Editor's key points

- Older adults with cognitive disorders are at particularly high risk of adverse drug events. Optimizing medications is a critical aspect of care.
- This review offers a practical approach to medication use in older adults with cognitive impairment based on an accredited primary care memory clinic training program developed by the Centre for Family Medicine Primary Care Collaborative Memory Clinic.
- Medication changes should be implemented gradually following a thorough person-centred discussion of the potential risks of medication adverse effects with increasing age and with cognitive impairment, and ensuring treatment goals are aligned with the person's preferences and values.

Optimizing medications in older adults with cognitive impairment

Considerations for primary care clinicians

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Abstract

Objective To provide primary care physicians with an approach to medication optimization in older adults with cognitive impairment.

Sources of information The approach is based on an accredited memory clinic training program developed by the Centre for Family Medicine Primary Care Collaborative Memory Clinic.

Main message Dementia increases the risk of medication-related adverse events and adds to the complexity and challenge of providing optimal care for these older adults. Considerations include medication adherence, appropriate therapeutic targets for comorbid conditions, minimized use of medications with potentially adverse cognitive effects, and rational use and monitoring of cognition-enhancing drugs. Medication management plans must be individualized and based on goals of care.

Conclusion Primary care physicians must consider many factors in optimizing medications for those with cognitive impairment.

Because older adults with cognitive disorders are at particularly high risk of adverse drug events,[1] optimizing medications is a critical aspect of care for the primary care clinician. More than 1 in 9 emergency department visits involve drug-related adverse events,[2] and older adults are nearly 7 times more likely than younger persons to require hospitalization related to adverse drug events.[3] The presence of dementia increases the risk of medication adverse events[1] and adds to the complexity and challenge of providing optimal care.[4,5]

Case description

Helen is an 89-year-old woman who had been living independently in her apartment until her hospitalization 5 weeks ago due to persistent right leg pain and "failure to cope." In hospital, investigations revealed no relevant cause of her leg pain other than long-standing sciatica. She remained in hospital awaiting transfer to long-term care because of "heavy care needs." Corroborated history from her sons revealed memory difficulties for the past 2 years, which had worsened in the past several months, with inability to prepare meals, poor hygiene, and considerable anxiety resulting in very frequent telephone calls to her sons. Memory symptoms had been noted to be worse with initiation of various pain medications, including hydromorphone. She has a grade 8 education level and worked in a factory for years. Her husband died 10 years ago. Medical history includes coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease, hyperlipidemia, colon cancer with colostomy, and sciatica. Cranial computed tomography scan in hospital revealed mild microangiopathic change. Her sitting blood pressure

was 135/75 mm Hg, with a heart rate of 73 beats/min; standing blood pressure was 130/70 mm Hg, with a heart rate of 91 beats/min.

Medications include 3 mg of controlled-release hydromorphone every 12 hours and 1 mg every 6 hours as needed; 7.5 mg of zopiclone at bedtime; 0.5 mg of lorazepam twice daily as needed (last taken 1 week ago); 40 mg of pantoprazole once daily; a 0.4-mg nitroglycerine patch once daily; 4 mg of candesartan twice daily; 110 mg of dabigatran twice daily; 1000 µg of vitamin B12 once daily; 18 µg of tiotropium inhaled once daily; and 975 mg of acetaminophen twice daily.

Cognitive testing demonstrates a Montreal Cognitive Assessment score of 10 out of 30 (corrected for education level), with intact digit spans, 0 of 5 words on delayed recall, and 7 *f* words. Her Cornell Scale for Depression in Dementia score is 8, which is borderline for depression.

Could medications be contributing to Helen's cognitive symptoms? If so, how might medications be optimized?

Sources of information

The approach described in this article is based on an accredited primary care memory clinic training program[6] developed by the Centre for Family Medicine (CFFM) Primary Care Collaborative Memory Clinic.

Main message

This article focuses on a practical approach to medication use in older adults with cognitive impairment. These medication considerations are included in steps 3 (Is there a reversible cause?) and 6 (How will you manage this?) of the CFFM Memory Clinic[7,8] clinical reasoning model, a structured primary care approach to assessing persons with memory difficulties previously published in *Canadian Family Physician*.[9]

Based on the CFFM Memory Clinic training program for Primary Care Collaborative Memory Clinics, **Box 1** summarizes a 5-step checklist of medication considerations for older adults with cognitive impairment. Medication changes should be implemented gradually following a thorough person-centred discussion of the potential risks of medication adverse effects with increasing age and with cognitive impairment, and ensuring treatment goals are aligned with the person's preferences and values.

