Health Outcomes Associated with Polypharmacy in Community-Dwelling Older Adults: A Systematic Review

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OBJECTIVES: To summarize evidence regarding the health outcomes associated with polypharmacy, defined as number of prescribed medications, in older community-dwelling persons.

DESIGN: Systematic review of MEDLINE (OvidSP 1946 to May, Week 3, 2014).

SETTING: Community.

PARTICIPANTS: Observational studies examining health outcomes according to number of prescription medications taken.

MEASUREMENTS: Association between number of medications and health outcomes. Because of the importance of comorbidity as a potential confounder of the relationship between polypharmacy and health outcomes, articles were assessed regarding the quality of their adjustment for confounding.

RESULTS: Of the 50 studies identified, the majority that were rated good in terms of their adjustment for comorbidity demonstrated relationships between polypharmacy and a range of outcomes, including falls, fall outcomes, fall risk factors, adverse drug events, hospitalization, mortality, and measures of function and cognition. However, a number of these studies failed to demonstrate associations, as did a substantial proportion of studies rated fair or poor.

CONCLUSION: Data are mixed regarding the relationship between polypharmacy, considered in terms of number of medications, and adverse outcomes in community-dwelling older persons. Because of the challenge of confounding, randomized controlled trials of medication discontinuation may provide more-definitive evidence regarding this relationship than observational studies can provide. **J Am Geriatr Soc 62:2261–2272, 2014.**

Key words: polypharmacy; observational studies; systematic review

The majority of older persons have multimorbidity, the coexistence of multiple chronic conditions. In a study using 100% Medicare claims data from 2008 (with 83.5% of beneficiaries aged ≥65), 67% of all beneficiaries had two or more chronic conditions. The prevalence increased with age, to 81.5% for beneficiaries aged 85 and older.[1] A consequence of multimorbidity is the use of multiple medications. In a 2003 survey of Medicare beneficiaries, nearly 90% were taking at least one prescription medication, and 46% of these were taking five or more medications.[2] The use of multiple medications is called polypharmacy, although there are other definitions for the term, such as use of inappropriate medications, and even when defined according to number of medications, no consensus exists regarding the number of medications at which polypharmacy begins. There are concerns about the consequences of polypharmacy in persons with multimorbidity. Increasing the number of medications exponentially increases the number of combinations of medications, which in turn increases the risk of adverse drug reactions and drug–drug interactions.[3] One study that applied clinical practice guidelines to the care of an older adult with five common chronic coexisting conditions (hypertension, diabetes mellitus, osteoarthritis, chronic obstructive pulmonary disease, and osteoporosis) found that she would be prescribed 12 medications, requiring a complex administration schedule with the potential for multiple drug–drug and drug–disease interactions.[4] Because data regarding the benefits and harms of medications have come largely from randomized controlled trials excluding persons with multimorbidity, the marginal benefits and harms associated with prescribing additional medications for persons who are already taking other medications are not known.[5]

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Although reviews of polypharmacy defined as the receipt of multiple medications have concluded that number of medications is associated with adverse outcomes in older adults,[3,6] the full range of outcomes potentially associated with polypharmacy is not well understood. Several prior reviews of polypharmacy focused on the epidemiology of and interventions to reduce polypharmacy rather than on outcomes.[6,7] One review examining outcomes associated with polypharmacy used the key words "polypharmacy" or "multiple medications" as identifiers of studies examining the use of multiple medications.[3] Examination of articles suggested that relevant studies were not uniformly indexed using these terms, so a systematic review of the literature was undertaken to examine the health outcomes associated with polypharmacy, employing a number of strategies to identify studies that examined the use of multiple medications.

METHODS

Data Sources and Searches

The search was constructed to address the question, "In community-living persons aged 65 and older receiving outpatient care, what are the clinical outcomes associated with polypharmacy related to medications taken for chronic conditions?" MEDLINE was searched for relevant studies (OvidSP 1946 to Week 3, May 2014). The search strategies used synonymous free text words in addition to controlled vocabulary terms to capture the concept of polypharmacy by identifying studies examining the prescription of four or more medications or drug burden in persons aged 65 and older. The search strategy was not limited by study design or language of publication. The full strategy is shown in the Appendix.

Study Selection

In the absence of consensus regarding the definition of polypharmacy, articles were included if they compared outcomes associated with more and fewer medications, regardless of what these numbers were. Because multiple articles described population-based studies regardless of site of residence, these articles were included, but if the population consisted entirely of persons living in assisted living facilities or nursing homes, the articles were excluded. Observational designs other than cohort or case–control studies (e.g., case series) were excluded. Articles were excluded if they examined hospitalized individuals and individuals receiving emergency department care, because these represented selected cohorts. Articles were also excluded if they did not examine a health-related outcome; an example of such an exclusion was medication adherence. A final exclusion criterion was the prescription of inappropriate medications or number of medications in a specific medication class as the sole measure of polypharmacy without also examining the number of medications prescribed, because of a specific interest in examining the evidence regarding the relationship between number of medications and outcomes regardless of the appropriateness of each medication considered individually. Studies of individuals taking possibly inappropriate medications were not excluded if they had polypharmacy defined according to total number of medications. Three of the investigators independently reviewed 50 titles and abstracts to confirm uniformity in the process of excluding articles. One of two investigators initially reviewed the titles and abstracts of the remaining references, and a third investigator re-reviewed articles that were not excluded to achieve consensus regarding inclusion. Full-text review was performed for these articles. The reference lists for the final set of articles identified using this search, as well as for articles that did not meet inclusion criteria but provided reviews or conceptual discussions of polypharmacy, were also examined to identify additional articles meeting inclusion criterion.

