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Prevalence of polypharmacy and risk of drug-drug interactions in geriatric patients

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Abstract
Polypharmacy—commonly defined as the concurrent use of five or more medications—has become widespread among older adults due to increasing multimorbidity, advances in disease-specific therapies, and fragmented care delivery. Recent global meta-analyses estimate that roughly one in three to two in five older adults meet commonly used thresholds for polypharmacy, with hyperpolypharmacy (≥10 medications) present in a substantial minority of patients; prevalence varies by region, setting (community, outpatient, inpatient), and study definition. Polypharmacy increases the risk of clinically significant drug–drug interactions (DDIs), adverse drug events (ADEs), hospitalizations, cognitive impairment, falls, and mortality. Mechanistically, age-related pharmacokinetic and pharmacodynamic changes (reduced renal and hepatic clearance, altered body composition, increased sensitivity of target organs) compound risks from complex drug regimens. Observational and pharmacoepidemiologic studies report DDI prevalence estimates among older adults that range widely but consistently identify potentially clinically significant interactions in a notable proportion (often ~10–30% depending on the population and detection method). Key contributors include cardiovascular polytherapy (antiplatelets, anticoagulants, statins, antihypertensives), psychotropics (antidepressants, benzodiazepines, antipsychotics), analgesics (opioids, NSAIDs), and combinations involving enzyme inhibitors/inducers and narrow therapeutic index drugs. Tools such as the AGS Beers Criteria, STOPP/START, and electronic DDI-checkers help identify risky combinations; deprescribing interventions and pharmacist-led medication reconciliation reduce medication burden and some ADEs. However, evidence of sustained clinical benefit at scale remains mixed, and implementation barriers persist. This review synthesizes contemporary prevalence data, underlying mechanisms, clinical consequences, common problematic drug pairs, preventive strategies, and research gaps, and offers recommendations for clinicians and health systems to mitigate DDI risk in older adults.

Keywords: Polypharmacy; elderly; drug–drug interactions; adverse drug events; deprescribing; Beers Criteria

Introduction
Population aging and improved survival from chronic diseases have led to a growing segment of older adults living with multiple chronic health conditions. Multimorbidity—commonly defined as the co-occurrence of two or more chronic diseases—drives prescribing complexity, and many older adults receive therapeutic regimens from multiple specialists. The term *polypharmacy* is used variably in the literature; the most frequently used operational definition is the concurrent use of five or more medications, whereas *hyperpolypharmacy* often denotes use of ten or more medications. Other conceptual approaches classify polypharmacy qualitatively (appropriate vs inappropriate) rather than by count alone, recognizing that some multi-drug regimens are evidence-based and beneficial while others are unnecessary or harmful [1-3].

Epidemiology — prevalence and trends
Recent systematic reviews and meta-analyses show that polypharmacy is common in older adults across settings and regions. A large 2024 meta-analysis that pooled over 57 million individuals reported an overall prevalence of polypharmacy of approximately 39.1% (95% CI 35.5–42.7%) and hyperpolypharmacy of 13.3% (95% CI 10.4–16.5%) among older populations worldwide[1]. Other systematic reviews and global analyses have reported similar

pooled prevalence estimates around the mid-30% range, with marked heterogeneity across countries, healthcare settings, and study methodologies [2, 15]. For example, community-dwelling older adults typically show lower prevalence than hospitalized or long-term care populations, where polypharmacy prevalence often exceeds 50% [2, 11, 15]. Temporal trends in some high-income settings indicate increasing prevalence over the last two decades, attributable to expanded guideline-directed therapies for conditions such as cardiovascular disease, diabetes and osteoporosis [11].

Regional variability is notable. Studies from low- and middle-income countries (LMICs) demonstrate wide ranges—some community studies in India and other settings report prevalence ranging from low single digits to over 50% depending on sampling and definitions used—underscoring differences in access to care, prescribing patterns, and data capture [3, 12]. Age stratification shows higher prevalence with advancing age: prevalence estimates often rise from ~30% among those aged 65–74 to >40–50% in those aged 75 and older in pooled analyses [19].

