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SAFER PRESCRIBING IN ELDERLY PATIENTS

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Abstract

Within the senior population, the percentage of long-term drug users taking multiple medications is rising with the increasing prevalence of chronic conditions.[1] Patients aged 60–79 years fill an average of 35 prescriptions per year.[2,3] This is estimated to increase to 74 prescriptions per year in patients aged over 80 years, suggesting the risk of adverse drug reactions is high.[2,3]

According to Hamilton and colleagues, over 25% of patients aged 65 years and over admitted with acute illness to a university teaching hospital had an adverse drug event.[4] In 67%, the adverse drug events were deemed to be causal or contributory to the reason for admission. Within this group, 69% of the adverse drug reactions were considered avoidable or potentially avoidable.[4]

With the increasing aging demographic, the need for safer prescribing practices and effective medication management is imperative.

Résumé

Dans la population âgée, le pourcentage de personnes qui prennent plusieurs médicaments pendant une période prolongée augmente avec la prévalence des maladies chroniques[1]. Les patients de 60 à 79 ans reçoivent en moyenne 35 prescriptions chaque année[2,3]. On estime que ce nombre passe à 74 prescriptions par an après 80 ans, ce qui laisse croire que le risque d'effets indésirables est élevé [2,3]. Selon Hamilton et coll. (2011), plus de 25 % des patients de 65 ans et plus admis dans un hôpital universitaire à cause d'une affection aiguë subissaient les effets indésirables de médicaments[4]. Dans 67 % des cas, ces effets indésirables avaient entraîné l'hospitalisation ou y avaient contribué, et de ces effets indésirables, 69 % ont été jugés évitables ou potentiellement évitables[4]. Avec le vieillissement de la population, il est impératif de mettre en place des pratiques de prescription plus sûres et une gestion efficace des médicaments.

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Case

Mr. S is an 89-year-old man, weighing 55 kg (121 lb) and living in a nursing home. His medical history is significant for benign prostatic hypertrophy, atrial fibrillation, chronic kidney disease, hypertension, "indigestion," chronic pain secondary to degenerative disc disease (DDD), bilateral osteoarthritis of the knees, moderate to severe Alzheimer's dementia, and depression/anxiety. There is also a history of worsening falls over the last few months.

Mr. S's medication list is as follows: amitriptyline 25 mg orally (po) every night at bedtime (qhs), amlodipine 2.5 mg po daily, calcium carbonate 2500 mg po daily, docusate sodium 200 mg po daily, domperidone 10 mg po four times a day (qid), donepezil 10 mg po daily, ibuprofen 400 mg po every eight hours (q8h), lansoprazole 30 mg po daily, lorazepam 1 mg po qhs, risedronate 35 mg po weekly, sennosides 2 tablets po qhs as needed (prn), sertraline 50 mg po daily, terazosin 5 mg po daily, acetaminophen with codeine 1–2 tablets po every six hours (q6h) prn, vitamin D 1000 units po daily, and warfarin 3 mg po daily.

Mr. S developed foul-smelling urine. A nurse sent off the urine for culture and sensitivity, which came back positive for gram-negative bacilli. She asked about an antibiotic. Our knee-jerk reaction as health care providers may be to prescribe an antibiotic such as ciprofloxacin. However, this prescribing behaviour raises a number of questions and safety concerns in this elderly patient.

1) Is there really a need to treat the bacteriuria?
2) What considerations are required for drug choice, dosing, and monitoring?

This patient also had an increase in the number of falls over the last two months, thus it was vital that a complete medication review be performed.

1) Which medications may be contributing to this patient's falls?

