

# The Impact of Sex and Gender on Prescribing Cascades in Older Adults

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## Abstract

Prescribing cascades occur when an adverse drug event is misinterpreted as a new medical condition, leading clinicians to prescribe an additional medication. Studies using ICES data have detected a number of common prescribing cascades, particularly among older adult populations. These findings have contributed to international initiatives aimed at optimizing prescribing practices in this population, with the goal of minimizing the risk of drug-related harms. Examining prescribing cascades through a sex and gender lens will better inform guidelines and recommendations tailored to older men and women.

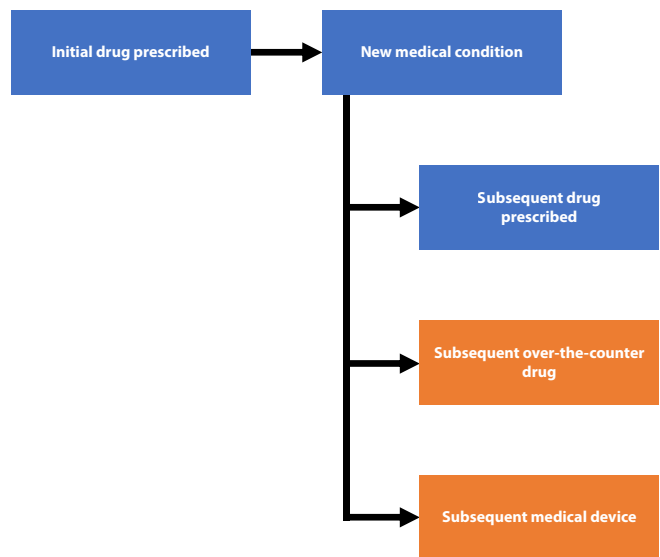
## Background

Polypharmacy is generally defined as the simultaneous use of five or more medications, although there is no consensus on this definition (Masnoon et al. 2017). The practice of prescribing multiple drug therapies can be appropriate in some cases, particularly for older adults who may require different medications to manage complex health conditions (Duerden et al. 2013).

Problematic polypharmacy occurs when multiple medications are prescribed without clear indications or when there is strong evidence for drug interactions and poor adherence to medication (Rochon et al. 2021). Prescribing cascades are part of the concept of inappropriate polypharmacy, when adverse events from one drug therapy are treated with additional medications (Sternberg et al. 2021a).

Prescribing cascades were described in the 1990s by Rochon and Gurwitz (1997), and the concept was revised in a 2017 publication for *The Lancet* to include over-the-counter drug therapies and medical devices (Rochon and Gurwitz 2017) (Figure 1). For over two decades, numerous prescribing cascades have been identified in the medical literature, and the data have underscored the impact on the health and well-being of adults older than 65 years.

**FIGURE 1.**  
Prescribing cascade: Revised



Source: Adapted with permission from Rochon and Gurwitz (2017).

Older adults are more susceptible to drug interactions, are at a higher risk of falls and other adverse events and are more likely to be living in long-term care homes (WHO 2019). These risks are compounded for people with multiple chronic conditions.

Researchers at ICES have used administrative healthcare data to detect several prescribing cascades that are common in older adults: Parkinson’s medications following lithium use (Marras et al. 2016), cholinesterase inhibitors and anticholinergic drugs (Gill et al. 2015), calcium channel blockers and diuretics (Savage et al. 2020), gabapentinoids and diuretics (Read et al. 2021) and sodium glucose cotransporter 2 inhibitors and an antibiotic or antimycotic agent (Lega et al. 2019).

Despite these advances, prescribing cascades remain under-researched in older women compared with older men.

### Why a Sex and Gender Lens?

Discounting sex-based (biological) or gender-based (socio-cultural) differences in prescribing can place women at a greater risk of drug-related harm, because women and men respond differently to drug therapies (Soldin and Mattison 2009). Evidence shows that women experience adverse drug reactions nearly twice as often as men and are also more likely than men to use two or more medications concurrently (Zucker and Prendergast 2020).

More importantly, research on age-related differences among women has been largely overlooked in clinical research (Rochon et al. 2020). Older women are at an increased poly-pharmacy risk, partly due to pharmacokinetic and pharmacodynamic changes in drug absorption, metabolism and elimination that occur as they age (Soldin and Mattison 2009).

Beyond these biological considerations, gender-based socio-cultural factors can influence prescribing behaviours, adherence to medication and access to healthcare. Evidence of prescribing practices show that women are more likely to be prescribed medications for conditions such as depression and sleeping problems (Regitz-Zagrosek 2012). On the other hand, men receive prescriptions more often for physical health-related issues, such as preventive treatment for heart disease (Franconi and Campesi 2014).

