HOW NOT TO HARM YOUR PATIENTS: TIPS ON PRESCRIBING FOR THE ELDERLY

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Polypharmacy increases the risk of adverse drug reactions (ADRs) in the elderly.[1] It has been estimated that by the year 2041, 25% of the Canadian population will be over the age of 65 years, although more recent census data suggest that this may happen sooner.[2] The fact that patients aged 60–79 years fill an average of 35 prescriptions per year, which is estimated to increase to 74 per year in patients over the age of 80 years, suggests the risk of ADRs is high.[3] Indeed, the risk is underestimated given that 68% of older adults also use over-the-counter (OTC) medications.[4] A study looking at ADRs in the community determined that 95% of ADRs are predictable and that 28% are preventable.[5] Notable ADRs in the elderly include falls, cognitive impairment, constipation, insomnia, and mortality.

Clinicians should attempt to optimize medication therapy while aiming to improve outcomes and reduce ADRs. The process of conducting periodic medication reviews is a practical way of achieving this goal and can lead to discontinuing inappropriate medications, changing medications to those documented to be safer in older adults, reducing dosages, or employing additional therapy.

New signs and symptoms should be investigated before being treated, and ADRs should be included in the differential diagnosis. This may lead to the discovery of an ADR and avoid a harmful and unnecessary prescribing cascade (Figure 1).

The following patient case highlights some commonly prescribed medications in elderly patients and the risks associated with these drugs. The resolution of the case follows a discussion of potentially harmful medications in this population.

Case Report

Ms. P was an 81-year-old woman admitted to hospital with a right hip fracture. She presented with a 2-week history of progressive left leg edema, pain, and erythema that contributed to instability and resulted in a fall while walking to the bathroom at night. Her past medical history included hypertension, atrial fibrillation (AF), renal insufficiency, osteoporosis, osteoarthritis, and urinary frequency.

Her medications included acetylsalicylic acid (ASA) 81 mg daily, metoprolol 25 mg bid, digoxin 0.0625 mg daily, amitriptyline 50 mg qhs, warfarin 2 mg daily, calcium 500 mg daily, vitamin D 1,000 units daily, alendronate 70 mg weekly, lorazepam 1 mg qhs prn, tolterodine 2 mg bid prn, and ibuprofen 200 mg qid prn. A comprehensive geriatric assessment was requested by her orthopedic team.

Potentially Inappropriate Medications

This patient was taking a number of medications that may have contributed to her fall and subsequent admission to hospital. Outlined below are five medications or classes of medications that

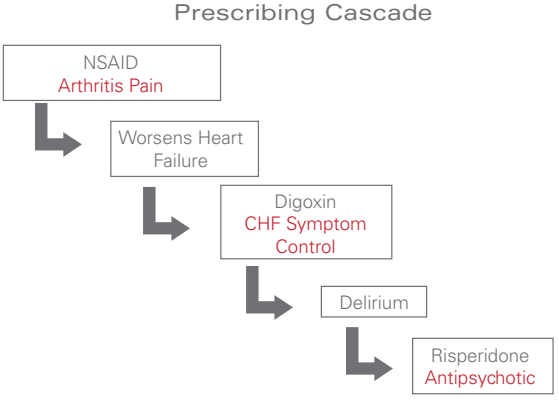

Figure 1. Example of a prescribing cascade.
CHF = congestive heart failure; NSAID = nonsteroidal anti-inflammatory drug. Source: Reprinted from *The Lancet* 346(8966), Rochon PA and Gurwitz JH, Drug therapy, 32–6, Copyright 1995, with permission from Elsevier.[6]

have been identified by the Beers criteria[7] and are potentially unsafe for use in elderly patients. The rationale for avoiding these medications is provided, and safer alternatives are suggested.

Digoxin for AF and Congestive Heart Failure

Age-related changes to total body water, lean muscle mass, and renal function predispose older patients to developing digoxin toxicity. This toxicity presents as nausea, blurred vision, weakness, and confusion; patients with more severe cases can experience heart block, delirium, and psychosis. In older patients, these ADRs also occur at serum concentrations considered to be in the therapeutic range (1–2.6 nmol/L).[8]

β-Blockers and non-dihydropyridine calcium channel blockers (e.g., verapamil, diltiazem) are preferred as initial therapy for rate control of AF as they more effectively control heart rate (HR) during exercise. The addition of digoxin can be considered in those patients whose HR remains refractory despite optimal therapy.[8]