Table 1. Pharmacokinetic Changes with Aging (5-9)

Pharmacokinetic Phase	Mechanism		Examples
Absorption	Decreased active transport decreases bioavailability for some drugs		↑ Calcium with achlorhydria
	Reduced first-pass metabolism and/or gut wall metabolism (reduced liver mass and blood flow)	Increases bioavailability of some drugs	↑Metoprolol ↑Propranolol ↑Calcium channel blockers ↑Tricyclic antidepressants ↑Morphine
		Decreases the bioavailability of some pro-drugs	↑Clopidogrel ↑Enalapril
Distribution	Increased body fat prolongs half-life of fat-soluble drugs		↑Diazepam ↑Amitriptyline
	Decreased body water increases serum concentration of water-soluble drugs		↑Digoxin ↑Ethanol ↑Levodopa ↑Morphine
Metabolism	Hepatic disease or reduced hepatic volume and blood flow results in reduced oxidative metabolism (reduced metabolism through CYP450) and higher steady-state concentrations of some drugs		↑Diazepam ↑Alprazolam ↑Flurazepam* ↑Metoprolol ↑Phenytoin ↑Theophylline ↑Warfarin
Excretion	Decreased cardiac output (e.g. heart failure) results in less perfusion of kidneys and liver, which reduces elimination of high extraction ratio drugs		↑Imipramine ↑Morphine ↑Propranolol
	Reduced kidney function which reduces elimination of renally excreted drugs or metabolites and higher steady-state concentration of many drugs		↑Digoxin ↑Cephalexin ↑Ciprofloxacin ↑Co-trimoxazole ↑Morphine ↑Meperidine ↑Gabapentin ↑Sotalol ↑Lisinopril ↑Ramipril ↑Metformin

Table 2. Pharmacodynamic Drug Changes Associated with Aging

Drug Class	Pharmacodynamic Change with Aging	Outcome in the Elderly
Antipsychotics e.g. Olanzapine, Haloperidol	Decreased dopamine receptor/neurons	Increased sedation, risk of extrapyramidal symptoms, anticholinergic effects, delirium, orthostatic hypotension, arrhythmias
Benzodiazepines e.g. Diazepam	Increased sensitivity of receptors	Increased sedation at lower doses and lower plasma concentrations, postural sway, falls/fractures
Calcium Channel Blockers e.g. Verapamil	Increased sensitivity to the negative inotropic and vasodilator effects as well as diminished baroreceptor sensitivity	Decreased sensitivity to cardiac conduction effects and greater blood pressure and heart rate effects
Opiates e.g. Morphine	Increased density and affinity of opiate receptors in the brain (proposed explanation)	Higher risk of respiratory depression, increased hallucinations and cognitive impairment may increase risk of falls/fractures
Vitamin K Antagonists e.g. Warfarin	Increased inhibition of synthesis of Vitamin K dependent clotting factors at similar warfarin plasma concentrations in elderly compared to younger patients (mechanism unknown)	Increased INRs for the same dose, risk of bleeding

Medication Appropriateness Index

Questions to ask about each individual medication

1. Is there an indication for the medication?
2. Is the medication effective for the condition?
3. Is the dosage correct?
4. Are the directions correct?
5. Are the directions practical?
6. Are there clinically significant drug-drug interactions?
7. Are there clinically significant drug-disease/condition interactions?
8. Is there unnecessary duplication with other medication(s)?
9. Is the duration of therapy acceptable?
10. Is this medication the least expensive alternative compared to others of equal utility?

Figure 1.
Taken from: Holmes HM, Cox Hayley D ,et al. Reconsidering medication appropriateness for patients late in life. Arch Intern Med 2006;166:605–9.

Pharmacological Changes of Aging

Aging may have a significant effect on prescribing choices and outcomes in older patients. Table 1 summarizes the pharmacokinetic changes of aging ("the course of the drug in the body").[5–9]

The most significant pharmacokinetic change with aging is the decreased elimination of renally cleared drugs. A creatinine clearance must be calculated when prescribing renally eliminated drugs in the elderly (for a CrCl calculator see http://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation/). Because there is decreased muscle mass in the elderly, with a resulting lower production of creatinine, a normal serum creatinine is not a reliable indicator of renal function. For example, Mr. S.'s serum creatinine of 105 μmol/L falls within the normal range of 58–110 μmol/L however, when age and weight are considered, his CrCl is only 33 mL/min, requiring the dose adjustment of many renally eliminated drugs and contraindicating others altogether.

