BETTER PRESCRIBING IN THE ELDERLY

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Medication-related problems are common, costly, associated with poor outcomes, and potentially preventable in older adults. Potentially inappropriate medications (PIMs) continue to be prescribed and used as first-line treatments for the most vulnerable older adults despite better therapeutic choices and evidence of poor outcomes.[1] 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, suggesting that the risk of adverse drug reactions (ADRs) is high (Figure 1).[2]

Inappropriate use of medications in elderly patients is of major concern to clinicians and public health authorities. Inappropriate prescribing is an important and possibly preventable risk factor for ADRs in the elderly and is associated with drug-related hospital admissions in up to 10–30% in older people.[3] The incidence of PIMs is about 20% in community-dwelling elderly and up to 40% of long-term care residents (Figure 2).[4] Moreover, ADRs occur during hospital admission in up to half of patients.[5] The financial burden of ADRs to the health care system is substantial. A US study by Wu et al. calculated the mean cost of treating an ADR causing a hospital admission to be $9,491 per patient, with 60% of this cost being the room and board charges alone.[6]

A recent study found 42% of elderly in-patients were prescribed at least one drug without valid indication and that dosage or duration was inappropriate in about half of these patients.[7] Conversely, medicines for conditions such as heart failure or osteoporosis remained under-prescribed in 20–70% of patients.[3] Medication errors are also frequent during the transition between acute and post-acute care, in part due to incomplete discharge instructions.[3] It is imperative to ensure good prescribing in primary care to avoid these costly consequences, both from a financial perspective and, more importantly, from a morbidity and mortality perspective.

The goal of this article is to present the importance of PIMs in the elderly, with a review of different criteria and tools developed over the last decade.

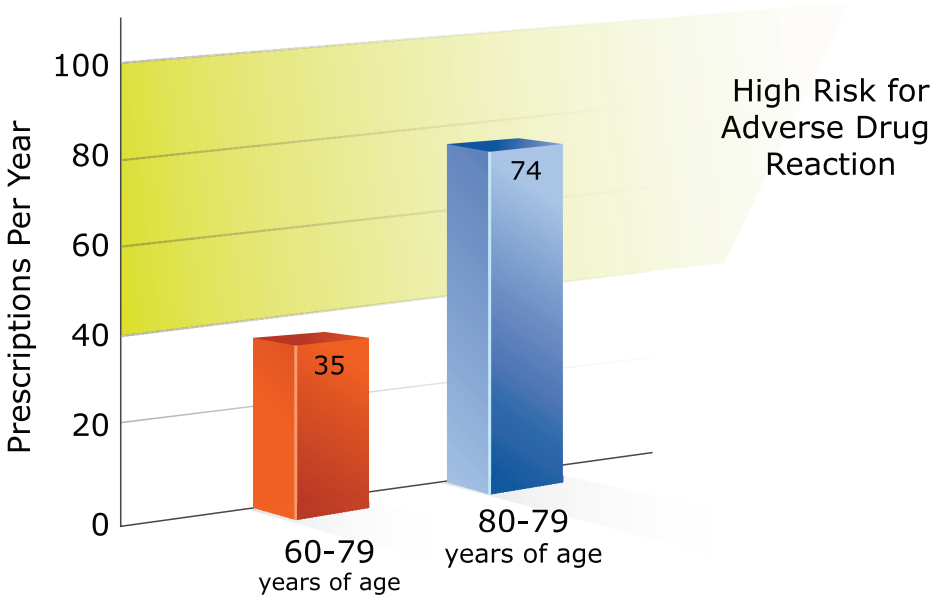

Figure 1. The risk of adverse drug reactions in older patients is high due to their increased number of prescriptions.

