REVIEW ARTICLE

WHEN TREATMENT BECOMES THE TRIGGER: POLYPHARMACY AS A HIDDEN CAUSE OF ACUTE CLINICAL DETERIORATION IN INTERNAL MEDICINE

Eneida Hoxha, Ledio Collaku, Somida Kuka, Pandush Pojani, Xhesika Habilaj, Margarita Gjata
Department of Internal Medicine, University Hospital Center "Mother Teresa", Tirana, Albania
Corresponding Email: eneida_hoxha@yahoo.com

ABSTRACT

Polypharmacy is increasingly common among older and multimorbid patients and represents one of the most frequent yet underrecognized challenges in internal medicine. Although traditionally defined as the concurrent use of five or more medications, its clinical relevance extends beyond the number of prescribed drugs. The risk emerges from the complex interaction between medications, comorbidities, organ dysfunction, frailty, acute illness, and changing therapeutic goals. In acute care settings, clinical deterioration is often attributed to disease progression, while the cumulative therapeutic burden may remain overlooked. This narrative clinical review aims to reframe polypharmacy as a hidden and potentially modifiable contributor to acute clinical deterioration in internal medicine. Particular attention is given to drug–drug and drug–disease interactions, renal impairment, hemodynamic vulnerability, electrolyte disturbances, bleeding risk, delirium, falls, and prescribing cascades. High-risk clinical phenotypes include patients with chronic kidney disease, heart failure, atrial fibrillation, diabetes, frailty, anemia, and acute infection. The review also emphasizes medication reconciliation, renal dose adjustment, structured prescribing tools such as STOPP/START and Beers Criteria and deprescribing as essential components of clinical reasoning. Polypharmacy should not be approached merely as a numerical threshold or a pharmacological problem, but as a dynamic clinical syndrome with diagnostic and therapeutic implications. Before escalating treatment or attributing deterioration solely to underlying disease, internists should ask whether treatment itself has become the trigger.

Keywords. Polypharmacy; Internal medicine; Multimorbidity; Deprescribing; Acute clinical deterioration

KUR TRAJTIMI BËHET SHKAKTAR: POLIFARMACIA SI SHKAK I FSHEHUR I PËRKEQËSIMIT AKUT KLINIK NË MJEKËSINË INTERNE.

ABSTRAKT

Polifarmacia është gjithnjë e më e shpeshtë te pacientët e moshuar dhe ata me multimorbiditet, duke përfaqësuar një nga sfidat më të zakonshme, por shpesh të

nënvlerësuara, në mjekësinë interne. Megjithëse tradicionalisht përkufizohet si përdorimi i njëkohshëm i pesë ose më shumë barnave, rëndësia e saj klinike shkon përtej numrit të medikamenteve të përshkruara. Rreziku lind nga ndërveprimi kompleks midis barnave, komorbiditeteve, disfunksionit të organeve, brishtësisë, sëmundjes akute dhe ndryshimit të objektivave terapeutikë. Në kujdesin akut, përkeqësimi klinik shpesh i atribuohet progresionit të sëmundjes, ndërkohë që barra terapeutike kumulative mund të mbetet e pavlerësuar. Ky rishikim narrativ klinik synon ta riformulojë polifarmacinë si një kontribues të fshehur dhe potencialisht të modifikueshëm në përkeqësimin klinik akut në mjekësinë interne. Vëmendje e veçantë i kushtohet ndërveprimeve bar-bar dhe bar-sëmundje, dëmtimit renal, vulnerabilitetit hemodinamik, çrregullimeve elektrolitike, rrezikut për hemorragji, deliriumit, rrëzimeve dhe kaskadave të përshkrimit medikamentoz. Fenotipet klinike me rrezik të lartë përfshijnë pacientët me sëmundje kronike renale, insuficiencë kardiake, fibrilacion atrial, diabet, sindromë të brishtësisë, anemi dhe infeksion akut. Rishikimi thekson gjithashtu rëndësinë e rakordimit të listës së barnave, përshtatjes së dozave sipas funksionit renal, mjeteve të strukturuara të përshkrimit si STOPP/START dhe Kriteret e Beers, si edhe depreskribimit (ndërprerja e strukturuar e barnave të panevojshme) si pjesë thelbësore e arsyetimit klinik. Polifarmacia nuk duhet të trajtohet thjesht si një prag numerik apo problem farmakologjik, por si një sindromë klinike dinamike me implikime diagnostike dhe terapeutike. Përpara përshkallëzimit të trajtimit ose atribuimit të përkeqësimit vetëm të sëmundjes bazë, internistët duhet të pyesin nëse vetë trajtimi është bërë shkaktari.

