Prevalence And Definitions of Polypharmacy: A Systematic Review And Meta-Analysis

Mahin Delara

Queen's University

Lauren Murray

Queen's University

Behnaz Jafari

University of Calgary

Anees Bahji

University of Calgary

Zahra Goodarzi

University of Calgary

Julia Kirkham

University of Calgary

Dallas P. Seitz (✉ dallas.seitz@ucalgary.ca)

Queen's University

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Abstract

INTRODUCTION: Polypharmacy is common associated with several adverse health outcomes. There are currently no systematic reviews or meta-analyses on the prevalence of polypharmacy and associated factors. We aimed to identify population-based observational studies reporting on the prevalence of polypharmacy and factors associated with polypharmacy.

METHODS: MEDLINE, EMBASE, and Cochrane databases with no restriction on date. Population-based observational studies with cross-sectional, case-control, or cohort designs using administrative databases or registries to define or measure polypharmacy among individuals over 19. Using a standardized form, two reviewers independently extracted study characteristics, a crude prevalence rate of polypharmacy and its standard error with 95% confidence intervals (CIs). The risk of bias and quality of studies was assessed using the Newcastle-Ottawa Scale. The main outcome was the prevalence of polypharmacy and factors associated with polypharmacy. Using a random-effects model, pooled prevalence estimates with 95% CI was reported. Subgroup analysis was performed if significant heterogeneity was explored. Meta-regression analysis was conducted to predict polypharmacy prevalence.

RESULTS: 106 full-text articles were identified using 21 unique terms with 138 descriptive definitions of polypharmacy. The pooled estimated prevalence polypharmacy in studies reporting all medication classes was 37% (95% CI: 31%-43%). Differences in polypharmacy prevalence were reported for studies using different numerical threshold and polypharmacy was also associated with study year in meta-regression. Sex, study geography, study design and study setting were not associated with differences in polypharmacy prevalence.

DISCUSSION: Our review highlights that polypharmacy is common particularly among older adults and those in inpatient settings. A variety of definitions are used to define polypharmacy and differences in polypharmacy definitions may have implications for understanding the burden of polypharmacy and outcomes associated with polypharmacy.

CONCLUSIONS AND IMPLICATIONS: Clinicians should be aware of the common occurrence of polypharmacy in all populations and undertake efforts to minimize inappropriate polypharmacy whenever possible.

Introduction

While medications are often necessary to manage acute and chronic health conditions, polypharmacy is a significant problem related to prescribing medications. Polypharmacy refers to a situation where an individual uses multiple medications simultaneously. The World Health Organization (WHO) defines polypharmacy as “the administration of many drugs at the same time or the administration of an excessive number of drugs”. [1] While there is no consensus on the medication threshold and means of

measurement, polypharmacy is often commonly defined as concomitant use of 5 or more medications.[1, 2]

Prescribing multiple medications is often clinically required (appropriate polypharmacy). However, exposure to multiple medicines may lead to harm or the ongoing use of medications no longer indicated (inappropriate polypharmacy).[2, 3] Polypharmacy can be associated with numerous poor health outcomes, especially among older adults with multimorbidity, including an increased risk of death, falls, drug interactions, non-adherence, and hospitalization.[2, 3] Polypharmacy has become a substantial health care burden. It is associated with an annual estimated US \$50 billion costs, which is increasing over time.[4] To avoid such cost and prevent adverse events, identification of individuals receiving inappropriate polypharmacy is essential.[3]

Some research indicates that inappropriate polypharmacy can affect up to one-third of the population under study.[4] However, there is no comprehensive and global definition of polypharmacy and factors associated with polypharmacy have not been well-described. We conducted this systematic review and meta-analysis of population-based observational studies to estimate polypharmacy prevalence and identify factors associated with polypharmacy. We also described the terminology and definitions used to define polypharmacy in the research literature.

Methods

We registered our review protocol on PROSPERO (CRD42019130998). This systematic review is written following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[5]

Eligibility Criteria

We included population-based observational studies with cross-sectional, case-control, or cohort designs using administrative databases or registries to define or measure polypharmacy among individuals over 19. We excluded studies that focused on children and adolescents (aged 0-19) and duplicate articles and non-original studies (e.g. editorials). We included all publication dates and limited articles to the English language only. The primary study objective outcome was to estimate polypharmacy prevalence and identify factors associated with polypharmacy. Our secondary objectives were to identify definitions and measurements of polypharmacy using administrative databases or registries.

Search Strategy and Study Selection

We developed a search strategy in consultation with a librarian specializing in health databases. We searched EMBASE, MEDLINE, and Cochrane Library from inception to March 30, 2019, using individualized search strategies prepared for each database. We limited results to studies conducted in humans and available in the English language. We used exploded MeSH terms (e.g. polypharmacy, polytherapy, poly medication, poly prescription, multi medication, multi prescription, multidrug therapy,

multiple drug treatment, multiple pharmacotherapies, administrative data, databases, registries) and combinations of relevant keywords and their variants by grouping polypharmacy and administrative database associated terms. The MEDLINE search strategy is presented in online supplementary materials (Appendix 1). We also hand-searched for additional publications using a reference list of relevant papers. Reference management and citation screening were performed using EndNote™ (V.X7).[6] Using a two-step process for study selection, two of three reviewers (MD, LM) independently screened each citation's title and abstract to determine whether a study met the broad inclusion criteria. The full texts of all relevant citations were retrieved for formal review. Two reviewers (MD, LM) independently assessed the full-text reports. Conflicts were resolved by discussion between reviewers.

Data Extraction and Management

We used a standardized and piloted data extraction form. Reviewers (MD, LM) extracted data independently, using a standardized form, with conflicts resolved through consensus. The extracted study characteristics were bibliographic references, country, year of publication, sample size, setting, study design, age and sex. Appendix 2 illustrates the baseline data extracted from each study. Other data items extracted from the retrieved articles included a crude prevalence rate of polypharmacy and its standard error, 95% confidence intervals (CIs), and polypharmacy definitions. Definitions were broken down based on medication threshold, duration of therapy, overlapping days, measurement indicators, and type of drug assessment. Additional related to studies are provided in Appendix 3.

Quality Assessment

We assessed the risk of bias and quality of the included studies using the Newcastle-Ottawa Scale.[7] This tool consists of 7 to 8 domains depending on the type of study design; each domain is rated 'low risk,' 'unclear risk,' or 'high risk.' Studies were categorized based on total scores as either high quality (total scores ≥ 7) or low quality (total score < 7).

Data Analysis

The included studies' data were summarized in frequency tables and analyzed using RStudio (version 3.6.1). Meta-analyses were performed using random effects. Using inverse variance, we expressed pooled continuous data as prevalence estimates and reported 95% CI. Heterogeneity was determined using the I-squared (I^2) statistic (low $< 25\%$, moderate $25-50\%$, high $> 50\%$).[8] If significant heterogeneity was suspected, further analysis, including subgroup analysis, was conducted. Publication bias was assessed for the prevalence of polypharmacy using funnel plot techniques as appropriate, given the known limitations of these methods.[9] We also used meta-regression analysis to predict polypharmacy prevalence using the identified factors in a linear regression model.

Subgroup Analyses

We restricted subgroup analyses to situations where a minimum of 4 studies were available for each categorical study-level variable.[10] A total of nine subgroup analyses were planned based on: mean age (< 65 vs ≥ 65); sex of participants (male vs female), location of study (North America vs elsewhere),

health care setting (inpatient vs outpatient vs community), study design (cross-sectional vs case-control vs cohort), methodological quality (low vs high); medication threshold (2 vs 5), measurement indicator (simultaneous vs cumulative).

