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

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Abstract

Background/Objectives—Polypharmacy is receiving increased attention as a potential problem for older persons, who frequently have multiple chronic conditions. The purpose of this study was to summarize evidence regarding the health outcomes associated with polypharmacy, defined as number of prescribed medications,among 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 the number of prescription medications taken.

Measurements—Association of number of medications with 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 total of 50 studies identified, the majority studies that were rated as "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 those studies rated as "fair" or "poor."

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Conclusions—Data are mixed regarding the relationship between polypharmacy, considered in terms of number of medications, and adverse outcomes among community-dwelling older persons. Because of the challenge of confounding, randomized controlled trials of medication discontinuation may provide more definitive evidence regarding this relationship.

Keywords

Polypharmacy; observational studies; systematic review

INTRODUCTION

The majority of older persons have multimorbidity, the co-existence of multiple chronic conditions. In a study using 100% Medicare claims data from 2008(with 83.5% of beneficiaries age ≥ 65 years), 67% of all beneficiaries had two or more chronic conditions. The prevalence increased with age, to 81.5% for beneficiaries 85 years of age or 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, among these persons, 46% were taking five or more medications.[2] The use of multiple medications has been given the namepolypharmacy, 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 among 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 patient with five common chronic co-existing conditions(hypertension, chronic heart failure, stable angina, atrial fibrillation, hypercholesterolemia, diabetes mellitus, osteoarthritis, chronic obstructive pulmonary disease, and osteoporosis)found that she would be prescribed twelve 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]

While reviews of polypharmacy defined as the receipt of multiple medications have concluded that number of medications is associated with adverse outcomes among 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] Our examination of key articles suggested that relevant studies were not uniformly indexed using these terms. We therefore sought to undertake a systematic review of the literature 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, "Among community-living persons age 65 years and older receiving outpatient care, what are the clinical outcomes associated with polypharmacy related to medications taken for chronic conditions?" The following databases were searched for relevant studies with in the dates shown: MEDLINE (OvidSP 1946 to May Week 3 2014).The search strategies used synonymous free text words in addition to controlled vocabulary terms and to capture the concept of polypharmacy by identifying studies examining the prescription of 4 or more medications and/or drug burden in persons age 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 examined outcomes associated with a greater number of medications as compared to a lesser number, regardless of what these numbers were. Because multiple articles enrolled population-based studies regardless of site of residence, we included these articles, but excluded articles if the population consisted entirely of persons living in assisted living facilities or nursing homes. We excluded observational designs other than cohort or case-control studies (e.g. case series).Articles were excluded if they examined hospitalized patients and patients receiving emergency room care, as 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. We did this because of our specific interest in examining the evidence regarding the relationship between number of medications and patient outcomes regardless of the appropriateness of each medication considered individually. We did not exclude studies of patients on possibly inappropriate medications if they had polypharmacy defined according to total number of medications.A total of 50 titles and/or abstracts were reviewed independently by three of the investigators to confirm uniformity in the process of excluding articles. The titles and/or abstracts of the remaining references were initially reviewed by one of two investigators, and articles that were not excluded were re-reviewed by a third investigator to achieve consensus regarding inclusion. Full text review was performed for these articles. The reference lists for the final set of articles identified by 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 the following data elements: 1) study design; 2) study population; 3) measure of polypharmacy; 4) main findings. Disagreements were resolved through discussion. Many of the customary measures of quality utilized 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, we focused on the issue of confounding. 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. We therefore evaluated each study for the adequacy of adjustment for confounding, rating each study 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 did include other characteristics associated with health, such as age, self-reported health, and/or 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 done.

Data Synthesis and Analysis

We organized studies according to the outcome examined. Because of the heterogeneity in design, population, and definition of polypharmacy, we did not attempt to combine the results.

RESULTS

Identification of Articles

The literature search yielded 2,552 articles, including 50 duplicates. A total of 78 articles passed the title/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 the identification of an additional17 articles, for a total of 58 (Figure).