Fjalë kyç: Polifarmacia; Mjekësia interne; Multimorbiditeti; Reduktimi i barnave; Përkeqësimi
akut klinik.

INTRODUCTION

In internal medicine, acute clinical deterioration is often interpreted as the natural consequence of disease progression, advanced age, or multimorbidity. However, in older and clinically complex patients, deterioration may also result from the cumulative therapeutic burden imposed on a fragile physiological system. This distinction is clinically important because medication-related harm is potentially preventable, frequently underrecognized, and may mimic the progression of underlying disease (1-3).

Polypharmacy is commonly defined as the concurrent use of five or more medications, although definitions vary across studies and clinical settings (3,4). While this numerical threshold is useful for epidemiological purposes, it does not capture the full clinical complexity of medication-related risk. The relevance of polypharmacy depends not only on the number of prescribed drugs, but also on the interaction between medications, comorbidities, renal and hepatic function, frailty, acute illness, and therapeutic goals. Multiple evidence-based therapies may be justified, but they may become harmful when continued without reassessment, duplicated, poorly monitored, or used in combinations that increase the risk of adverse outcomes (3,5).

Patients admitted to internal medicine wards are particularly vulnerable because chronic kidney disease (CKD), heart failure (HF), diabetes mellitus (DM), atrial fibrillation (AF),

chronic obstructive pulmonary disease (COPD), anemia, frailty, recurrent infections, and cognitive impairment frequently coexist. These conditions reduce physiological reserve, alter pharmacokinetics and pharmacodynamics, and increase susceptibility to adverse drug events (2,6). Acute illness may further transform a previously tolerated medication regimen into a source of harm (1,2).

Medication safety has become a major international priority. The World Health Organization's *Medication Without Harm* initiative identifies polypharmacy, high-risk situations, and transitions of care as key areas for reducing avoidable medication-related harm (1,7). Structured tools such as STOPP/START version 3 and the 2023 American Geriatrics Society Beers Criteria provide practical frameworks for identifying potentially inappropriate medications in older adults (8,9).

This narrative clinical review examines polypharmacy as a hidden and potentially modifiable contributor to acute clinical deterioration in internal medicine. By reframing polypharmacy as a dynamic clinical syndrome rather than a simple medication count, internists may better recognize when treatment itself has become the trigger.

Polypharmacy beyond the number of medications

Polypharmacy should not be interpreted solely as the presence of multiple medications. In many patients with multimorbidity, the use of several drugs may be clinically appropriate when each medication has a clear indication, proven benefit, appropriate dosage, acceptable safety profile, and defined monitoring strategy. The central issue is therefore not the number of medications itself, but whether the therapeutic regimen remains coherent, individualized, and periodically reassessed (3).

The distinction between appropriate and inappropriate polypharmacy is therefore essential. Appropriate polypharmacy refers to the use of multiple medications when they are indicated, optimized, monitored, and aligned with the patient's current clinical condition and therapeutic goals. Inappropriate polypharmacy occurs when medications are unnecessary, duplicated, excessively dozed, poorly monitored, harmful in the context of comorbid disease, or no longer consistent with the patient's prognosis and priorities. The World Health Organization emphasizes that medication safety in polypharmacy requires systematic medication review, patient-centered prescribing, multidisciplinary collaboration, and attention to high-risk patients and transitions of care (1).

Medication burden is dynamic. A regimen that is appropriate in stable outpatient conditions may become unsafe during acute illness. Dehydration, infection, reduced oral intake, hypotension, acute kidney injury (AKI), liver dysfunction, or hospitalization may change the risk–benefit balance of previously tolerated medicate

ons. Diuretics, renin–angiotensin–aldosterone system inhibitors, anticoagulants, antidiabetic agents, sedatives, and non-steroidal anti-inflammatory drugs may all become harmful when physiological reserve declines or organ function changes (1,2,10).