Why polypharmacy matters in older adults

The clinical importance of polypharmacy lies not only in the numerical burden of medications but in associated risks: adverse drug events (ADEs), drug–drug interactions (DDIs), medication nonadherence, increased risk of falls and fractures, hospitalizations, cognitive decline, and increased mortality. Older adults are physiologically more vulnerable to medication harms because of age-related pharmacokinetic and pharmacodynamic alterations—reduced renal and hepatic clearance, decreased lean body mass and total body water, increased body fat fraction influencing volume of distribution, and altered receptor sensitivity—making dose–response relationships less predictable and increasing the propensity for accumulation and toxicity [9].

Polypharmacy complicates care transitions: incomplete medication reconciliation at admission or discharge is a frequent source of unintended omissions or duplications and contributes to DDI risk. Fragmented care across multiple prescribers and insufficient communication are major drivers of complex regimens [11, 21].

Conceptualizing drug–drug interactions (DDIs)

DDIs occur when one drug modifies the pharmacokinetics (absorption, distribution, metabolism, excretion) or pharmacodynamics (additive, synergistic, or antagonistic effects) of another, altering efficacy or safety. Clinically significant DDIs are those that are likely to cause harm or require therapy change or monitoring. Polypharmacy increases the pairwise number of potential interactions exponentially; with N drugs there are $N(N-1)/2$ possible pair interactions, but clinically meaningful interactions depend on specific mechanisms and patient susceptibility.

Pharmacokinetic interactions commonly involve cytochrome P450 (CYP) enzyme inhibition or induction, P-glycoprotein transport alterations, or competition for renal excretion. Pharmacodynamic interactions can include additive CNS depressant effects (e.g., benzodiazepines + opioids), additive bleeding risk (antiplatelet + anticoagulant), or antagonism (e.g., NSAIDs blunting antihypertensive efficacy) [9, 13].

Prevalence of DDIs and their clinical consequences

Several systematic reviews and population studies estimate that potentially clinically significant DDIs are common among older adults. A systematic review of community-dwelling older adults reported DDI prevalence estimates that varied by study design and detection method, but many studies identified potentially clinically significant interactions in ~10–30% of older adults, with higher figures reported in inpatient and polypharmacy-heavy cohorts [6, 21].

DDIs account for a proportion of ADE-related hospital admissions and emergency department visits; meta-analyses of hospital admission studies attribute a non-trivial fraction of drug-related hospitalizations to DDIs and avoidable medication harms [2, 4].

Beyond immediate ADEs such as bleeding, hypoglycemia, or arrhythmias, chronic outcomes include cognitive impairment and falls, which may be precipitated by sedative combinations or hypotensive additive effects. Multidrug interactions—where three or more agents contribute to a combined effect—further complicate risk prediction and may produce emergent adverse outcomes not easily predicted by pairwise assessments alone [13].

Common high-risk drug classes and interaction examples

Certain classes are repeatedly implicated in harmful DDIs in older adults:

- **Antithrombotics (antiplatelet + anticoagulant)**: combination therapy increases major bleeding risk; DDIs with CYP inhibitors may raise DOAC concentrations.
- **Polypharmacy with psychotropics**: combinations of antidepressants, antipsychotics, benzodiazepines, and opioids increase sedation, respiratory depression, falls, and QT prolongation risk.
- **Cardiovascular polytherapy**: combinations that influence conduction or potassium homeostasis (e.g., antiarrhythmics + certain antibiotics) increase arrhythmia risk.
- **Drugs affecting CYP enzymes**: potent CYP3A4 inhibitors (e.g., certain azole antifungals, macrolide antibiotics) can increase concentrations of statins, calcium channel blockers, or certain anticoagulants, raising toxicity risk.
- **NSAIDs with antihypertensives/antiplatelets**: NSAIDs can blunt antihypertensive effects and increase bleeding/renal risk when combined with antithrombotics [17, 13].

Tools, criteria and risk identification

Clinical tools assist in identifying potentially inappropriate medications (PIMs) and DDIs: the American Geriatrics Society (AGS) Beers Criteria highlights PIMs for older adults and drug–drug or drug–disease interactions to avoid; STOPP/START criteria provide European guidance to stop potentially inappropriate medications and start underused beneficial therapies. Electronic prescribing systems with integrated DDI-checkers, clinical decision support (CDS), and pharmacy-led medication reviews are operational methods to flag interactions [10, 14].

However, tools vary in sensitivity and specificity, and not every flagged interaction is clinically meaningful in a given patient. Decision-making requires contextual clinical judgment considering indications, frailty, life expectancy, and patient preferences.