Data Extraction

For each of the included studies, two investigators independently extracted information on study design, study population, measure of polypharmacy, and main findings. Disagreements were resolved through discussion. Many of the customary measures of quality used for systematic reviews that are designed to assess the risk of bias in randomized controlled trials, such as adequacy of randomization, blinding, and completion of outcome reporting, were not applicable to the observational studies included in the current review.[8] Instead, confounding was focused on. Adjustment for chronic illnesses was particularly important to consider because of the possibility that the outcomes examined were associated with the multiple diseases for which medications were prescribed rather than the medications themselves. Each study was therefore evaluated for the adequacy of adjustment for confounding, and each was rated as good, fair, or poor. A rating of good was assigned if the study used specific assessments of comorbid conditions (e.g., comorbidity index, number of chronic conditions, presence or absence of multiple individual conditions). A rating of fair was assigned if the study did not assess a full complement of chronic conditions but included other characteristics associated with health, such as age, self-reported health, and function. A rating of poor was assigned if the study did not include any of these adjustments or if the methods section did not explicitly describe how adjustment was made.

Data Synthesis and Analysis

Studies were organized according to the outcome examined. Because of the heterogeneity in design, population, and definition of polypharmacy, the results were not combined.

RESULTS

Identification of Articles

The literature search yielded 2,552 articles, including 50 duplicates; 78 passed the title and abstract screening process. Full-text review resulted in the exclusion of 37 articles. Review of the reference lists for the remaining 41 articles and articles identified as not meeting inclusion criteria but providing a review of polypharmacy resulted in

Table 1. Outcomes Associated with Polypharmacy

Author, Year	N	Study Design	Follow-Up	Population	Measure of Polypharmacy	Main Findings
Falls, fractures, dizziness						
Good quality of adjustment for chronic illness						
Agostini, 2004[9]	885	Cohort: cross-sectional (weight loss) longitudinal (impaired balance)	1 year	Probability sample; single U.S. city, aged ≥72	1–2, 3–4, ≥5 vs 0 medications	Impaired balance: NS for 1–2 medications; OR = 1.72, 95% CI = 1.09–2.71 for 3–4 medications; OR = 1.80, 95% CI = 1.02, 3.19 for ≥5 medications
Beer, 2011[10]	4,260	Cohort: cross-sectional		Population-based; single Western Australia city; men aged 65–83	Continuous	Falls: OR = 1.06, 95% CI = 1.02–1.09
Campbell, 1989[11]	761	Cohort: longitudinal	1 year	Population-based; rural New Zealand community, aged ≥70	1–3, ≥4 vs 0 medications	Falls: significant for women only. RR = 2.6, 95% CI = 1.2–5.5 for 1–3 medications; RR 4.5, 95% CI = 1.9–10.6 for ≥4 medications
Clough-Gorr, 2008[12]	1,644	Cohort: longitudinal	1 year	Population-based; three European cities, aged ≥65	≥4 vs 0–3 medications	Falls or ever fallen: OR = 1.3, 95% CI = 1.0–1.8
Fletcher, 2009[13]	453	Cohort: cross-sectional		Participants in five Canadian fall prevention studies, mean age 80.7	Continuous	1 fall: OR = 1.19, 95% CI = 1.09–1.30; ≥2 falls: OR = 1.21, 95% CI = 1.02–1.43
Gassman, 2009[14]	620	Cohort: cross-sectional and longitudinal	2 years	Population-based; three German cities aged ≥65	≥4 vs 0–3 medications	Dizziness at baseline: OR = 2.36, 95% CI = 1.62–3.44; at follow-up: OR = 1.60, 95% CI = 1.11–2.32 Falls: NS
Gnjidic, 2012[15]	1,242	Cohort: longitudinal	2 years	Population-based; single Australian city, aged ≥70	Continuous	Falls: OR = 1.07, 95% CI = 1.03–1.12
Gomez, 2011[16]	1,692	Cohort: cross-sectional		Population-based; four suburban and rural Colombian communities, aged ≥60	≥4 vs 0–3 medications	Dizziness: NS
Huang, 2009[17]	46,946	Cohort: longitudinal	5 years	Health maintenance organization disease registry of individuals with diabetes mellitus; single U.S. city, aged ≥18	2–3, 4–5, 6–7, ≥7 vs 0–1 medications	Falls: NS for 2–3 medications. OR = 1.22, 95% CI = 1.04–1.43 for 4–5 medications; OR = 1.33, 95% CI = 1.12–1.58 for 6–7 medications; OR = 1.59, 95% CI = 1.34–1.89 for ≥8 medications
Lawlor, 2003[18]	4,050	Cohort: cross-sectional		General practice lists; three U.K. towns, women aged 60–79	Continuous	Falls: NS
Murphy, 2002[19]	433	Cohort: cross-sectional		Probability-sample; single U.S. city, aged ≥72	≥5 vs 0–4 medications	Fear of falling or activity restriction: NS
Tinetti, 2000[20]	1,087	Cohort: cross-sectional		Probability-sample; single U.S. city, aged ≥72	≥5 vs 0–4 medications	Dizziness: RR = 1.3, 95% CI = 1.01–1.63
Vellas, 1998[21]	482	Cohort: longitudinal	2 years	Volunteers from two prior U.S. studies; aged ≥60	Continuous	Falls: RR = 1.05, 95% CI = 1.00–1.11 Injurious falls: RR 1.13, 95% CI = 1.02–1.26
Ziere, 2005[25]	6,928	Cohort: cross-sectional		Population-based; Dutch city, aged ≥55	3, ≥4 vs 0 medications	Falls: NS for 3 medications; OR = 1.6, 95% CI = 1.1–2.1 for ≥4 medications No increased risk if not on individual medication associated with falls in adjusted model