Pharmacodynamic changes ("the clinical effects of the drug on the body") involve altered drug sensitivity in the elderly due to changes in the receptors in various systems. For a review of pharmacodynamic changes pertaining to commonly used drugs, please see Table 2.[9]

Impact of Multiple Medications

Polypharmacy, defined by the number of medications, as well as the appropriateness of each drug for the patient, is a major concern with older people. It is essential to perform regular medication reviews and routine monitoring to make certain the drugs are achieving the expected clinical benefit, without significant adverse effects. Many adverse drug reactions can be avoided by asking the elderly patient what else they are taking, because there may be other prescriptions provided from walk-in clinics, covering MDs, specialists, or emergency room visits. Remembering to ask about other herbal or natural supplements, vitamins, and over-the-counter medications (OTCs) will provide a more complete picture when considering adverse drug reactions and potential drug interactions.

A family physician or interdisciplinary team may choose to use structured tools to identify potentially inappropriate medications

Table 3. Possible Negative Outcomes Secondary to Initiation of Antibiotics in Mr. S.

Potential failure due to local resistance patterns
Contributed to increased resistance rates for fluoroquinolones
Cost of at least $ 10/day
Potential INR increase → increasing risk for bleed → holding warfarin → more INR testing → subtherapeutic INRs → increased risk of stroke
Increased risk for QT prolongation → risk of torsades de pointes
Calcium administration time adjustment
Ten more tablets for nurse to administer and patient to swallow
Increased risk of c. Difficile

INR = International Normalized Ratio.

Table 4. Commonly Prescribed QTc-Prolonging Drugs

Category of Drug	Examples
Anti-infectives	Macrolides, Fluoroquinolones
Anti-arrhythmics	Amiodarone
Antipsychotics	Haloperidol, Phenothiazines, Risperidone, Paliperidone, Quetiapine
Antidepressants	Tricyclic antidepressants, SSRIs
Anti-emetics	Domperidone, Metoclopramide

SSRI = selective serotonin reuptake inhibitors.

(PIMs). The Medication Appropriateness Index (MAI) reviewed in Figure 1 is one such tool that is geared towards individualizing the assessment of a patient's medications.[10] Other methods include Beers Criteria (2012) and the STOPP/START, depicted on Table 2 of http://www.canadiangeriatrics.ca/default/index.cfm/linkservid/BE34AED2-D5B7-B425-A21527A9E6498A4D/showMeta/0/,[11,12] which can be used as a guideline to start, optimize, or stop drugs in elderly patients. Updated Beers Criteria is provided as a free pocket card on the American Geriatric Society website: http://www.americangeriatrics.org/files/documents/beers/2012BeersCriteria_JAGS.pdf

A patient's adherence should receive particular attention, as "Drugs don't work in patients who don't take them."[13] In a study of elderly patients with at least two or more chronic conditions, mean adherence with prescription drugs taken once or twice daily was 72%, whereas those taken 3–4 times daily had a mean adherence rate of just 54%.[14] Studies show that risk of non-adherence is greatest with poor medication knowledge, three or more drugs, living alone, prescribing by more than one physician, and pre-dementia symptoms.[15]

Focusing on limiting the medications to those making a positive difference, minimizing the frequency, improving medication knowledge, and scanning the medications at each visit—not just for what's there, but also what's not there (as per the START criteria) may prevent non-adherence and the resulting adverse drug reactions. Other key points to improve adherence include considering the cost of medication and available coverage when prescribing, encouraging the use of compliance aids (e.g., dosettes, blister packs, and downloadable apps) when appropriate, and providing clear and specific instructions rather than "as directed." Following up on a recently prescribed medication on the next visit helps to instill the importance of taking the medications appropriately. It also provides an opportunity to correct misunderstandings and make any necessary adjustments.

