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Perspective

Polypharmacy and Medication Outcome Reporting Bias in Older Patients with COVID-19

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Abstract: Polypharmacy, the use of multiple and potentially inappropriate medications, is an increasing problem among older adults. The global polypharmacy prevalence is 34.6% in patients with COVID-19, and polypharmacy in COVID-19 increases with age. The present paper proposes that polypharmacy in older adults with COVID-19 and other comorbid conditions is linked to the medication outcome reporting bias of randomized controlled trials. Outcome reporting bias can occur when treatment efficacy is reported as relative risk reductions, which overestimates medication benefits and exaggerates disease/illness risk reductions compared to unreported absolute risk reductions. The comorbidities common in patients with COVID-19 include high blood pressure, cardiovascular disease, dementia or cerebrovascular disease, and diabetes. Accordingly, the present paper reassesses the relative and absolute risk reductions in clinical trials from a small convenience sample of antihypertension, statin, anticoagulant, and antihyperglycemic medications. Examples demonstrate a wide gap between reported relative risk reductions and unreported absolute risk reductions in medication clinical trials. This paper concludes that medication clinical trial outcome reporting bias is an important upstream factor that contributes to biased medication benefits and poor clinical decision making, leading to polypharmacy in older adults with COVID-19 and other comorbid conditions. Public health campaigns are urgently needed to educate the public about the link between polypharmacy and medication outcome reporting bias.

Keywords: polypharmacy; outcome reporting bias; potentially inappropriate medications; COVID-19; comorbid conditions; clinical trials; absolute risk reduction; relative risk reduction; number needed to treat

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1. Introduction

Polypharmacy is the use of multiple and potentially inappropriate medications (PIMs) that lack sufficient evidence of benefits and/or increase the risks of adverse drug reactions [1]. The prevalence of polypharmacy is high among older populations [2], which increases health risks in older adults who are already burdened with chronic diseases and infectious illnesses such as COVID-19. Recently, polypharmacy in older adults with cardiovascular disease has almost doubled annual U.S. healthcare expenditures and tripled pharmacy costs [3]. The risk factors for polypharmacy in older adults include inappropriate prescribing by physicians [4], but other contributing factors need to be investigated to address this growing healthcare problem.

A cross-sectional study of seven European cities recently found that polypharmacy is common among relatively healthy older adults and that factors such as being a woman, older age, a greater body mass index, and a greater number of comorbidities were associated with increased odds of polypharmacy [5]. Despite having a high level of medication knowledge, public service workers in France who used "multiple sources of trustworthy information" had increased exposure to polypharmacy, including the overuse of antibiotics and hypnotics that induce sleep [6]. The position statement of the International Group for Reducing Inappropriate Medication Use & Polypharmacy (IGRIMUP) asserts that, when

prescribing without definitive benefits, "less is more" for many older adults [7]. IGRIMUP advocates for "a shift in medical education, research, and diagnostic frameworks, and re-examination of the measures used as quality indicators."

The present paper proposes that polypharmacy in older adults with COVID-19 and other comorbid conditions is linked to poor clinical decisions based on the medication outcome reporting bias of randomized controlled trials (RCTs). The determinants of outcome reporting bias include financial incentives that encourage brand name pharmaceutical manufacturers to omit the reporting of unfavorable outcomes in order to increase the use of their products in clinical practice [8]. Medication outcome reporting bias can occur when the treatment efficacy of an RCT is reported solely as relative risk reductions (RRRs), which overestimate medication benefits and exaggerate disease/illness risk reductions compared to unreported absolute risk reductions (ARRs). For example, a recent study of COVID-19 antiviral medications to reduce the risks of COVID-19 severity, hospitalizations, and deaths noted that the RRRs for paxlovid, remdesivir, and molnupiravir are 88.88%, 86.48%, and 30.41% respectively, but the corresponding ARRs are much lower at 5.73%, 4.58%, and 2.96% [9]. "Publication of complete trial results is important to allow clinicians, consumers, and policy makers to make better informed decisions about healthcare" [10].

Medication outcome reporting bias in RCTs can be reduced by following proper reporting procedures established by the Consolidated Standards of Reporting Trials (CONSORT), which states, "For binary outcomes, presentation of both absolute and relative effect sizes is recommended" [11]. Nevertheless, a review of general medical and public health journals found that only 7% of published articles reported both absolute and relative effects in the full text [12]. The present paper proposes that reducing medication outcome reporting bias can reveal insufficient evidence of benefits, improve clinical decisions by identifying and eliminating PIMs, and reduce polypharmacy in older patients with COVID-19 or other comorbid conditions However, relying on regulatory agencies, pharmaceutical manufacturers, and journals to enforce transparent outcome reporting standards may not be as effective as developing public health campaigns to alert the public directly about overexaggerated and misleading medication benefits disseminated by healthcare providers.