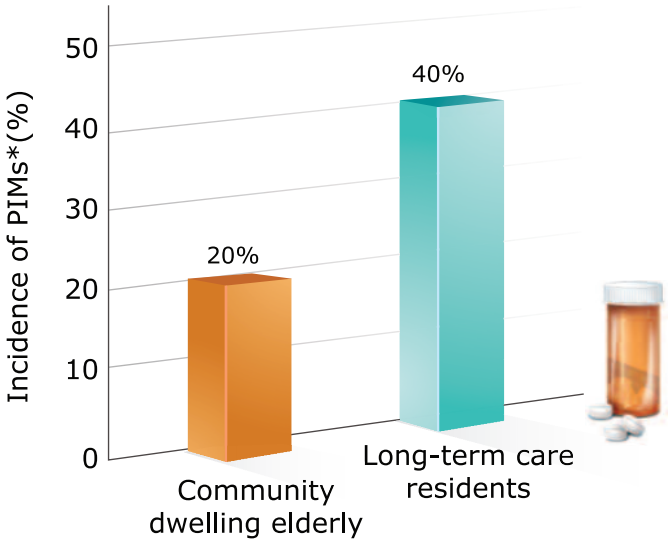

Figure 2. Inappropriate prescribing is an important and possibly preventable risk factor for ADRs in the elderly. *PIM = potentially inappropriate medication.

Table 1. Why Are the Elderly at Such High Risk for ADRs?

• Higher prevalence of chronic and multiple medical conditions leading to polypharmacy (≥6 medications increases significantly risk of ADRs) and increased side effects
• Age-associated physiological changes altering pharmacokinetics and pharmacodynamics (decreased GI transit, increased fat-to-lean body ratio, decreased oxidative phase of liver metabolism, reduced renal clearance and GFR)[26]
• Homeostenosis (decreased reserve in body system to adapt to change) with increased vulnerability to ADRs (delirium, CHF, etc.)[27]
Increased risk of the following: • Falls • **Prescribing cascades*** (process whereby the side effects of drugs are misdiagnosed as symptoms of another problem resulting in more new medications and new side effects/drug interactions) • Iatrogenic suffering • Cognitive impairment – delirium and dementia • Health care resource utilization (emergency room visits, hospitalization) • Morbidity and mortality
• Exclusion from participation in pharmaceutical research, making dosing unclear, side effects uncertain and effectiveness ambiguous.[27] The typical drug trial patient is young, male, disease free, and on no other drugs. The typical recipient is old, is female, and has multiple comorbidities and medications.
Summary: Elderly people are at increased risk of suffering from polypharmacy, drug-drug interactions, drug-disease interactions, and ADRs.

ADR = adverse drug reaction; CHF = congestive heart failure; GI = gastrointestinal; GFR = glomerular filtration rate.

*The term *prescribing cascade* first appeared in "Optimizing Drug Treatment for Elderly People: The Prescribing Cascade," by Paula Rochon and Jerry Gurwitz, *BMJ* 1997;315(7115), Volume 315.

Table 2. Medication Appropriateness Index

Indication
Effectiveness
Dosage
Correct directions
Drug-drug interactions
Drug-disease considerations
Practical directions
Expense
Duplication
Duration

Source: Data from Hanlon and Schmader.[9]

The Ottawa Top Ten Tool (OTTT) and the anticholinergic risk score (ARS) are two simplified guides that have been developed and are used to help clinicians enhance safer prescribing and reduce the risk of ADRs in their older patients (Table 1). The guides provide an approach to stopping PIMs through the use of a discontinuation algorithm.

Try a "Trial of Discontinuation"

There is a growing body of evidence showing that discontinuing specific medications in certain patient populations does not worsen outcomes, that it decreases the risk of ADRs, and that it reduces costs attributable to medications.[8] Therefore, strategies to improve the discontinuation of medications and the need to integrate this process into health care are needed. This is why we want to introduce the concept of a "trial of discontinuation" (Figure 3). The outcomes of discontinuation can result in the patient feeling better (fewer side effects, lower drug cost), the patient feeling the same (less drug load and less cost), or the patient feeling worse (but recurrence of symptoms are predictable and the patient is able to monitor this).