Another important concept is the prescribing cascade. This occurs when an adverse drug effect is misinterpreted as a new medical condition, leading to the prescription of an additional medication rather than recognition of the original drug-related problem (11-13). In internal medicine, where nonspecific symptoms such as dizziness, confusion, edema, fatigue,

constipation, hypotension, and renal dysfunction are common, the risk of prescribing cascades is particularly high.

Thus, polypharmacy should be understood as a dynamic clinical condition rather than a fixed medication count. The key question is not only how many medications the patient is taking, but whether one or more of them could be contributing to the current deterioration.

Why internal medicine patients uniquely vulnerable

The internal medicine patient is rarely a single-disease patient. Most patients admitted to internal medicine wards present with overlapping chronic conditions, reduced physiological reserve, and acute stressors that interact with one another. Chronic kidney disease, heart failure, diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disease, anemia, liver dysfunction, frailty, cognitive impairment, and recurrent infections often coexist, creating a clinical context in which medication safety becomes more complex than the evaluation of any single drug. Frailty, multimorbidity, and polypharmacy are closely interrelated and have been associated with higher healthcare use, unscheduled hospital admissions, and mortality (6,14).

This vulnerability is partly explained by altered pharmacokinetics and pharmacodynamics. Ageing and chronic disease are associated with reduced renal and hepatic clearance, altered drug distribution, increased sensitivity to central nervous system-active medications, impaired baroreflexes, and reduced homeostatic reserve. As a result, medications that are appropriate in stable or younger patients may produce exaggerated effects in older and frail individuals. Sedatives may precipitate delirium or falls, antihypertensives may cause orthostatic hypotension, anticholinergic drugs may worsen cognition or urinary retention, and diuretics may contribute to dehydration, electrolyte disorders, or renal dysfunction (2,9).

Renal impairment is one of the most important amplifiers of medication-related harm. Many commonly used drugs, including anticoagulants, antibiotics, antidiabetic agents, analgesics, digoxin, and cardiovascular medications, require dose adjustment or close monitoring in chronic kidney disease. KDIGO 2024 emphasizes drug stewardship in chronic kidney disease, including assessment of kidney function for drug dosing, avoidance of nephrotoxic agents when possible, and adjustment of medication use according to kidney function and clinical context (15). Importantly, renal function is not static during acute illness. Infection, hypovolemia, hypotension, contrast exposure, and nephrotoxic medications may transform stable chronic kidney disease into acute kidney injury, increasing the risk of drug accumulation and toxicity (15).

Heart failure illustrates the same tension between therapeutic benefit and vulnerability. Patients with heart failure often receive combinations of diuretics, renin–angiotensin–aldosterone system inhibitors, beta-blockers, mineralocorticoid receptor antagonists, sodium–glucose cotransporter 2 inhibitors, anticoagulants, and therapies for coexisting diseases. These treatments may be lifesaving in stable conditions, yet during acute illness, they may contribute to hypotension, renal dysfunction, electrolyte abnormalities, bradycardia, dehydration, or symptomatic intolerance. Thus, medication safety in internal medicine cannot be judged drug by drug in isolation; it must be interpreted dynamically within the whole clinical context.

Mechanisms by which treatment becomes the trigger

Polypharmacy contributes to acute deterioration through several overlapping mechanisms. In internal medicine, these mechanisms rarely act independently; they interact with multimorbidity, organ dysfunction, frailty, and acute physiological stress, making medication-related harm difficult to distinguish from disease progression (1-3).

Drug–drug and drug–disease interactions are central mechanisms. Pharmacokinetic interactions may alter absorption, metabolism, protein binding, or elimination, leading to reduced efficacy or toxicity, while pharmacodynamic interactions may produce additive effects such as sedation, hypotension, bleeding, bradycardia, or electrolyte imbalance. Drug–disease interactions are equally important: non-steroidal anti-inflammatory drugs (NSAIDs) may worsen hypertension, heart failure, gastrointestinal bleeding risk, and renal dysfunction; anticholinergic medications may aggravate cognitive impairment, constipation, urinary retention, and delirium; sedatives and hypnotics may increase the risk of falls, respiratory depression, and prolonged confusion. Polypharmacy has been associated with adverse drug events, drug–drug interactions, non-adherence, functional decline, cognitive impairment, falls, and hospitalization (2,16).