In addition to the aforementioned COVID-19 antivirals, the RRRs and ARRs of RCTs for several other medications commonly used by older adult patients with COVID-19 were selected from a small convenience sample, assessed, and presented as examples in the present paper. The data for RCTs were obtained through Pub Med/MEDLINE, Google, and Google Scholar. An iterative grounded theory literature review method [13], summarized below, was used in researching and writing the present paper, which added rigor and objectivity during the inductive synthesis of new knowledge from relevant findings in the research literature. A grounded theory literature review begins with a purposive selection of articles about the subject under investigation. Unlike a systematic review, however, information may be included from an unlimited number and variety of credible literature sources. Through a comparative analysis, evidence is grouped into concepts, and concepts form themes as a novel explanatory theory begins to emerge. Additional sources and keywords are selected to fill in knowledge gaps as the trail of evidence is followed. For example, keywords for medications to treat hypertension, high cholesterol, heart disease, and diabetes were used to search the research literature. The final novel theory provides insights and new directions for further research on polypharmacy and medication outcome reporting bias in older adults. A limitation of this paper is that it provides the unique perspective of a single author, and the selection, analysis, interpretation, and reporting of findings in the paper may not reflect those of other perspectives.

2. Polypharmacy in Older Adults with COVID-19

Harvard researchers estimated that, during the COVID-19 pandemic, adults over 65 years of age accounted for 80% of hospitalized COVID-19 cases and had a 23 times higher risk of death than people under 65 years [14]. A meta-regression analysis of approximately 190,000 patients with COVID-19 found that the global polypharmacy prevalence is 34.6%

and that polypharmacy increases with age in patients with COVID-19 [15]. The authors also noted that people with polypharmacy have an increased risk and severity of COVID-19, along with more kidney problems, more drug interactions, and an increased mortality.

Researchers found that almost one-third of older adult patients with COVID-19 in a Malaysian population had been prescribed a PIM [16], based on Beers assessment tool criteria [17] and criteria from the Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (STOPP) [18]. Beers 2019 criteria are intended to "improve medication selection; educate clinicians and patients; reduce adverse drug events; and serve as a tool for evaluating quality of care, cost, and patterns of drug use of older adults" [17].

A Canadian population-based cohort study that analyzed data from the Quebec Integrated Chronic Disease Surveillance System found that the use of 5–9 medications by older adults with COVID-19 was associated with a 1.11 relative risk of hospitalizations compared to the use of 0–4 medications, and the relative risks ranged up to 1.62 for 20 or more medications [19]. Deaths among patients with COVID-19 were also associated with a relative risk of 1.13 for 5–9 medications, ranging up to 1.97 for 20 or more. Importantly, the researchers of the cohort study had adjusted for the confounding effects of age and comorbid chronic diseases, suggesting that polypharmacy may impose an iatrogenic burden on patients.

Of relevance, the most common chronic conditions in U.S. adults 65 years and older receiving Medicare benefits in 2010 were high blood pressure (61%), high cholesterol (48%), ischemic heart disease (34%), arthritis (31%), and diabetes (28%) [20]. Similarly, a more recent retrospective cohort study of older Italian adults hospitalized with COVID-19 found that the most common comorbidities included high blood pressure, cardiovascular disease, dementia or cerebrovascular disease, and diabetes [21].

3. RCT Analyses for Medications in Polypharmacy

This section presents a small sample of analyses of data reported in clinical trials for medications to treat the most common chronic conditions in older adults, including older adults with COVID-19. The types of medications analyzed include an antihypertensive for high blood pressure, a statin for high cholesterol, an anticoagulant for ischemic heart disease, and an antihyperglycemic agent for diabetes. A comprehensive review and meta-analysis of RCTs for each type of medication are beyond the scope of the present paper. Accordingly, the analyses in this paper are not representative of the body of literature and are purposively selected from a convenience sample to demonstrate examples of large discrepancies between reported RRRs and unreported ARRs. More research of a wider selection of medications commonly used by older adults is needed to verify the important implications of the analyses in the present paper.

The ARRs in the medication clinical trial analyses presented below are calculated by subtracting the rate of events in the trial's treatment group from the rate of events in the placebo group. The RRRs are calculated by dividing the trial's ARR by the rate of events in the placebo group. The number needed to treat (NNT), the number of people who need to be treated to reduce one event, is calculated as the reciprocal of the ARR, and 95% confidence intervals are calculated using formulas provided elsewhere [22].