Measures and Tools to Decrease Inappropriate Prescribing

To assist clinicians with a trial of discontinuation, two different indicators have been developed to assess the appropriateness of prescription: implicit criteria (judgement based) and explicit criteria (consensus based).

Implicit Criteria

Implicit criteria such as the medication appropriateness index (MAI) from Hanlon (1992)[9] are used to assess each medication prescribed for a patient. The MAI consists of a 10-item checklist for consideration to determine the appropriateness of medication (Table 2). The index uses a three-point scale. For each criterion, a rating of 1 represents appropriate medication use, a rating of 2 represents marginally appropriate medication use, and a rating of 3 represents inappropriate use. Those reviewing a patient's medications (often clinical pharmacists) need to have a comprehensive knowledge of medications to confidently determine their appropriateness.

Explicit Criteria

Explicit criteria are usually established by expert consensus to create a list of medications to be avoided in older adults, either in general or in

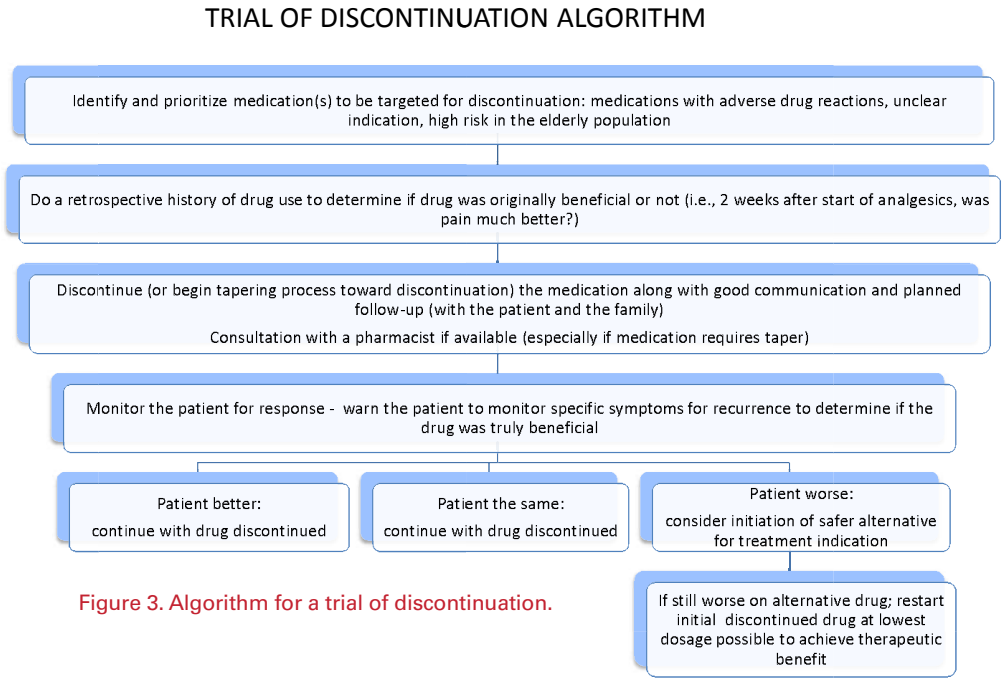

Figure 3. Algorithm for a trial of discontinuation.

Table 3. Similarities and Differences among Seven Criteria on PIMs

Similarities
Long-acting benzodiazepines: • Considered inappropriate by all 7 criteria • Associated with an increased risk of confusion, sedation, falls, and hip fracture
Short-acting benzodiazepines: strongly associated with fall-related injuries
Tricyclic antidepressants: strong anticholinergic effect introducing risks of impaired cognitive function, falls, constipation, urinary retention, and cardiotoxicity
Drug-disease interaction: • Listed in at least 4 criteria • Anticholinergic medications, NSAIDs, alpha-adrenoreceptor antagonists, and benzodiazepine listed for specific medical problems such as falls, peptic ulcers, urinary incontinence, or cognitive impairment
Drug-drug interactions: concomitant use of NSAIDs and warfarin was mentioned in 6 criteria
Differences
Variation of inappropriateness of certain medications, Europe versus North America: amiodarone, doxazosin, fluoxetine

