PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #354
DEPRESCRIBING CHOLINESTERASE INHIBITORS AT THE END OF LIFE
Pamela Liao MD CCFP, Giulia Anna Perri MD CCFP (COE) (PC)

Background Cholinesterase inhibitors (CHEIs) are the most commonly prescribed agents to delay the progression of cognitive decline from dementia, Parkinson's disease, and other degenerative neurologic diseases. Yet, as dementia progresses, the effectiveness of CHEIs diminish while adverse effects can mount. Other *Fast Facts* addressed dementia's natural history (# 150) and tension points in medical-decision-making (#84). This *Fast Fact* addresses deprescribing considerations for CHEIs.

Dementia Severity (1)
- Mild: characterized by specific areas of functional dependence, such as trouble managing finances
- Moderate: characterized by multiple areas of dependence on others, particularly being unable to drive and having difficulty with bathing and shopping.
- Severe: characterized by total dependence and motor and balance impairments.

Therapeutic Rationale of CHEIs for Dementia Although there are many types of dementia, Alzheimer's disease is the most common and its progression is associated with loss of cholinergic neurons and decreased levels of acetylcholine (2,3). CHEIs inhibit the cholinesterase enzyme from breaking down acetylcholine and thereby increases both the level and duration of action of acetylcholine in the brain. Three CHEIs are approved for mild to moderate dementia -- donepezil, galantamine, and rivastigmine -- with no notable differences in effectiveness. Donepezil is also approved for severe Alzheimer's disease (4). Each is available in oral form, but only rivastigmine is available in a transdermal patch (5). CHEIs have been studied in multiple types of cognitive decline including vascular dementia and Parkinson-related illnesses (6). Even though they are associated with a mild but statistically significant improvement in cognitive function, behavior, and activities of daily living (ADLs) for various types of cognitive decline (6,7), prescribing beyond Alzheimer's disease is off-label.

Deprescribing Considerations for CHEIs CHEIs have not been shown to slow the progression of dementia, prolong survival, nor prevent nursing home admissions (8). Therefore, it can be hard to justify continuing CHEIs for dementia patients who become bedbound or dependent on all ADLs. CHEIs are associated with significant adverse effects. Nausea, vomiting, and diarrhea are common reasons for discontinuation of CHEIs as are dizziness and headaches (9). CHEIs also increase the risk of syncope, falls, and fractures in patients who have or develop bradycardia or cardiac conduction disease. The usual monthly cost for CHEIs is approximately $200 (US) and they usually are not covered by hospice agencies if the admitting diagnosis is dementia. Considering these factors, clinicians should consider CHEI discontinuation in the following clinical scenarios (10):
- Intolerable side effects or poor adherence.
- Significant cognitive or functional decline: e.g. patient progresses from moderate to severe dementia.
- A comorbid illness that limits life expectancy to < 1 year.
- Prior to hospice admission.
- Sentinel medical events such as aspiration pneumonia, a fracture, dysphagia, or frequent falls.

Counseling About CHEI Deprescription The discussion about deprescribing CHEIs can be stressful for families, especially if done at a time of a significant change in condition or a medical crisis. Clinicians can prepare families for these discussions by counseling them about appropriate times to deprescribe CHEIs when initiating CHEIs and revisiting this discussion at regular intervals (e.g. quarterly or annually) throughout the illness trajectory. Exploring the understanding of the role of CHEIs in the disease trajectory, its side effects, and what to expect once deprescribed, may help facilitate this discussion.

Tapering CHEIs Avoid abrupt discontinuation. If possible, taper by reducing the CHEI dose 25-50% every 1-2 weeks, to avoid withdrawal symptoms (9,11,12). This can be done by adjusting the oral dose or changing to a transdermal route for patients who cannot swallow safely oral medications anymore.

CHEI Withdrawal Symptoms usually emerge 3 to 7 days after CHEI discontinuation and can take up to 3 weeks to resolve (13,14). They are predominantly neuropsychiatric in nature and can vary in severity from subtle (e.g. difficulty concentrating, insomnia, and a labile mood) to more overt (e.g. hallucinations,

delusions, altered consciousness, and agitation) (14). Recognition is vital, as withdrawal symptoms can be mistaken for depression or delirium.

CHEI Withdrawal Management Although there are a no guidelines for the management of withdrawal symptoms, the following steps based on expert opinion may be reasonable:

- Close observation for new neuropsychiatric withdrawal symptoms whenever CHEIs are discontinued.
- If withdrawal symptoms are distressing, consider re-starting the CHEI at the lowest possible dose.
- If restarting the CHEI is not possible or inappropriate, supportive care for withdrawal symptoms often include anti-dopaminergic agents such as haloperidol (15).
- If an oral route is unavailable, there is evidence that the rivastigmine transdermal patch either started immediately or after 7 days of discontinuation of the CHEI, is safe and well tolerated (16).

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Authors' Affiliations: University of Toronto; Toronto ON; Baycrest Health Science Centre, Toronto ON.

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