Importantly, relative risk measures are useful in uncontrolled observational studies to compare proportions of associations between exposures and disease risks, while absolute risk measures are useful to evaluate the strength of causative relationships in experimentally controlled studies, such as RCTs [23]. Furthermore, RCTs with identical RRRs can have different ARRs depending on differences in the baseline risk or placebo group event rate. For example, an RCT with a 50% RRR will have an ARR of only 1% if the baseline risk is 2%. However, the RRR remains at 50% if the ARR and baseline risk double to 2% and 4%, respectively.

3.1. Antihypertensive for High Blood Pressure

Table 1 is an analysis based on published data from the Systolic Hypertension in the Elderly (SHEP) trial to reduce stroke risk in older adults with chlorthalidone/atenolol/reserpine [24]. The numbers in parentheses are the numbers of participants.

Table 1. Chlorthalidone/atenolol/reserpine compared to placebo based on SHEP trial data to reduce risk of stroke in older adults. Values are unadjusted for participant demographics [24].

Antihypertensive	Stroke	RRR	95% CI	ARR	95% CI	NNT
Chlorthalidone/atenolol/reserpine (2365)	103	35.06%	17.33–48.98%	2.35%	1.05–3.65%	43
Placebo (2371)	159					

According to data from the 2017 Behavioral Risk Factor Surveillance System, analyzed by the U.S. Centers for Disease Control and Prevention, hypertension was self-reported by almost one-third of U.S. adults, and antihypertension medication was used by 63 million people [25]. Antihypertension medications to lower blood pressure, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), β-blockers, calcium channel blockers, and diuretics, are intended to reduce the risk of major cardiovascular events, such as stroke [26,27]. Although systolic hypertension was lowered by antihypertension medications in the SHEP trial (an average decrease of 26/9 mm Hg), the unpublished absolute risk of stroke was reduced by only 2.35% with an NNT of 43 patients compared to the published RRR, which was adjusted by the researchers to 36%. The weak benefits provided by low ARRs in the SHEP trial, and in other RCTs of antihypertension medications, could alter clinical decisions, reassess these medications as PIMs, and reduce polypharmacy in older adult patients with COVID-19 and other comorbid conditions.

3.2. Statin for High Cholesterol

Table 2 analyzes published data based on the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, with primary endpoints of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke using pravastatin [28].

Table 2. Pravastatin compared to placebo based on PROSPER trial data, with secondary endpoint of death from coronary heart disease (CHD) or non-fatal myocardial infarction (MI) in older adults [28].

Statin	CHD Death/Non-Fatal MI	RRR	95% CI	ARR	95% CI	NNT
Pravastatin (2891)	292	17.35%	4.37–28.58%	2.12%	0.50–3.74%	48
Placebo (2913)	356					

An average of 21.35 million prescriptions for statins were purchased annually in the United States between 2002 and 2018, and the average age of users was 63.5 years [29]. The analysis in the present paper showed that pravastatin in the PROSPER trial reduced serum levels of low-density lipoprotein (LDL) cholesterol by 34% in older adults at risk of cardiovascular disease, but the statin had no effect on stroke risk as part of the trial's primary endpoint. A data analysis of the trial's secondary endpoint showed that the RRR for coronary heart disease death or non-fatal myocardial infarction is 17.35%, but the unpublished ARR is only 2.12% with an NNT of 48 patients. Furthermore, new cancers were diagnosed 25% more frequently in the pravastatin group compared to the placebo group. In addition, a systematic review and meta-analysis of 21 randomized clinical trials for statins reported RRRs of 9% for all-cause mortality, 29% for myocardial infarction, and 14% for stroke, with lower ARRs of 0.8% for all-cause mortality, 1.3% for myocardial infarction, and 0.4% for stroke [30]. However, the researchers warned that their pooled ARR results may not be reliable due to the high heterogeneity of the trials included in the analysis. Pooled ARR results in a meta-analysis are only advised if the baseline risks

of the trials are similar [23]. Nevertheless, a comparison of trials in a meta-analysis is not necessary to demonstrate that ARRs are substantially lower and are often unreported compared to RRRs. The most reliable source of information for patients considering a specific medication may be a direct comparison of the medication's RRR and ARR in clinical trials [31].