We are all guilty of participating in prescribing cascades (see Table 4 of Kwan and Farrell's article) http://www.canadiangeriatrics.ca/default/index.cfm/linkservid/BE34AED2-D5B7-B425-A21527A9E6498A4D/showMeta/0/). It is easy to misinterpret an adverse reaction from a medication as a new medical condition, resulting in the prescription of another drug, possibly leading to further adverse effects. For example, a patient with mild to moderate dementia started on a cholinesterase inhibitor (e.g., donepezil) presents to the family physician with urinary incontinence caused by the cholinergic effect of the cholinesterase inhibitor and then is prescribed oxybutynin (an anticholinergic that will block the effect of the cholinesterase inhibitor). The patient then returns with worsening cognition, dizziness, and falls, and the cascade continues. Another example is the use of a nonsteroidal anti-inflammatory drug (NSAID; could be OTC), such as ibuprofen, which results in hypertension. Amlodipine is then prescribed, followed by furosemide for peripheral edema, followed by potassium supplementation. This example highlights the importance of asking about OTCs during medication histories.

Knowledge of which common medications contribute to which common geriatric signs and symptoms can be very helpful. Examples worth highlighting include falls, which can be secondary to the use of sedatives, anticholinergics, and antidepressants. Cognitive impairment can be the result of drug effects from benzodiazepines, antihistamines, or tricyclic antidepressants (See article by Dyks and Sadowski in this edition (p.23). Incontinence could be linked to alpha-blocker use, antidepressants, benzodiazepines, or diuretics. For further examples, see Table 3 in Kwan and Ferrell. http://www.canadiangeriatrics.ca/default/index.cfm/linkservid/BE34AED2-D5B7-B425-A21527A9E6498A4D/showMeta/0/

The important take-home message is that patients with new symptoms require a review of their medications for adverse effects before any new treatment is initiated. Ask yourself, "Can this new symptom be explained by any medications and, if so, can that medication be decreased or discontinued?" Taking a good medication history and doing regular medication reviews is vital and highlights the

Reassessing patients on proton pump inhibitors (PPIs)

Questions to think about when reassessing patients on PPIs:

Why is the patient on a PPI?

How long has the patient been on a PPI?

Is it causing any drug interactions?

Can the dose of the PPI be reduced?

Do vitamin B12 (recommended in elderly and those with insufficient dietary intake*) and magnesium levels need to be checked?

Would the patient be appropriate for tapering the dose and/or a discontinuation trial?

Figure 2.

importance of working within an interdisciplinary team. Managing frail and elderly patients can be overwhelming, and recruiting the expertise of a pharmacist (e.g., team pharmacists or a patient's community pharmacist) for medication history, drug interaction, adverse reaction assessment, and assistance with adherence can be very helpful.

Optimization Exercise

Review Mr. S's medication list, identify potential problem areas, and "optimize" his medications. Next, review the medication list again, but this time, apply the Medication Appropriateness Index (Figure 1) to each medication. You will notice how this structured review, while labour-intensive, results in many more issues being identified. (See **Table 2** of Kwan and Ferrell. http://www.canadiangeriatrics.ca/default/index.cfm/linkservid/BE34AED2-D5B7-B425-A21527A9E6498A4D/showMeta/0/) The Beers Criteria or STOPP/START can also be used to ensure that potentially harmful drugs are avoided and that potentially helpful medications have not been missed. Consider how you can leverage your interdisciplinary team members to assist you in optimizing his medications, so that this can be achieved in your everyday practice.

UTI: Diagnosing a symptomatic urinary tract infection in the elderly can be challenging. A helpful source for practical guidelines is provided by McGeer and colleagues (see http://ac.els-cdn.com/0196655391901545/1-s2.0-0196655391901545-main.pdf?_tid=c68ab57e-1430-11e4-a973-00000aacb360&acdnat=1406316225_0e09233ad0e78756c70a8a891d60074d.16) As Mr. S does not have an indwelling urinary catheter, at least three signs and symptoms are suggested for the diagnosis of UTI, of which foul-smelling urine is just one. Mr. S does not have any other new urinary symptoms (frequency and occasional urinary incontinence due to BPH has not changed), and no new non-specific symptoms, such as worsened confusion or acute change in function, have been identified. You should therefore not initiate antibiotics, but encourage fluids and monitor.