Results

Of 525 unique citations with available abstracts, we retrieved and reviewed 179 full texts. Of these, 106 studies met inclusion criteria (Appendix 4). The studies were published from 1989 to 2019. Figure 1 depicts a PRISMA flowchart of citations reviewed. While two studies were multicentre, most studies were conducted in Europe (n=59), followed by Asia (n=21), North America (n=20), Australia (n=2), and South America (n=2). The healthcare setting was specified in 50 studies (49.1%) including community (n=15), inpatient (n=15), outpatient (n=13) or a combination of these settings (n=7). Nearly 75% percent of the studies were cross-sectional (n=80). The studies included a different number of participants varying from 248 to 12,301,537 individuals. The mean age of participants ranged from 26 to 87 years old. Studies were overall adjudicated to be at low risk of bias or high quality (101 studies, 95.3%), and five studies were judged to be at high risk of bias or low quality. The details of the study characteristics varied across studies (Appendix 2).

Definitions of Polypharmacy

Fifty-seven studies used the term polypharmacy (54%) followed by polytherapy (n=18 studies, 17%), co-prescribing (2 studies, 1.9%), multiple medication use (1 study, 0.9%), concurrent medication (1 study, 0.9%), poly medication (1 study, 0.9%), concomitant use (1 study, 0.9%) and comedication (1 study, 0.9%) (Appendix 3). Out of the 106 identified articles, 96 (90.6%) included descriptive definitions of polypharmacy resulting in 124 different definitions. All definitions had a numerical component ranging from 2 to 21 medications. A common descriptive definition was identified for polypharmacy with five or more medications (33 studies, 31.1%) followed by polypharmacy with two or more medications (16 studies, 15.1%). The descriptive definition with a medication threshold of 2 (52 studies, 49%) was most frequently used after combining these terms, followed by 5 (39 studies, 37%). All descriptive definitions had a time component, including the duration of therapy, minimum days of overlap, time interval, or assessment frequency. Three studies expressly incorporated an allowable gap of 12, 14, and 15 days in their definitions, and one study reported a grace period of 28 days.

Measuring Polypharmacy

As illustrated in Appendix 3, techniques for operationalizing polypharmacy varied across studies as follows: 59 studies used simultaneous approach (55.7%), 45 used cumulative method (42.5%), and two studies examined a combination of simultaneous, cumulative and continuous approaches (1.9%). In the simultaneous process, the most common sub-indicator was described as the concurrent use of medications with at least one day overlap (47 studies, 44%). Among studies using a cumulative approach, the summing up of different medications taken over 90 days was identified as the most frequent sub-indicator (9 studies, 9%). The timing of polypharmacy assessment also differed across

studies. The minimum overlap days required for the simultaneous evaluation ranged from 1 day to 1 year. Studies using the cumulative approach specified a period between 14 to 730 days. The time frame ranged from 180 to 360 days in the continuous approach.

Prevalence of Polypharmacy

Overall Prevalence

Ninety-four studies (100 single reports) contributed raw data for the prevalence of polypharmacy terms. Of the 94 studies, 54 reported on polypharmacy incorporating all medications while the remaining studies only reported polypharmacy related to specific medication classes (e.g. psychotropic polypharmacy, polypharmacy with antiepileptic medications). The pooled estimated prevalence of polypharmacy among the 54 studies reporting on polypharmacy including all medications was 37% (95% CI: 31% - 43%). There was a high degree of heterogeneity observed in this estimate ($\text{Tau}^2=0.0424$, $\text{Chi}^2=22194826$, $\text{df}=53$, $\text{I}^2=100\%$) (Figure 2).

Factors Associated with Polypharmacy

Subgroup analyses were undertaken using the 54 studies reporting polypharmacy including all medication classes (Table 1). These subgroup analyses includes sex, numerical threshold (≥ 2 medications vs ≥ 5 medications), study geography (North America vs other), study design (cross-sectional, case-control, or cohort) and study setting (community, outpatient and inpatient) or study location (North America vs outside North America). Meta-regression was used to assess the associations between mean age of participants and study year. A summary of the subgroup analyses are provided in Table 1.

Table 1
Summary of Subgroup Analyses of Polypharmacy Prevalence

Variable	Pooled Prevalence (95% CI)	Chi ²	df	p-value
Mean age of participants	36 (29,43)	10.88	1	<0.01
Non-elderly (< 65)	25(16,35)	238592.68	20	<0.0001
Elderly (≥ 65)	45 (37,54)	4378199.84	25	<0.0001
Sex	32 (26,39)	0.04	1	0. 85
Male	32 (22,41)	1484546.49,	21	0
Female	33 (23,43)	1754816.42	21	0
Health care setting	40 (32,49)	13.55	2	<0.01
Inpatient	52 (38,66)	36809.71	10	0
Outpatient	47 (33,62)	910219.51	12	0
Community	20 (6,35)	12462667.1	10	0
Numerical cut off for medications	32 (26,38)	2.60	1	0.11
2 medications	29 (27,37)	1615476.66	40	<0.0001
5 medications	37 (30,43)	12019635.95	31	<0.0001
Measurement indicator	33 (28,38)	0.01	2	P = 0.91
Simultaneous	33 (27,40)	9353584.02	50	<0.0001
Cumulative	33 (25,41)	12926693.67	37	<0.0001
Methodological quality	33(28,38)	0.37	1	0.54
High quality	34(29,39)	21220449.4	83	<0.0001
low quality	27 (0,57)	5005.5	4	<0.0001
Country of publication	33 (28,38)	0.15	1	0.70
North America	35 (21,49)	463188.05	17	<0.0001
Non-North America	32 (27,38)	22176139.61	70	<0.0001
Study design	33 (28,38)	9.93	2	<0.01
Cross-sectional	37(31,43)	20427507.22	63	<0.0001
Chi ² = Chi-squared; df = degrees of freedom; Number of reports exceeding the total number of included studies indicates that some studies contributed more raw data at different study periods, age groups or etc.				

Variable	Pooled Prevalence (95% CI)	Chi ²	df	p-value
Cohort	23 (9,38)	326083.41	11	<0.0001
Case-control	24 (17,31)	365802.26	12	<0.0001
Chi ² = Chi-squared; df = degrees of freedom; Number of reports exceeding the total number of included studies indicates that some studies contributed more raw data at different study periods, age groups or etc.				

There was a significant difference in the prevalence of polypharmacy in subgroup analyses for studies using a threshold of ≥ 2 medications (40%, 95% CI: 0% – 47%) when compared to studies using a threshold of ≥ 5 medications (22%, 95% CI: 10% - 35%; $P < 0.01$, *Appendix 4*). There were no differences in polypharmacy prevalence in subgroup analyses based on sex (*Appendix 5*), study design (*Appendix 6*), healthcare setting (*Appendix 7*) or study location (*Appendix 8*) (. Meta-regression demonstrated that more recent studies were associated with a higher prevalence of polypharmacy (estimate = 0.0175, $p = 0.003$). Age was not associated with the prevalence of polypharmacy in meta-regression (estimate = -0.0204, $p = 0.4$).