In their review on statins, Diamond and Ravnskov assessed ARRs in three clinical trials: the JUPITER trial, the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA), and the British Heart Protection Study (HPS) [32]. The aim stated in Diamond and Ravnskov's review was to "illustrate how statistical deception has magnified the unimpressive effects of statin treatment in the medical literature and in the media using RRR." The authors also reported numerous adverse effects from statin use, "including increased rate of cancer, cataracts, diabetes, cognitive impairment and musculoskeletal disorders."

3.3. Anticoagulant for Ischemic Heart Disease

Table 3 is an analysis of published data based on the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) in mostly older adults given warfarin, with a primary endpoint of ischemic stroke [33].

Table 3. Warfarin compared to placebo based on BAATAF trial data to reduce risk of ischemic stroke [33].

Anticoagulant	Ischemic Stroke	RRR	95% CI	ARR	95% CI	NNT
Warfarin (212)	2	84.91%	33.93–96.55%	5.31%	1.77–8.84%	19
Placebo (208)	13					

The use of oral anticoagulants to prevent and treat venous thromboembolism increased by 54% among U.S. Medicare beneficiaries from 2012 to 2017, and oral anticoagulant use increased by 71% in the United Kingdom from 2012 to 2018 [34]. The BAATAF trial of the anticoagulant warfarin to prevent ischemic stroke was terminated early based on the strength of the high RRR (in the mid-80% range), which is recalculated in the present paper as 84.91%. By comparison, the unreported ARR based on the published data from the BAATAF trial is 5.31% with an NNT of 19 patients.

3.4. Antihyperglycemic Agent for Diabetes

Table 4 analyzes published data based on the UK Protective Diabetes Study 34 (UKPDS 34) to test the effects of metformin in patients with overweight newly diagnosed with type II diabetes (mean age of 53 years) against conventional dietary treatment for diabetes [35].

Table 4. Metformin compared to conventional dietary treatment to reduce risk of diabetes-related death [35].

Antihyperglycemic Agent	Diabetes Death	RRR	95% CI	ARR	95% CI	NNT
Metformin (342)	28	38.82%	5.78–60.27%	5.19%	0.80–9.59%	20
Conventional Dietary Treatment (411)	55					

Approximately 553.3 million prescriptions to treat diabetes with the antihyperglycemic agent metformin were dispensed in the United States between 2000 and 2015 [36]. The British UKPDS 34 trial of metformin for diabetes in adults with overweight reported a 42% reduced risk of diabetes-related death compared to the group that received conventional dietary advice. However, the analysis of UKPDS 34 data in the present paper recalculated the RRR for diabetes-related death at just under 39%, and the unreported ARR at a much lower 5.19% with an NNT of 20 patients. Importantly, the UKPDS 34 trial found that metformin added to sulphonyl-urea treatment increased patient deaths.

3.5. Analgesic for Arthritis

Arthritis is a chronic condition common in older adults, but clinical trials of analgesic drugs to treat pain from arthritis generally do not use relative risk measures, relying instead on subjective perceptions of pain-relieving efficacy compared to pain reductions from placebo. Nevertheless, the adverse effects of opioid analgesics can be serious while providing few additional benefits [37], and the use of analgesics should be moderated in older adults to minimize adverse drug events from PIMs.

4. Determinants and Effects of Polypharmacy

The determinants and effects of polypharmacy apply to COVID-19 as well as chronic conditions in older adults. Figure 1 is a directed acyclic graph (DAG) created by the present author to show the relationship of the findings in the present paper. The DAG shows that medication clinical trial reporting bias and unreported ARRs are upstream determinants leading to the downstream effects of biased medication benefits, poor clinical decision making, PIMs, and patient adverse effects from polypharmacy. Obviously, patients, clinicians, public health administrators and policy makers, pharmacists, pharmaceutical companies, researchers, educators, regulators, consumers, and other people involved with prescription medications are all eventually affected by upstream outcome reporting bias in medication RCTs.

