

Turning over the rocks

Role of anticholinergics and benzodiazepines in cognitive decline and falls

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Optimizing the function of elderly patients is critical for them to live in their homes for as long as possible. Elderly patients frequently present to their family physicians with signs and symptoms of cognitive decline and functional deterioration. Recognizing and addressing potential causes of and contributors to cognitive and functional decline is paramount if we are to prevent unnecessary institutionalization and improve quality of life. In particular, elderly people are more likely than younger patients to develop cognitive or functional impairment as a result of taking medications. Both the number of medications that elderly patients use and physiologic changes in these patients make them more susceptible to developing toxicity. Continued use of unnecessary medications contributes to polypharmacy and carries with it an increased risk of falls, adverse drug events, and mortality.¹

In this article, we illustrate how the quality of life and functioning of an elderly person with multiple medical problems was affected by medication review, tapering and deprescribing of medications, and contributions of an interprofessional team during admission to the Bruyère Continuing Care Geriatric Day Hospital (GDH) in Ottawa, Ont.

Case

A 69-year-old woman was referred to the GDH for concerns about polypharmacy, mobility, cognition, and recurrent falls. Her medical history was relevant for 3 cerebral vascular accidents (CVAs), hypertension, asthma, gastroparesis, recurrent esophageal strictures requiring monthly dilation, controlled severe depression, hypothyroidism, chronic functional bowel problems, and meningioma. The CVAs resulted in a substantial decline in her overall functional abilities, including left hemiplegia and deterioration in balance. Short-term memory concerns, word-finding difficulties, and episodes of confusion were also attributed to the CVAs. Owing to weakness in her left upper extremity, she required assistance from her husband for all instrumental activities of daily living. Results of blood work were normal, and calculated creatinine clearance was 67 mL/min (using the Cockcroft-Gault equation with ideal body weight).

The patient had difficulty recalling medications, and her husband assisted her with reminders and by dispensing her medications from snap-cap vials.

The initial assessment by the physician identified falls, poor mobility, poor cognition, polypharmacy, and inadequate medication management as the most important issues. The patient was falling 2 to 3 times each week, but had yet to sustain any serious injuries. She had no premonitory symptoms before or at the time of the falls. Falls occurred when changing directions or moving from a lying to a standing position. She had recently undergone a neuropsychological evaluation and was found to have considerable global cognitive impairment consistent with a diagnosis of dementia. The patient's husband indicated that he was tired and overwhelmed. To address these issues, the GDH physiotherapist, occupational therapist, nurse, social worker, recreation therapist, and pharmacist were consulted. The pharmacist conducted a medication assessment, which included a 45-minute comprehensive patient interview, chart review, and communication with both the family and the community pharmacist. Each medication was assessed for indication, effectiveness, safety, compliance, and patient understanding.² The results of the initial part of this assessment are outlined in **Table 1**.

Stop here. If you are using this case report for group discussion, you can obtain instructions, discussion questions, and a blank worksheet on identifying drug-related problems and developing an interprofessional care plan from **CFPlus**.^{*} You might print out the above case description and **Table 1** for discussion before moving on to reading about the results of the medication assessment.

^{*}Instructions, discussion questions, and worksheets on **identifying drug-related problems and developing an interprofessional medication care plan and planning interventions** are available at www.cfp.ca. Go to the full text of the article online and click on **CFPlus** in the menu at the top right-hand side of the page.

EDITOR'S KEY POINTS

- Do not assume cognitive decline is caused by a neurodegenerative process. Thoroughly evaluate the patient for underlying medical comorbidities or adverse effects of medications when diagnosing dementia.
- Reduce fall risk by minimizing benzodiazepines and anticholinergics.
- This case demonstrates the meaningful improvements made by a pharmacist-physician dyad addressing medication-related issues, and several interprofessional team members working together to optimize functioning and quality of life.