Renal and hemodynamic vulnerability represent another major pathway. Chronic kidney disease reduces drug clearance and narrows the therapeutic margin of many medications, while acute illness may rapidly worsen renal function and convert a previously tolerated regimen into a toxic one (15). The combination of renin–angiotensin–aldosterone system inhibitors, diuretics, and NSAIDs, commonly referred to as the “triple whammy”, is a classic example of treatment-related renal vulnerability and has been associated with increased risk of acute kidney injury (17,18). Similarly, antihypertensives, diuretics, vasodilators, beta-blockers, nitrates, and heart failure therapies may be beneficial in stable chronic disease but may contribute to hypotension, syncope, renal hypoperfusion, or falls during sepsis, reduced oral intake, diarrhea, bleeding, or dehydration.

The clinical expressions of harmful polypharmacy are often nonspecific. Electrolyte disturbances, hypoglycemia, bleeding, and neurocognitive effects may present as weakness, confusion, falls, arrhythmia, hypotension, or functional decline. Hyperkalemia, hyponatremia, hypoglycemia, occult bleeding, and delirium may therefore be interpreted as isolated clinical problems unless the medication regimen is reviewed as a potential contributor (2,5,6).

A final and frequently overlooked mechanism is the prescribing cascade. This occurs when an adverse drug effect is misinterpreted as a new clinical condition, prompting the addition of another medication rather than recognition and correction of the original drug-related problem. Calcium-channel blocker-induced edema may lead to unnecessary diuretic therapy; drug-induced dizziness may be interpreted as a neurological disorder; and sedative-related confusion may be treated as worsening dementia or infection. Prescribing cascades are increasingly recognized as contributors to inappropriate polypharmacy, particularly among older adults (11-13).

For the internist, these mechanisms should shift diagnostic reasoning from a single question, that disease explains deterioration, to a broader one: which treatment, interaction, or therapeutic accumulation could be contributing to it?

High-risk clinical phenotypes in internal medicine

Harmful polypharmacy does not occur randomly. In internal medicine, it often emerges from recognizable clinical phenotypes in which multimorbidity, organ dysfunction, acute stressors, and high-risk medication clusters converge. Identifying these patterns may help internists move beyond a passive review of medication lists toward a targeted search for treatment-related harm.

One common phenotype is the patient with chronic kidney disease, hypertension, and heart failure receiving multiple cardiovascular and renal protective therapies. Renin–angiotensin–aldosterone system inhibitors, mineralocorticoid receptor antagonists, sodium–glucose cotransporter 2 inhibitors, and diuretics may provide substantial long-term benefit. However, during dehydration, infection, hypotension, or acute kidney injury, these same therapies may contribute to renal hypoperfusion, hyperkalemia, volume depletion, or symptomatic hypotension. The addition of NSAIDs further increases the risk of acute kidney injury, particularly in patients already receiving a renin–angiotensin system inhibitor and a diuretic (15,17).

Other vulnerable phenotypes include patients with atrial fibrillation, coronary artery disease, chronic kidney disease, or anemia receiving antithrombotic therapy; frail older adults exposed to central nervous system-active or anticholinergic medications; patients with diabetes mellitus and declining renal function treated with insulin or sulfonylureas; patients with chronic pain, chronic kidney disease, heart failure, or hypertension exposed to NSAIDs; and patients undergoing transitions of care, when medications may be duplicated, omitted, or unintentionally restarted. Antithrombotic combinations require particular attention because bleeding risk is amplified by advanced age, renal disease, anemia, prior bleeding, falls, and concomitant NSAID or antiplatelet use (8,19).

These patterns illustrate that harmful polypharmacy often arises from predictable combinations of vulnerable patients, acute stressors, and medication clusters. Recognizing them transforms medication review into a clinically directed diagnostic intervention.

Table 1. High-risk polypharmacy phenotypes in internal medicine

Clinical phenotype	High-risk medication cluster	Potential deterioration	Key clinical action
CKD + hypertension + HF	RAAS inhibitors + diuretics ± MRA ± NSAIDs	AKI, hyperkalemia, hypotension	Check renal function, potassium and volume status; reassess NSAIDs and temporarily unsafe combinations
AF + CAD + CKD/anemia	Anticoagulant + antiplatelet ± NSAID	Bleeding, anemia, hypotension	Reassess indication, dose, duration, renal adjustment and bleeding risk
Frail older adult	Benzodiazepines, hypnotics, opioids, anticholinergics	Delirium, falls, sedation	Reduce CNS-active drugs and anticholinergic burden; consider deprescribing
DM + CKD/acute illness	Insulin or sulfonylureas during reduced intake or renal decline	Hypoglycemia, confusion, falls	Adjust therapy to renal function, oral intake and glycemic trends
Chronic pain + CKD/HF/hypertension	NSAIDs ± RAAS inhibitors ± diuretics	AKI, fluid retention, gastrointestinal bleeding	Avoid or minimize NSAIDs; choose safer analgesia
Admission/discharge transition	Duplicated, omitted, or unintentionally restarted medications	Toxicity, undertreatment, readmission	Perform medication reconciliation at every transition