(Continued)

Table 1 (Contd.)

Author, Year	N	Study Design	Follow-Up	Population	Measure of Polypharmacy	Main Findings
Fair quality of adjustment for chronic illness						
Curcio, 2006[23]	1,668	Cohort: cross-sectional		Volunteers; Colombian towns, aged ≥60	≥4 vs 0–3 medications	Fear of falling: OR = 1.56, 95% CI = 1.14–2.14
Jacqmin-Gadda, 1998[24]	3,216	Cohort: longitudinal	5 years	Population-based; random sample; two communities in France, aged ≥65	>3 nonpsychotropic drugs vs ≤3	Hip fractures: NS Non-hip fractures: OR = 1.36, 95% CI = 1.04–1.78
Kojima, 2012[26]	172	Cohort: longitudinal	2 years	Consecutive individuals seen in single outpatient Japanese geriatric clinic, aged ≥65	≥5 versus 0–4 medications	Falls: OR = 4.50, 95% CI = 1.66–12.20
Kao, 2001[25]	262	Cohort: cross-sectional		Individuals in single U.S. geriatric assessment center, aged ≥60	3+ vs 0–2 medications	Dizziness: NS
Lord, 1994[27]	704	Cohort: longitudinal	1 year	Population-based; single Australian city, women aged ≥65	≥4 vs, 0–3 medications	Falls: RR = 1.28, 95% CI = 1.03–1.58
Wu, 2013[28]	671	Cohort: cross-sectional		Random sample of persons participating in free health examination; single Taiwanese city, aged ≥55	≥4 vs 0–3 medications	Falls: OR = 2.17, 95% CI = 1.18–3.97
Poor quality of adjustment for chronic illness						
Buatois, 2010[29]	1,618	Cohort: longitudinal	25 months	Persons presenting for senior medical examination; single French city, aged ≥65	≥4 medications vs 0–3 medications	Falls: OR = 1.66, 95% CI = 1.06–2.60
Lai, 2010[63]	9,312	Retrospective case–control		Population-based sample of Taiwanese residents, aged ≥65	2–4, 5–7, 8–9, ≥10 vs 0–1 medications	Hip fracture: OR = 1.65, 95% CI = 1.47–1.83 for 2–4 medications, OR = 3.21, 95% CI = 2.77–3.73 for 5–7 medications, OR = 5.54, 95% CI = 3.77–8.13 for 8–9 medications, OR = 8.42, 95% CI = 4.73, 15.0 for ≥10 medications
Liu, 1995[30]	100	Cohort: longitudinal	1 year	Volunteers; single Canadian city, mean age 83	Continuous	Falls: NS
Adverse drug reactions or events						
Good quality of adjustment for chronic illness						
Calderón-Larrañaga, 2012[31]	79,089	Retrospective cohort: longitudinal	1 year	Patients of 7 urban primary care centers; single Spanish city aged ≥14	≥6 vs 0–5 medications	ADE coded in electronic medical record: OR = 1.34, 95% CI = 1.11–1.63
Chrischilles, 2007[32]	689	Cohort: longitudinal	1 year	Population-based Iowa Medicare beneficiaries with mobility limitation, aged ≥65	4–6, 7–9, 10–13, 14–34 vs 0–3 medications	Self-reported ADE, unwanted reaction: increasing OR under unadjusted and 2 adjusted models. Only 14–34 medications with significant OR
Field, 2004[33]	30,397	Cohort: longitudinal	1 year	Patients of large multispecialty group practice; single U.S. city, aged ≥65	2–4, 5–7, ≥8 vs 0–1 medications	Preventable drug-related injury: NS for 2–4 medications; OR = 2.4 for 5–7 medications; OR = 3.1 for ≥8 medications
Field, 2007[34]	30,000	Cohort: longitudinal	1 year	Patients of large multispecialty group practice; single U.S. city, aged ≥65	3–4, 5–6, ≥7 vs 0–2 medications	Drug-related injury: NS for 3–4 medications; OR = 3.1 for 5–6 medications; OR = 3.3 for ≥7 medications

(Continued)

Table 1 (Contd.)

