

# A Decision Tree Estimating Total Cost of Care Using Exposure-Adjusted Discontinuation: Capsaicin 8% Versus Oral Treatments for Painful Diabetic Neuropathy in the United States

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## Background and Rationale

Diabetic peripheral neuropathy (DPN) remains a common complication of diabetes, with estimates reporting that up to 50%-66% of patients with diabetes will develop DPN during their lifetime<sup>1</sup> and approximately 20%-40% of these patients will experience pain associated with DPN, known as painful DPN (PDPN).<sup>2</sup>

The standard of care for PDPN has historically been led by oral treatments<sup>3-6</sup>; however, these therapies have been associated with high discontinuation rates due to adverse effects, limited efficacy, dose titration challenges, worsening symptoms, or patient dissatisfaction.<sup>7-9</sup> Inadequate pain control can lead to increased healthcare utilization, including outpatient visits, diagnostic testing, medication changes, and in severe cases, emergency department visits and hospitalizations.<sup>6-8,10,11</sup> Medical claims-based studies have demonstrated that patients with lower medication adherence incur higher total healthcare costs, which provides a structural justification for this model.<sup>12,13</sup>

While economic evaluations of PDPN therapies have traditionally emphasized drug acquisition cost, these analyses do not account for how differences in treatment discontinuation and persistence may influence healthcare utilization. Thus, modeling the redistribution of annual resource use during periods of undertreated PDPN may provide a clearer estimate of total cost of care.

## High-Concentration Capsaicin (8%) Topical System (HCCTS)

HCCTS is a chemoneurolytic agent that is approved by the FDA for neuropathic pain associated with postherpetic neuralgia (2009) and DPN of the feet (2020).<sup>14-16</sup>

In clinical trials, it has provided pain relief for up to 3 months following a single application, with low treatment-related discontinuation rates.<sup>14</sup>

## Objective

To estimate the 12-month total cost of care associated with treatment discontinuation for HCCTS versus oral PDPN therapies from a US payer perspective, as existing PDPN economic models inadequately capture the costs associated with therapy withdrawal and related medical care.

## Methods

A decision tree economic model was developed to estimate total direct healthcare costs following initiation of therapy for PDPN adjusting for exposure and discontinuation.

### Model Structure

- The model compared HCCTS with five commonly used oral PDPN treatments: amitriptyline, duloxetine, gabapentin, pregabalin, and venlafaxine.
- A simulated group of 1,000 adults initiating PDPN treatment was followed over 12 months, representing 12,000 total person-months of observation.
- Starting at treatment initiation with HCCTS or oral therapy, the decision tree branches at 3-month intervals into continuation or discontinuation; using these intervals enables comparability of discontinuation across all PDPN treatments (Figure 1).
- Medication discontinuation was estimated and calculated as person-time, and resource use was applied during the off-treatment periods.

### Identification of Data Sources

- A systematic literature search informed all model inputs.
- Treatment-specific discontinuation rates were derived from 78 randomized clinical trials (~15,092 patients), healthcare utilization from 14 US claims-based cohorts (~2.06 million patients), resource unit costs from 10 cohorts (~401,202 patients), and diagnostic testing patterns and costs from 7 studies (~207,436 patients).

## Methods (cont.)

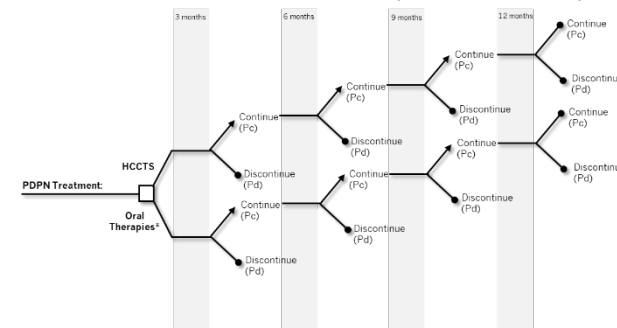
### Base Case Analysis

- When therapy is discontinued (time off treatment), patients enter an undertreated PDPN state and diagnostic evaluation pathway with increased healthcare resource use and, where applicable, therapy switching; with continued therapy (time on treatment), patients accrue drug and routine care costs.
- Healthcare utilization includes emergency room (ER) visits, inpatient hospital admissions, outpatient encounters, physician office visits, and diagnostic testing. Drug acquisition costs include all administration-related costs.

### Sensitivity Analysis

- Probabilistic sensitivity analysis used Monte Carlo simulation to jointly vary discontinuation and cost parameters.