Abbreviations: AF, atrial fibrillation; AKI, acute kidney injury; CAD, coronary artery disease; CKD, chronic kidney disease; CNS, central nervous system; DM, diabetes mellitus; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NSAIDs, non-steroidal anti-inflammatory drugs; RAAS, renin–angiotensin–aldosterone system.

Polypharmacy in acute internal medicine

In the emergency department and acute medical ward, polypharmacy may become both a diagnostic challenge and a therapeutic hazard. Patients are frequently admitted with nonspecific manifestations such as confusion, falls, hypotension, acute kidney injury, electrolyte disturbances, bleeding, bradycardia, hypoglycemia, or functional decline. These presentations are often attributed to infection, dehydration, ageing, or progression of chronic disease, while medication-related harm may remain insufficiently explored (2,5,6).

Medication history should therefore be considered a diagnostic intervention, not merely an administrative task. A structured review of prescribed drugs, over-the-counter medications, herbal products, recent dose changes, adherence patterns, and newly introduced therapies may reveal clinically relevant triggers. Particular attention should be given to medications initiated shortly before deterioration, drugs requiring renal dose adjustment, combinations associated with hypotension or bleeding, and agents with central nervous system or anticholinergic effects (1,4,20).

Acute illness can rapidly change the safety profile of chronic treatment. Sepsis, vomiting, diarrhea, reduced oral intake, dehydration, hypotension, and acute kidney injury may transform a previously appropriate regimen into a source of harm. During hospitalization, therapeutic plans are often modified by multiple clinicians, increasing the risk of duplication, omission, inappropriate continuation, or unintentional re-prescribing. These risks are especially important at admission and discharge, when medication reconciliation may be incomplete or fragmented. Medication reconciliation has therefore been emphasized as a key safety strategy during transitions of care (4,20).

In acute care, the central question should not be limited to which new diagnosis explains deterioration. It should also include whether one or more medications could be contributing to the current presentation. In acute internal medicine, medication review should be triggered not only by admission or discharge, but by any unexplained deterioration.

Deprescribing and safer prescribing: a structured approach for the internist

Deprescribing should not be understood as simple medication withdrawal, but as a structured process of clinical reasoning aimed at improving safety, reducing harm, and aligning treatment with the patient's current condition, prognosis, and goals of care. It has been defined as the planned and supervised process of dose reduction or discontinuation of medications that may be causing harm or may no longer provide meaningful benefit (10,21). The objective is not to reduce medication numbers indiscriminately, but to identify therapies whose risks exceed their benefits, whose indication is no longer valid, or whose continuation has become unsafe in the context of acute illness, frailty, organ dysfunction, or limited physiological reserve.

Several structured tools may support this process. STOPP/START criteria provide an explicit framework for identifying potentially inappropriate medications and clinically indicated treatments that may be omitted, while the American Geriatrics Society Beers Criteria help recognize medications associated with delirium, falls, cognitive impairment, anticholinergic burden, bleeding risk, and renal dosing concerns in older adults (7,8). Anticholinergic burden is particularly relevant in frail older patients, as it has been associated with delirium and other adverse neurocognitive outcomes (22,23). These tools are useful for standardizing medication review, but they should not be applied mechanically. A medication may be inappropriate in one clinical context, temporarily necessary in another, or safe only under close monitoring.