Author, Year	N	Study Design	Follow-Up	Population	Measure of Polypharmacy	Main Findings
Gandhi, 2000[35]	2,248	Retrospective cohort: longitudinal	1 year	Patients of 11 ambulatory practices; single U.S. city, aged 20–75	Continuous	Self-reported ADR and ADR in medical record: NS
Green, 2007[36]	405	Retrospective cohort: cross-sectional		Medicare managed care enrollees; single U.S. city, aged ≥65	Continuous	Self-reported ADE: NS (as ≥5 medications or continuous)
Hutchinson, 1986[37]	1,026	Cohort: longitudinal	1 year	Patients of internal medicine practice; single Canadian city, mean age 55 ± 16	Number of drug courses: 1, 2, 3–5, 6–10, ≥11	Risk of ADE to newly started medication: NS
Sarkar, 2011[38]	[a]	Cohort: cross-sectional		Nationally representative U.S. probability sample, aged ≥25	1–3, 4–5, 6–8 vs 0 medications	Outpatient visit for ADE: OR = 2.8, 95% CI = 1.66–4.74 for 1–3 medications; OR = 3.61, 95% CI = 1.92–6.78 for 4–5 medications; OR = 3.83, 95% CI = 2.2–6.65 for 6–8 medications
Fair quality of adjustment for chronic illness						
Chrischilles, 1992[39]	3,170	Cohort: cross-sectional		Probability sample; 2 rural U.S. counties, aged ≥65	Continuous	Self-reported ADR: OR = 1.25, 95% CI = 1.18–1.33
Schneider, 1992[40]	463	Cohort: longitudinal	1 year	Outpatients of geriatric and general medicine clinics in single U.S. city, aged ≥70	Continuous	ADRs or symptoms linked to medication by clinician or investigator: NS
Poor quality of adjustment for chronic illness						
Bourgeois, 2010[41]	[a]	Cohort: cross-sectional		Nationally representative U.S. probability sample, all ages	3–4, ≥5 vs 0–2 medications	Outpatient or ED visit for ADE: OR = 1.45, 95% CI = 1.25–1.58 for 3–4 medications; OR = 1.88, 95% CI = 1.58–2.25 for ≥5 medications
Gandhi, 2003[42]	661	Cohort: longitudinal	3 months	Patients of four ambulatory practices; U.S., aged ≥18	Continuous	ADE or symptoms linked by investigator to medication: for each additional medication, mean number of ADEs per individual increased by 10%, 95% CI = 6–15%
Reason, 2012[43]	3,132	Cohort: cross-sectional		Nationally representative Canadian probability sample, aged ≥65	≥5 vs 1–2, 3–4 medications	Self-reported ADE requiring office or ED visit: 5% for 1–2 medication, 6% for 3–4 medications, 12% for ≥5 medications ($P < .001$)
Veehof, 1999[44]	2,185	Retrospective cohort: cross-sectional		Patients of three general practices; single Dutch city, aged ≥65	2–3, 4–5, ≥5 vs 0–1 medications	ADR as recognized by clinician: NS
Hospitalization or mortality						
Good quality of adjustment for chronic illness						
Beer, 2011[10]	4,260	Cohort: longitudinal	4.5 years	Population-based; single Western Australia city; men aged 65–83	Continuous	Hospital admission: HR = 1.04, 95% CI = 1.03–1.06 Cardiovascular events: HR = 1.09, 95% CI = 1.06–1.12 Mortality: HR = 1.04, 95% CI = 1.00–1.07
Gnjidic, 2012[15]	1,242	Cohort: longitudinal	2 years	Population-based; single Australian city, aged ≥70	Continuous	Mortality: OR = 1.09, 95% CI = 1.04–1.15

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Table 1 (Contd.)

