

# Tricyclic antidepressants and diabetic peripheral neuropathy: Deprescribing considerations for brain health

Moises Martinez III, PharmD<sup>1</sup>; Jasmine Gonzalvo, PharmD, BC-ADM, CDCES, FADCES<sup>1,2</sup>; Ana Hernández Calderón, PharmD<sup>1</sup>; Nathan Macatangay, PharmD<sup>1</sup>; Noll Campbell, PharmD, MSc<sup>1,2,3</sup>

<sup>1</sup> Purdue University College of Pharmacy, West Lafayette, IN; <sup>2</sup>Eskenazi Health, Indianapolis, IN; <sup>3</sup>Indiana University Center for Aging Research, Indianapolis, IN

## Background

- Anticholinergic medications are consistently associated with cognitive decline and incident dementia in epidemiologic studies.
- Tricyclic antidepressants (TCAs) are a treatment option for painful diabetic peripheral neuropathy (DPN).
- Treatment guidelines poorly highlight these risks and alternative approaches among those with DPN.

## Specific Aims

- Aim 1:** Highlight existing evidence supporting the risk of long-term anticholinergic use.
- Aim 2:** Review current DPN guidelines for content related to cognitive burden associated with long-term TCA use.
- Aim 3:** Propose guidance on drug-free intervals and counseling points for providers to facilitate deprescribing treatments for painful DPN.

## Methods

A literature review was conducted, identifying treatment guidelines with recommendations for painful DPN and literature that supports cognitive risk of long-term anticholinergic use.

Both guidelines and literature were assessed/reviewed on their recommendations to use TCAs, side effects discussed regarding TCAs, and any recommendation for drug-free intervals to facilitate deprescribing.

Literature was further reviewed for association of TCAs with mild cognitive impairment (MCI) and incident dementia to inform and propose guidance on drug-free intervals to facilitate deprescribing.

## Results

**9**  
total guidelines recommend TCAs for painful DPN

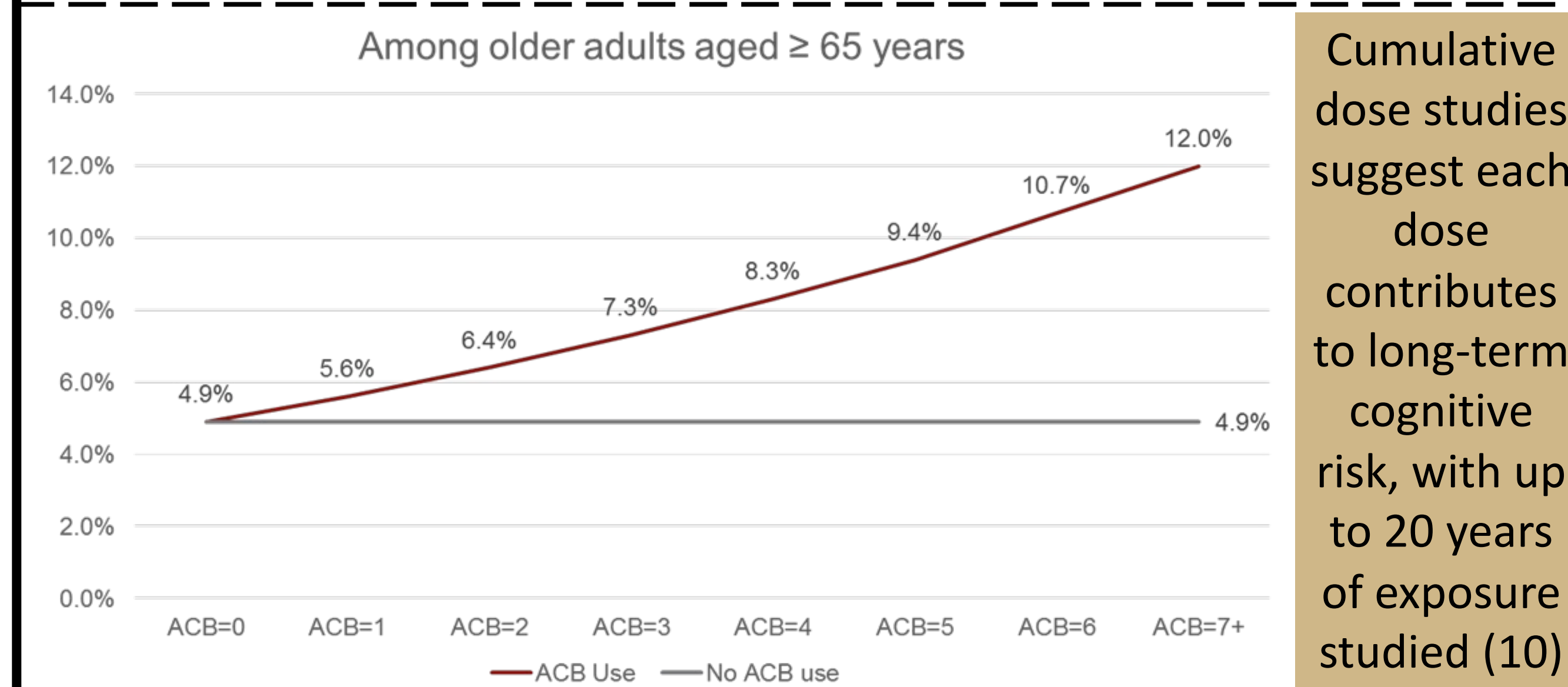
**2**  
of those guidelines discuss any cognitive risks (increased fall risk in older adults)