For the internist, medication review should be structured, repeated, and clinically triggered. First, obtain an accurate medication history, including prescription drugs, over-the-counter medications, herbal products, recent dose changes, adherence patterns, and medications prescribed by different specialists. Second, identify high-risk drugs and combinations,

particularly anticoagulants, antiplatelet agents, diuretics, renin–angiotensin–aldosterone system inhibitors, mineralocorticoid receptor antagonists, insulin, sulfonylureas, NSAIDs, opioids, benzodiazepines, anticholinergics, and drugs requiring renal dose adjustment. Third, evaluate whether one or more medications could plausibly contribute to the current presentation, such as delirium, falls, hypotension, acute kidney injury, electrolyte imbalance, bleeding, hypoglycemia, or functional decline. Finally, decide whether treatment should becontinued, monitored, reduced, substituted, temporarily withheld, or discontinued (16,21).Clear documentation and communication across transitions of care are essential to avoid unintentional re-prescribing, therapeutic omission, or abrupt discontinuation without follow-up (4,20). In this framework, deprescribing is not therapeutic nihilism; it is a safety-oriented intervention that complements evidence-based prescribing. Medication review becomes a proactive diagnostic and therapeutic intervention rather than a retrospective safety exercise.

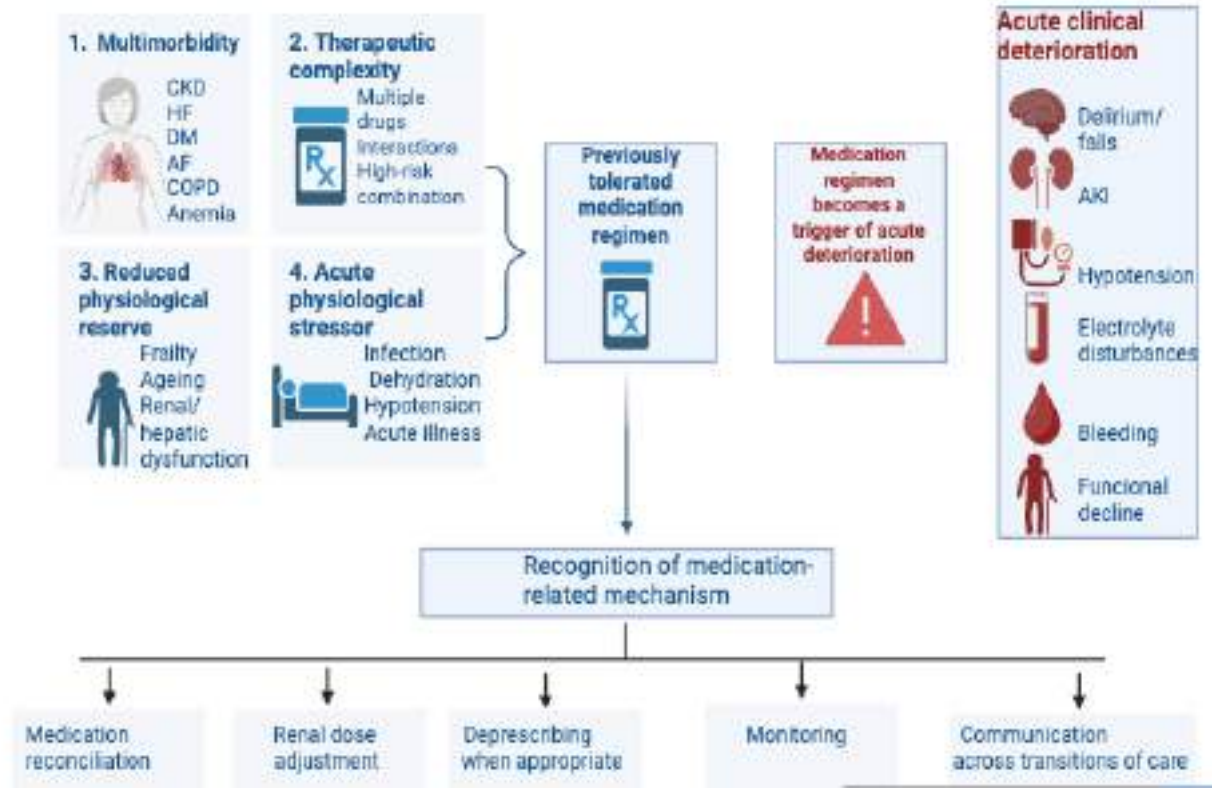

Figure 1. The Internal Medicine Polypharmacy Trigger Model**.** Polypharmacy-related harm in internal medicine emerges from the interaction between multimorbidity, therapeutic complexity, reduced physiological reserve, and acute physiological stressors. These factors may transform a previously tolerated medication regimen into a trigger of acute deterioration. Recognition of medication-related mechanisms should prompt structured medication reconciliation, renal dose adjustment, deprescribing when appropriate, monitoring, and clear communication across transitions of care.