Type of Studies Identified

All of the studies were observational, with the majority of these being cross-sectional or longitudinal cohort studies;[9-62] the remainder of the observational studies were case-control.[63-66] Many were population-based or enrolled participants from disease or medical practice registries and represented persons from multiple countries. The largest number of studies (23) examined falls or a fall-related outcome (e.g. dizziness, fear of falling, fracture) as the outcome of interest.[9-30,63]A total of 14 studies 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] Hospitalization and/or mortality were the outcomes examined in ten studies,[10,15,45-51,65] and a total of 15 studies examined a variety of outcomes, including general markers of health as well as specific symptoms, function, cognition, and, in one study, risk of developing a new disease, Parkinson's.[9,15,52-62,64,66]

Study Findings

Of the 23 studies that examined falls or fall-related outcomes, 14were rated as good in terms of adjustment for chronic conditions.[9-22] Among these studies, 12 found at least one positive association between polypharmacy and the outcome of interest.[9-15,17,18,20-22]Of the 12, one study found an association between polypharmacy and falls among women but not among 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 did find associations for categories including a higher number of medications.[9,17,22] In one study, the authors stratified the participants according to whether they were taking a medication that was individually found to be associated with falls, or a “risk” medication, and reported that polypharmacy was associated with falls only among those taking a risk medication.[22] The remaining nine studies were assessed fair or poor in terms of adjustment for chronic conditions;[23-30,63] among these studies, seven found at least one positive association between polypharmacy and the outcome of interest.[23,24,26-29,63]

A total of eight of the studies examining ADEs were rated as good in their adjustment for chronic conditions.[31-38]Of these, five 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]Of the five, one found a significant associated only for 14 or more medications.[35]Of the six studies rated as fair or poor in their adjustment, four found an association between number of medications and ADEs.[39,41-43]

Of the ten studies examining hospitalization and/or mortality, four were rated as good in their adjustment for comorbidity and associations were found between number of medications and all-cause hospitalization and/or mortality in three of the studies[10,15,45] and flu-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 in an emergency room visit, hospitalization, or death.[50]

A total of 15 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 eleven studies rated as 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 only found an association 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 the outcomes associated with polypharmacy, demonstrated marked heterogeneity among studies in terms of definition of polypharmacy and outcomes studied. Because the number of medications cannot be

assigned to patients, these studies are observational, and therefore the issue of confounding is particularly important, since 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. However, 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 of polypharmacy with 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, while other studies failed to find these associations.

Our expectation was that studies with less adequate 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 the patient's underlying health status. The results of the review showed that, for falls and fall-related outcomes, a greater proportion of studies assessed as good in terms of adjustment for confounding demonstrated an association with polypharmacy as compared to studies assessed as fair or poor. For the other outcomes included in the review, some studies assessed as good as well as those assessed as fair or poor demonstrated associations while others did not. It is unclear why studies doing 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/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 among older persons found that medications for which there is no evidence of mortality benefit, including non-steroidal anti-inflammatory agents and benzodiazepines, were nonetheless associated with a lower risk of death among 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 by comorbidity, as 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 by this term in Medline increased three-fold 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 our 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 established by expert consensus to be inappropriate for some or all older persons.[75,76]Our review

identified a study finding that individuals who were prescribed a greater number of medications had a greater likelihood of taking a medication associated with fall risk after adjusting for age, gender, 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 the receipt of inappropriate medications, there is also the question of whether it is also a marker for under prescribing. 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 outcome, it may result, at least in part, from underuse of appropriate medications. The challenge, however, is a lack of data regarding which medications are appropriate for older persons with multiple chronic conditions. These patients are systematically excluded from participation in clinical trials, with the result that trials underestimate the harms these patients may experience from medications.[78] In addition, a recent study demonstrated that, because of lower life expectancy, older persons with chronic kidney disease derive much less benefit from medications to prevent end-stage renal disease than do younger patients.[79]Taken together, these studies highlight the complexity of the relationship between medications and outcomes, suggesting that number of medications alone may not be sufficient indicator of the quality of a patient's medication regimen.