Assessment of Study Quality

The assessment of study quality according to the Newcastle-Ottawa Scale risk of bias assessments for cohort, case-control and cross-sectional studies are provided in Appendix 8. Overall, 10/13 cohort (77%), 11/13 of case-control (85%) and 80/80 cross-sectional studies (100%) were reported to be of high quality.

Publication Bias Assessment

A funnel plot analysis was used to investigate publication bias which did not demonstrate any evidence of publication bias.

Discussion

Overall, our review indicates that polypharmacy is common (33%) regardless of the definitions used to define it. Older age, inpatient clinical settings and cross-sectional study design were associated with an increased prevalence of polypharmacy. Our review also identified several definitions used to define polypharmacy in the literature. However, the term polypharmacy and a threshold of ≥ 2 medications were the most common definitions found in the literature. However, we did not find that these differing definitions significantly impacted the overall prevalence of polypharmacy in our meta-analysis.

To date, only one systematic review has addressed the multiple definitions of polypharmacy. In their review, Masnoon et al.[3] identified 110 articles that assessed polypharmacy. However, in contrast to our study, Manson et al. did not incorporate a meta-analysis reporting the overall prevalence of polypharmacy or factors associated with polypharmacy. However, these authors highlighted the diverse range of terms

used to define polypharmacy, such as minor, major, severe, excessive, hyper, appropriate, persistent, chronic, long term, and pseudo-polypharmacy.[3] Both our review and this previous review highlight the variety of terms used to define polypharmacy and emphasize the need for researchers to create standardized definitions of polypharmacy in the future.

Awareness of polypharmacy is important as it is associated with several adverse outcomes such as the increased risk of drug-drug interactions, hospitalizations, functional decline and mortality.[11–14] When the number of prescribed medicines increases, the number of drug combinations increases exponentially, increasing the risk of adverse drug reactions and drug-drug interactions.[15] Whether polypharmacy is directly causing these outcomes or if it is a marker for frailty or general vulnerability to poor outcomes is not always clear. However, the presence of polypharmacy may be an indicator for clinicians to identify individuals at risk for adverse outcomes who may benefit from preventative health measures and medication review. It has been suggested that different methods of measuring polypharmacy may have different clinical implications in this respect.[1] To reduce adverse events or assess prescription appropriateness, cumulative indicators of polypharmacy may be more useful, whereas simultaneous assessments of polypharmacy may be more helpful for exploring drug-drug interactions. Continuous indicators may be more appropriate for assessing economic costs associated with polypharmacy or chronic disease burden measures. While our review could not incorporate contextual information related to comorbid medical conditions into our assessment of polypharmacy, this information is also critical to understanding if polypharmacy is appropriate or not at an individual level.

Several strategies can be employed to reduce inappropriate prescribing and/or polypharmacy. Medication review (by pharmacists, physicians, or multidisciplinary teams), education and training, and the use of screening tools to identify potentially inappropriate prescribing (e.g. Screening Tool of Older Persons' Potentially Inappropriate Prescription (STOPP)) have all been found to be effective for reducing polypharmacy in various populations.[16–20] Digital technologies (for example, automatically generated alerts in electronic prescribing programs) have shown promising results in lowering polypharmacy in various settings but have not been widely adopted or investigated.[21] Most of these studies focus on interventions to reduce polypharmacy in settings of greatest concern, such as among older adults or those in residential care settings. However, interventions to reduce polypharmacy vary widely, and the most effective aspects of interventions are still unclear.[20] Deprescribing does not appear to increase adverse outcomes,[22] but whether reducing polypharmacy results in better outcomes is questionable. Studies incorporating clinical outcomes have had mixed findings on the impact on the quality of life, falls, disease-specific outcomes, and hospitalizations.[17–20] Several reviews of interventions to reduce polypharmacy found no effect on all-cause mortality.[16, 18, 22]

Polypharmacy is a complex issue and may differ in appropriateness and implications for medically compromised individuals compared to those who are healthier. In general, polypharmacy needs to be justified and limited as much as possible, especially in older or frail adults. Several strategies have been proposed to reduce polypharmacy, such as deprescribing, reducing the use of unnecessary and inappropriate drugs, and underuse of medications. Still, their clinical significance is not well known.[15]

One of the main challenges is to disentangle the effects of removed drugs from reducing the overall burden of medicines that cause no harm.[15] As well, the use of polypharmacy definitions in clinical practice and informatics systems depends on their operationalization and utility.[1] Therefore, the evidence base of the suggested approaches merits more exploration.

This study is a novel and comprehensive review summarising the range of definitions and measurements of polypharmacy and alternative terms available in the literature. This is the first meta-analysis of polypharmacy prevalence. Our study included multiple electronic database searches and hand searching of bibliographies of included studies. This review also provided a high quality of evidence, as 95% of the included studies were at low risk of bias.

Despite these strengths, we acknowledge that this work has some limitations. Most studies operationalized polypharmacy as multiple medication use, so we could not distinguish between appropriate and inappropriate prescriptions. The prevalence estimates in this review were based mainly on raw and dispensing data available in some studies. The included studies did not use a homogenous, evidence-based approach to reporting the proportional rates of polypharmacy. This is likely one reason for the considerable heterogeneity observed across studies. While the observed difference among some subgroups was not significant, the high heterogeneity within those subgroups may reflect the presence of unmeasured factors influencing heterogeneity such as comorbidities, prescription patterns, medication dosage, or genetic factors. We could not obtain enough data from studies to examine these factors' effect on pooled estimates' variations.

Conclusion And Implications

The current study reviewed 106 studies[1, 23–127] (*See Appendix 3*) published from 1989 to 2019 which met inclusion criteria. Regardless of the employed definitions and measure indicators, polypharmacy is a common phenomenon. Given the adverse outcomes associated with polypharmacy, it is essential to understand which definitions of polypharmacy are strongly related to adverse effects and which populations are most susceptible to polypharmacy-related adverse events. Clinicians should routinely assess patients for the presence of polypharmacy and institute measures to reduce inappropriate polypharmacy when it is possible to do so. There were also numerous approaches to define polypharmacy. Still, due to considerable heterogeneity among studies, we failed to identify a comprehensive, clear, and universal definition of polypharmacy and its measurement to address safety and efficacy concerns in the clinical setting. While a numerical cut-off to define polypharmacy may be somewhat arbitrary, it can be a starting point to identify patients at potential risk of developing adverse events due to inappropriate therapy. Depending on the purpose, different measurement indicators of polypharmacy may be required. To make definitions more clinically relevant, adding new components to present comorbidities and treatment appropriateness are recommended.

Abbreviations

CI: Confidence Interval; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis; STOPP: Screening Tool of Older Persons' Potentially Inappropriate Prescription

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for Publication: Not applicable

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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References

1. Monégat M, Sermet C, Perronnin M, Rococo E. Polypharmacy: Definitions, measurement and stakes involved - Review of the literature and measurement tests. *Quest d'économie la Santé*. 2014; 204:1–8.
2. Davies LE, Spiers G, Kingston A, Todd A, Adamson J, Hanratty B. Adverse outcomes of polypharmacy in older people: Systematic review of reviews. *J Am Med Dir Assoc*. 2020; 21(2):181–187. <https://doi.org/10.1016/j.jamda.2019.10.022>.
3. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatr*. 2017; 17(1):1–10. <https://doi.org/10.1186/s12877-017-0621-2>.
4. Moriarty F, Hardy C, Bennett K, Smith SM, Fahey T. Trends and interaction of polypharmacy and potentially inappropriate prescribing in primary care over 15 years in Ireland: A repeated cross-sectional study. *BMJ Open*. 2015; 5(9):1–7. <https://doi.org/10.1136/bmjopen-2015-008656>.
5. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Int J Surg*. 2010; 8(5):336–341. <https://doi.org/10.1371/journal.pmed.1000097>.
6. Superior Business Solutions. EndNote solution: Your smarter way to research. 2021. <https://sbs-me.com/blogs/endnote-your-smarter-way-to-research/> Accessed May 4, 2021.