NSAIDs = nonsteroidal anti-inflammatory drugs.

the presence of specific comorbidities. These criteria are often easy to implement in routine clinical practice because only limited numbers of medications and clinical conditions are specified.[10] Physicians familiar with explicit criteria may prescribe fewer PIMs when treating elderly patients. Throughout the years, explicit criteria have been proposed by groups around the world, such as PRISCUS, Najanjo, Laroche's French consensus, McLeod, Winit-Watjana, Australian Prescribing, Zhan, ACOVE, HEDIS, DUR, STOPP-START, and Beers in 1991, 1997, 2003, and most recently 2012.[1]

For more than 20 years, the Beers criteria for PIM use in older adults has been the most used source of information about the safety of prescribing medications in older adults. The revised criteria (an update sponsored by the American Geriatric Society) is an evidence-based approach that rates the quality of the evidence for every recommendation.[1] It also recommends a removal of drugs no longer available since the 2003 version, and introduces new drugs to make the criteria as up to date as possible.[1]

Comparison among the Seven Explicit Criteria/Tools to Guide Initial Prescribing and Trial of Discontinuation

In 2010, Chang and Chan[11] looked at the seven most popular criteria/tools (Fick et al. – Beers,[12] McLeod et al.,[13] Rancourt et al.,[14] Laroche et al.,[15] O'Mahoney et al. – STOPP and START,[16] Winit-Wajana et al.,[17] and Rognstad et al. – Norwegian General Practice [NORGEP][18]) and identified similarities and differences. In their summary, they state that the STOPP,[16] Rancourt,[14] and Laroche[15] criteria came closest to fully meeting the optimal explicit criteria (Table 3).