Author, Year	N	Study Design	Follow-Up	Population	Measure of Polypharmacy	Main Findings
Hak, 2001[65]	315	Case–control		Population-based; throughout Netherlands, with chronic disease	Continuous	Influenza hospitalization or mortality: OR = 1.3, 95% CI = 1.1–1.5
Richardson, 2011[45]	12,423	Cohort: longitudinal	18 years	Population-based; three urban and two rural communities; Great Britain, aged ≥65	≥5 medications	2-year mortality: HR = 1.42, 95% CI = 1.28–1.58 for men; HR = 1.3, 95% CI = 1.19–1.41 for women
Fair quality of adjustment for chronic illness						
Espino, 2006[46]	1,823	Cohort: longitudinal	8 years	Probability sample; 4 southwest U.S. cities, Mexican Americans aged 65–99	>4 vs 1 medication	Mortality: HR = 1.27, 95% CI = 1.04–1.56
Jensen, 2001[47]	386	Cohort: longitudinal	1 year,	Members of single managed Medicare plan, aged ≥65	≥3 vs 0–2 medications	Hospitalization: OR = 3.79, 95% CI = 1.33–10.90
Jyrkka, 2009[48]	601/339	Cohort: longitudinal, measured at 2 time points	9 years	Population-based; single Finnish city, aged ≥75	6–9, ≥10 vs 0–5 medications	Mortality: no association in first phase; in second phase, NS for 6–9 medications; OR = 2.23, 95% CI = 1.21–4.12 for ≥10 medications
Pozzi, 2010[49]	568	Cohort: longitudinal	4 years	Population-based; single small Italian town, aged ≥65	≥5 medications	Mortality: NS
Shorr, 1997[50]	19,932	Retrospective cohort: longitudinal	5 years	Population-based; Tennessee Medicaid enrollees, aged ≥65 using insulin or sulfonylureas	≥5 vs 0–4 medications	Serious hypoglycemia resulting in ED visit, hospitalization, or death: RR = 1.3, 95% CI = 1.1–1.5
Poor quality of adjustment for chronic illness						
Hershman 1995[51]	488	Cohort: longitudinal	2–10 years	Volunteers; single New York city, aged 75–85	Continuous	Mortality: NS
Miscellaneous						
Good quality of adjustment for chronic illness						
Agostini, 2004[9]	885	Cohort: cross-sectional (weight loss); longitudinal	1 year (impaired balance)	Probability-sample; single U.S. city, aged ≥72	1–2, 3–4, ≥5 vs 0 medications	Weight loss: NS for 1–2 medications, OR = 1.96, 95% CI = 1.08–3.54 for 3–4 medications, OR = 2.78, 95% CI = 1.38–5.60 for ≥5 medications
Fu, 2004[52]	22,601	Cohort: longitudinal	4 years	Nationally representative; probability sample of U.S. residents, aged ≥65	Continuous	Self-perceived health status: Ordered probit model: total number of medications, $P = .01$
Gnjidic, 2012[53]	1,242	Cohort: longitudinal	2 years	Population-based; single Australian city, aged ≥70	≥5 vs 0–5 medications.	Frailty: OR = 4.97, 95% CI = 3.04–8.14
Gnjidic, 2012[53]	1,242	Cohort: longitudinal	2 years	Population-based; single Australian city, aged ≥70	Continuous	Frailty: OR = 1.13, 95% CI = 1.06–1.21; ADL disability: OR = 1.08, 95% CI = 1.00–1.15; Cognitive impairment: NS
Jyrkka, 2011[54]	294	Cohort: longitudinal	3 years	Population-based; single Finnish city, aged ≥75	6–9, ≥10 vs 0–5 medications	Decline in Mini Nutritional Assessment Short-Form: NS for 6–9 medications, $\beta = -0.62$, 95% CI = −0.27 to −0.98) for ≥10 medications; decline in instrumental ADLs: $\beta = -0.29$, 95% CI = −0.10 to −0.47) for 6–9 medications, $\beta = -0.53$, 95% CI = −0.26 to −0.81) for ≥10 medications; Decline in MMSE: NS for 6–9 medications, $\beta = -1.36$, 95% CI = −0.63 to −2.10 for ≥10 medications

(Continued)

Table 1 (Contd.)

Author, Year	N	Study Design	Follow-Up	Population	Measure of Polypharmacy	Main Findings
Lai, 2012[66]	35,675	Case–control		Population-based sample of Taiwanese residents, aged ≥65	2–4, 5–9, ≥10 vs 0–1 medications	Dementia: OR = 1.28, 95% CI = 1.18–1.38 for 2–4 medications, OR = 1.34, 95% CI = 1.23–1.46 for 5–9 medications, OR = 1.56, 95% CI = 1.38–1.76 for ≥10 medications
Lai, 2011[64]	14,135	Case–control		Population-based sample of Taiwanese residents, aged ≥65	2–4, 5–7, 8–9, ≥10 vs 0–1 medications	Parkinson's disease: OR = 1.53, 95% CI = 1.34–1.75 for 2–4 medications, OR: 2.08, 95% CI = 1.79–2.42 for 5–7 medications, OR = 2.64, 95% CI = 2.19–3.18 for 8–9 medications, OR = 2.95, 95% CI = 2.73–3.59 for ≥10 medications
Magaziner, 1989[55]	609	Cohort: longitudinal	1 year	Population-based random sample; single U.S. city, women aged ≥65	Continuous	Decline in MMSE score: NS; increase in Center for Epidemiologic Studies Depression Scale score: $\beta = 0.13$ ($P < .01$); decline in IADL: $\beta = 0.12$ ($P < .001$); decline in physical ADLs: NS
Pugh, 2007[56]	3,050	Cohort: longitudinal	7 years	Probability sample; 4 southwest U.S. cities, Mexican Americans aged 65–99	≥5 vs 0–5 medications	Lower extremity functional limitation: regression estimate –0.014 ($P = .004$)
Rosso, 2013[57]	29,544	Cohort: longitudinal	3 years	Population-based; from areas surrounding 40 clinical centers in 24 U.S. states and the District of Columbia	≥5 vs 0–5 medications	Incident ADL disability: RR = 1.95, 95% CI = 1.54–2.46
Starr, 2004[58]	478	Retrospective cohort: longitudinal	69 years (age 11 and 80)	Survivors of earlier population-based cohort; single urban region, Scotland, 80 years old	Continuous	Change in IQ from age 11 to 80: lower IQ scores with more medications ($F = 12.2$, $P = .001$).
Fair quality of adjustment for chronic illness						
Monastero, 2006[59]	718	Retrospective cohort: longitudinal	3–4 years	Population-based district of Stockholm, aged ≥75	1–4, ≥5 vs 0 medications	Cognitive impairment no dementia: NS for 1–4 medications; OR = 2.6, 95% CI = 1.1, 6.1 for ≥5 medications
Poor quality of adjustment for chronic illness						
Cohen, 1998[60]	1,611	Cohort: cross-sectional		Population-based random sample; electoral role of Australia, aged ≥60	Continuous	Self-reported symptoms of postprandial and postural hypotension: OR = 1.17, 95% CI = 1.05–1.31
Kadam, 2011[61]	4,506	Cohort: longitudinal	5 years	Patients of six general practices England, aged ≥50	5–7, 8–11, ≥12 vs 1–4 medications	Worsening physical and mental health as measured by Medical Outcomes Study 12-item Short-Form Survey: OR = 1.55, 95% CI = 1.2–2.1 for 5–7 medications; OR = 2.25, 95% CI = 1.7–3.1 for 8–11 medications; OR = 2.91, 95% CI = 2.0–4.2 for ≥12 medications
Pilotto, 2005[62]	5,515	Cohort: cross-sectional		General practice patients throughout Italy, aged ≥65	0, 1–3, 4–6, ≥7 medications	Upper gastrointestinal symptoms: Prevalence increased as number of medications increased in bivariate analysis (0, 1–3, 4–6, or ≥7 medications) ($P < .001$)

