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Short communication

Medication triads: mapping high-risk drug combinations in geriatric pharmacotherapy

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Introduction

Traditional pairwise drug-interaction screenings often overlook cumulative risks in geriatric polypharmacy, given the age-related pharmacokinetic and pharmacodynamical changes and vulnerability to multi-drug synergies. Shifting clinical risk assessment to medication clusters is essential for accurate mapping of multi-drug risks in this setting.
The objective of this paper is to evaluate the physiological mechanisms and clinical safety implications behind the use of three high-risk medication triads in older adults.

Materials and methods

The PubMed base was searched for literature published from 2000 to 2026 to evaluate three high-risk medication triads in older adults (aged > 65 years) in hospital and outpatient settings: (1) Renal (ACEIs/ARBs + Diuretics + NSAIDs), (2) Hemorrhagic (Anticoagulants/antiplatelets + SSRIs + NSAIDs), and (3) Arrhythmogenic triad (TMP-SMX + Spironolactone + ACEIs/ARBs). Search terms combined MeSH descriptors and keywords for each drug alongside clinical outcomes (acute kidney injury, hemorrhage, hyperkalemia, arrhythmia). Eligible literature comprised 10 peer-reviewed studies investigating adverse drug-drug interactions.

Discussion

Renal triad: ACEI/ARB + Diuretic + NSAID

Combining ACEIs/ARBs, diuretics, and NSAIDs compromises the glomerular filtration rate (GFR), precipitating pre-renal acute kidney injury (AKI). Diuretics induce hypovolemia, NSAIDs inhibit afferent arteriolar vasodilation, and ACEIs/ARBs block efferent arteriolar vasoconstriction. Observational data of AKI hospitalizations shows that 78% patients were over the age of 70 (Camin et al., 2015). NSAIDs act as easiest precipitant of AKI when added to ACEIs/ARBs and diuretics, across all NSAID types (Akimoto et al., 2023; Kunitsu et al., 2025). Exposure to this triad in elderly hospitalized significantly affects serum creatinine levels and clearance (Loboz & Shenfield, 2004).

Hemorrhagic triad: Anticoagulant/Antiplatelet + SSRI + NSAID:

Synergistic bleeding risk arises when anticoagulants/antiplatelets are prescribed alongside NSAIDs or SSRIs. SSRIs inhibit platelet aggregation by depleting intra-platelet serotonin while NSAIDs suppress thromboxane A2 and compromise gastric mucosal integrity. Concomitant use with anticoagulants/antiplatelets further impairs hemostasis. Large-scale database studies demonstrate that co-prescribing SSRIs or NSAIDs with warfarin significantly increases major systemic hemorrhage

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(Hauta-Aho et al., 2009). Use of SSRIs or NSAIDs with DOACs significantly raises overall and major bleeding risks (Lee et al., 2020). Ultimately, concurrent use of NSAIDs, anticoagulants and antidepressants serves as primary driver of gastrointestinal bleeding, a vulnerability exacerbated in elderly patients (Lee & Katz,2021; Uskur & Kurt 2025).

Arrhythmogenic triad: TMP-SMX + Spironolactone + ACEI/ARB

Co-prescription of TMP-SMX with spironolactone and ACEI/ARB in elderly patients synergistically disrupts renal potassium elimination, introducing a dangerous, under-recognized risk. This combination pairs aldosterone suppression (ACEIs/ARBs) and mineralocorticoid receptor blockade (spironolactone) with trimethoprim's amiloride-like (potassium sparing) effect, the latter independently reducing renal potassium excretion by roughly 40% (Antoniou et al., 2015). Introduction of the full triad predisposes to adverse outcomes such as severe hyperkalemia, bradyarrhythmia, acute kidney injury, and sudden cardiac death. Population-based studies in older adults show that combining TMP-SMX with ACEIs/ARBs or spironolactone increases severe hyperkalemia risk and related hospitalization risk roughly sevenfold and twelvefold, respectively (Antoniou et al., 2010). TMP-SMX exposure in spironolactone users more than doubles the risk of sudden death, likely driven by hyperkalemia-induced arrhythmias (Antoniou et al., 2015).

Conclusion

Evaluating high-risk medication clusters is essential in geriatric care, where adding a third agent often creates a tipping point for severe cumulative harm. Clinical pharmacists must proactively identify these triads and recommend targeted de-prescribing. Removing even a single component markedly reduces preventable adverse events and enhances patient safety in the geriatric setting.

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