Table 4. The Ottawa Top Ten Tool: Drug Classes to Avoid in the Elderly

Drug	Why Stop?	Alternatives	Indications to Continue	Special Monitoring/ Considerations
Anticholinergics (not included in other categories): H1 histamine blockers (diphenhydramine, hydroxyzine) Cyclobenzaprine Benztropine Dimenhydrinate *See also Table 5*	Potent anticholinergic properties Should not be used as hypnotics Impair cognition Delirium Falls Prolongation Q–T interval	Allergy symptoms: non-sedating non-anticholinergic anti-histamines (cetirizine, loratadine, desloratadine) Pain/muscle spasm: non-pharmacological muscle relaxation, physiotherapy, massage Nausea: ondansetron, low-dose domperidone	If diphenhydramine use for allergic reaction, use the smallest dosage possible Exception: anaphylaxis and transfusion reaction	Clinical monitoring for anticholinergic side effects: bladder outflow obstruction, constipation, delirium, worsening cognition in patients with dementia ECG for QTc
Tricyclic antidepressants Amitriptyline, doxepin, imipramine, clomipramine, trimipramine	Strong peripheral anticholinergic side effects (constipation, dry mouth, orthostatic hypotension, cardiac arrythmias) and central anticholinergic side effects (sedation, confusion, delirium) Cognitive deficit Increased risk of falling Can exacerbate glaucoma/BPH/heart block	SSRIs (citalopram, escitalopram, sertraline) Mirtazapine Non-pharmacological (behavioural therapy) SNRIs	Long use with no apparent side effects No cognitive issues Relapse with trial of discontinuation	Monitor for anticholinergic side effects, suicidality, fall risk, cognition ECG (QT prolongation, proarrhythmics) Therapeutic drug monitoring if risk of intoxication **Avoid doses >20 mg of citalopram, if used; monitor QTc for risk of prolongation**
Benzodiazepines Long-acting benzodiazepines: flurazepam, diazepam, bromazepam, clonazepam Short-acting benzodiazepines (lorazepam, oxazepam, alprazolam, temazepam) Non-benzodiazepines hypnotics zolpidem, zopiclone (>3.75 mg/day)	Extreme long half-life producing prolonged sedation and reaction times Elderly more sensitive Risk of falls, fractures Psychiatric reactions can be paradoxical (agitation, irritability, hallucinations, psychosis) Cognitive impairment Depression May cause dependency	Sleep: very low-dose short-acting benzodiazepines for short duration only, low-dose zopiclone, trazodone Sedative antidepressant for concomitant insomnia and depression (mirtazapine) Non-pharmacological treatment of sleep disturbance/sleep hygiene Anxiety disorder: anti-depressant (citalopram, escitalopram, venlafaxine)	Use lowest possible dose, shortest possible duration of treatment May be appropriate for seizure disorders, ethanol withdrawal, and end-of-life care. Zolpidem, zopiclone: use for short period <90 days	Clinical monitoring for adverse effects (cognitive function, vigilance, regular fall history, gait steadiness testing, psychopathology, ataxia) May exacerbate depression May worsen cognition If patient is on chronic benzodiazepines (over 1 month), yearly documentation and discussion of risks, and attempts to taper and discontinue For longer use (>1 month), taper down slowly (may be done in consultation with specialist or pharmacist for complex cases)
Older SSRIs/NDRIs Fluoxetine, paroxetine Bupropion	Fluoxetine = long half-life, multiple drug interactions – not unique to the elderly CNS side effects (nausea, insomnia, dizziness, confusion) Hyponatremia If risk of seizure (bupropion)	Another SSRI (sertraline, citalopram, escitalopram) Mirtazapine Non-pharmacological: (behavioural therapy)	Very good clinical response, no side effects, in consultation with geriatric psychiatrist	Clinical monitoring of CNS function Monitor of renal function and serum electrolytes **Avoid doses >20 mg of citalopram, if used; monitor QTc for risk of prolongation**
Antipsychotics Atypical: olanzapine, clozapine, risperidone, quetiapine – 40% lower mean oral clearance in the elderly Typical: haloperidol	Anticholinergic and EPS side effects (tardive dyskinesia), but less than typicals, parkinsonism, hypotonia, sedation, fall risk, all anti-psychotic agents associated with increased risk of all-cause mortality in patients with dementia Stroke, lowers seizure threshold Clozapine = increased risk of agranulocytosis and myocarditis	Atypical antipsychotics with favourable risk/benefit profile (risperidone) Quetiapine = if used for insomnia, use low-dose trazodone (25–100 mg)	Short term (<3 months) with reassessment of benefit/worsening/need to continue Advise patient/family of possible increased risk of stroke and mortality Haloperidol in acute psychosis (short duration: <3 days), avoid single dose over 2 mg, avoid IV formulation (risk of postural hypotension and cardiovascular collapse)	Clinical monitoring for adverse effects, anticholinergic, and EPS Fall history Neurological and cognitive function (parkinsonism) Monitoring of cardiovascular function (hypotension, ECG/Q–T interval) Clozapine = blood pressure monitoring No psychoactive medication used to treat neuropsychiatric symptoms of dementia should be continued indefinitely, and attempts at drug withdrawal should be made regularly (e.g., every 3–6 months)[19]