Deprescribing and interventions

Deprescribing—systematic reduction or cessation of medications that are unnecessary or harmful—has emerged as a pragmatic approach to reduce polypharmacy and DDI risk. Randomized trials and implementation studies of pharmacist-led medication reconciliation, comprehensive geriatric assessment, and structured deprescribing protocols have demonstrated reductions in medication counts and PIMs; some show reductions in falls and improvements in prescribing appropriateness, but consistent evidence of reduced mortality is limited and heterogeneous across studies. Implementation challenges include clinical inertia, prescriber disagreement, fear of withdrawal or disease recurrence, patient resistance, and lack of reimbursement or system support [14].

Rationale and objectives of this review

Given the high and variable prevalence of polypharmacy and the documented contribution of DDIs to ADEs in older adults, clinicians and health systems require a concise synthesis of current prevalence estimates, mechanistic explanations, common high-risk interactions, evidence for interventions, and practical recommendations. This review draws on recent systematic reviews, meta-analyses, and high-quality observational studies to (1) summarize contemporary prevalence estimates of polypharmacy and of potentially clinically significant DDIs in older adults, (2) explain physiologic and pharmacologic mechanisms that increase DDI susceptibility, (3) identify commonly implicated drug classes and interactions, (4) appraise tools and interventions to reduce risk, and (5) highlight research gaps and system-level recommendations to improve medication safety for older patients.

Discussion

Prevalence—interpretation, heterogeneity and drivers

Large pooled analyses show that polypharmacy affects a substantial proportion of older adults globally, with pooled prevalence estimates typically in the 30–40% range for the commonly used threshold of ≥5 medications and hyperpolypharmacy (~≥10 meds) in the low-teens [1, 2, 15]. Heterogeneity is substantial across studies because of differences in definitions (count thresholds, whether OTC and supplements are included), settings (community vs hospital vs long-term care), data sources (prescription claims, medical records, self-report), and populations (age strata, comorbidity burden). For example, hospitalized and nursing home populations have consistently higher prevalence due to acute and chronic disease complexity [11, 12].

Key drivers include: (a) guideline-driven polytherapy for evidence-based control of multiple chronic diseases (e.g., post-MI drug regimens, heart failure therapies), (b) prescribing cascades—where new drugs are prescribed to treat side effects of existing drugs (e.g., anticholinergic-induced constipation treated with laxatives), (c) specialist-driven prescribing without central coordination, (d) poor medication reconciliation at transitions of care, and (e) patient factors such as multiple prescribers, use of complementary and alternative medicines (often unrecorded), and self-medication [3, 5, 12].

Drug–drug interaction prevalence and clinical significance

The reported prevalence of potential DDIs among older adults is wide-ranging—many studies rely on electronic DDI databases that flag potential interactions without clinical adjudication, leading to higher prevalence estimates. Systematic work focusing on potentially clinically significant DDIs (those likely to lead to measurable patient harm or requiring therapy modification) finds prevalence commonly in the range of ~10–30% among older community-dwelling individuals, with higher rates in settings with higher medication counts [6, 21]. Importantly, prevalence depends heavily on the DDI list used (some lists are inclusive, others restrict to high-risk pairs) and on whether OTC and herbal products are considered.

Clinical consequences of DDIs include increased emergency visits and hospital admissions. Reviews estimate that a meaningful fraction of ADE-related admissions in older adults is attributable to interactions or inappropriate prescribing, though precise attributable fractions vary by study and methodologic approach [2, 4]. Examples of severe DDI outcomes include major bleeding with combined antiplatelet/anticoagulant therapy or DOAC interactions, profound sedation and respiratory depression with opioid-benzodiazepine co-prescribing, hypoglycemia with sulfonylurea–CYP inhibitors, and torsades de pointes from combined QT-prolonging agents.

Mechanistic vulnerability of older adults

Aging alters pharmacokinetics (PK) and pharmacodynamics (PD) in ways that amplify interaction consequences. On the PK side, reductions in hepatic blood flow and phase I metabolism, decreased renal function (common as estimated glomerular filtration rate declines with age), and changes in body composition (reduced total body water, increased fat) alter drug distribution and clearance. On the PD side, increased receptor sensitivity (e.g., CNS receptors) and reduced homeostatic reserve mean that smaller pharmacologic effects can produce clinical harm (e.g., orthostatic hypotension). Thus, a mild pharmacokinetic increase in concentration due to enzyme inhibition may lead to disproportionately severe outcomes in older patients [9, 13].