**0**  
guidelines recommend drug-free intervals or deprescribing for any medication used to treat DPN

Our recommendations are based on published literature of antidepressant deprescribing / withdrawal publications and opinion-based strategies

### Literature Evaluation – Landmark Evidence for Adverse Cognitive Effects:

Association between ACh & Dementia			Association between ACh & MCI		
Strong ACh over 6 yrs	OR: 1.54 (1.21-1.96)	(2)	All Strong ACB (Norm to MCI)	OR: 1.15 (1.01-1.31)	(4)
Strong ACB total score	OR: 1.36 (1.17-1.58)	(3)	Musc ACB (Norm to MCI)	OR: 1.34 (1.09-1.65)	
Strong ACh for ≥ 3/10 yrs	OR: 1.54 (1.21-1.96)	(6)	Musc ACB (Reversion: MCI to Norm)	OR: 0.63 (0.40-0.99)	
Strong ACh for ≥ 4/20 yrs	OR: 1.40 (1.30-1.50)	(10)			



Recommendation: Gradual deprescribing taper of TCAs over two to four weeks

Additional prospective research is necessary to address whether stopping anticholinergics reduces dementia risk

## 3 Key Takeaways

Several current guidelines for treatment of painful DPN include TCAs as treatment options without discussing the risk for long-term cognitive decline. None of the current guidelines encourage drug-free intervals to facilitate deprescribing medications used to treat DPN. To our knowledge, there is no available data specific to patients experiencing diabetes and risk of MCI.

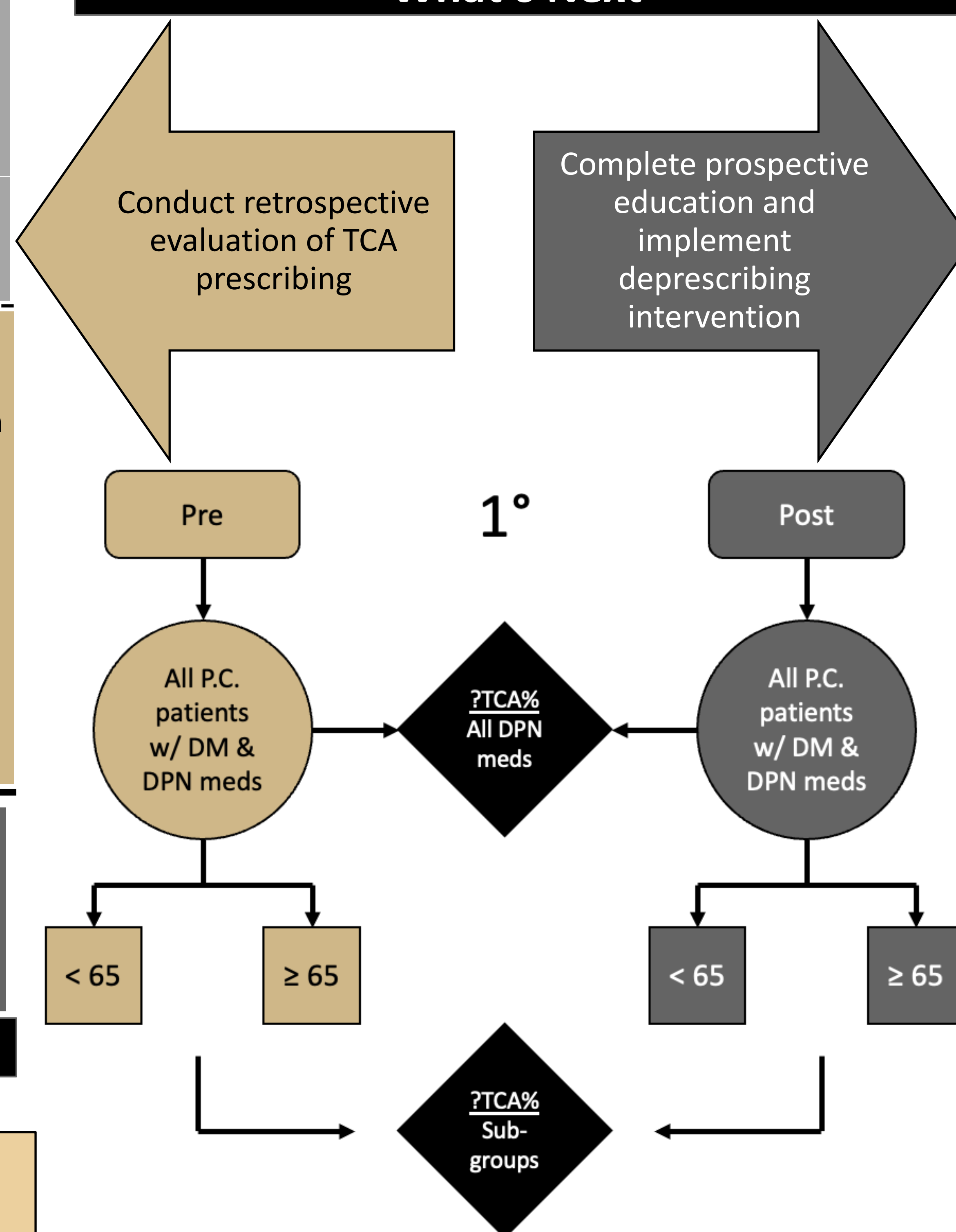
A growing body of evidence associates use of anticholinergic medications with mild cognitive impairment and incident dementia. The association is consistent across multiple studies, including exposure over a decade prior to diagnosis of dementia. Consistently among the culprits are TCAs, particularly amitriptyline.