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Table 1. History of medication experience: *The patient's allergies and intolerances included penicillin (rash, fever, short of breath), levofloxacin (myalgias), venlafaxine (agitation), and citalopram, nefazodone, bupropion, and trazodone (headaches, light-headedness, dizziness, falls).*

| MEDICATION | REASON FOR USE (IF KNOWN) | KNOWLEDGE, EFFICACY, COMPLIANCE, GOALS, SAFETY ASSESSMENT | DURATION (IF KNOWN) |
|---|--|--|---------------------|
| 2.5 mg of ramipril daily | Hypertension | <ul style="list-style-type: none"> Patients' BP measurements at GDH ranged from 116/64 to 156/70 mm Hg in first 3 weeks of admission (4 of 8 above target) Target BP < 140/90 mm Hg | Years |
| 75 mg of clopidogrel once daily | Secondary prevention | <ul style="list-style-type: none"> 3 CVAs in the past (March and May 2002 and June 2003) | Months |
| 30 mg of domperidone 4 times daily | For IBS when symptoms are primarily constipation | <ul style="list-style-type: none"> Dose recently reduced from 40 mg 4 times daily | Years |
| 250 mg of erythromycin 3 times daily as needed | | <ul style="list-style-type: none"> Patient's husband states erythromycin has made no difference in symptoms | Months |
| 3 tbsp of lactulose 3-4 times daily as needed | | <ul style="list-style-type: none"> Uses after 6-7 days of constipation for 2 days until diarrhea appears | Years |
| 30 mL of psyllium laxative twice daily as needed | For IBS when symptoms are primarily diarrhea | <ul style="list-style-type: none"> Uses after 6-7 days of constipation for 2 days until diarrhea appears | Years |
| 50 mg of pinaverium 3 times daily | | <ul style="list-style-type: none"> Patient unsure if helping | Years |
| 2 mg of loperamide every 6 hours as needed | | <ul style="list-style-type: none"> Uses 5, 2-mg capsules over several hours when diarrhea appears until diarrhea stops | Years |
| 5 mg of chlordiazepoxide with 2.5 mg of clidinium 2-3 times daily | IBS | <ul style="list-style-type: none"> Unsure if helping | Years |
| 200 mg of amitriptyline every night at bedtime | Depression | <ul style="list-style-type: none"> History of severe depression; controlled now | Since 1994 |
| Half-capsule of acetylsalicylic acid, butalbital, codeine, and caffeine as needed | Esophageal spasm | <ul style="list-style-type: none"> Patient states she gets no relief from it; patient states using once weekly, but refill records suggest 4 times weekly | Unknown |
| 30 mg of lansoprazole daily | Heartburn | <ul style="list-style-type: none"> Still having nightly heartburn; uses 3 calcium carbonate antacid tablets each evening | 2 years |
| Calcium carbonate antacid tablets as needed | | | Unknown |
| 0.088 µg of levothyroxine each morning | Hypothyroidism | <ul style="list-style-type: none"> Thyroid-stimulating hormone level is 0.67 mU/L | Years |
| Codeine with acetaminophen as needed (average 2 per day) | Headaches | <ul style="list-style-type: none"> Relieves "tight band" headaches within 20-30 minutes but not "noise-light" headaches | Years |
| Acetaminophen with phenylephrine hydrochloride as needed | NA | NA | Years |
| 10 mg of loratadine once daily | Environmental allergies | NA | Years |
| 2 puffs of budesonide-formoterol inhaler twice daily | Asthma | <ul style="list-style-type: none"> Uses terbutaline every morning (husband states was prescribed because could not use salbutamol inhaler but now using both); hates taste | Years |
| 2 puffs of terbutaline inhaler daily as needed | | | Years |
| 2 puffs of 200-µg-dose salbutamol inhaler every 4 hours as needed | | <ul style="list-style-type: none"> Uses salbutamol 4-5 times daily; has difficulty pressing canister down owing to thumb weakness | Years |

BP—blood pressure, CVA—cerebrovascular accident, GDH—Bruyère Continuing Care Geriatric Day Hospital, IBS—irritable bowel syndrome, NA—not available.

Signs and symptoms were assessed to determine potential drug causes, and drug-related problems were identified.³ The complete medication assessment is outlined in Table 2.

Stop here. If you are using this case report for group discussion, you can obtain instructions, discussion questions, and a blank worksheet on planning interventions from **CFPlus**.^{*} You might print out the above case description and **Table 2** for discussion before reading about how the care plan was implemented.