Ensure medication adherence. Unintentional medication nonadherence must be identified in persons with dementia because it might prevent medication-related hospitalizations.[10-15] Dementia often affects a patient's ability to follow instructions and to adhere to complex medication dosing regimens[16]; indeed, difficulties in self-managing medications might be one of the earliest identified areas of functional impairment.[17] The estimated prevalence of medication nonadherence in those with cognitive impairment has ranged from 2% to 59%,[18] and it is influenced by effects of cognitive loss on capacity, memory, and executive functioning.[13] In addition, low performance on cognitive screening tests has been associated with difficulty using medication devices. For example, those unable to copy intersecting pentagons might have difficulty learning to use a Turbuhaler[19] or metered-dose inhaler,[20] and impaired clock drawing has been associated with difficulty learning to self-administer insulin.[21] It is critical to ensure those with cognitive impairment are taking medications safely and appropriately.

Box 1. Considerations in medication management for older adults with cognitive impairment

Consider the following when assessing medications for patients with cognitive impairment:

1. Is there medication adherence?
2. If the person is taking medications for hypertension, are treatment targets appropriate based on functional blood pressure? Is orthostatic hypotension a concern?
3. If the person is taking medications for diabetes mellitus, are treatment targets appropriate? Is hypoglycemia a concern?
4. Can medications with the potential for cognitive adverse effects be minimized? These include ...
   -highly anticholinergic drugs,
   -benzodiazepines and non-benzodiazepine hypnotics,
   -antipsychotics, and
   -opioids
5. If the person is taking cognition-enhancing medications for dementia, is this being appropriately monitored?

Assessing a person's ability to manage medications can be challenging in the context of the busy clinical setting. While performance on cognitive screening tests might be useful as initial screening, it is inadequate to rely on cognitive test scores alone because of a lack of established cutoff scores clearly indicating the inability to safely manage medications.[15,22] Patients themselves might overestimate their management abilities[23]; if caregivers are available they can provide helpful information.[16,23] Several validated performance-based tools[13,24] have been developed to assess patients' abilities to manage medications. These, however, require time to administer and must be part of a comprehensive assessment that considers other factors affecting medication use and adherence, such as the person's beliefs, goals, preferences, routines, and supports.[15] These assessments might be best conducted by trained health care professionals, such as pharmacists and nurses, who can assist the primary care physician in developing an appropriate plan for safe medication management.

Ensure treatment targets for hypertension are appropriate. Based on observational studies, there is

increasing awareness that overtreatment of hypertension might be associated with accelerated cognitive decline in persons with mild cognitive impairment or dementia.[25] Several large cross-sectional studies have demonstrated better cognitive functioning associated with higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) in older adults.[26-30] Although moderate blood pressure control (<150/90 mm Hg) in hypertensive older adults has been associated with reduced mortality, stroke, and cardiac events, lower blood pressure treatment targets have been associated with adverse effects such as syncope.[31] In one study, elderly persons with mild cognitive impairment or dementia who were taking antihypertensive drugs had more rapid cognitive decline associated with ambulatory SBP maintained below 129 mm Hg.[32] Some studies have suggested worsened cognitive functioning associated with DBP below 77 to 85 mm Hg.[26,27]

Orthostatic hypotension (OH) might affect up to 30% of adults older than 70 years of age,[33] and in those with cognitive impairment, it might be related to autonomic dysfunction and neurocardiovascular instability.[34] Orthostatic blood pressure should be monitored because OH has been associated with worsened cognitive functioning in persons who are cognitively impaired.[35-37] Orthostatic hypotension is defined as a drop in SBP of greater than 20 mm Hg or a drop in DBP of greater than 10 mm Hg within 3 minutes of standing.[38] The medication classes most likely to induce OH include α-blockers, antihypertensives, antipsychotics, narcotic analgesics, tricyclic antidepressants, vasodilators, and medications used for Parkinson disease.[39] If OH is identified, it might be helpful to switch to medications less likely to cause OH. Nonpharmacologic approaches can also be helpful.[39] Referral to a geriatric specialist should be considered for severe or complex cases. Further information on OH is available in the *Canadian Geriatrics Society Journal of CME*.[40,41]

Ensure appropriate treatment targets for diabetes mellitus. For older adults with diabetes and cognitive impairment, treatment benefits and therapeutic targets for glycemic control should be carefully weighed against the considerable risks of hypoglycemia. Diabetes is a proven independent risk factor for developing dementia,[42] with a prevalence of cognitive impairment or dementia in persons with diabetes estimated to be between 13% and 23%.[43] Persons with dementia have greater risk of severe hypoglycemia[44] because dementia can affect the person's ability to adhere to medication dosing schedules and to safely self-administer insulin.[10] In older persons with type 2 diabetes, the occurrence of severe hypoglycemic episodes has been independently associated with late-life cognitive decline and dementia.[45]