Providers should review the benefits and risks of long-term use of TCAs with persons with diabetes. While recommendations for deprescribing strategies are not yet evidence-based, for individuals taking TCAs for long-term management of DPN, deprescribing with a taper over two to four weeks represents a reasonable approach consistent with prescribing recommendations.

## Conclusions

- Diabetes care and education specialists must discuss the long-term cognitive effects of TCA use in individuals experiencing DPN.
- Currently, no evidence-based guidelines for deprescribing exist, which presents an opportunity to study the advantages and disadvantages of deprescribing.
- Drug-free intervals might facilitate deprescribing of TCAs.
- Dose reduction and deprescribing slowly over 2-4 weeks could be introduced to help weigh benefits against future risk of dementia.

## What's Next



## Disclosures

There is no source of funding to report for this research.

## References

- Boyle J, Eriksson MEV, Gribble L, et al. Randomized, Placebo-Controlled Comparison of Amitriptyline, Duloxetine, and Pregabalin in Patients With Chronic Diabetic Peripheral Neuropathic Pain. *Diabetes Care* 35:2451–2458, 2012. doi:10.2337/dc12-0656.
- Campbell NL, Boustani MA, Lane KA, et al. Use of anticholinergics and the risk of cognitive impairment in an African American population. *Neurology*. 2010; 75(2):152-159.
- Campbell NL, Perkins AJ, Bratt P, et al. Association of Anticholinergic Burden with Cognitive Impairment and Health Care Utilization Among a Diverse Ambulatory Older Adult Population. *Pharmacotherapy*. 2016; 36(2):196-202.
- Campbell NL, Lane KA, Gao S, et al. Anticholinergics Influence Transition from Normal Cognition to Mild Cognitive Impairment in Older Adults in Primary Care. *Pharmacotherapy*. 2018; 38(5):511-519.
- Draznin B, Aroda VR, Bakris G, et al. Retinopathy, Neuropathy, and Foot Care: Standards of Medical Care in Diabetes—2022. *Diabetes Care* 2022;45:S185–S194. doi:10.2337/dc22-S012
- Gray SL, Anderson ML, Dublin S, et al. Cumulative Use of Strong Anticholinergics and Incident Dementia - A Prospective Cohort Study. *JAMA Intern Med*. 2015; 175(3):401-407.
- Lindsay TJ, Rodgers BC, Savath V, Hettinger K. Treating Diabetic Peripheral Neuropathic Pain. *Am Fam Physician*. 2010;82(2):151-158.
- Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care* 2017;40:136–154 doi:10.2337/dc16-2042
- Price R, Smith D, Franklin G, et al. Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary. *Neurology*® 2022;98:31-43. doi:10.1212/WNL.0000000000013038
- Richardson, K, Fox C, Maidment I, et al. Anticholinergic drugs and risk of dementia: case-control study. *BMJ* 2018;361:k1315