Because of the issues 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. In addition, additional studies provide ancillary evidence of benefits of medication reduction. Several studies have examined on interventions to reduce inappropriate prescribing, including the use of unnecessary and inappropriate medications as well as underuse of medications. An early study utilizing a clinical pharmacist demonstrated a 25% reduction in the likelihood of an ADE, although this result did not reach statistical significance,[80] and a more recent study of outpatient geriatric care demonstrated a significant 35% reduction in serious ADEs.[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, dizziness. These participants received the targeted intervention of medication review.[82,83] Overall, the intervention reduced the risk of falls by 31% and also reduced the likelihood of taking four or more medications (86% in the control group versus 63% in the intervention group.)[82]A second study examined the feasibility of reducing medications among 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 among 64 participants, of whom 88% reported improvement in their general health.[84] Taken together, this evidence provides support for the efficacy of interventions to improve medication regimens. Whether,

however, reduction in polypharmacy*per se* results in better patient outcomes is still unknown, and studies addressing this issue 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 of polypharmacy with these outcomes. However, the heterogeneity in study populations and in definitions of polypharmacy made direct comparisons among the studies highly challenging. Second, we found a sizeable proportion of the studies included in the review through the reference lists of other articles. This suggests that, while we attempted to make our search strategy as broad as possible, by using text words as well as formal subheadings, we may have missed other relevant articles.Third, the studies included in the review were heterogeneous in terms of the types of medications they examined. While some studies specified the exclusion of over-the-counter medications and/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/ excluded.

In summary, this systematic review addressing the question of the health outcomes associated with polypharmacy provides mixed evidence regarding these associations. While some articles that were assessed as good in terms of adjusting for comorbidities that likely confound the relationship between medication use and outcomes demonstrated an association between polypharmacy and falls, adverse drug events, 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 #	Search	Result
1	polypharmacy/	2344
2	polypharmacy.tw.	2703
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

Step #	Search	Result
6	1 or 2 or 3 or 4 or 5	4786
7	limit 6 to humans	4678
8	limit 7 to ‘all aged (65 and over)’	2552

Appendix

Conflict of Interest:

Elements of Financial/Personal Conflicts	TRF		JO		VT		MKG		MT		DKM	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X		X		X		X
Grants/Funds		X		X		X		X		X		X
Honoraria		X		X		X		X		X		X
Speaker Forum		X		X		X		X		X		X
Consultant		X		X		X		X		X		X
Stocks		X		X		X		X		X		X
Royalties		X		X		X		X		X		X
Expert Testimony		X		X		X		X		X		X
Board Member		X		X		X		X		X		X
Patents		X		X		X		X		X		X
Personal Relationship		X		X		X		X		X		X

Author contributions:

Concept and Design: TRF

Acquisition of data: TRF

Analysis and interpretation of data: JO'L, VT, MKG, MT, DKM

Preparation of manuscript: TRF, JO, VT, MKG, MT, DKM

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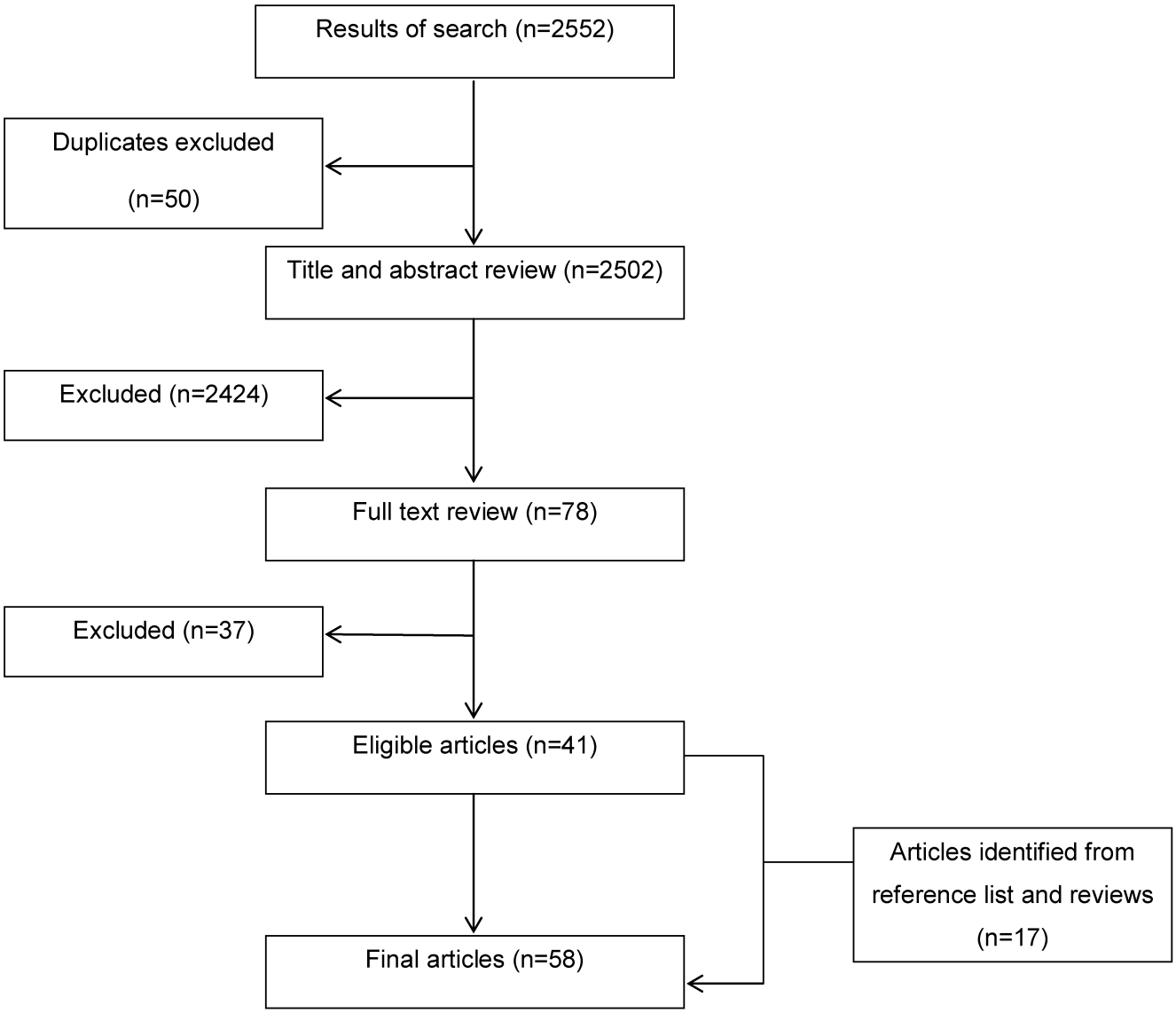

Figure.
Summary of literature search and selection

Table

Outcomes associated with polypharmacy*

Outcome:FALLS/FRACTURES/DIZZINESS				
Author/ Year	**Study Design, Follow-up, & N**	**Population**	**Measure of Polypharmacy**	**Main Findings**
Agostini, 2004	Cohort: cross-sectional (weight loss); longitudinal 1 year (impaired balance) N= 885	Probability-sample single U.S. city, age 72+ years	1-2, 3-4, 5+ vs. 0 meds	Impaired balance: NS for 1-2 meds, OR (95% confidence interval) 1.72 (1.09, 2.71) for 3-4 meds, 1.80 (1.02, 3.19) for 5+ meds.
Beer, 2011	Cohort: cross-sectional N= 4,260	Population-based single city Western Australia; males ages 65-83 years	Continuous	Falls: OR 1.06 (1.02, 1.09)
Campbell, 1989	Cohort: longitudinal 1 year N= 761	Population-based rural New Zealand community, age 70+ years	1-3, 4+ vs. 0 meds	Falls: Significant for women only. RR2.6 (1.2, 5.5) for 1-3 meds; RR 4.5 (1.9, 10.6) for 4+ meds
Clough- Gorr, 2008	Cohort: longitudinal 1 year N= 1,644	Population-based three European cities, age 65+ years	4+ vs. 0-3 meds	Falls or ever fallen: OR: 1.3 (1.0, 1.8)
Fletcher, 2009	Cohort: cross-sectional N= 453	Participants in five Canadian fall prevention studies, mean age 80.7 years	Continuous	1 fall: OR 1.19 (1.09, 1.3) 2+falls: OR 1.21 (1.02, 1.43)
Gassman, 2009	Cohort: cross-sectional and longitudinal 2 years N= 620	Population-based three German cities age 65+ years	4+ vs 0-3 meds	Dizziness at baseline: OR 2.36 (1.62, 3.44); at follow-up: OR 1.60 (1.11, 2.32) Falls: NS
Gnjidic, 2012	Cohort: longitudinal 2 years ISM,242	Population-based single Australian city, age 70+ years	Continuous	Falls: OR 1.07 (1.03, 1.12)
Gomez, 2011	Cohort: cross-sectional N= 1,692	Population-based four suburban/rural Columbian communities, age 60+ years	4+ vs 0-3 meds	Dizziness: NS
Huang, 2009	Cohort: longitudinal 5 years N= 46,946	HMO disease registry of patients with DM single U.S. city, age 18+ years	2-3, 4-5, 6-7, >7 vs. 0-1 meds	Falls: NS for 2-3 meds. OR 1.22 (1.04, 1.43) for 4-5 meds; OR 1.33 (1.12, 1.58) for 6-7 meds; OR 1.59 (1.34, 1.89) for >7 meds.
Lawlor, 2003	Cohort: cross-sectional N= 4,050	General practice lists three U.K. towns, women, age 60-79 yrs	Continuous	Falls: NS.
Murphy, 2002	Cohort: cross-sectional N= 433	Probability-sample single U.S. city, age 72+ years	5+ vs. 0-4 meds	Fear of falling/activity restriction: NS