In patients with congestive heart failure (CHF) whose symptoms persist despite optimized first-line therapies, digoxin can be considered for symptomatic control. If initiated, digoxin should not be abruptly discontinued as this may lead to worsening heart failure and increase the risk of hospitalization.[9] A safe approach to the use of digoxin in elderly patients is to target lower serum concentrations. In studies, older patients whose digoxin levels were between 0.6 and 1.2 nmol/L did not experience worsening CHF symptoms compared with those whose serum levels were >1.3 nmol/L. A reduced risk of hospitalization and mortality was also observed with lower serum concentrations.[10,11]

Tricyclic Antidepressants for Depression, Insomnia, and Neuropathic Pain

A major concern with tricyclic antidepressants (TCAs) is the elevated anticholinergic activity and related adverse effects (cognitive impairment, constipation, dry mouth, dizziness, and falls), especially with first-generation agents such as amitriptyline and doxepin.[12] The rate of depression in the geriatric population has been reported as approximately 15%, and 15–25% of nursing home residents suffer from a major depressive disorder.[13] These numbers highlight the need for screening elderly patients and weighing the risks and benefits of therapy.

Key Points

Physiological changes combined with polypharmacy increase the risks of adverse drug reactions (ADRs) in elderly patients.
Routine medication reviews and a team-based approach may help reduce ADRs.
Medication therapy needs to be individualized (treatment plans created and goals of therapy established).
Thorough histories of signs and symptoms should be taken to avoid a prescribing cascade.
The medications discussed in this article carry an increased risk for ADRs in elderly patients; the risks associated with these drugs must be weighed against the potential benefits of treatment.

Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) are less anticholinergic than TCAs and are thus considered safer in elderly depressed patients.[14] These medications do carry their own risks, and the guiding principle of "start low and go slow" should still be applied. Studies comparing the efficacy of TCAs and SSRIs[15] have not shown either agent to be superior for treating depression, thus leaving TCAs as a viable option in older patients who cannot tolerate SSRIs. Among the TCAs, agents such as nortriptyline and desipramine have relatively lower anticholinergic activity and may be preferable in these situations.[16]

For older patients with untreated insomnia, non-pharmacological therapy including sleep hygiene, stimulus control, and cognitive behavioural therapy (CBT) should be preferred over medications. The need for TCAs to aid in sleep should be reassessed, and the use of TCAs over less anticholinergic options should be re-examined. Sedating antidepressants such as trazodone and mirtazapine may be preferred over TCAs in this setting because of the lower anticholinergic activity; however, evidence to support their use is lacking in patients without underlying depression.

TCAs have been used successfully to treat neuropathic pain. However, their anticholinergic effects limit their use in older patients. Gabapentin and pregabalin are other first-line agents that are not as anticholinergic as TCAs and can be considered, but slow dosage titration is necessary due to side effects such as sedation.[17] As discussed above, the lowest effective dosages should always be used and, in these cases, adjunct acetaminophen or low-dose opioids may help to lower dosages and reduce pain.

Nonsteroidal Anti-inflammatory Drugs for Pain

Musculoskeletal pain from injury or arthritis can be a common symptom in older patients and negatively impact their quality of life. Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective options for both chronic and acute pain; however, their mechanism of action (prostaglandin inhibition) can cause or worsen hypertension, CHF, acute renal failure, and upper gastrointestinal bleeds (UGIBs).[18,19] All drugs in the NSAID class appear to cause these adverse events, with the exception of UGIBs, at similar rates.[19] Cyclooxygenase 2 (COX-2) selective agents (e.g., celecoxib) appear to cause fewer gastrointestinal bleeds than do non-selective agents (diclofenac, ibuprofen, etc.).[20]

Non-pharmacological options such as structured physical activity can be effective in relieving pain in arthritic patients. If pain is unresponsive to activity, regularly dosed acetaminophen should be considered first-line therapy. If pain control is still insufficient, low-dose opioids can be added along with increased monitoring for side effects of constipation, sedation, and cognitive impairment.[21] NSAIDs remain an option but require a discussion with the patient of the benefits and risks, including the need for increased monitoring of cardiac and renal functions. The need for pain relief should also be assessed continually, which may prompt discontinuation of the drug.