NS = nonsignificant; OR = odds ratio; HR = hazard ratio; RR = risk ratio; ADE = adverse drug event; ADR = adverse drug reaction; ED = emergency department; ADL = activity of daily living; IADL = instrumental activity of daily living; MMSE = Mini–Mental State Examination; IQ = intelligence quotient; CI = confidence interval; NS = not significant; U.S. = United States.

[a]Unit of analysis was ambulatory visit.

the identification of an additional 17 articles, for a total of 58 (Figure 1).

Type of Studies Identified

All of the studies were observational, with the majority being cross-sectional or longitudinal cohort studies[9–62] and the rest being case–control.[63–66] Many were population based or enrolled participants from disease or medical practice registries and represented persons from multiple countries. Twenty-three studies examined falls or a fall-related outcome (e.g., dizziness, fear of falling, fracture) as the outcome of interest;[9–30,63] 14 examined adverse drug events (ADEs), although these studies varied in how they measured ADEs, including self-report, identification by investigator, recognition by clinician, and reason for outpatient visit;[31–44] 10 examined hospitalization or mortality;[10,15,45–51,65] and 15 examined a variety of outcomes, including general markers of health as well as specific symptoms, function, cognition, and in one study, risk of developing Parkinson's disease.[9,15,52–62,64,66]

Study Findings

Table 1 summarizes the details of the studies and their findings. Of the 23 studies that examined falls or fall-related outcomes, 14 were rated good in terms of adjustment for chronic conditions;[9–22] 12 of these found at least one positive association between polypharmacy and the outcome of interest;[9–15,17,18,20–22] one of these found an association between polypharmacy and falls in women but not in men,[11] and one found an association between polypharmacy and dizziness but not falls.[14] Several studies examining multiple categories of number of medications did not find associations between the use of one to two or two to three medications versus no medications and the outcome of interest but found associations for categories including a higher number of medications.[9,17,22] In one study, participants were stratified according to whether they were taking a medication that was individually found to be associated with falls (a "risk" medication), and polypharmacy was found to be associated with falls only in those taking a risk medication.[22] The remaining nine studies were rated fair or poor in terms of adjustment for chronic conditions;[23–30,63] seven of these studies found at least one positive association between polypharmacy and the outcome of interest.[23,24,26–29,63]

Eight of the studies examining ADEs were rated as good in their adjustment for chronic conditions;[31–38] five of these found an association between polypharmacy and ADEs measured in a number of different ways, including self-report, chart review, and outpatient visit,[31–34,38] and one of these found a significant association only for 14 or more medications.[35] Of the six studies rated as fair or poor in their adjustment for chronic conditions, four found an association between number of medications and ADEs.[39,41–43]

Of the 10 studies examining hospitalization or mortality, four were rated as good in their adjustment for comorbidity, and associations were found between number of medications and all-cause hospitalization or mortality in three of the studies[10,15,45] and influenza-related hospitalization and mortality in the fourth.[65] Of the six studies rated as fair or poor, three found associations between number of medications and mortality or hospitalization.[46–48] A fourth study included older persons using insulin or sulfonylureas and found an association between number of medications and serious hypoglycemia resulting