Outcome:FALLS/FRACTURES/DIZZINESS				
Author/ Year	**Study Design, Follow-up, & N**	**Population**	**Measure of Polypharmacy**	**Main Findings**
Tinetti, 2000	Cohort: cross-sectional N= 1,087	Probability-sample single U.S. city, age 72+ years	5+ vs. 0-4 meds	Dizziness: RR 1.3 (1.01, 1.63)
Vellas, 1998	Cohort: longitudinal 2 years N= 482	Volunteers from two prior U.S. studies, age 60+ years	Continuous	Falls: RR 1.054 (1.001, 1.109) Injurious falls: RR 1.135 (1.022, 1.260)
Ziere, 2005	Cohort: cross-sectional N= 6,928	Population-based Dutch city, age 55+ years	3, 4+ vs. 0 meds	Falls: NS for 3 meds; OR 1.6 (1.1, 2.1) for 4+ meds. No increased risk if not on individual med associated with falls in adjusted model.
Curcio, 2006	Cohort: cross-sectional N= 1,668	Volunteers Columbian towns, age 60+ years	4+ vs. 0-3 meds	Fear of falling: OR 1.56 (1.14, 2.14)
Jacqmin- Gadda, 1998	Cohort: longitudinal 5 years N= 3,216	Population-based random sample two communities in France, age 65+ years	>3 nonpsychotropic drugs vs. ≤3	Hip fractures: NS Non-hip fractures: OR 1.36 (1.04, 1.78)
Kojima, 2012	Cohort: longitudinal 2 years N=172	Consecutive patients seen in single outpatient Japanese geriatric clinic, age 65+ years	5+ versus 0-4 meds	Falls: OR 4.50 (1.66, 12.2)
Kao, 2001	Cohort: cross-sectional N= 262	Patients in single U.S. geriatric assessment center, age 60+ years	3+ vs. 0-2 meds	Dizziness: NS
Lord, 1994	Cohort: longitudinal 1 year N= 704	Population-based single Australian city, women age 65+ years	4+ vs, 0-3 meds	Falls: RR 1.28 (1.03, 1.58)
Wu, 2013	Cohort: cross-sectional N= 671	Random sample of persons participating in free health examination single Taiwanese city, age 55+ years	4+ vs. 0-3 meds	Falls: OR 2.17 (1.18, 3.97)
Buatois, 2010	Cohort: longitudinal 25 months; N= 1,618	Persons presenting for senior medical checkup singe French city, age 65+ years	4+ meds vs. 0-3 meds	Falls: OR 1.66 (1.06, 2.60)
Lai, 2010	Retrospective case-control N= 9,312	Population-based sample of Taiwanese residents, age 65+ years, age 65+ years	2-4, 5-7, 8-9, 10+ vs. 0-1 meds	Hip fracture: OR 1.65 (1.47, 1.83) for 2-4 meds, OR 3.21 (2.77, 3.73) for 5-7 meds, OR 5.54 (3.77, 8.13) for 8-9 meds, OR 8.42 (4.73, 15.0) for 10+ meds
Liu, 1995	Cohort: longitudinal 1 year N= 100	Volunteers single Canadian city, mean age 83 years	Continuous	Falls: NS

