



### Drug information question: What is a prescribing cascade? The case of calcium channel blocker induced peripheral edema and loop diuretics.

A [prescribing cascade](#) occurs when a drug-related adverse event leads to the addition of a subsequent medication to treat the adverse event.<sup>1</sup>

One of the BC Provincial Academic Detailing (PAD) Service's previous topics, [Hypertension in Older Adults \(PDF, 615KB\)](#), describes that calcium channel blockers (CCBs) can cause peripheral edema which is a dose and treatment-duration related adverse event.<sup>2</sup> In British Columbia, under the Reference Drug Program, [amlodipine is the reference drug \(PDF, 248KB\)](#) within the dihydropyridine CCB class.<sup>3</sup> The Health Canada prescribing information for amlodipine reports that the frequency of peripheral edema ranges from 3% to 11% across the 5 to 10 mg dose range.<sup>4</sup>

Two recent observational studies identified an association between the initiation of a CCB and the subsequent addition of a loop diuretic in people without heart failure.<sup>5,6</sup> Amlodipine was the most commonly prescribed CCB in both studies (90%, 80% respectively).<sup>5,6</sup>

- In a [2019 U.S. cohort study](#) of 1.2 million adults who had been initiated on a dihydropyridine CCB, 1.4% of people had a loop diuretic subsequently prescribed within a year.<sup>5</sup> The prescribing cascade occurred more often in older adults (2.3%) and in those prescribed a high dose of CCB (2.5%). High-dose amlodipine was defined as  $\geq 10$  mg per day.
- In a [2020 Ontario cohort study](#) of 41,086 older adults with hypertension who were newly-prescribed any CCB, 1.4% of people had a loop diuretic prescribed at 90 days. This increased to 3.5% at 1 year of follow up.<sup>6</sup> The risk of being prescribed a loop diuretic in the CCB group compared to those prescribed an ACEI or an ARB increased with time: the first 30 days (HR 1.68), the next 31-60 days (HR 2.26) and in the next 61-90 days (HR 2.40).

A 2019 interactive, clinically-focused, and accessible Tweetorial (educational Tweet thread) explains that the pathophysiology of CCB induced peripheral edema is likely multifactorial but probably not caused by sodium retention.<sup>7</sup> Diuretics are not known to be an effective treatment.<sup>7</sup>

Here is the link to the Tweetorial, "How do calcium channel blockers (e.g., amlodipine) cause edema?"<sup>7</sup>

▶ [https://twitter.com/tony\\_breu/status/1134521056167944192?s=20](https://twitter.com/tony_breu/status/1134521056167944192?s=20)

Further, loop diuretics may introduce additional adverse events, medication burden and laboratory monitoring.

**Conclusion: Given the uncertain value of loop diuretics as a treatment for calcium channel blocker induced peripheral edema, consider reducing the dose of the calcium channel blocker or switching to an alternative evidence-based antihypertensive.**

<sup>1</sup>MCCARTHY J *Am Geriatr Soc* 2019;67:1023-26 (PMID: 30747997); <sup>2</sup>BC PAD Hypertension Newsletter 2017; <sup>3</sup>British Columbia Reference Drug Program;

<sup>4</sup>Health Canada Drug Product Database; <sup>5</sup>VOURI *JAMA Netw Open* 2019;2:e1918425 (PMID: 31880802); <sup>6</sup>SAVAGE *JAMA Int Med* 2020;180:643-51

(PMID: 32091538); <sup>7</sup>BREU @tony\_breu Twitter May 31, 2019