DISCUSSION

Reframing polypharmacy as a clinical syndrome in internal medicine

Polypharmacy is often approached as a medication count, but in internal medicine, its clinical significance is broader and more dynamic. The central question is not simply whether a patient is taking five, eight, or ten medications, but whether the therapeutic regimen remains appropriate in the context of multimorbidity, organ dysfunction, frailty, acute illness, and evolving goals of care. This reframing shift polypharmacy from a pharmacological label to a clinical syndrome with diagnostic and therapeutic implications (1-3,16).

This perspective is particularly relevant in acute care, where medication-related harm may present nonspecific manifestations such as confusion, falls, hypotension, acute kidney injury, electrolyte disturbances, bleeding, anemia, bradycardia, hypoglycemia, or functional decline. These presentations are often attributed to infection, ageing, frailty, or progression of chronic disease, while the contribution of medications may be considered only after other causes have been excluded. Evaluating treatment-related deterioration early, in parallel with other diagnostic hypotheses, may reduce preventable harm and avoid unnecessary therapeutic escalation (1,2,6).

Importantly, this approach does not imply that complex patients should receive fewer medications by default. Many patients with heart failure, chronic kidney disease, diabetes mellitus, atrial fibrillation, or coronary artery disease benefit from multiple evidence-based therapies. The clinical challenge is to distinguish beneficial therapeutic complexity from harmful therapeutic burden. Appropriate polypharmacy requires indication, proportionality, monitoring, and reassessment. Inappropriate polypharmacy emerges when prescriptions accumulate without systematic review, adverse effects are treated as new diseases, organ function changes without dose adjustment, or treatment goals are no longer aligned with clinical reality (3,8,10).

The internist has a central role because internal medicine is the discipline of integration. Unlike single-disease approaches, internal medicine must interpret the whole patient: diseases, drugs, physiology, prognosis, function, and priorities. In this context, medication review is not a secondary administrative task, but a core component of clinical reasoning. Before adding another drug, escalating treatment, or attributing deterioration solely to disease progression, clinicians should ask whether the current therapeutic regimen may be contributing to the problem (24).

Digital tools and clinical decision support systems may help identify interactions, renal dosing problems, duplication, and high-risk combinations; however, they cannot replace clinical judgment. The final decision must remain individualized and anchored in the patient's current condition. Ultimately, reframing polypharmacy as a clinical syndrome does not weaken evidence-based medicine; it strengthens it. It reminds clinicians that evidence must be applied to a person, not only to a disease. In complex internal medicine patients, the safest treatment is not always the longest medication list, but the most coherent one (24).

CONCLUSIONS

Polypharmacy is one of the most frequent yet underrecognized challenges in internal medicine. Although often defined by the number of prescribed medications, its true clinical relevance lies in the interaction between drugs, diseases, organ function, frailty, acute illness, and therapeutic goals. In older and multimorbid patients, treatment itself may become a hidden trigger of acute deterioration, presenting as delirium, falls, hypotension, acute kidney injury, bleeding, electrolyte disorders, hypoglycemia, or functional decline.

For internists, medication review should be considered an essential part of diagnostic reasoning, particularly during acute deterioration, hospitalization, and transitions of care. Structured approaches such as medication reconciliation, renal dose adjustment, STOPP/START criteria, Beers Criteria, and deprescribing can support safer prescribing when applied within an individualized clinical context.

Polypharmacy should therefore be approached not merely as a pharmacological problem, but as a dynamic and potentially modifiable clinical syndrome. Before escalating therapy or attributing deterioration solely to disease progression, clinicians should ask whether treatment itself has become the trigger.

Conflict of interest: The author declares no conflict of interest.

Funding: No specific funding was received for this narrative review.

Author contribution: All authors conceptualized the review, drafted the manuscript, critically revised the content, and approved the final version for submission.