Outcome: ADVERSE DRUG REACTIONS or EVENTS				
Author/ Year	**Study Design, Follow-up, & N**	**Population**	**Measure of Polypharmacy**	**Main Findings**
Calderon-Larranaga, 2012	Retrospective cohort: longitudinal 1 year	Patients of 7 urban primary care centers single Spanish city age 14+	6+ versus 0-5 meds	ADE coded in electronic medical record: OR 1.344 (1.106, 1.634)
Chrischilles, 2007	N=79, 089 Cohort: longitudinal 1 year N= 689	Population-based Iowa Medicare beneficiaries with mobility limitation, age 65+	4-6, 7-9, 10-13, 14-34 vs. 0-3 meds	Self-reported ADE, unwanted reaction: increasing OR under unadjusted and 2 adjusted models. Only 14-34 meds w/ sig OR.
Field, 2004	Cohort: longitudinal 1 year N= 30,397	years Patients of large multispecialty group practice single U.S. city, age 65+ years	2-4,5-7, 8+ vs. 0-1 meds,	Preventable drug-related injury: NS for 2-4 meds; OR 2.4 for 5-7 meds; OR 3.1 for 8+ meds.
Field, 2007	Cohort: longitudinal 1 year N= 30,000	Patients of large multispecialty group practice single U.S. city, age 65+ years	3-4, 5-6, 7+ vs. 0-2 meds	Drug related injury: NS for 3-4 meds; OR 3.1 for 5-6 meds; OR 3.3 for 7+ meds.
Gandhi, 2000	Retrospect cohort: longitudinal 1 year N= 2,248	Patients of 11 ambulatory practices single U.S. city, ages 20-75 years	Continuous	Self-reported ADR and ADR in medical record: NS
Green, 2007	Retrospect cohort: cross-sectional. N= 405	Medicare managed care enrollee single U.S. city, age 65+ years	Continuous	Self-reported ADE: NS (either as 5+ meds or continuous)
Hutchinson, 1986	Cohort: longitudinal 1 year N= 1,026	Patients of internal medicine practice single Canadian city, mean age 55 (±16)	# drug courses 1, 2, 3-5, 6-10, 11 +	Risk of ADE to newly-started med: NS
Sarkar, 2011	Cohort: cross-sectional †	Nationally representative U.S. probability sample, age 25+ years	1-3, 4-5, 6-8 vs. 0 meds	Outpt visit for ADE: OR 2.8 (1.66, 4.74) for 1-3 meds; OR 3.61 (1.92, 6.78) for 4-5 meds; OR 3.83 (2.2, 6.65) for 6-8 meds
Chrischilles, 1992	Cohort: cross-sectional N= 3,170	Probability sample 2 rural U.S. counties, age 65+ years	Continuous	Self-reported ADR: OR 1.25 (1.18, 1.33)
Schneider, 1992	Cohort: longitudinal 1 year N= 463	Outpatients of geriatric and general medicine clinics in single U.S. city, age 70+ years	Continuous	ADRs or symptoms linked to medication by clinician/investigator: NS
Bourgeois, 2010	Cohort: cross-sectional †	Nationally representative U.S. probability sample, all ages	3-4, 5+ vs. 0-2 meds	Outpt/ER visit for ADE: OR 1.45 (1.25, 1.58) for 3-4 meds; OR 1.88 (1.58, 2.25) for 5+ meds
Gandhi, 2003	Cohort: longitudinal 3 months N= 661	Patients of four ambulatory practices U.S., age 18+ years	Continuous	ADE/pt symptoms linked by investigator to med: for each additional med, mean # of ADEs per pt increased by 10% (6, 15%)
Reason, 2012	Cohort: cross-sectional N=3132	Nationally representative Canadian probability sample age 65+ years	5+ vs. 1-2, 3-4 meds	Self-reported ADE requiring MD or ER visit: 5% for 1-2 med, 6% for 3-4 meds, 12% for 5+ meds (p=.0001)
Veehof, 1999	Retrospective cohort: cross-sectional. N= 2,185	Patients of three general practices single Dutch city, age 65+ years	2-3, 4-5, 5+ vs. 0-1 meds	ADR as recognized by clinician: NS