7. Wells GA, Shea B, O'Connell Da, Peterson J, Welch V, Losos M et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; 2011.
8. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002; 21(11):1539–1558. <https://doi.org/10.1002/sim.1186>.
9. Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: A large survey. *Can Med Assoc J*. 2007; 176(8):1091–1096. <https://doi.org/10.1503/cmaj.060410>.
10. Fu R, Gartlehner G, Grant M, Shamliyan T, Sedrakyan A, Wilt TJ et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011; 64(11):1187–1197. <https://doi.org/10.1016/j.jclinepi.2010.08.010>.
11. Leelakanok N, Holcombe AL, Lund BC, Gu X, Schweizer ML. Association between polypharmacy and death: A systematic review and meta-analysis. *J Am Pharm Assoc*. 2017; 57(6):729–738. e710. <https://doi.org/10.1016/j.japh.2017.06.002>.
12. Jyrkkä J, Enlund H, Lavikainen P, Sulkava R, Hartikainen S. Association of polypharmacy with nutritional status, functional ability and cognitive capacity over a three-year period in an elderly population. *Pharmacoepidemiol Drug Saf*. 2011; 20(5):514–522. <https://doi.org/10.1002/pds.2116>.
13. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: Population database analysis 1995–2010. *BMC Med*. 2015; 13(1):1–10. <https://doi.org/10.1186/s12916-015-0322-7>.
14. Lalic S, Sluggett JK, Ilomäki J, Wimmer BC, Tan EC, Robson L et al. Polypharmacy and medication regimen complexity as risk factors for hospitalization among residents of long-term care facilities: A prospective cohort study. *J Am Med Dir Assoc*. 2016; 17(11):1067. e1061–1067. e1066. <https://doi.org/10.1016/j.jamda.2016.08.019>.
15. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: A systematic review. *J Am Geriatr Soc*. 2014; 62(12):2261–2272. <https://doi.org/10.1111/jgs.13153>.
16. Johansson T, Abuzahra ME, Keller S, Mann E, Faller B, Sommerauer C et al. Impact of strategies to reduce polypharmacy on clinically relevant endpoints: A systematic review and meta-analysis. *Br J Clin Pharmacol*. 2016; 82(2):532–548. <https://doi.org/10.1111/bcp.12959>.
17. Hill-Taylor B, Walsh K, Stewart S, Hayden J, Byrne S, Sketris I. Effectiveness of the STOPP/START (Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert doctors to the Right Treatment) criteria: Systematic review and meta-analysis of randomized controlled studies. *J Clin Pharm Ther*. 2016; 41(2):158–169. <https://doi.org/10.1111/jcpt.12372>.
18. Kua C-H, Mak VS, Lee SWH. Health outcomes of deprescribing interventions among older residents in nursing homes: A systematic review and meta-analysis. *J Am Med Dir Assoc*. 2019; 20(3):362–372. e311. <https://doi.org/10.1016/j.jamda.2018.10.026>.

19. Martyn-St James M, Faria R, Wong R, Scope A. Evidence for the impact of interventions and medicines reconciliation on problematic polypharmacy in the UK: A rapid review of systematic reviews. *Br J Clin Pharmacol*. 2021; 87(1):42–75. <https://doi.org/10.1111/bcp.14368>.
20. Rankin A, Cadogan CA, Patterson SM, Kerse N, Cardwell CR, Bradley MC et al. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev*. 2018; 5(12):e009235–e009235. <https://doi.org/10.1002/14651858.CD008165.pub4>.
21. Clyne B, Bradley MC, Hughes C, Fahey T, Lapane KL. Electronic prescribing and other forms of technology to reduce inappropriate medication use and polypharmacy in older people: A review of current evidence. *Clin Geriatr Med*. 2012; 28(2):301–322. <https://doi.org/10.1016/j.cger.2012.01.009>.
22. Page AT, Clifford RM, Potter K, Schwartz D, Etherton-Beer CD. The feasibility and effect of deprescribing in older adults on mortality and health: A systematic review and meta-analysis. *Br J Clin Pharmacol*. 2016; 82(3):583–623. <https://doi.org/10.1111/bcp.12975>.
23. Abe J, Umetsu R, Uranishi H, Suzuki H, Nishibata Y, Kato Y et al. Analysis of polypharmacy effects in older patients using Japanese Adverse Drug Event Report database. *PLoS One*. 2017; 12(12):e0190102–e0190102. <https://doi.org/10.1371/journal.pone.0190102>.
24. Andrew T, Milinis K, Baker G, Wiesmann U. Self reported adverse effects of mono and polytherapy for epilepsy. *Seizure*. 2012; 21(8):610–613. <https://doi.org/10.1016/j.seizure.2012.06.013>.
25. Asranna A, Jose M, Philip RM, Sarma PS, Thomas SV. Do Anti-Epileptic Drug modifications after first trimester of pregnancy influence fetal malformation or cognitive outcome? *Epilepsy Res*. 2018; 146:121–125. <https://doi.org/10.1016/j.epilepsyres.2018.07.017>.
26. Åstrand E, Åstrand B, Antonov K, Petersson G. Potential drug interactions during a three-decade study period: A cross-sectional study of a prescription register. *Eur J Clin Pharmacol*. 2007; 63(9):851–859. <https://doi.org/10.1007/s00228-007-0326-0>.
27. Åstrand B, Åstrand E, Antonov K, Petersson G. Detection of potential drug interactions – A model for a national pharmacy register. *Eur J Clin Pharmacol*. 2006; 62(9):749–756. <https://doi.org/10.1007/s00228-006-0143-x>.
28. Baandrup L, Kruse M. Incident users of antipsychotics: Who are they and how do they fare? *Soc Psychiatry Psychiatr Epidemiol*. 2016; 51(4):505–512. <https://doi.org/10.1007/s00127-015-1129-8>.
29. Baandrup L, Sørensen J, Lublin H, Nordentoft M, Glenthøj B. Association of antipsychotic polypharmacy with health service cost: A register-based cost analysis. *Eur J Health Econ*. 2012; 13(3):355–363. <https://doi.org/10.1007/s10198-011-0308-0>.
30. Baek Y-H, Shin J-Y. Trends in polypharmacy over 12 years and changes in its social gradients in South Korea. *PLoS One*. 2018; 13(9):e0204018–e0204018. <https://doi.org/10.1371/journal.pone.0204018>.
31. Bjerrum L, Sjøgaard J, Hallas J, Kragstrup J. Polypharmacy: Correlations with sex, age and drug regimen: A prescription database study. *Eur J Clin Pharmacol*. 1998; 54(3):197–202. <https://doi.org/10.1007/s002280050445>.