REFERENCES

1. World Health Organization. *Medication Safety in Polypharmacy: Technical Report*. World Health Organization; 2019. Accessed May 16, 2026.
2. Zazzara MB, Palmer K, Vetrano DL, Carfì A, Onder G. Adverse drug reactions in older adults: a narrative review of the literature. *Eur Geriatr Med*. 2021;12(3):463-473. doi:10.1007/s41999-021-00481-9
3. Pazan F, Wehling M. Polypharmacy in older adults: a narrative review of definitions, epidemiology and consequences. *Eur Geriatr Med*. 2021;12(3):443-452. doi:10.1007/s41999-021-00479-3
4. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatr*. 2017;17(1):230. Published 2017 Oct 10. doi:10.1186/s12877-017-0621-2
5. Daltrey JF, Boyd MK, Burholt V, et al. Association of Clinical Indicators of Acute Deterioration and Morbidity and Mortality in the Residential Aged Care Population: A Retrospective Cohort Study of Routinely Collected Health Data. J Eval Clin Pract. 2025;31(3):e70068. doi:10.1111/jep.70068
6. Umegaki H. Frailty, multimorbidity, and polypharmacy: Proposal of the new concept of the geriatric triangle. *Geriatr Gerontol Int*. 2025;25(5):657-662. doi:10.1111/ggi.70046
7. World Health Organization. *Medication Safety in Transitions of Care*. World Health Organization; 2019. Accessed May 16, 2026.

8. O'Mahony D, Cherubini A, Guiteras AR, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 3. *Eur Geriatr Med*. 2023;14(4):625-632. doi:10.1007/s41999-023-00777-y
9. American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2023;71(7):2052-2081. doi:10.1111/jgs.18372
10. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med*. 2015;175(5):827-834. doi:10.1001/jamainternmed.2015.0324
11. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. *BMJ*. 1997;315(7115):1096-1099. doi:10.1136/bmj.315.7115.1096
12. Chen Z, Li Y, Wang J, et al. Research on prescribing cascades: a scoping review. *Front Pharmacol*. 2023;14:1147921. doi:10.3389/fphar.2023.1147921
13. Carollo M, Crisafulli S, Zerio M, et al. Prescribing cascades: an umbrella review and updated systematic review. *Drugs Aging*. 2026;43(5):397-424. doi:10.1007/s40266-026-01295-9
14. Vetrano DL, Palmer K, Marengoni A, et al. Frailty and Multimorbidity: A Systematic Review and Meta-analysis. *J Gerontol A Biol Sci Med Sci*. 2019;74(5):659-666. doi:10.1093/gerona/gly110
15. Kidney Disease: Improving Global Outcomes CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney International.* 2024;105(4S):S117–S314.
16. Kurczewska-Michalak M, Lewek P, Jankowska-Polańska B, et al. Polypharmacy Management in the Older Adults: A Scoping Review of Available Interventions. *Front Pharmacol*. 2021;12:734045. Published 2021 Nov 26. doi:10.3389/fphar.2021.734045
17. Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. *BMJ*. 2013;346:e8525. Published 2013 Jan 8. doi:10.1136/bmj.e8525
18. Loboz KK, Shenfield GM. Drug combinations and impaired renal function -- the 'triple whammy'. *Br J Clin Pharmacol*. 2005;59(2):239-243. doi:10.1111/j.0306-5251.2004.2188.x
19. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024;149(1):e1-e156. doi:10.1161/CIR.0000000000001193
20. Tomlinson J, Cheong VL, Fylan B, et al. Successful care transitions for older people: a systematic review and meta-analysis of the effects of interventions that support medication continuity. *Age Ageing*. 2020;49(4):558-569. doi:10.1093/ageing/afaa002

21. Elbeddini A, Sawhney M, Tayefehchamani Y, et al. Deprescribing for all: a narrative review identifying inappropriate polypharmacy for all ages in hospital settings. *BMJ Open Qual*. 2021;10(3):e001509. doi:10.1136/bmjoq-2021-001509
22. Egberts A, Moreno-Gonzalez R, Alan H, Ziere G, Mattace-Raso FUS. Anticholinergic Drug Burden and Delirium: A Systematic Review. *J Am Med Dir Assoc*. 2021;22(1):65-73.e4. doi:10.1016/j.jamda.2020.04.019
23. Braithwaite E, Todd OM, Atkin A, et al. Interventions for reducing anticholinergic medication burden in older adults-a systematic review and meta-analysis. *Age Ageing*. 2023;52(9):afad176. doi:10.1093/ageing/afad176
24. National Institute for Health and Care Excellence. *Multimorbidity: Clinical Assessment and Management*. NICE Guideline NG56. National Institute for Health and Care Excellence; 2016