Given that several medications, particularly the benzodiazepine and the anticholinergics the patient was taking, could have been contributing to the cognitive decline and falls, the following changes were made: chlordiazepoxide and clidinium were stopped, the amitriptyline dose was reduced to 150 mg nightly, and codeine with acetaminophen was stopped. By discharge, there was evidence of substantial improvement in all areas of mental function using multiple standardized psychometric tests, ruling out an underlying progressive dementing process. Her Mini-Mental State Examination

Table 2. Medication care plan

| DRUG-RELATED PROBLEM | ACTION PLAN | MONITORING |
|--|---|---|
| Medications that might contribute to cognitive decline symptoms and fall risk: <ul style="list-style-type: none"> • Chlordiazepoxide • Clidinium • Amitriptyline (also contributing to QT prolongation with erythromycin and domperidone) | <ul style="list-style-type: none"> • Stop chlordiazepoxide and clidinium (tapering not required owing to long benzodiazepine half-life) • Taper amitriptyline to 150 mg at bedtime and consult with geriatric psychiatrist regarding further tapering | Benzodiazepine withdrawal starting at 7–10 days, then for 6 weeks after stopping: insomnia, anxiety, etc Improvement in cognitive symptoms Improvement in anticholinergic symptoms (eg, dry mouth, constipation, dizziness) |
| Constipation–diarrhea cycle might be contributed to by periodic overuse of psyllium laxative and lactulose, followed by loperamide | <ul style="list-style-type: none"> • Change to routine psyllium laxative 1 tsp daily (each morning with water) and lactulose 1–2 tsp every 2–3 days if no bowel movement • Will provide IBS symptom diary | Bowel movements (IBS diary); need for loperamide |
| Might not require all 3 of erythromycin, domperidone, and pinaverium; risk of additive side effects (eg, diarrhea, nausea, vomiting, QT prolongation) | <ul style="list-style-type: none"> • Once psyllium laxative and lactulose use is stable, consider tapering erythromycin • Taper domperidone when effect of erythromycin is known • Taper pinaverium once effect of above is known | Bowel movements (IBS diary) With domperidone tapering, monitor for worsening symptoms of esophageal spasms or reflux |
| Ongoing heartburn (with esophageal strictures); might need lansoprazole increase | <ul style="list-style-type: none"> • Increase lansoprazole to 30 mg twice daily | Heartburn; use of calcium carbonate antacids |
| Half-capsule of acetylsalicylic acid, butalbital, codeine, and caffeine, and acetaminophen with codeine might be contributing to heartburn, constipation, dizziness, and confusion; limited effectiveness of each | <ul style="list-style-type: none"> • Will discuss limiting acetylsalicylic acid, butalbital, codeine, and caffeine dosing with patient • Reduce acetaminophen with codeine to 1 only for “tight band” headache | Esophageal spasms Headache |
| BP higher than target; might benefit from ramipril increase | <ul style="list-style-type: none"> • Increase ramipril to 5 mg | Cough; serum creatinine and electrolyte levels in 1–2 weeks BP target < 140/90 mm Hg |
| At risk of additive side effects owing to overuse of 2 short-acting β_2 -agonists | <ul style="list-style-type: none"> • Stop regular terbutaline inhaler and use only salbutamol inhaler as needed, with hand-grip attachment and antistatic valved holding chamber if necessary | Ability to use salbutamol inhaler |

BP—blood pressure, IBS—irritable bowel syndrome.

score improved from 24 to 30 (out of 30) at discharge and she demonstrated improved attention, concentration, short-term memory, and problem solving. There was substantial improvement in balance, with her Berg Balance Scale score increasing from 12 to 33 (out of 56), and standing tolerance improving from 5 minutes to 30 minutes; her 6-minute walking distance improved from 120 m to 225 m at discharge. There were no reported falls in the final 2 months of her GDH admission. Finally, the patient's gait, strength, and upper extremity function improved dramatically, with lower extremity strength improving from 3 and greater to 4 (out of 5), functional use of her left hand improving from 10% to 80%, and her grip strength improving from 33 mm Hg to 90 mm Hg. Other medication changes were made in order to optimize pharmacotherapy, but these were not

believed to be contributing to the falls and cognitive issues. Her terbutaline inhaler was stopped, lansoprazole was increased, psyllium laxative and lactulose doses were reduced and switched to daily doses, and calcium and vitamin D were added (Box 1). A final medication list is presented in Box 2. During the patient's admission, her husband met with the GDH social worker to address issues of caregiver stress.