32. Bjerrum L, Rosholm J, Hallas J, Kragstrup J. Methods for estimating the occurrence of polypharmacy by means of a prescription database. *Eur J Clin Pharmacol*. 1997; 53(1):7–11.
<https://doi.org/10.1007/s002280050329>.
33. Blozik E, Rapold R, von Overbeck J, Reich O. Polypharmacy and potentially inappropriate medication in the adult, community-dwelling population in Switzerland. *Drugs Aging*. 2013; 30(7):561–568.
<https://doi.org/10.1007/s40266-013-0073-0>.
34. Broeks SC, Horsdal HT, Ingstrup KG, Gasse C. Psychopharmacological drug utilization patterns in pregnant women with bipolar disorder – A nationwide register-based study. *J Affect Disord*. 2017; 210(Supplement 3):158–165. <https://doi.org/10.1016/j.jad.2016.12.001>.
35. Byrne CJ, Cahir C, Curran C, Bennett K. High-risk prescribing in an Irish primary care population: trends and variation. *Br J Clin Pharmacol*. 2017; 83(12):2821–2830.
<https://doi.org/10.1111/bcp.13373>.
36. Calderón-Larrañaga A, Gimeno-Feliu LA, González-Rubio F, Poblador-Plou B, Lairla-San José M, Abad-Díez JM et al. Polypharmacy patterns: Unravelling systematic associations between prescribed medications. *PLoS One*. 2013; 8(12):e84967–e84967.
<https://doi.org/10.1371/journal.pone.0084967>.
37. Carey IM, De Wilde S, Harris T, Victor C, Richards N, Hilton SR et al. What factors predict potentially inappropriate primary care prescribing in older people? *Drugs Aging*. 2008; 25(8):693–706.
<https://doi.org/10.2165/00002512-200825080-00006>.
38. Caughey G, Barratt J, Shakib S, Kemp-Casey A, Roughead E. Medication use and potentially high-risk prescribing in older patients hospitalized for diabetes: A missed opportunity to improve care? *Diabet Med*. 2017; 34(3):432–439. <https://doi.org/10.1111/dme.13148>.
39. Chang C-M, Wu C-S, Huang Y-W, Chau Y-L, Tsai H-J. Utilization of psychopharmacological treatment among patients with newly diagnosed bipolar disorder from 2001 to 2010. *J Clin Psychopharmacol*. 2016; 36(1):32–44. <https://doi.org/10.1097/JCP.0000000000000440>.
40. Charlton RA, Weil JG, Cunnington MC, Ray S, de Vries CS. Comparing the general practice research database and the UK epilepsy and pregnancy register as tools for postmarketing teratogen surveillance. *Drug Saf*. 2011; 34(2):157–171. <https://doi.org/10.2165/11584970-000000000-00000>.
41. Chiapella LC, Menna JM, Mamprin ME. Assessment of polypharmacy in elderly patients by using data from dispensed medications in community pharmacies: Analysis of results by using different methods of estimation. *Int J Clin Pharm*. 2018; 40(5):987–990. <https://doi.org/10.1007/s11096-018-0663-3>.
42. Cho H, Choi J, Kim Y-S, Son SJ, Lee KS, Hwang H-J et al. Prevalence and predictors of potentially inappropriate prescribing of central nervous system and psychotropic drugs among elderly patients: A national population study in Korea. *Arch Gerontol Geriatr*. 2018; 74:1–8.
<https://doi.org/10.1016/j.archger.2017.08.013>.
43. Constantine RJ, Andel R, Tandon R. Trends in adult antipsychotic polypharmacy: Progress and challenges in Florida's Medicaid program. *Community Ment Health J*. 2010; 46(6):523–530.

<https://doi.org/10.1007/s10597-009-9288-2>.

44. Curkendall SM, Thomas N, Bell KF, Juneau PL, Weiss AJ. Predictors of medication adherence in patients with type 2 diabetes mellitus. *Curr Med Res Opin.* 2013; 29(10):1275–1286. <https://doi.org/10.1185/03007995.2013.821056>.
45. De las Cuevas C, Sanz EJ. Polypharmacy in psychiatric practice in the Canary Islands. *BMC Psychiatry.* 2004; 4(1):1–8. <https://doi.org/10.1186/1471-244X-4-18>.
46. Dolk H, Jentink J, Loane M, Morris J, de Jong–van den Berg LT. Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? *Neurology.* 2008; 71(10):714–722. <https://doi.org/10.1212/01.wnl.0000316194.98475.d8>.
47. Ekstam AK, Elmståhl S. Do fall-risk-increasing drugs have an impact on mortality in older hip fracture patients? A population-based cohort study. *Clin Interv Aging.* 2016; 11:489–496. <https://doi.org/10.2147/CIA.S101832>.
48. Degli Esposti L, Sangiorgi D, Mencacci C, Spina E, Pasina C, Alacqua M et al. Pharmaco-utilisation and related costs of drugs used to treat schizophrenia and bipolar disorder in Italy: The IBIS study. *BMC Psychiatry.* 2014; 14(1):1–9. <https://doi.org/10.1186/s12888-014-0282-z>.
49. Fano V, Chini F, Pezzotti P, Bontempi K. Estimating the prevalence and the determinants of polypharmacy using data from a health administrative database: A comparison of results obtained employing different algorithms. *Adv Pharmacoepidemiol Drug Saf.* 2014; 3(151):2167–1052.10001. <https://doi.org/10.4172/2167-1052.1000151>.
50. Faught E, Helmers S, Thurman D, Kim H, Kalilani L. Patient characteristics and treatment patterns in patients with newly diagnosed epilepsy: A US database analysis. *Epilepsy Behav.* 2018; 85:37–44. <https://doi.org/10.1016/j.yebeh.2018.05.019>.
51. Feng X, Tan X, Riley B, Zheng T, Bias TK, Becker JB et al. Prevalence and geographic variations of polypharmacy among West Virginia Medicaid beneficiaries. *Ann Pharmacother.* 2017; 51(11):981–989. <https://doi.org/10.1177/1060028017717017>.
52. Fereshtehnejad S-M, Johnell K, Eriksdotter M. Anti-dementia drugs and co-medication among patients with Alzheimer’s disease. *Drugs Aging.* 2014; 31(3):215–224. <https://doi.org/10.1007/s40266-014-0154-8>.
53. Fontanella CA, Hiance-Steelesmith DL, Guirgis H, Campo JV. Trends in and predictors of long-term antipsychotic polypharmacy use among Ohio Medicaid patients with schizophrenia, 2008–2014. *Psychiatr Serv.* 2018; 69(9):1015–1020. <https://doi.org/10.1176/appi.ps.201800052>.
54. Franchi C, Tettamanti M, Pasina L, Djignefa CD, Fortino I, Bortolotti A et al. Changes in drug prescribing to Italian community-dwelling elderly people: The EPIFARM–Elderly Project 2000–2010. *Eur J Clin Pharmacol.* 2014; 70(4):437–443. <https://doi.org/10.1007/s00228-013-1621-6>.
55. Franchi C, Cartabia M, Risso P, Mari D, Tettamanti M, Parabiaghi A et al. Geographical differences in the prevalence of chronic polypharmacy in older people: Eleven years of the EPIFARM–Elderly Project. *Eur J Clin Pharmacol.* 2013; 69(7):1477–1483. <https://doi.org/10.1007/s00228-013-1495-7>.