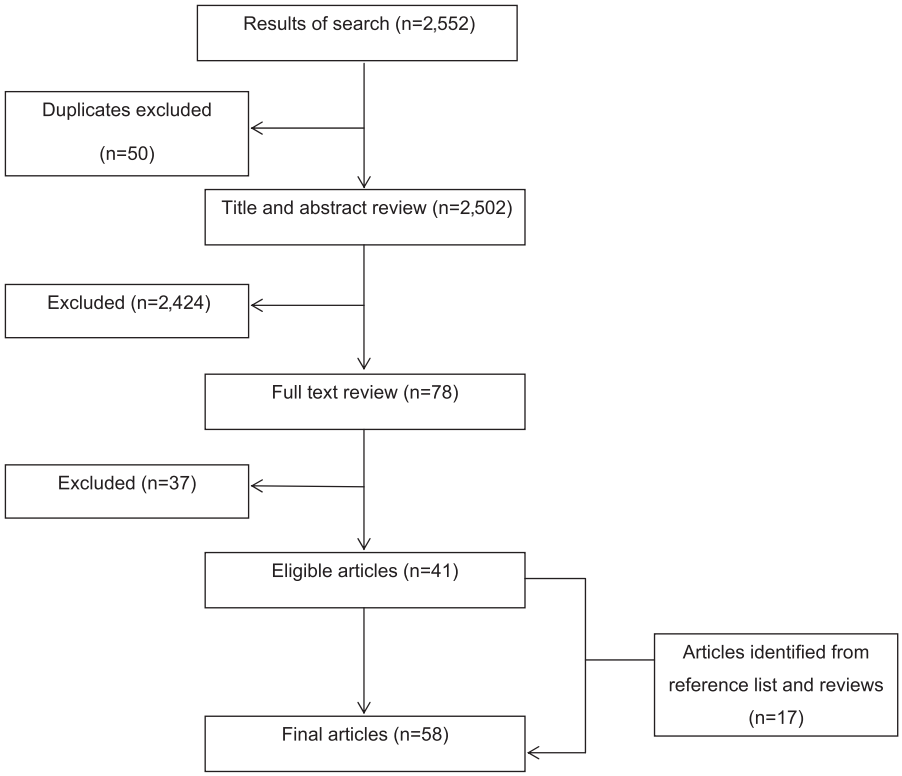

Figure 1. Summary of literature search and selection.

in an emergency department visit, hospitalization, or death.[50]

Fifteen studies examined a broad range of outcomes, including weight loss, self-perceived health status, physical performance, function, cognition, symptoms, and disease development.[9,15,52–62,64,66] Of the 10 studies rated good regarding adjustment for comorbidities, all found an association between number of medications and at least one outcome of interest,[9,15,52–58,64,66] although one study examining the outcomes of nutritional, functional, and cognitive status found an association only for 10 or more medications.[54] The remaining studies, rated fair or poor, also found associations.[59–62]

DISCUSSION

This systematic review, designed to address the question of outcomes associated with polypharmacy, demonstrated marked heterogeneity among studies in terms of definition of polypharmacy and outcomes studied. Because number of medications cannot be assigned to participants, these studies are observational, and therefore the question of confounding is particularly important, because individuals who take more medications are likely to have poorer health than those who take fewer. The studies in this review also varied widely in their approaches to and adequacy of adjustment for chronic conditions, although the majority of studies involved large and often population-based cohorts, suggesting that the study cohorts were representative of persons taking multiple medications. The results of the studies were mixed, with some studies demonstrating an association between polypharmacy and falls, fall risk factors, and fall-related injury; adverse drug events; hospitalization; mortality; and a variety of measures of symptoms and physical and cognitive function, whereas other studies failed to find these associations.

The expectation was that studies with poorer adjustment for confounding would be more likely to demonstrate an association between polypharmacy and adverse outcomes, because polypharmacy is likely to be a marker of an individual's underlying health status. The results of the review showed that, for falls and fall-related outcomes, a greater proportion of studies rated as good in terms of adjustment for confounding demonstrated an association with polypharmacy than of studies rated as fair or poor. For the other outcomes included in the review, some studies rated as good as well as those rated as fair or poor demonstrated associations, whereas others did not. It is unclear why studies making less-adequate adjustment failed to demonstrate associations, but this finding highlights the multifactorial nature of the outcomes examined in the studies included in this review. To the extent that these negative studies reflect a lack of association between health status or chronic diseases and the outcomes examined, they support the conclusion that findings of associations between polypharmacy and the various outcomes reflect a true independent relationship. However, it may also be that even good adjustment for comorbidities cannot account for differences in health associated with differential receipt of medications. A study examining the relationship between the use of individual medications and mortality in older persons found that medications for which there is no evidence of mortality benefit, including nonsteroidal antiinflammatory agents and benzodiazepines, were nonetheless associated with a lower risk of death in a large cohort of older persons. Adjustment for comorbidity had little effect on this association, leading the authors to conclude that the prescription of these medications was a marker of better health status not captured according to comorbidity, because physicians would be reluctant to prescribe these medications to their sickest patients.[67]