Outcome: HOSPITALIZATION OR MORTALITY

Author/ Year	Study Design, Follow-up, & N	Population	Measure of Polypharmacy	Main Findings
Beer, 2011	Cohort: longitudinal 4.5 years N= 4,260	Population-based single city Western Australia; males ages 65-83 years	Continuous	Hospital admission: HR 1.04 (1.03, 1.06) Cardiovascular events: HR 1.09 (1.06, 1.12) Mortality: HR 1.04 (1.00, 1.07)
Gnjidic, 2012	Cohort: longitudinal 2 years N=1,242	Population-based single Australian city, age 70+ years	Continuous	Mortality: OR 1.09 (1.04, 1.15)
Hak, 2001	Case-control N= 315	Population-based throughout Netherlands with chronic disease	Continuous	Flu hospitalization or mortality: OR 1.3 (1.1, 1.5)
Richardson 2011	Cohort: longitudinal 18 years N= 12,423	Population-based three urban and two rural communities Great Britain, age 65+ years	5+ meds	2-year mortality: HR 1.42 (1.28, 1.58) for men; HR 1.3 (1.19, 1.41) for women.
Espino, 2006	Cohort: longitudinal 8 years N= 1,823	Probability sample 4 Southwest U.S. cities, Mexican Americans age 6599 years	>4 vs. 1 med	Mortality: HR 1.27 (1.04, 1.56)
Jensen, 2001	Cohort: longitudinal 1 year, N= 386	Members of single managed Medicare plan, age 65+ years	3+ vs. 0-2 meds	Hospitalization: OR 3.79 (1.33, 10.90)
Jyrkka, 2009	Cohort: longitudinal, measured at 2 time points, 9 years. N= 601/339	Population-based single Finnish city, age 75+ years	6-9, 10+ vs. 0-5 meds	Mortality: No association in 1st phase In 2nd phase, NS for 6-9 meds; OR 2.23 (1.21, 4.12) for 10+ meds.
Pozzi, 2010	Cohort: longitudinal 4 years N=568	Population-based single small town Italy, age 65+ years	5+ meds	Mortality: NS
Shorr, 1997	Retrospective cohort: Longitudinal 5 years N= 19,932	Population-based Tennessee Medicaid enrollees, age 65+ years using insulin or sulfonylureas	5+ vs. 0-4 meds	Serious hypoglycemia resulting in ER visit, hospitalization, or death: RR 1.3 (1.1, 1.5)
Hershman 1995	Cohort: longitudinal 2-10 years N= 488	Volunteers single New York city, ages 75-85 years	Continuous	Mortality: NS

Outcome: MISCELLANEOUS

Author/ Year	Study Design & N	Population	Measure of Polypharmacy	Outcome: Main Findings
Agostini, 2004	Cohort: cross-sectional (weight loss); longitudinal 1 year (impaired balance) N= 885	Probability-sample single U.S. city, age 72+ years	1-2, 3-4, 5+ vs. 0 meds	Weight loss: NS for 1-2 meds, OR 1.96 (1.08, 3.54) for 3-4 meds, OR 2.78 (1.38, 5.60) for 5+ meds
Fu, 2004	Cohort: longitudinal 4 years N= 22,601	Nationally representative probability sample of U.S. residents, age 65+ years	Continuous	Self-perceived health status: Ordered probit model: total # meds p= .01
Gnjidic, 2012	Cohort: longitudinal 2 years ISM,242	Population-based single Australian city, age 70+ years	5+ vs. 0-5 meds.	Frailty: OR 4.97 (3.04, 8.14)
Gnjidic, 2012	Cohort: longitudinal 2 years ISM,242	Population-based single Australian city, age 70+	Continuous	Frailty: OR 1.13 (1.06, 1.21); ADL disability: OR 1.08 (1.00, 1.15); Cognitive impairment: NS