Discussion

Addressing medication-related cognitive impairment. Both anticholinergic burden and benzodiazepine use are associated with cognitive decline, including lower Mini-Mental State Examination and Trail Making Test scores and diagnosis of dementia.^{4–9} Increased

blood-brain barrier permeability and age-related declines in cholinergic neurotransmission, as well as increased sensitivity to benzodiazepine medications with age are contributing factors. Discontinuing anticholinergics and benzodiazepines has been shown to decrease the risk of cognitive decline.^{4,10}

The fixed-combination medication chlordiazepoxide-clidinium has been used for the short-term treatment of irritable bowel syndrome, but has limited benefit given the risks associated with long-term use.¹¹ The active metabolite of the benzodiazepine chlordiazepoxide has a half-life of up to 200 hours and, with clearance

delayed in elderly patients, can result in prolonged duration of action and increased adverse effects. Resulting confusion, memory loss, dizziness, daytime sleepiness, falls and fractures, and depressed mood can lead to severe functional status impairment.¹² After the patient's chlordiazepoxide-clidinium was stopped, there were substantial improvements in memory and cognitive function. Although long-term use of benzodiazepines is associated with adverse withdrawal symptoms, the long half-life of this agent likely was the reason that the patient tolerated an abrupt discontinuation. However, 2 months after discontinuation, the patient experienced a generalized tonic-clonic seizure and was started on 300 mg of phenytoin daily by an emergency department physician (eventually tapered to 200 mg daily at the GDH owing to symptoms of fatigue and dizziness, accompanied by a phenytoin level of 109 µmol/L). While

Box 1. Intervention timeline: *Initial pill burden = 24; initial number of medications = 20; final pill burden = 9; final number of medications = 14.*

Week 1

- No new medication changes

Week 2

- Stop chlordiazepoxide-clidinium
- Decrease amitriptyline to 150 mg at bedtime

Week 3

- No new medication changes

Week 4

- No new medication changes

Week 5

- No new medication changes

Week 6

- Change psyllium laxative to 1 tbsp each morning with water and lactulose to 1-2 tbsp every 2-3 days if no bowel movement and complete an irritable bowel syndrome diary
- Educate regarding hand-grip adapter to help with salbutamol inhaler administration

Week 7

- Emergency department physician started 300 mg of phenytoin daily

Week 8

- No new medication changes

Week 9

- No new medication changes

Week 10

- Start calcium and vitamin D supplements at supper
- Decrease phenytoin to 250 mg daily
- Increase psyllium laxative to 3 tbsp daily and lactulose to 2 tbsp daily

Week 11

- No new medication changes

Week 12

- Decrease phenytoin to 200 mg daily

Week 13

- No new medication changes

Week 14

- Increase lansoprazole to 30 mg twice daily

Week 15

- No new medication changes

Box 2. Medication schedule at discharge

Morning

- 30 mg of lansoprazole
- 2.5 mg of ramipril
- 0.088 µg of levothyroxine
- 200 mg of phenytoin
- 30 mg of domperidone
- 2 puffs of budesonide-formoterol inhaler
- 50 mg of pinaverium
- 75 mg of clopidogrel
- 250 mg of erythromycin
- 2 tbsp of lactulose
- 2 tbsp of psyllium laxative

Afternoon

- 30 mg of domperidone
- 50 mg of pinaverium
- 250 mg of erythromycin

Supper

- 30 mg of lansoprazole
- 500 mg of calcium
- 1000 IU of vitamin D
- 30 mg of domperidone
- 2 puffs of budesonide-formoterol inhaler
- 50 mg of pinaverium
- 250 mg of erythromycin

Bedtime

- 150 mg (2 × 75 mg) of amitriptyline

As needed

- 1 puff of salbutamol inhaler
- 10 mg of loratadine
- 2 mg of loperamide
- Acetaminophen with codeine
- Half-capsule of acetylsalicylic acid, butalbital, codeine, and caffeine
- Calcium carbonate antacid
- Acetaminophen with phenylephrine hydrochloride

seizures occur rarely following benzodiazepine withdrawal, the patient had a number of risk factors (meningioma, multiple CVAs) and it was unclear whether the chlordiazepoxide had been masking a seizure disorder or whether this was a single adverse drug withdrawal event. As the risks associated with long-term use of chlordiazepoxide (especially in terms of its contribution to her incorrect diagnosis of dementia) outweigh its ability to prevent seizures, a more appropriate anticonvulsant seemed warranted.