Considering these risks, hemoglobin A_{1c} levels of up to 8.5% might be a reasonable therapeutic target to avoid metabolic decompensation while minimizing the risk of hypoglycemia.[46] The 2013 Canadian Diabetes Association guidelines recommends a hemoglobin A_{1c} level of 8.5% or lower and preprandial and fasting plasma glucose levels between 5 and 12 mmol/L in frail older adults with high functional dependency.[47,48] Of the different types of antihyperglycemic agents, insulin and sulfonylureas, such as glyburide, carry the highest risk of hypoglycemic episodes; their use should be reviewed, adjusted, or avoided to reduce the risk of hypoglycemic events. Medication adherence and administration technique for both oral and nonoral medications must be closely assessed and monitored because progressive cognitive decline and executive dysfunction might affect the person's ability to safely self-administer medications such as insulin.[21] If insulin is required, administration technique and adherence must be closely monitored and educational support should be adapted to focus on individual therapeutic goals and avoidance of severe hypoglycemia. Further information is available in the *Canadian Geriatrics Society Journal of CME*.[49]

Minimize the use of drugs with adverse cognitive effects. Psychotropic drugs are among the most frequently implicated causes of adverse drug reactions in older adults with cognitive impairment.[1]

Benzodiazepines and non-benzodiazepine hypnotics: In Canada, it has been estimated that 15%[50] to 25%[51] of persons aged 65 years and older use benzodiazepines. In those who are cognitively intact, use of benzodiazepines can adversely affect memory as well as attention and reaction time.[52] Several large studies have found that benzodiazepine users have increased occurrence of cognitive deficits,[53-56] whereas evidence implicating non-benzodiazepine derivatives has been less consistent.[52] Of recent concern are several large population-based and database studies suggesting that use of benzodiazepines, particularly long-acting benzodiazepines and longer-term use, is strongly associated with increased risk of developing dementia.[57-62] Although a causal relationship cannot be established, a systematic review demonstrated a 1.78-fold increased risk of developing dementia in persons whose cumulative benzodiazepine use exceeded 30 days.[59] In persons with Alzheimer dementia, benzodiazepine use has been associated with accelerated cognitive decline and limited benefits.[63]

Reduction in benzodiazepine use should involve gradual tapering of a 25% to 50% dose reduction every 1 to 2 weeks, or more slowly for the very elderly or for those with chronic use. The taper can be slowed even further once titrated down to 50% of the original dose; for example, consider reducing the dose by 10% every 2 to 4 weeks. If necessary, switching the benzodiazepine to the equivalent dose of liquid diazepam might facilitate incremental dose reductions. Comparative diazepam doses of various benzodiazepines are listed in **Table 1**.[64]

Anticholinergic drugs: In older adults, there is strong evidence for adverse cognitive effects with the use of

Table 1. Benzodiazepine dosing: ***Comparative doses are the equivalent of 5 mg of diazepam.***

DRUG	COMPARATIVE DOSE, MG	T_{MAX} FOR AN ORAL DOSE,* H	ELIMINATION HALF LIFE, H
Alprazolam	0.5	1-2	6-27
Bromazepam	3.0	0.5-4	8-30
Chlordiazepoxide	25.0	1-4	4-29 (parent) 28-100 (metabolites)
Clonazepam	0.25	1-4	19-60
Clorazepate	10.0	0.5-2	1-120
Diazepam	5	1-2	14-80 (parent) 30-200 (metabolites)
Estazolam	1	0.5-6.0	8-24
Flurazepam	15	0.5-1	0.3-3 (parent) 40-250 (metabolites)
Lorazepam	1	1-6	8-24
Nitrazepam	2.5	0.5-7	15-48
Oxazepam	15	1-4	3-25
Quazepam	7.5	1.5	15-40
Temazepam	10	2.5	3-25
Triazolam	0.25	1-2	1.5-5

*T_{max} is the time to peak plasma concentration after taking regular-release oral formulations.
Data from Virani et al.[64]

medications that have highly anticholinergic properties.[65] Anticholinergic drugs have been associated with deleterious effects on divided attention and reaction time, and reduced performance in tasks requiring attention and vigilance.[52] A recent study suggests that higher cumulative anticholinergic use is associated with increased risk of dementia and that this increased dementia risk might persist following discontinuation of therapy.[66] For example, in that study persistent increased dementia risk was associated with 5 mg of oxybutynin, 2.5 mg of olanzapine, or 10 mg of doxepin given daily for more than 3 years. Evidence supports limiting the use of drugs with highly anticholinergic properties in older adults with cognitive impairment and, if these drugs are required over the longer term, having an informed discussion with patients and caregivers, balancing the benefits and harms. More comprehensive listings of highly anticholinergic drugs have been described elsewhere.[67-69]