Table 3 summarizes the possible negative impact of antibiotics for asymptomatic bacteriuria in Mr. S.

Falls: With respect to Mr. S's risk of falls, a medication review reveals many medications that may be contributing to his falls. These include lorazepam, amitriptyline, sertraline, amlodipine, terazosin, and codeine. For a detailed review of medications that cause falls, please see the article by Dyks and Sadowski in this edition (p. 23) There is a useful algorithm for a trial of discontinuation of medications found in Lemay and Dalziel (see Figure 3. at http://www.canadiangeriatrics.ca/default/index.cfm/linkservid/86F27E6A-B4AE-C03B-7BC1839EF84D70A1/showMeta/0.[2] When we reflect on Mr. S's medication list, we see that the relatively high dose lorazepam 1mg po qhs in this small elderly gentleman should be considered for tapering with eventual discontinuation (especially given the dementia and history of falls). Further recommendations on psychotropic weaning are provided by Hogan and others.[17] Terazosin, which causes dizziness (10–20%) and orthostatic hypotension (1–4%), could be replaced with a 5-alpha reductase inhibitor such as dutasteride (incidence of dizziness < 1%). Amitriptyline is a major cause of orthostatic hypotension and falls and, upon checking his postural blood pressures, you may consider weaning and then discontinuing it. This would also relieve concern regarding the use of amitriptyline (anticholinergic) with donepezil (cholinesterase inhibitor), where the opposing effects might result in decreased therapeutic outcomes, despite the continued risk of adverse effects.

Mr. S is taking sertraline, amitriptyline, and domperidone; and treating the asymptomatic bacteriuria might have resulted in the addition of a fluoroquinolone. An EKG should be considered whenever QTc prolonging drugs such as those listed above are used. The possibility that Mr. S is falling due to presyncope or syncope related to a domperidone-induced arrhythmia should be evaluated. As per the Health Canada Black box warning http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2012/15857a-eng.php, his risk of domperidone-induced arrhythmia is increased due to his being aged over 60 years old and his use of domperidone exceeding 30 mg per day.[18] Mr. S's chronic kidney disease will increase his elimination half-life of domperidone from 7 hours to approximately 20 hours, and his intake of the CYP 3A4 inhibitor sertraline will further increase the domperidone level. In addition, Mr. S is on three other QTc-prolonging drugs! See Table 4 for further examples of QTc- prolonging drugs. This is a perfect example of how complicated

medication management can be in elderly patients and the need to critically evaluate medication regimens, the appropriateness of which are influenced by so many factors.

Chronic kidney disease in this patient also raises concern regarding his use of ibuprofen. NSAIDs may compromise existing renal function. Did Mr. S have a prescribing cascade with the pain resulting in OTC ibuprofen, causing indigestion, resulting in the prescription for lansoprazole? An NSAID is also not recommended in a patient taking warfarin. Could you instead switch the warfarin to a new oral anticoagulant and avoid the INR testing? Not in this patient, who has a borderline CrCl of 33 mL/min!

Now that amitriptyline and ibuprofen are discontinued, you will need something for his chronic pain. Scheduled acetaminophen, such as the long-acting arthritis preparation at 650–1300 mg q8h is a much safer suggestion (ideally keeping it to 2–3 g/day due to the renal function). Tylenol3 should be decreased and, if possible, discontinued, to maintain acceptable daily acetaminophen exposure. Codeine is also not a favourable drug in elderly patients as it has a higher incidence of sedation, nausea, and constipation.[2] Consider close monitoring of the INR over the next 2–3 weeks.