Polypharmacy adds complexity: not only do pairwise interactions matter, but combinations of multiple agents may produce additive or supra-additive pharmacodynamic effects (e.g., multiple CNS depressants) or complex metabolic pathway competition (e.g., multiple CYP substrates and inhibitors), complicating prediction and monitoring [13].

Common problematic drug combinations — clinical examples

Several interactions recur across diverse settings:

1. **Anticoagulant + antiplatelet or interacting co-medications**: Combined antiplatelet and anticoagulant therapy increases major bleeding risk; combinations of DOACs with potent CYP/P-gp inhibitors can lead to supratherapeutic anticoagulant exposures and bleeding.
2. **Opioids + benzodiazepines / gabapentinoids**: Co-prescribing increases risk of respiratory depression, oversedation and falls — a frequent concern in older patients with chronic pain and insomnia/anxiety. Policies and warnings have sought to reduce such combinations, but co-prescribing persists in many populations.

3. **NSAIDs + antihypertensives/diuretics/ACE inhibitors**: NSAIDs can blunt antihypertensive efficacy and precipitate acute kidney injury when combined with ACE inhibitors/ARBs and diuretics (the "triple whammy"), particularly in older patients with reduced renal reserve.
4. **CYP3A4 inhibitors + statins (e.g., simvastatin)**: Potent inhibitors can raise statin levels causing myopathy and rhabdomyolysis; newer guidelines limit high-risk statin/inhibitor combinations.
5. **QT-prolonging combinations**: Concomitant use of multiple drugs that prolong QT interval (certain antipsychotics + macrolide antibiotics + antiemetics) increases torsades risk, especially with hypokalemia or structural heart disease.
6. **Anticholinergic burden**: Additive anticholinergic effects from multiple agents (antihistamines, tricyclic antidepressants, bladder antimuscarinics) increase cognitive impairment, constipation, dry mouth, and urinary retention.

These examples illustrate both pharmacokinetic and pharmacodynamic pathways to harm; importantly, many involve drugs commonly used in older adults, making vigilance essential [9, 13].

Identification and risk stratification strategies

Medication reconciliation at all care transitions (admission, transfer, discharge) is the foundational process to capture a complete medication list (including OTCs, supplements) and identify potentially problematic combinations. Pharmacist-led medication review (comprehensive medication review) using explicit criteria such as Beers, STOPP/START, or clinical judgment increases detection of PIMs and DDIs. Electronic health record (EHR)-integrated clinical decision support can automatically flag DDIs but often suffers from alert fatigue due to overly sensitive thresholds and nonspecific warnings; tailoring alert thresholds for older adults and integrating patient-specific factors (renal function, frailty) can improve usefulness.

Risk stratification approaches combine medication count, presence of high-risk classes (anticoagulants, insulin, opioids), renal/hepatic impairment, and history of falls or prior ADEs. Several validated tools estimate risk for ADEs; however, no single widely adopted global "DPI" (drug interaction risk index) has replaced individual clinical judgment [13, 14].

Interventions to reduce polypharmacy and DDI risk

1. **Deprescribing interventions**: Structured protocols to taper or stop PIMs (e.g., benzodiazepines, long-acting sulfonylureas, antipsychotics used off-label) have shown efficacy in reducing medication counts and PIM prevalence. Some randomized and pragmatic trials demonstrate reduced falls or improved prescribing appropriateness, though evidence for reduced mortality remains inconclusive and heterogeneous [14].
2. **Pharmacist-led services**: Pharmacist involvement in primary care, inpatient teams, or transitional care results in improved medication appropriateness, fewer PIMs, and sometimes fewer readmissions. Collaborative models where pharmacists have deprescribing authority or can propose changes to prescribers are effective.
3. **Clinical decision support (CDS) and EHR integration**: Well-designed CDS that prioritizes high severity interactions and reduces non-actionable alerts can improve prescriber response. Interoperability challenges and the need to include OTC/ herbal medication data remain barriers.
4. **Patient-centred strategies**: Shared decision-making that accounts for patient goals, life expectancy, and quality of life is crucial. Older patients often prioritize symptom control and functional independence; deprescribing plans tailored to these goals are more acceptable and sustainable.
5. **Education and systems interventions**: Provider education, audit and feedback, multidisciplinary case conferences (geriatric review teams), and policy-level interventions (e.g., formulary restrictions, prescribing metrics) help but require sustained investment and measures to prevent under-treatment of conditions.