Table 4. Cont'd

Drug	Why Stop?	Alternatives	Indications to Continue	Special Monitoring/ Considerations
Digoxin Dosage >0.125 mg/d	Dosage should not exceed 0.125 mg/d because of decreased renal clearance Risk of toxicity	For tachycardia/atrial fibrillation use beta-blockers (metoprolol, bisoprolol, carvedilol)	Use for heart failure (NYHA III) Use in difficult to control atrial arrhythmias	Monitor renal function Monitor cardiovascular function Therapeutic drug monitoring (target 0.5–1 ng/mL in elderly) *ONLY* if renal dysfunction, ECG changes, drug-drug interaction, or signs/symptoms of toxicity
NSAIDs Diclofenac, indomethacin, meloxicam, naproxen, ketorolac, Including OTC-NSAIDs: ibuprofen, naproxen	Indomethacin = most CNS side effects Potential for GI bleeding/perforation, renal failure, hypertension, CHF. Avoid concomitant use of ASA/warfarin/dabigatran/ clopidogrel OTC not perceived by patient as dangerous; often not mentioned to physician	Acetaminophen, weak opioid (morphine, hydromorphone), tramadol **Avoid codeine – higher incidence of sedation, nausea, and constipation**	Short duration (<14 days) 2-week trial: if no clinical significant benefit, discontinue as risk too high	Use in combination with PPI Follow up GI manifestations (note that 70% of GI bleeds have no GI prodrome) Monitor renal function Monitor BP, signs of CHF
Urological spasmolytic agents Oxybutynin, non-SR tolterodine, solifenacin	Anti-cholinergic side effects, sedation, weakness ECG changes – prolonged Q–T May worsen: prostatism, glaucoma, constipation, dementia	Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapies)	May use tolterodine SR with close monitoring if patient cognitively intact and good response to medication	Clinical monitoring for anticholinergic side effects (bladder outflow obstruction, constipation, cognition, falls)
Laxatives Stimulant (senna, dulcolax) Softener (ducosate)	Long-term use results in cathartic colon and bowel dysfunction Diarrhea, fecal incontinence, urgency Refractory constipation, obstruction	Fibre, hydration Osmotic laxatives (lactulose, polyethylene glycol 3350; magnesium hydroxide if GFR ≥60)	Short course during opioid use	
Hypoglycemics Long-acting sulfonylurea: glyburide chlorpropamide TZDs: pioglitazone, rosiglitazone	Can cause severe prolonged hypoglycemia Increase risk of HF and MI, avoid if liver disease	Metformin Gliclazide Repaglinide		Glucoscan Avoid metformin if impaired renal function (adjust dose if GFR falls <60 mL/min, discontinue when GFR falls <30 mL/min) TZDs – avoid if history of HF/edema/CAD Note that insulin has been listed as a high-alert medication; use with close monitoring to avoid hypoglycemic episodes (often asymptomatic)

BP = blood pressure; BPH = benign prostatic hyperplasia; CAD = coronary artery disease; CHF = congestive heart failure; CNS = central nervous system; ECG = electrocardiography; EPS = extrapyramidal symptoms; GFR = glomerular filtration rate; HF = heart failure; IV = intravenous; MI = myocardial infarction; NDRI = norepinephrine-dopamine reuptake inhibitor; NYHA = New York Heart Association (classification); OTC = over the counter; PPI = proton pump inhibitor; SNRIs = serotonin-norepinephrine reuptake inhibitors; SR = slow release; SSRIs = selective serotonin reuptake inhibitors; TZD = thiazolidinedione.

OTTT: Drug Classes Considered Inappropriate to Use in the Elderly

A thorough review of the literature and available tools and criteria for PIMs resulted in this summary of the top 10 drug classes considered inappropriate to use in the elderly. This simplified version is applicable in Canada, is arranged in categories, and concentrates on common high-risk drugs (with a higher potential for side effects and ADRs) for easier use. It includes simple explanations as well as safer alternatives. OTTT was created with the assistance and expertise of eight geriatric medicine specialists at The Ottawa Hospital and two expert geriatric pharmacists through use of rating scales for prioritization of relevance and importance, followed by formal discussions at geriatric academic rounds (Table 4).

Table 5. Modified Anticholinergic Risk Scale

3 Points	2 Points	1 Point
Amitriptyline	Amantadine	Carbidopa-levodopa
Atropine/scopolamine	Baclofen	Entacapone
Benztropine	Cetirizine	Haloperidol
Chlorpromazine	Cimetidine	Methocarbamol
Clomipramine	Clozapine	Metoclopramide
Dicyclomine	Cyclobenzaprine	Mirtazapine
Diphenhydramine	Desipramine	Paroxetine
Doxepin	Loperamide	Pramipexole
Fluphenazine	Loratadine	Quetiapine
Flurazepam	Nortriptyline	Ranitidine
Hydroxyzine	Olanzapine	Risperidone
Hyoscyamine products	Prochlorperazine	Selegiline
Imipramine	Pseudoephedrine	Trazodone
Meperidine	Tiprolidine	Ziprasidone
Nitrazepam	Tolterodine	
Oxybutynin		
Perphenazine		
Solifenacin		
Trimipramine		