56. Frandsen R, Baandrup L, Kjellberg J, Ibsen R, Jennum P. Increased all-cause mortality with psychotropic medication in Parkinson's disease and controls: A national register-based study. *Parkinsonism Relat Disord*. 2014; 20(11):1124–1128. <https://doi.org/10.1016/j.parkreldis.2014.07.012>.
57. French DD, Campbell R, Spehar A, Cunningham F, Foulis P. Outpatient medications and hip fractures in the US. *Drugs Aging*. 2005; 22(10):877–885. <https://doi.org/10.2165/00002512-200522100-00006>.
58. Gamble J-M, Hall JJ, Marrie TJ, Sadowski CA, Majumdar SR, Eurich DT. Medication transitions and polypharmacy in older adults following acute care. *Ther Clin Risk Manag*. 2014; 10:189–196. <https://doi.org/10.2147/TCRM.S58707>.
59. Gaviria AM, Franco JG, Aguado V, Rico G, Labad J, de Pablo J et al. A non-interventional naturalistic study of the prescription patterns of antipsychotics in patients with schizophrenia from the Spanish Province of Tarragona. *PLoS One*. 2015; 10(10):e0139403–e0139403. <https://doi.org/10.1371/journal.pone.0139403>.
60. Gidal BE, French JA, Grossman P, Le Teuff G. Assessment of potential drug interactions in patients with epilepsy: Impact of age and sex. *Neurology*. 2009; 72(5):419–425. <https://doi.org/10.1212/01.wnl.0000341789.77291.8d>.
61. Gören JL, Meterko M, Williams S, Young GJ, Baker E, Chou C-H et al. Antipsychotic prescribing pathways, polypharmacy, and clozapine use in treatment of schizophrenia. *Psychiatr Serv*. 2013; 64(6):527–533. <https://doi.org/10.1176/appi.ps.002022012>.
62. Guidoni CM, Obreli-Neto PR, Pereira LRL. Pharmacoepidemiologic study of warfarin prescription in a Brazilian tertiary hospital. *J Thromb Thrombolysis*. 2014; 37(4):542–548. <https://doi.org/10.1007/s11239-013-1030-9>.
63. Guilcher SJ, Hogan M-E, Calzavara A, Hitzig SL, Patel T, Packer T et al. Prescription drug claims following a traumatic spinal cord injury for older adults: A retrospective population-based study in Ontario, Canada. *Spinal Cord*. 2018; 56(11):1059–1068. <https://doi.org/10.1038/s41393-018-0174-z>.
64. Haider SI, Johnell K, Weitoft GR, Thorslund M, Fastbom J. The influence of educational level on polypharmacy and inappropriate drug use: A register-based study of more than 600,000 older people. *J Am Geriatr Soc*. 2009; 57(1):62–69. <https://doi.org/10.1111/j.1532-5415.2008.02040.x>.
65. Hamann J, Ruppert A, Auby P, Pugner K, Kissling W. Antipsychotic prescribing patterns in Germany: A retrospective analysis using a large outpatient prescription database. *Int Clin Psychopharmacol*. 2003; 18(4):237–242.
66. Helgadóttir B, Laflamme L, Monárrez-Espino J, Möller J. Medication and fall injury in the elderly population: Do individual demographics, health status and lifestyle matter? *BMC Geriatr*. 2014; 14(1):1–8. <https://doi.org/10.1186/1471-2318-14-92>.
67. Hoffmann F, van den Bussche H, Wiese B, Schön G, Koller D, Eisele M et al. Impact of geriatric comorbidity and polypharmacy on cholinesterase inhibitors prescribing in dementia. *BMC Psychiatry*. 2011; 11(1):1–8. <https://doi.org/10.1186/1471-244X-11-190>.

68. Horváth L, Fekete K, Márton S, Fekete I. Outcome of antiepileptic drug treatment of 1282 patients with epilepsy, their pharmacovigilance reports and concomitant medication on CNS in an East-Hungarian adult database. *J Neurol Sci.* 2016; 369:220–226.
<https://doi.org/10.1016/j.jns.2016.08.039>.
69. Hovstadius B, Petersson G, Hellström L, Ericson L. Trends in inappropriate drug therapy prescription in the elderly in Sweden from 2006 to 2013: Assessment using national indicators. *Drugs Aging.* 2014; 31(5):379–386. <https://doi.org/10.1007/s40266-014-0165-5>.
70. Hovstadius B, Hovstadius K, Åstrand B, Petersson G. Increasing polypharmacy-An individual-based study of the Swedish population 2005-2008. *BMC Clin Pharmacol.* 2010; 10(1):1–8.
<https://doi.org/10.1186/1472-6904-10-16>.
71. Hsieh L-P, Huang C-Y. Antiepileptic drug utilization in Taiwan: Analysis of prescription using National Health Insurance database. *Epilepsy Res.* 2009; 84(1):21–27.
<https://doi.org/10.1016/j.eplepsyres.2008.11.018>.
72. Hung CH, Tang TC, Wang CJ, Liu LK, Peng LN, Chen LK. Impact of living arrangements on clinical outcomes among older patients with dementia or cognitive impairment admitted to the geriatric evaluation and management unit in Taiwan. *Geriatr Gerontol Int.* 2017; 17:44–49.
<https://doi.org/10.1111/ggi.13036>.
73. Ivanova I, Elseviers M, Wettermark B, Schmidt Mende K, Vander Stichele R, Christiaens T. Electronic assessment of cardiovascular potentially inappropriate medications in an administrative population database. *Basic Clin Pharmacol Toxicol.* 2019; 124(1):62–73. <https://doi.org/10.1111/bcpt.13095>.
74. Jaffe AB, Levine J. Antipsychotic medication coprescribing in a large state hospital system. *Pharmacoepidemiol Drug Saf.* 2003; 12(1):41–48. <https://doi.org/10.1002/pds.783>.
75. Kadra G, Stewart R, Shetty H, MacCabe J, Chang CK, Taylor D et al. Long-term antipsychotic polypharmacy prescribing in secondary mental health care and the risk of mortality. *Acta Psychiatr Scand.* 2018; 138(2):123–132. <https://doi.org/10.1111/acps.12906>.
76. Kadra G, Stewart R, Shetty H, MacCabe JH, Chang C-K, Kesserwani J et al. Antipsychotic polypharmacy prescribing and risk of hospital readmission. *Psychopharmacology.* 2018; 235(1):281–289. <https://doi.org/10.1007/s00213-017-4767-6>.
77. Källén B, Robert E, Mastroiacovo P, Martinez-Frias M, Castilla E, Cocchi G. Anticonvulsant drugs and malformations is there a drug specificity? *Eur J Epidemiol.* 1989; 5(1):31–36.
<https://doi.org/10.1007/BF00145041>.
78. Kim H-A, Shin J-Y, Kim M-H, Park B-J. Prevalence and predictors of polypharmacy among Korean elderly. *PLoS One.* 2014; 9(6):e98043–e98043. <https://doi.org/10.1371/journal.pone.0098043>.
79. Kragh A, Elmståhl S, Atroshi I. Older adults' medication use 6 months before and after hip fracture: A population-based cohort study. *J Am Geriatr Soc.* 2011; 59(5):863–868.
<https://doi.org/10.1111/j.1532-5415.2011.03372.x>.
80. Kulaga S, Sheehy O, Zargarzadeh AH, Moussally K, Bérard A. Antiepileptic drug use during pregnancy: Perinatal outcomes. *Seizure.* 2011; 20(9):667–672.

<https://doi.org/10.1016/j.seizure.2011.06.012>.