Effectiveness, limitations, and evidence gaps

While many interventions reduce medication counts and PIMs, translating these process improvements into robust outcome benefits (reduced hospitalizations, mortality) is challenging. Heterogeneity in study populations, intervention intensity, follow-up duration, and outcome definitions explains part of the mixed evidence. Pragmatic barriers—limited time in primary care, competing clinical priorities, fear of disease destabilization when stopping medications—limit broad adoption. Additionally, most DDI-detection systems do not adequately account for patient-specific characteristics like frailty, organ function, or pharmacogenetic variability.

Emerging research priorities include: (a) improved predictive algorithms for clinically meaningful DDIs that integrate laboratory data, genomics, and frailty measures; (b) scalable deprescribing pathways that are acceptable to patients and prescribers; (c) better outcome trials with longer follow-up and patient-centred outcomes; and (d) implementation science to translate promising interventions into routine care with measurement of fidelity and sustainability.

Practical clinical recommendations

For clinicians caring for older adults, pragmatic steps to reduce DDI risk include:

- **Obtain a comprehensive medication list** at each visit, explicitly asking about OTCs, supplements and alternative remedies.
- **Prioritize medication reconciliation** during care transitions and ensure updated lists are communicated to all providers and caregivers.
- **Use evidence-based explicit tools** (AGS Beers Criteria, STOPP/START) as augmenting aids, not as determinants divorced from clinical context[10].
- **Identify high-risk patients** (≥5 medications, recent hospitalization, renal impairment, cognitive impairment) and arrange medication review—preferably pharmacist-led.
- **Apply deprescribing gradually** for nonessential or high-risk medications with monitoring plans and clear documentation of rationale.
- **Customize DDI alerts** where possible; act on high-severity alerts and contextualize others based on patient comorbidity and monitoring capacity.

- **Engage patients and caregivers** in shared decisions about trade-offs, expected benefits, and realistic goals of therapy.
- **Monitor outcomes** after changes—watch for withdrawal effects, disease recurrence, or unmasked symptoms.

Systems-level recommendations

Health systems should invest in structured medication review programs, incentivize pharmacist integration into primary care and transitional care teams, and refine EHR CDS systems to reduce alert fatigue while prioritizing high-risk interactions. Policies that facilitate interoperability of medication data across care settings (community pharmacy, primary care, hospitals) will reduce unintentional duplications and omissions. Training clinicians in deprescribing approaches and embedding prompts in workflows can foster safer prescribing culture.

Notable gaps include standardized definitions of clinically relevant DDIs, better evidence linking specific DDI combinations to patient-centered outcomes in varied settings, and strategies to scale effective deprescribing interventions with proven long-term patient benefits. Research on how polypharmacy interacts with frailty, cognitive impairment, and social determinants in driving ADEs is warranted. Finally, trials of CDS systems that incorporate dynamic patient data (renal function, drug levels, pharmacogenomics) should be prioritized.

Conclusion

Polypharmacy is a prevalent and growing challenge among older adults globally, with recent pooled estimates placing prevalence commonly in the 30–40% range and hyperpolypharmacy affecting a significant minority. Polypharmacy mechanically increases the pool of potential drug–drug interactions; when combined with age-related physiologic vulnerability, diminished homeostatic reserve, and frequent care transitions, the result is a marked increase in risk for adverse drug events, hospitalizations, falls, and cognitive harms. Evidence shows that potentially clinically significant DDIs occur in a noteworthy proportion of older patients—especially in inpatient and multimorbid populations—and that particular classes (antithrombotics, psychotropics, opioids, NSAIDs, CYP-interacting agents) account for many high-risk interactions.

Tools such as the AGS Beers Criteria and STOPP/START can help identify potentially inappropriate medications, and pharmacist-led medication reviews and structured deprescribing interventions can reduce medication burden and some harms.

Clinicians and health systems must balance disease-targeted therapy benefits with the cumulative risks of complex regimens, always centering decisions on the individual patient's goals and vulnerability.

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