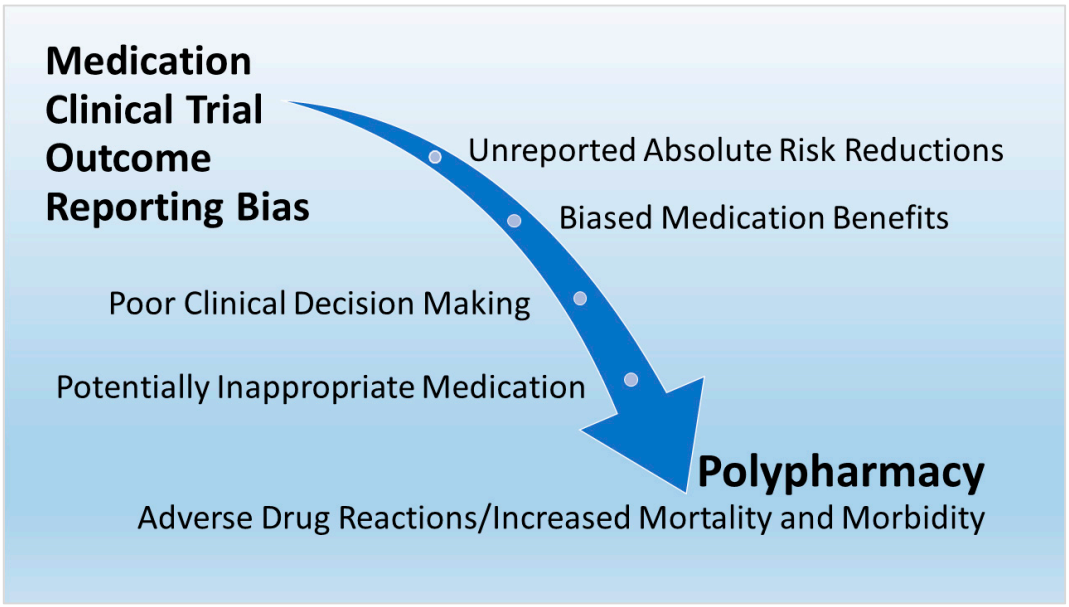

Figure 1. Upstream determinants and downstream effects of polypharmacy.

A recent qualitative study that interviewed pharmacists and general practitioners explored the determinants of polypharmacy, but none of the interviewed participants appeared to challenge the reliability of the reported clinical trial outcomes of the medications that they prescribed and dispensed to patients [38]. An American national action plan to eliminate medication overload confirms that "health care providers do not have clear, accurate, up-to-date information on the harms and benefits of medications when making prescribing decisions", and "clinicians and patients lack critical information and skills they need to appraise the evidence" [39]. The present paper provides critical information from analyses of unreported outcomes in medication clinical trials to help clinicians and patients reappraise evidence and improve medication decision making. Considering the pervasiveness of outcome reporting bias throughout the research literature, much more work lies ahead in establishing preventive measures to reduce outcome reporting bias in published RCTs [40].

The U.S. National Institute on Aging (NIA) notes that scientists are just beginning to explore the new field of deprescribing, and NIA has established a US Deprescribing Research Network to reduce polypharmacy harm in older adults [41]. Future deprescribing research should address outcome reporting bias in RCTs as a key (and often overlooked) upstream factor of polypharmacy. Additionally, "pharmaceutical companies are suspected of putting profits above public interest, using marketing techniques to distort scientific evidence, and actively influencing both physicians and health policy makers" [42].

An editorial in *The Journal of the American Medical Association* emphasized that patients "need to have trust in treatments recommended by clinicians during the time of COVID-19, including taking medications indefinitely for chronic conditions" [43]. The editorial described how patients must be reassured that their best personal needs are considered above the financial interests of others, but the editorial also pointed out that many factors have contributed to the public's declining trust in the healthcare system over the past half century, which has been exacerbated by challenges of the COVID-19 pandemic. The editorial further pointed out that regaining the public's trust requires "a broad, multifaceted approach, including expanding diversity within the scientific community, engaging communities in the design of clinical trials and the interpretation of results, and increasing the number of underrepresented minority groups in clinical trials." Relevant to polypharmacy discussed in the present paper, public health campaigns are urgently needed to disseminate information and educate the public about medication outcome reporting bias as a determinant of the inappropriate use of medications in older adults.

5. Conclusions

Polypharmacy, the use of multiple PIMs, is an increasing problem among older adults. The present paper proposes that polypharmacy in older adults with COVID-19 and other comorbid conditions is linked to medication outcome reporting bias from randomized controlled trials, which overestimates medication benefits and exaggerates disease/illness risk reductions. The common comorbidities in patients with COVID-19 include high blood pressure, cardiovascular disease, dementia or cerebrovascular disease, and diabetes. Assessments of risk reductions in several clinical trials for antihypertension, statin, anticoagulant, and antihyperglycemic medications demonstrated a wide gap between reported relative risk reductions and unreported absolute risk reductions. This paper concludes that medication clinical trial outcome reporting bias is an important upstream factor that contributes to biased benefits and poor clinical decision making, leading to polypharmacy in older adults with COVID-19 and other comorbid conditions. Alerting the public to outcome reporting biases in medication clinical trials is urgently needed to help reduce the inappropriate use of medications and polypharmacy in older adults.

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