For patients in later life stages, research has shown that older men with advanced dementia are more likely to receive aggressive interventions and antibiotics in their final days of life, even when these therapies have been deemed unnecessary and burdensome to patients (Stall et al. 2019). Gender differences also exist at the level of the prescriber. Evidence suggests that female physicians are more conservative prescribers and prescribe at lower doses than male physicians (Mishra et al. 2020).

Finally, socio-economic status can impact a woman's ability to pay for prescription medications as women are less likely to have pensions or drug benefits compared with men. This is largely due to overrepresentation of women in low-wage and part-time jobs (Cheff et al. 2019).

### A Global Problem with Global Solutions

The world's population is aging rapidly. According to the United Nations, by 2050, the number of people aged 65 years or over will be more than twice the number of children under age five (United Nations Department of Economic and Social Affairs 2022).

On September 17, 2022, the World Health Organization identified medication safety as the theme for World Patient Safety Day, reaffirming their "Medication Without Harm" campaign that was launched in 2017 (WHO 2017). The goal of that campaign was to reduce avoidable medication-related harm by 50% globally over five years (WHO 2022).

International initiatives and clinical tools are needed to identify inappropriate prescribing practices and take steps toward prevention of new cascades or deprescribing for older people who are experiencing harms from cascades.

An international and multidisciplinary consortium launched the project "Identifying Key Prescribing Cascades in Older People" (iKASCADE) and the group is working to address drug safety through a sex and gender lens by:

1. creating an international inventory of prescribing cascades that impact older adults;
2. examining the differences in the frequency of prescribing cascades by sex and country within three healthcare settings: the community (including the home), the hospital and long-term care facilities; and
3. exploring the development and impact of prescribing cascades through a sex and gender lens (Sternberg et al. 2021b).

The iKASCADE consortium includes experts on aging, geriatric pharmacotherapy and sex and gender research, and utilizes population health data from six countries: Canada, USA, Ireland, Italy, Belgium and Israel. Using a modified Delphi process, the consortium developed a consensus-based tool called "ThinkCascades," which includes nine clinically important cascades that are examples of potentially inappropriate prescribing affecting older people (Figure 2) (McCarthy et al. 2022).

Clinicians across different healthcare settings can use this list as a tool to guide shared decision making about prescription medications with older patients. The tool can also prompt clinicians to review certain medications for potentially inappropriate prescribing.

### Looking Forward

The transnational and collaborative work that has been accomplished helps to raise awareness about prescribing cascades in older adults and emphasizes the need for effective policy interventions to prevent and manage medication-related harm. Greater awareness can also empower patients and their caregivers to become more active in medication management and to better communicate any concerning side effects that they may be experiencing (Richards 2022).

As part of the research for ThinkCascades, the authors found that there was less consistency among general practitioners and nurses in how prescribing cascades are defined, suggesting that there are different factors that determine their clinical importance (McCarthy et al. 2022). Future research should explore differences in clinicians' gender, country and other socio-demographic characteristics that might impact prescribing practices in general.

**FIGURE 2.**  
Clinically important prescribing cascades affecting older people, by physiological system

Drug A		Side effect		Drug B
<b>Cardiovascular System (n = 2)</b>				
Calcium channel blocker	→	Peripheral edema	→	Diuretic
Diuretic	→	Urinary incontinence	→	Overactive bladder medication
<b>Central Nervous System (n = 4)</b>				
Antipsychotic	→	Extrapyramidal symptoms	→	Antiparkinsonian agent
Benzodiazepine	→	Cognitive impairment	→	Cholinesterase inhibitor or memantine
Benzodiazepine	→	Paradoxical agitation or agitation secondary to withdrawal	→	Antipsychotic
Selective serotonin reuptake inhibitor (SSRI) / Serotonin-norepinephrine reuptake inhibitor (SNRI)	→	Insomnia	→	Sleep agent (e.g., benzodiazepines, benzodiazepine receptor agonists, sedating antidepressants, melatonin)
<b>Musculoskeletal System (n = 1)</b>				
NSAIDs	→	Hypertension		Antihypertensive
<b>Urogenital System (n = 2)</b>				
Urinary anticholinergics		Cognitive impairment		Cholinesterase inhibitor or memantine
Alpha-1 receptor blocker		Orthostatic hypotension, dizziness		Vestibular sedatives (e.g., betahistine, antihistamines, benzodiazepines)

NSAIDs = non-steroidal anti-inflammatory drugs.

Source: Figure reprinted with permission from McCarthy et al. (2022).

Finally, there is a need for interventions and guidelines that target inappropriate prescribing, with the goal to interrupt or reduce prescribing cascades in older adults.

By raising global awareness of the disproportionate burden of medication-related harm on older women and men, we can improve medication safety and support healthier aging worldwide. **HQ**

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