In addition, diclofenac or capsaicin are available in several different topical preparations. They may be applied for temporary symptomatic relief of pain associated with acute localized muscle or joint injuries, as an adjunct. Zupcapsaicin is a derivative of capsaicin, available as a cream, used for relief of severe pain in adults with osteoarthritis of the knee (not controlled with oral COX-2 inhibitors or NSAIDs alone). These topicals should be avoided in patients with hypersensitivity and areas of irritated or broken skin barrier. In addition, they should not be used where other topical medications are used and not on the face or genitals.

Hydromorphone (safer than morphine in poor kidney function and not a pro-drug like codeine) can be used if Mr. S needs stronger pain management, along with a bowel regimen, which should always accompany prescriptions for opiates.

In the current literature, docusate sodium has not been shown to be effective and is adding to the patient's pill count, decreasing his chances of adhering to his other medications. Lactulose and polyethylene glycol (e.g., RestoraLAX®, Lax-A-Day®) are safe and effective osmotic agents. Sennosides or bisacodyl are safe and effective peristaltic agents, which can be used in elderly patients. Milk of magnesia should be avoided in any patient with a CrCl approaching 30 mL/min due to risk of magnesium accumulation.

Patients on long-term use of proton pump inhibitors (PPIs) should be reassessed at least every 6–12 months, and where a clear prescribing indication no longer exists, a discontinuation trial should be considered as per BEERs and STOPP criteria.[11] Abrupt discontinuation of chronic PPI use can provoke rebound symptoms, and tapering by 50% weekly in those on higher doses or long-term use should be considered. Not only will discontinuation assist with medication adherence pill counts and costs, but also PPI's are increasingly reported to have significant adverse drug reactions. Patients receiving a PPI are four times more likely to have clostridium difficile-associated disease (CDAD).[19] With a more alkaline environment, certain nutrients (e.g., magnesium and vitamin B12)[19] and drugs (e.g., iron and bisphosphonates) may not be optimally absorbed.[8] As well, PPIs may inhibit the cytochrome P450 system, affecting the metabolism of certain drugs. An example of this is clopidrogel, which is a pro-drug. It needs to be metabolized by CYP2C19 to become active. PPIs inhibit this enzyme to varying degrees (most significantly, omeprazole), reducing the antiplatelet effects and increasing cardiovascular risk. Pantoprazole, which minimally inhibits CYP2C19, is the safer of the PPIs to be used with clopidogrel. Please refer to Figure 2 for a list of questions to think about when reassessing patients taking PPIs.

Reassessment of risedronate in Mr. S is warranted, as it is contraindicated at a CrCl of less than 30 mL/min, and any illness or dehydration could easily worsen his renal function. Proton pump inhibitors (and H2 blockers) should not be used with the delayed-release form of risedronate, due to premature dissolution of the delayed release tablet and a 60% increase in risedronate concentration. Consider switching to the regular release risedronate given on an empty stomach if the proton pump inhibitor cannot be discontinued. Denosumab may also be considered in this patient with a low CrCl. Denosumab is administered subcutaneously every six months. Any patient on this drug with CrCl < 20 mL/min should be monitored for increased risk of hypocalcemia. In Ontario, however, denosumab is not covered for men and would require a review of this patient's affordability or private insurance coverage.

Patients should be counselled to avoid calcium doses in excess of 500 mg (elemental) due to limits on single-dose absorption. Finally, remind Mr. S to avoid grapefruit and grapefruit juice. This is important information for those patients taking medications metabolized by CYP3A4, including selected statins, amlodipine, sertraline, and domperidone, where drug levels can also be increased thereby increasing the risk of adverse drug reactions.

Conclusion

This paper has used Mr. S's medication list to highlight the complexity, challenges, and satisfaction of medication review in frail elderly persons. We would like to leave you with one last thought, in fact a famous quote by our predecessor Paracelsus (toxicologist, 1493—1541): "All drugs are poisons; there is none that is not a poison. The right dose differentiates a poison from a remedy." For every one of our elderly patients, we must periodically reassess the role of each drug, optimize their dosing to the minimally effective dose, and ensure the benefits outweigh the potential harms

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