81. Laflamme L, Monárrez-Espino J, Johnell K, Elling B, Möller J. Type, number or both? A population-based matched case-control study on the risk of fall injuries among older people and number of medications beyond fall-inducing drugs. *PLoS One*. 2015; 10(3):e0123390–e0123390. <https://doi.org/10.1371/journal.pone.0123390>.
82. Lai SW, Lin CH, Liao KF, Su LT, Sung FC, Lin CC. Association between polypharmacy and dementia in older people: A population-based case–control study in Taiwan. *Geriatr Gerontol Int*. 2012; 12(3):491–498. <https://doi.org/10.1111/j.1447-0594.2011.00800.x>.
83. Lai SW, Su LT, Lin CH, Tsai CH, Sung FC, Hsieh DPH. Polypharmacy increases the risk of Parkinson's disease in older people in Taiwan: A population-based study. *Psychogeriatrics*. 2011; 11(3):150–156. <https://doi.org/10.1111/j.1479-8301.2011.00369.x>.
84. Lai S-W, Liao K-F, Liao C-C, Muo C-H, Liu C-S, Sung F-C. Polypharmacy correlates with increased risk for hip fracture in the elderly: A population-based study. *Medicine*. 2010; 89(5):295–299. <https://doi.org/10.1097/MD.0b013e3181f15efc>.
85. Landmark CJ, Fossmark H, Larsson PG, Rytter E, Johannessen SI. Prescription patterns of antiepileptic drugs in patients with epilepsy in a nation-wide population. *Epilepsy Res*. 2011; 95(1-2):51–59. <https://doi.org/10.1016/j.eplepsyres.2011.02.012>.
86. Lin S-K, Tsai Y-T, Lai J-N, Wu C-T. Demographic and medication characteristics of traditional Chinese medicine users among dementia patients in Taiwan: A nationwide database study. *J Ethnopharmacol*. 2015; 161:108–115. <https://doi.org/10.1016/j.jep.2014.12.015>.
87. Lizano-Díez I, Modamio P, López-Calahorra P, Lastra CF, Gilabert-Perramon A, Segú JL et al. Profile, cost and pattern of prescriptions for polymedicated patients in Catalonia, Spain. *BMJ Open*. 2013; 3(12):e003963–e003963. <https://doi.org/10.1136/bmjopen-2013-003963>.
88. Lu W-H, Wen Y-W, Chen L-K, Hsiao F-Y. Effect of polypharmacy, potentially inappropriate medications and anticholinergic burden on clinical outcomes: A retrospective cohort study. *Can Med Assoc J*. 2015; 187(4):E130–E137. <https://doi.org/10.1503/cmaj.141219>.
89. Malm H, Martikainen J, Klaukka T, Neuvonen PJ. Prescription of hazardous drugs during pregnancy. *Drug Saf*. 2004; 27(12):899–908. <https://doi.org/10.2165/00002018-200427120-00006>.
90. McIsaac DI, Wong CA, Bryson GL, van Walraven C. Association of polypharmacy with survival, complications, and healthcare resource use after elective noncardiac surgery: A population-based cohort study. *Anesthesiology*. 2018; 128(6):1140–1150. <https://doi.org/10.1097/ALN.0000000000002124>.
91. McLean G, Hindle JV, Guthrie B, Mercer SW. Co-morbidity and polypharmacy in Parkinson's disease: Insights from a large Scottish primary care database. *BMC Neurol*. 2017; 17(1):1–8. <https://doi.org/10.1186/s12883-017-0904-4>.
92. Mizokami F, Mizuno T, Mori T, Nagamatsu T, Endo H, Hirashita T et al. Clinical medication review tool for polypharmacy: Mapping approach for pharmacotherapeutic classifications. *Geriatr Gerontol Int*. 2017; 17(11):2025–2033. <https://doi.org/10.1111/ggi.13014>.

93. Moisan J, Grégoire J-P. Patterns of discontinuation of atypical antipsychotics in the province of Québec: A retrospective prescription claims database analysis. *Clin Ther.* 2010; 32:S21–S31. <https://doi.org/10.1016/j.clinthera.2010.01.003>.
94. Morin L, Johnell K, Laroche M-L, Fastbom J, Wastesson JW. The epidemiology of polypharmacy in older adults: Register-based prospective cohort study. *Clin Epidemiol.* 2018; 10:289–298. <https://doi.org/10.2147/CLEP.S153458>.
95. Onder G, Bonassi S, Abbatecola AM, Folino-Gallo P, Lapi F, Marchionni N et al. High prevalence of poor quality drug prescribing in older individuals: A nationwide report from the Italian Medicines Agency (AIFA). *J Gerontol A Biol Sci Med Sci.* 2014; 69(4):430–437. <https://doi.org/10.1093/gerona/glt118>.
96. Onishi Y, Hinotsu S, Furukawa TA, Kawakami K. Psychotropic prescription patterns among patients diagnosed with depressive disorder based on claims database in Japan. *Clin Drug Investig.* 2013; 33(8):597–605. <https://doi.org/10.1007/s40261-013-0104-y>.
97. Palmsten K, Huybrechts KF, Michels KB, Williams PL, Mogun H, Setoguchi S et al. Antidepressant use and risk for preeclampsia. *Epidemiology.* 2013; 24(5):682–691. <https://doi.org/10.1097/EDE.0b013e31829e0aaa>.
98. Park H-Y, Park J-W, Song HJ, Sohn HS, Kwon J-W. The association between polypharmacy and dementia: A nested case-control study based on a 12-year longitudinal cohort database in South Korea. *PLoS One.* 2017; 12(1):e0169463–e0169463. <https://doi.org/10.1371/journal.pone.0169463>.
99. Park H-Y, Park J-W, Sohn HS, Kwon J-W. Association of parkinsonism or parkinson disease with polypharmacy in the year preceding diagnosis: A nested case–control study in South Korea. *Drug Saf.* 2017; 40(11):1109–1118. <https://doi.org/10.1007/s40264-017-0559-5>.
100. Pergolizzi Jr JV, Labhsetwar SA, Puenpatom RA, Joo S, Ben-Joseph R, Summers KH. Exposure to potential CYP450 pharmacokinetic drug–drug interactions among osteoarthritis patients: Incremental risk of multiple prescriptions. *Pain Pract.* 2011; 11(4):325–336. <https://doi.org/10.1111/j.1533-2500.2010.00438.x>.
101. Pottegård A, Christensen Rd, Houji A, Christiansen CB, Paulsen MS, Thomsen JL et al. Primary non-adherence in general practice: A Danish register study. *Eur J Clin Pharmacol.* 2014; 70(6):757–763. <https://doi.org/10.1007/s00228-014-1677-y>.
102. Preskorn SH, Silkey B, Shah R, Neff M, Jones TL, Choi J et al. Complexity of medication use in the Veterans Affairs healthcare system: Part I: Outpatient use in relation to age and number of prescribers. *J Psychiatr Pract.* 2005; 11(1):5–15.
103. Rossini M, Viapiana O, Adami S, Idolazzi L, Buda S, Veronesi C et al. Medication use before and after hip fracture: A population-based cohort and case-control study. *Drugs Aging.* 2014; 31(7):547–553. <https://doi.org/10.1007/s40266-014-0184-2>.
104. Ruwald MH, Hansen ML, Lamberts M, Hansen CM, Numé A-K, Vinther M et al. Comparison of incidence, predictors, and the impact of co-morbidity and polypharmacy on the risk of recurrent