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Outcome: MISCELLANEOUS				
Author/ Year	**Study Design & N**	**Population**	**Measure of Polypharmacy**	**Outcome: Main Findings**
		years		
Jyrkka, 2011	Cohort: longitudinal 3 years N= 294	Population-based single Finnish city, age 75+ years	6-9, 10+ vs. 0-5 meds	Decline in MNA-SF: NS for 6-9 meds, p -.62 (-.27, -.98) for 10+ meds; Decline in IADL: p -.29 (-.10, -.47) for 6-9 meds, p -.53 (-.26, -.81) for 10+ meds; Decline in MMSE: NS for 6-9 meds, P -1.36 (-.63, -2.10) for 10+ meds.
Lai, 2012	Case-control N=35,675	Population-based sample of Taiwanese residents, age 65+ years	2-4, 5-9, 10+ vs. 0-1 meds	Dementia: OR 1.28 (1.18, 1.38) for 2-4 meds, OR 1.34 (1.23, 1.46) for 5-9 meds, OR 1.56 (1.38, 1.76) for 10+ meds
Lai, 2011	Case-control N= 14,135	Population-based sample of Taiwanese residents, age 65+ years	2-4, 5-7, 8-9, 10+ vs. 0-1 meds	Parkinson's disease: OR 1.53 (1.34, 1.75) for 2-4 meds, OR: 2.08 (1.79, 2.42) for 5-7 meds, OR 2.64 (2.19, 3.18) for 8-9 meds, OR 2.95 (2.73, 3.59) for 10+ meds:
Magaziner, 1989	Cohort: longitudinal 1 year N= 609	Population-based random sample single U.S. city, females age 65+ years	Continuous	Decline in MMSE: NS; Increase in CES-D: p = .13 (p<01); Decline in IADL: p = .12 (p<001); Decline in PADL: NS.
Pugh, 2007	Cohort: longitudinal 7 years N= 3,050	Probability sample 4 Southwest U.S. cities, Mexican Americans age 65-99 years	5+ vs. 0-5 meds	Lower extremity functional limitation: regression estimate -.014 (p=.004).
Rosso, 2013	Cohort: longitudinal 3 years N= 29,544	Population-based from areas surrounding forty clinical centers in 24 US states and the District of Columbia	5+ vs. 0-5 meds	Incident ADL disability: RR 1.95 (1.54, 2.46)
Starr, 2004	Retrospective cohort: longitudinal 69 yrs (age 11 and 80) N= 478	Survivors of earlier population-based cohort single urban region Scotland, age 80 years	Continuous	Change in IQ from age 11 to age 80: lower IQ scores w/ great number of meds (F=12.2, D= 001V
Monastero, 2006	Retrospective cohort: longitudinal 3-4 yrs N= 718	Population-based district of Stockholm, age 75+ years	1-4, 5+ vs. 0 meds	CIND: NS for 1-4 meds; OR 2.6 (1.1, 6.1) for 5+ meds.
Cohen, 1998	Cohort: cross-sectional N= 1,611	Population-based random sample electoral role of Australia, age 60+ years	Continuous	Self-reported symptoms of postprandial & postural hypotension: OR 1.17 (1.05, 1.31)
Kadam, 2011	Cohort: longitudinal 5 years N= 4,506	Patients of six general practices England, age 50+ years	5-7, 8-11, 12+ vs. 1-4 meds	Worsening physical and mental health as measured by SF-12:: OR 1.55 (1.2, 2.1) for 5-7 meds; OR 2.25 (1.7, 3.1) for 8-11 meds; OR 2.91 (2.0, 4.2) for 12+ meds.
Pilotto, 2005	Cohort: cross-sectional N= 5,515	General practice patients throughout Italy, age 65+ years	0, 1-3, 4-6, 7+ meds	Upper GI symptoms: Prevalence increased as # of meds increased in bivariate analysis (0, 1-3, 4-6, or 7+ meds) (p<.0001)

NS = non-significant

OR = Odds ratio

HR = Hazard ratio

RR= Risk ratio

ADE = adverse drug event

ADR = adverse drug reaction

MNA-SF = Mini Nutritional Assessment Short-Form

IADL = Instrumental Activities of Daily Living

MMSE = Mini-Mental State Examination

PADL = Physical Activities of Daily Living

ADL = Activity of Daily Living

CIND = cognitive impairment not dementia

IQ = intelligence quotient

GI = gastrointestinal

* The shading of the box indicates the quality of adjustment for chronic illness. No shading = good; light gray = fair; dark gray = poor. See text for details.

†Unit of analysis was ambulatory visit