of the funders or sponsors in the review.	Appendix
Competing interests	26	Declare any competing interests of review authors.	Cover letter
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Cover letter

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. A

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 2. Search Strategy and Results

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 practi*[Title]) OR (family medicine) OR (family medicine[Title]))) AND ("1999/01/01"[PDAT] : "2020/12/31"[PDAT]) AND English[lang]) AND (primary[Title] OR family[Title] OR internal[Title] OR general[Title] OR ambulatory[Title] 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 'general practitioner':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	ITLE-ABS-KEY ("drug related side effects" OR "adverse drug event" OR "drug event" OR "medication error" OR "medication errors") 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**

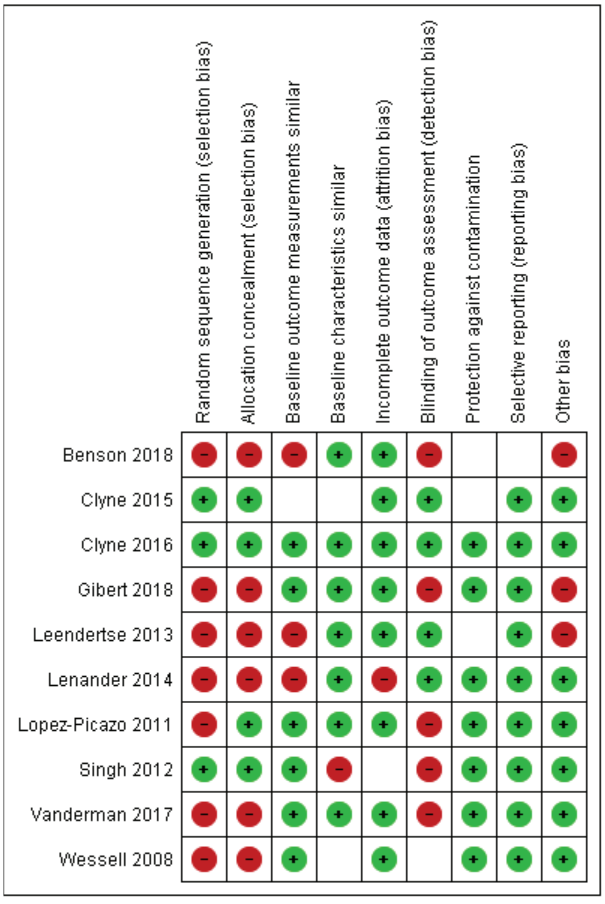
Appendix Table 3. Risk of Bias of Identified Studies

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

Paper	Sample frame	Study participants	Sample size	Subjects described	Analysis coverage	Valid methods to ID condition	Measured standard reliable	Appropriate stats	Response rate adequate	Bias/Quality Assessment
Aspinall	+	-	+	+	+	+	-	+	+	High risk
Clark	+	+	+	+	+	-	+	+	+	High risk
Diaz-Hernandez	-	+	+	+	+	+	-	+	+	High risk
Gnadinger	+	+	+	+	+	-	-	+	+	High risk
Kheir	-	-	-	+	+	+	+	+	+	High risk.
Kovacevic	-	-	+	+	+	-	-	+	+	High risk
Kunac	+	+	+	+	+	+	-	+	+	Some concern
Miller	+	+	+	+	+	+	-	+	+	Some concern
Trinkley	-	+	+	+	+	+	+	+	+	Some concern
Wallace	+	+	+	+	+	+	+	+	+	Low risk
Wucherer	+	+	+	+	+	+	-	+	+	Some concern

Appendix Table 3. Risk of Bias for Intervention Studies

Risk of Bias for Quasi-Experimental Intervention Studies



Risk of Bias for interrupted time series studies