- syncope in patients < 85 versus $\geq$ 85 years of age. *Am J Cardiol.* 2013; 112(10):1610–1615.
<https://doi.org/10.1016/j.amjcard.2013.07.041>.
105. Salahudeen MS, Hilmer SN, Nishtala PS. Comparison of anticholinergic risk scales and associations with adverse health outcomes in older people. *J Am Geriatr Soc.* 2015; 63(1):85–90.
<https://doi.org/10.1111/jgs.13206>.
106. Sanglier T, Saragoussi D, Milea D, Auray JP, Valuck RJ, Tournier M. Comparing antidepressant treatment patterns in older and younger adults: A claims database analysis. *J Am Geriatr Soc.* 2011; 59(7):1197–1205. <https://doi.org/10.1111/j.1532-5415.2011.03457.x>.
107. Sinnige J, Braspenning JC, Schellevis FG, Hek K, Stirbu I, Westert GP et al. Inter-practice variation in polypharmacy prevalence amongst older patients in primary care. *Pharmacoepidemiol Drug Saf.* 2016; 25(9):1033–1041. <https://doi.org/10.1002/pds.4016>.
108. Slabaugh SL, Maio V, Templin M, Abouzaid S. Prevalence and risk of polypharmacy among the elderly in an outpatient setting. *Drugs Aging.* 2010; 27(12):1019–1028.
<https://doi.org/10.2165/11584990-000000000-00000>.
109. Subesinghe S, Rutherford AI, Byng-Maddick R, Leanne Hyrich K, Benjamin Galloway J. Recurrent serious infections in patients with rheumatoid arthritis—Results from the British Society for Rheumatology Biologics Register. *Rheumatology.* 2018; 57(4):651–655.
<https://doi.org/10.1093/rheumatology/kex469>.
110. Suokas JT, Suvisaari JM, Haukka J, Korhonen P, Tiihonen J. Description of long-term polypharmacy among schizophrenia outpatients. *Soc Psychiatry Psychiatr Epidemiol.* 2013; 48(4):631–638.
<https://doi.org/10.1007/s00127-012-0586-6>.
111. Targownik LE, Metge C, Roos L, Leung S. The prevalence of and the clinical and demographic characteristics associated with high-intensity proton pump inhibitor use. *Am J Gastroenterol.* 2007; 102(5):942–950.
112. Thunander SL, Hedborg K. Association between prescribed antidepressants and other prescribed drugs differ by gender: A nationwide register-based study in Sweden. *Nord J Psychiatry.* 2019; 73(1):73–79. <https://doi.org/10.1080/08039488.2018.1536766>.
113. Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P. Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. *Arch Gen Psychiatry.* 2012; 69(5):476–483. <https://doi.org/10.1001/archgenpsychiatry.2011.1532>.
114. van de Vorst I, Vaartjes I, Sinneker L, Beks L, Bots M, Koek H. The validity of national hospital discharge register data on dementia: A comparative analysis using clinical data from a university medical centre. *Neth J Med.* 2015; 73(2):69–75.
115. van den Akker M, Vaes B, Goderis G, Van Pottelbergh G, De Burghgraeve T, Henrard S. Trends in multimorbidity and polypharmacy in the Flemish-Belgian population between 2000 and 2015. *PLoS One.* 2019; 14(2):e0212046–e0212046. <https://doi.org/10.1371/journal.pone.0212046>.
116. van den Bemt PM, Chaaouit N, van Lieshout EM, Verhofstad MH. Noncompliance with guidelines on proton pump inhibitor prescription as gastroprotection in hospitalized surgical patients who are

- prescribed NSAIDs. *Eur J Gastroenterol Hepatol*. 2016; 28(8):857–862.
<https://doi.org/10.1097/MEG.0000000000000634>.
117. van Erning F, Zanders M, Kuiper J, van Herk-Sukel M, Maas H, Vingerhoets R et al. Drug dispensings among elderly in the year before colon cancer diagnosis versus matched cancer-free controls. *J Clin Pharm Ther*. 2016; 41(5):538–545. <https://doi.org/10.1111/jcpt.12434>.
118. Veehof L, Stewart R, Haaijer-Ruskamp F, Jong BM-d. The development of polypharmacy. A longitudinal study. *Fam Pract*. 2000; 17(3):261–267. <https://doi.org/10.1093/fampra/17.3.261>.
119. Wang L-J, Chen Y-C, Chen C-K, Chou W-J, Chou M-C. Trends in anxiolytic-hypnotic use and polypharmacy in Taiwan, 2002–2009: A nationwide, population-based survey. *Psychiatr Serv*. 2014; 65(2):208–214. <https://doi.org/10.1176/appi.ps.201300066>.
120. Wastesson JW, Cedazo Minguez A, Fastbom J, Maioli S, Johnell K. The composition of polypharmacy: A register-based study of Swedes aged 75 years and older. *PLoS One*. 2018; 13(3):e0194892–e0194892. <https://doi.org/10.1371/journal.pone.0194892>.
121. Wastesson JW, Morin L, Laroche ML, Johnell K. How chronic is polypharmacy in old age? A longitudinal nationwide cohort study. *J Am Geriatr Soc*. 2019; 67(3):455–462.
<https://doi.org/10.1111/jgs.15717>.
122. Wawruch M, Zatko D, Wimmer G, Luha J, Wimmerova S, Kukumberg P et al. Non-persistence with antiplatelet therapy in elderly patients after a transient ischemic attack. *Aging Clin Exp Res*. 2017; 29(6):1121–1127. <https://doi.org/10.1007/s40520-017-0745-4>.
123. Weissman EM. Antipsychotic prescribing practices in the Veterans Healthcare Administration–New York metropolitan region. *Schizophr Bull*. 2002; 28(1):31–42.
<https://doi.org/10.1093/oxfordjournals.schbul.a006924>.
124. Wong MC, Tam WW, Cheung CS, Tong EL, Sek AC, Cheung N et al. Antihypertensive prescriptions over a 10-year period in a large Chinese population. *Am J Hypertens*. 2013; 26(7):931–938.
<https://doi.org/10.1093/ajh/hpt049>.
125. Xiang Y-T, Dickerson F, Kreyenbuhl J, Ungvari GS, Wang C-Y, Si T-M et al. Common use of antipsychotic polypharmacy in older Asian patients with schizophrenia (2001–2009). *J Clin Psychopharmacol*. 2012; 32(6):809–813. <https://doi.org/10.1097/JCP.0b013e3182726623>.
126. Yeh CC, Lussier EC, Sun Y-T, Lan T-Y, Yu H-Y, Chang T-Y. Antiepileptic drug use among women from the Taiwanese Registry of Epilepsy and Pregnancy: Obstetric complications and fetal malformation outcomes. *PLoS One*. 2017; 12(12):e0189497–e0189497.
<https://doi.org/10.1371/journal.pone.0189497>.
127. Yu N-W, Chen P-J, Tsai H-J, Huang C-W, Chiu Y-W, Tsay W-I et al. Association of benzodiazepine and Z-drug use with the risk of hospitalisation for fall-related injuries among older people: A nationwide nested case–Control study in Taiwan. *BMC Geriatr*. 2017; 17(1):1–9.
<https://doi.org/10.1186/s12877-017-0530-4>.

Figures

Figure 1

Flow Diagram for Study Selection

Figure 2- Prevalence of Polypharmacy Across Included Studies

Figure 2

Prevalence of Polypharmacy Across Included Studies

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