Antipsychotic drugs: Numerous systematic reviews and meta-analyses have suggested modest benefits for use of antipsychotic drugs in the management of psychosis and aggression in persons with dementia.[70-72] The potential harms have been well documented and include increased risk of stroke and mortality.[70,71,73] Recent evidence suggests the degree of risk might vary with the type of antipsychotic prescribed.[72,73] Use of antipsychotic medications has also been associated with considerable cognitive adverse effects in persons with dementia.[70,74] Despite these risks, antipsychotic medications are sometimes necessary when behavioural symptoms put the person with dementia or others at risk of serious harm and other treatment options, both pharmacologic and nonpharmacologic, have been considered. Antipsychotic medications must be used cautiously in persons with dementia and prescribed at the lowest effective dose for the shortest period possible, with close monitoring and balancing of the risks and benefits to ensure use is justified and consistent with improving quality of life.[71,75,76]

Detailed guidelines for use of antipsychotic medications in persons with dementia are available from **https://thewellhealth.ca/dementia**.

Opioids: Cognitive effects of opioid drugs can include inattention, concentration difficulties, memory deficits, executive dysfunction, and delirium.[77] Opioids might increase the risk of delirium by to 2- to 3-fold[78]; of the opioids, meperidine has been associated with highest risk of delirium.[79] If opioids are necessary, judicious use is recommended, with low starting doses and titration to the minimum doses needed based on response.[80] In general, meperidine should be avoided in older adults and tramadol should be used with caution in older persons with renal impairment or who are at high risk of falls and fractures.[81] Alternative medications to manage pain might be helpful, such as acetaminophen for managing mild to moderate musculoskeletal pain.[82]

Cognition-enhancing medications. A primary care approach to the use of cognition-enhancing drugs for persons with dementia is available in the *Canadian*

Geriatrics Society Journal of CME.[83] Persons using cholinesterase inhibitors should be monitored regularly for potential adverse effects such as bradycardia, syncope,[84] and weight loss.[85] Unintentional weight loss is a known predictor of mortality in persons with dementia, particularly when weight loss is severe (>8%).[86] In persons with dementia being treated with an cholinesterase inhibitor, it is important that highly anticholinergic drugs are not concomitantly prescribed because these drugs are mechanistically in pharmacologic opposition, potentially reducing the effectiveness of one or both drugs and potentially worsening functional decline.[87]

The decision to continue or discontinue these cognition-enhancing medications should be individualized and based on regular reassessments of the benefits and harms. A rational guide to deprescribing cholinesterase inhibitors is available online.[88]

Case resolution

Working through the CFFM Memory Clinic clinical reasoning model approach,[9] medication adverse effects of lorazepam, zopiclone, and hydromorphone were identified as potentially reversible causes of Helen's cognitive dysfunction, contributing to memory symptoms due to a probable underlying mixed dementia. Lorazepam was discontinued and zopiclone was gradually discontinued over 2 weeks. For mood symptoms and pain management, duloxetine was initiated and increased to 60 mg daily after 1 week. For sleep difficulties, 25 mg of trazodone every evening was prescribed with monitoring of postural blood pressure. Gradual deprescribing of hydromorphone began 4 weeks later, allowing for adequate time for the duloxetine to take effect. Candesartan was also discontinued during hospitalization and the dose of pantoprazole was reduced. As stated in her hospital discharge summary, "When she was first admitted, she was somnolent, unable to get out of bed, and very weak. Her medications were revised and many were discontinued. This caused her to wake up and she engaged more in activities. Slowly, she began to participate in some leisure activities including painting. She was gradually weaned from narcotics and continues to do well with respect to her pain." Instead of continued prolonged hospitalization awaiting transfer to long-term care, Helen's improved condition enabled discharge to a retirement home setting where she continues to enjoy a good quality of life.

While Helen's medication adjustments were made in hospital, these medication changes might have been proactively implemented by the primary care clinician on an outpatient basis, potentially averting the original need for hospital admission. In this case, medication optimization has helped to delay long-term care institutionalization and to improve Helen's quality of life.

Conclusion

Optimizing medications is a challenging but critical aspect of care for older adults with cognitive impairment. Considerations include medication adherence, appropriate therapeutic targets for comorbid conditions, minimized use of medications with potentially adverse cognitive effects, and rational use and monitoring of cognition-enhancing drugs. Medication management plans must be individualized and based on goals of care.

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Contributors
All authors contributed to the literature review and interpretation, and to preparing the manuscript for submission.

Competing interests
None declared

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