Oxybutynin and Tolterodine for Overactive Bladder

Overactive bladder occurs in an estimated 18% of the Canadian population and negatively impacts quality of life for patients. The

anticholinergic agents oxybutynin and tolterodine have an antispasmodic effect on the detrusor muscle, which decreases urinary urgency and frequency. They are the most commonly used and effective agents available[22] because of their potent anticholinergic effects, which can be amplified in older patients. The combination of bladder training, pelvic muscle exercise, relaxation, and voiding diaries with these agents may help to lower the required dosage of these medications and reduce the risks of ADRs.[22]

In order to individualize therapy, there are a number of formulations that exist: immediate- and extended-release tablets and capsules and a transdermal oxybutynin patch. Available data suggest that there is no difference in efficacy between immediate- and extended-release products, and neither oxybutynin nor tolterodine offers a clinical advantage over the other. However, a Cochrane Review found oxybutynin use to be more likely to result in discontinuation of therapy secondary to adverse events.[23] The transdermal and oral preparations appear to have similar efficacy and ADRs.[24]

The results of one study were analyzed to look at whether there is a treatment difference in older (>65 years) compared with younger patients. It was found that treatment was more effective than placebo, with similar adverse event rates. However, older patients suffered from more episodes of dry mouth.[25]

Benzodiazepines for Insomnia

Benzodiazepines have been shown to be effective for the short-term treatment of insomnia, but use for extended periods has been linked to cognitive and memory impairment and poor sleep structure. Another concern is daytime sedation, especially with longer-acting agents, which can predispose patients to falls, fractures, and motor vehicle accidents. Patients have also experienced tolerance and withdrawal syndromes with long-term use.[26]

These agents should be periodically reassessed and, if possible, plans should be made to taper the dosage slowly and eventually remove these agents.[27] Patients on short-acting agents are more likely to experience withdrawal, and this can be managed by first switching to a long-acting agent prior to the discontinuation of therapy.

Patients should be assessed for other conditions that may be causing the insomnia, and these underlying issues should be treated first. For the management of insomnia, non-pharmacological therapies such as stimulus control and sleep hygiene[28] should be first-line therapy. If required, short courses (i.e., <1 week) of benzodiazepines are preferred. Trazodone remains an option for insomnia and can be considered, but data for its use in non-depressed individuals are lacking.[29] Non-benzodiazepine sedatives and hypnotics (i.e., zopiclone) can be tried, but again only for short periods of time as their effectiveness appears to diminish with prolonged use and next-day drowsiness may still be observed.[28,30]

A meta-analysis of sedative hypnotics in older patients countered the belief that non-benzodiazepines are safer than benzodiazepines. There was no significant difference in cognitive or psychomotor adverse events, and the same benefit seen in younger patients did not translate to elderly patients. The increased rate of adverse events (number needed to harm [NNH] for any adverse event rate = 6) suggests that these agents may not be suitable for elderly patients.[31]

Case Conclusion

On assessment, there was no evidence of delirium or history of cognitive impairment in Ms. P. Her physical examination was relatively unremarkable aside from erythema and peripheral edema in her lower extremities, with chronic venous skin changes. She also reported a history of functional incontinence due to her inability to get to the washroom on time, her long-standing history of chronic leg edema, and osteoarthritis.

ASA was discontinued because she was on warfarin and did not have strong indications for antiplatelet therapy. Metoprolol was continued as her preoperative blood pressure was 125/65 mm Hg and her heart rate was 75 bpm. The digoxin was stopped because she had no history of systolic CHF. Her digoxin level upon discharge was 1 nmol/L. Her amitriptyline dosage was reduced to 25 mg qhs, with further tapering instructions after discharge. She did not have a history of depression or a neuropathic component to her pain. Lorazepam and tolterodine were discontinued as they both have been associated with an increased risk of delirium. Moreover, the patient infrequently used lorazepam and reported grogginess in the morning after use. The ibuprofen was stopped because of renal insufficiency. Instead, Ms. P was started on acetaminophen 1 g tid and low-dose hydromorphone q4h prn for pain management.

After surgical repair of her hip, she developed mild CHF requiring diuresis. She did not tolerate the hypotensive effects of metoprolol and required the re-initiation of digoxin to optimize her arrhythmia control. She continued her medications for bone health, and an outpatient bone mineral density test was arranged.

Ultimately, Ms. P was successfully transferred to rehabilitation care, with the eventual goal of returning home to the community.

Discussion

All medications have inherent risks that need to be weighed against the benefits before initiating therapy. Elderly patients appear to be at an increased risk for adverse events, especially from select medication classes. Efforts to limit the prescribing and use of these agents in older patients can reduce harm and help to avoid dangerous prescribing cascades.

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