There is a burgeoning interest in polypharmacy, as reflected in the literature. The number of studies indexed using this term in Medline almost quadrupled in the last decade, from 77 articles 2002 to 286 in 2012. Moreover, multiple studies have been conducted with the aim of reducing polypharmacy, based on the hypothesis that polypharmacy is a risk factor for adverse outcomes.[68–71] The results of this review provide mixed support for this hypothesis. In addition, one of the studies included in the review raises the question of whether the number of medications per se is associated with adverse outcomes or whether the number of medications is a marker for the use of individual medications with a well-established risk of causing adverse events, such as psychotropic agents[72–74] and other medications that expert consensus has established as inappropriate for some or all older persons.[75,76] The current review identified a study finding that individuals who were prescribed more medications had a greater likelihood of taking a medication associated with fall risk after adjusting for age, sex, comorbidity, and disability and that polypharmacy was a risk for falling only if it included one of these individual medications.[22]

In addition to the question of whether number of medications is merely a marker for receipt of inappropriate medications, there is also the question of whether it is also a marker for underprescribing. In one study, approximately 40% of older veterans who were taking five or more medications were simultaneously taking one or more medications considered to be inappropriate and not taking a potentially beneficial medication.[77] This finding raises the possibility that, if there is a relationship between number of medications and adverse outcomes, it may result, at least in part, from underuse of appropriate medications. The challenge is a lack of data regarding which medications are appropriate for older persons with multiple chronic conditions. These individuals are systematically excluded from participation in clinical trials, with the result that trials underestimate the harms these individuals may experience from medications.[78] In addition, a recent study demonstrated that, because of shorter life expectancy, older persons with chronic kidney disease derive much less benefit from medications to prevent end-stage renal disease than do younger individuals.[79] Taken together, these studies highlight the complexity of the relationship between medications and outcomes, suggesting that number of medications alone may not be a sufficient indicator of the quality of an individual's medication regimen.

Because of the questions regarding confounding and the complex relationship between medication regimens and outcomes, it is likely that a more-definitive answer to the question of the outcomes associated with polypharmacy will require randomized controlled trials. The results of

this systematic review provide sufficient preliminary evidence to support such trials. Additional studies provide ancillary evidence of benefits of medication reduction. Several studies have examined interventions to reduce inappropriate prescribing, including the use of unnecessary and inappropriate medications and the underuse of medications. An early study demonstrated a 25% lower likelihood of an ADE with a clinical pharmacist intervention than with usual care, although this result did not reach statistical significance,[80] and a more-recent study demonstrated 35% fewer serious ADEs associated with an outpatient geriatric evaluation and management program than with usual outpatient care, a significant difference.[81] Additional studies have focused on medication reduction. A randomized controlled trial of a multifactorial falls prevention intervention targeting multiple risk factors included older persons taking four or more medications, including at least one centrally acting antihypertensive, nitrate, diuretic, histamine blocker, or nonsteroidal anti-inflammatory drug, who reported fatigue or dizziness. These participants received the targeted intervention of medication review.[82,83] Overall, the intervention reduced the risk of falls by 31% and reduced the likelihood of taking four or more medications (control group, 86%; intervention group, 63%).[82] A second study examined the feasibility of reducing medications in 70 older community-dwelling adults in a pre/post study design. This study resulted in discontinuation of 81% of medications for which a recommendation was made in 64 participants, 88% of whom reported improvement in their general health.[84] Taken together, this evidence provides support for the efficacy of interventions to improve medication regimens, but whether reduction in polypharmacy per se results in better outcomes is still unknown. Studies addressing this question will face the challenge of disentangling the effects of eliminating high-risk medications from the effects of reducing the overall burden of medications that individually are not generally associated with harm.

This review has a number of limitations. First, because a number of health outcomes were common to many of the studies, it would be ideal to have a summary measure of the association between polypharmacy and these outcomes, but the heterogeneity in study populations and in definitions of polypharmacy made direct comparisons of the studies highly challenging. Second, a sizable proportion of the studies included in the review were found through the reference lists of other articles. This suggests that, although it was attempted to make the search strategy as broad as possible, by using text words and formal subheadings, other relevant articles may have been missed. Third, the studies included in the review were heterogeneous in terms of the types of medications they examined. Although some studies specified the exclusion of over-the-counter medications or medications prescribed for a short course to address an acute condition, other studies included these, and still others did not provide sufficient data to determine which medications were included and excluded.

In summary, this systematic review addressing the question of the health outcomes associated with polypharmacy provides mixed evidence regarding these associations. Although some articles that were rated as good in terms of adjusting for comorbidities that probably confound the relationship between medication use and outcomes demonstrated an association between polypharmacy and falls, ADEs, hospitalization, and other outcomes, other such articles did not. More-definitive evidence regarding these associations will require randomized controlled trials testing the effects of medication discontinuation.

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APPENDIX:

SEARCH STRATEGY

Step no.	Search	Result
1	Polypharmacy/	2,344
2	Polypharmacy.tw.	2,703
3	(drug adj1 burden).mo.	70
4	((prescription* or medication (or polypharmacy) adj (number* or amount* or multiple*)).mp	237
5	((four or five or six or seven or eight or nine or ten) adj1 (prescription* or medication* or polypharmacy)).mp	440
6	1 or 2 or 3 or 4 or 5	4,786
7	Limit 6 to humans	4,678
8	Limit 7 to "all aged (65 and over)"	2,552