Anticholinergic medications are known to cause numerous side effects, notably constipation, dry mouth, urinary retention, dizziness, blurred vision, and confusion. The antispasmodic, clidinium, and tricyclic antidepressant, amitriptyline, both contributed substantially to anticholinergic load. While we were able to stop the chlordiazepoxide-clidinium with no substantial adverse withdrawal effects, stopping the amitriptyline was somewhat more difficult, as the patient's depression had been severe and resistant to multiple other medications in the past. The patient's geriatric psychiatrist recommended dose reduction to no lower than 150 mg at bedtime. With this dose reduction and eliminating the clidinium, the patient's anticholinergic burden was meaningfully reduced.

Addressing medication-related falls. Benzodiazepines and anticholinergic medications cause central nervous system depression and increase the risk of falls in elderly patients.^{13,14} These medications have an additive effect—similar to their effect on cognition—and the likelihood of falls increases when they are used in combination, especially when amplified by pre-existing medications. While the patient's previous CVAs and related impairment were contributing to fall risk, the chlordiazepoxide-clidinium and amitriptyline, and some dizziness likely caused by other medications, were important to consider. In addition to stopping chlordiazepoxide-clidinium and reducing amitriptyline, the GDH physiotherapist facilitated lower extremity strength training and implemented a stretching and balance exercise program. The occupational therapist provided gait, balance, and transfer training and educated the patient about fall prevention techniques. An improvement in Berg Balance Scale score of 5 points indicates a true change in functional balance.¹⁵ This patient's Berg Balance Scale score improved by 21 points. With strength, balance, and standing tolerance improved, the patient did not report any falls during the last 2 months of her GDH admission. The GDH recreation therapist assisted the patient in finding a community exercise program, which she readily agreed to attend.

Addressing other drug-related problems. While a number of medications used in the treatment of the patient's

bowel problems might have been contributing to dizziness and fall risk, the program admission period allowed for adjustments to her psyllium laxative and lactulose regimens with good effect. By discharge, bowel movements were regular, with 2 to 3 per week and no persistent symptoms of constipation or diarrhea; loperamide was no longer required. Improvement in constipation might also have been related to reduction in her anticholinergic load. The lansoprazole dosage was increased to twice daily for ongoing heartburn and this was effective in reducing symptoms. Her gastroenterologist was consulted regarding follow-up after GDH discharge.

Combined use of 2 β_2 -agonists for relief of asthma symptoms can contribute to additive adverse effects and so the patient was advised of their similarity and asked to stop terbutaline. Using a salbutamol inhaler with a hand-grip adapter and an antistatic valved holding chamber, she was ultimately able to use the appropriate technique to improve effectiveness and minimize systemic absorption from breathing in too quickly. Calcium and vitamin D were added to the medication regimen. Codeine with acetaminophen was no longer required by the end of the admission, as her headaches had resolved. No changes to her ramipril dose were needed as her blood pressure during the second half of admission was usually below the target range.

Conclusion

When assessing older patients for cognitive and functional decline, a full review of medical issues and medications is required. It is important not to assume that cognitive decline is dementia until you have turned over all the rocks. In this case, despite an initial diagnosis of dementia from a neuropsychologist, cognitive decline was not related to an underlying neurodegenerative process but rather was the result of medications that were also affecting fall risk. The case demonstrates the meaningful improvements made by a pharmacist-physician dyad addressing medication-related issues, and several interprofessional team members working together to optimize functioning and quality of life. The quality of life of the patient's husband also improved, as he felt considerably less stressed at discharge.

This patient was admitted to the GDH 3 years later following a minor stroke. At that time, she had maintained her gains in terms of balance and walking distance and showed no evidence of impaired cognition. Several of the gastrointestinal medications, as well as her amitriptyline and phenytoin, had been successfully stopped in the interim period. When this woman was contacted for consent regarding the case report 8 years after her first admission, she immediately recalled the names of team members. She readily provided consent, stating she had had no further falls and that the GDH team had "saved her life," demonstrating that these changes had a long-lasting effect. 

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Competing interests

None declared

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