Source: Adapted from Rudolph et al.[24]

Special Problem of Anticholinergic Load in the Elderly

Medications with anticholinergic properties have frequently been cited in the literature as causing an increase in adverse events.[20,21] This often leads to consequences such as falls, hospitalization, and a loss of independence.[22,23] Higher rates of cognitive dysfunction and delirium are found in patients experiencing a greater anticholinergic load. Evidence suggests that reducing anticholinergic medications is a modifiable risk factor to avoid associated morbidity.[24] Rudolph and colleagues have developed an ARS that can be used in geriatric evaluation and management (GEM) as well as a primary care setting.[24] It was demonstrated that a higher score increases the risk of anticholinergic adverse effects in GEM with a relative risk of 1.3 and in primary care of 1.9. A subsequent large study found greater risk of delirium, cognitive decline, and dementia with functional and behavioural issues in patients with a high anticholinergic load. These clinical side effects/symptoms later decreased if anticholinergics were decreased or discontinued.[25]

The ARS ranks medications for anticholinergic potential on a three-point scale (1 = moderate, 2 = strong, 3 = very strong) for each medication based on its anticholinergic potential. The ARS score for a patient is the sum of points for his or her number of medications. The anticholinergic adverse effects are divided into central (falls, dizziness, confusion) and peripheral (dry mouth, dry eyes, and constipation). Table 5 presents a simplified version of the ARS created with the expertise of geriatric medicine specialists and pharmacists for use in conjunction with the OTTT. Modifications to the scale include the removal of medication rated as "0" for no anticholinergic risk and the inclusion of only the most common medications for 1, 2, and 3 points of risk.

Summary

In summary, prescribing medications is a complex phenomenon, particularly in the older population. The assessment and review of every patient's medication list should be done every 6–12 months; all drugs should be reviewed, including over-the-counter drugs, and the *pro re nata* (PRN) should be key. Review should also be done at times of transitions: discharge from hospital, relocation to retirement home, or transfer to long-term care. There is no best tool for doing a medication review. The three simplified tools presented, MAI, OTTT, and ARS, could be incorporated together into routine practice as they are easy to use, relevant, accurate, and not time consuming. Appropriate initial prescribing, drug monitoring, drug regimen reassessment, and medication discontinuation are essential to optimizing prescribing and drug side effects in the elderly. Always consider drug side effects, including those of over the counter drugs, as a lead cause in the differential diagnosis of any new symptom.

Although criteria, prescribing tools, and guidelines provide invaluable information regarding prescribing for older patients, there are

Key Points

- *There is a growing body of evidence showing that discontinuing specific medications in certain patient populations does not worsen outcomes, that it decreases the risk of ADRs, and that it reduces costs attributable to medications.*
- *Those reviewing a patient's medications (often clinical pharmacists) need to have a comprehensive knowledge of medications to confidently determine their appropriateness.*
- *Medications with anticholinergic properties have frequently been cited in the literature as causing an increase in adverse events.*
- *Appropriate initial prescribing, drug monitoring, drug regimen reassessment, and medication discontinuation are essential to optimizing prescribing and drug side effects in the elderly.*

important caveats concerning their use. No criteria should substitute for professional judgment or dictate prescribing for patients. When in doubt, consider consulting with a pharmacist or geriatrician.

Acknowledgements

The authors would like to thank Debbie Ayotte (librarian), Dr. Barbara Power (geriatrician), Sarah Bhatti (Desjardins Pharmacy), and geriatricians Drs. N. Azad, L. Khoury, A. Byszewski, R. Ellen, F. Molnar, M. Hing, and M. Roy at The Ottawa Hospital for their invaluable support and participation in the creation of the OTTT.

This article was peer reviewed.

Conflict of interest: None declared.

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