Figure 1. Treatment Discontinuation Decision Tree (Base Case Model)

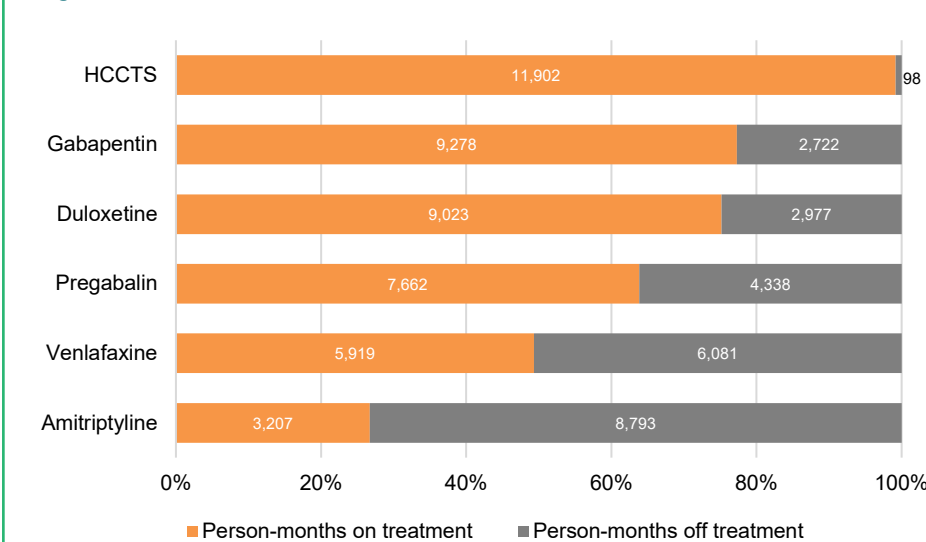


Decisions to continue or discontinue as recommended by healthcare provider and aligned with routine monitoring.

## Results

- HCCTS had the lowest discontinuation probabilities, resulting in 11,902 annual person-months on treatment vs 3,207-9,587 for orals out of a total 12,000 person-months (Figure 2).

Figure 2. Treatment Discontinuation Rates and Person-Months On vs Off Treatment



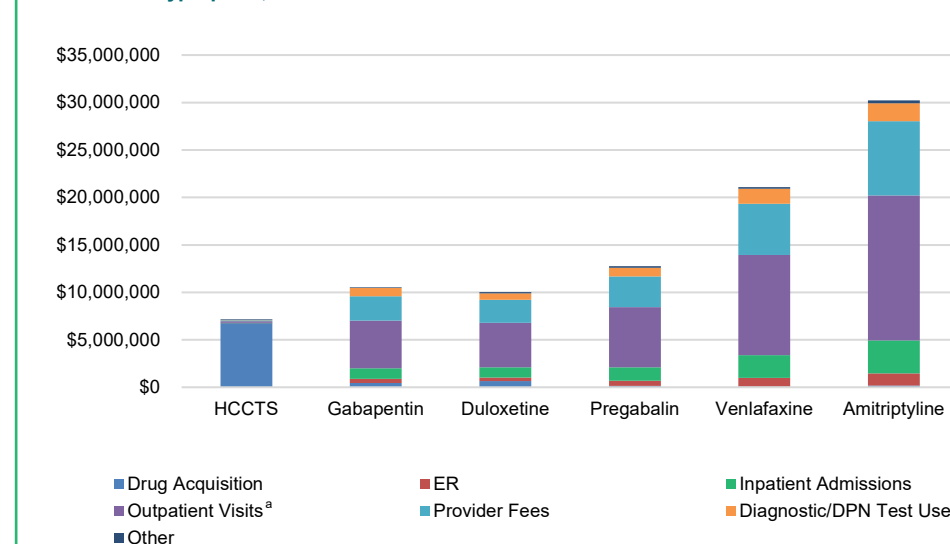
- With the greatest amount of time on treatment, HCCTS resulted in lower healthcare resource utilization and the lowest total 12-month cost among all studied PDPN treatments (Table 1).
  - Annual total costs savings with HCCTS vs all oral treatments ranged from \$2.9M-\$23.1M.
  - Monte Carlo sampling across parameters demonstrated a 90%-99% probability that oral therapies incurred higher total costs than HCCTS over 12 months.

Table 1. Probabilistic Sensitivity Analysis: Annual Total Cost of Care per 1,000 Patients

Treatment	Mean Annual Total Cost of Care (95% CI)	Incremental Cost vs HCCTS (\$)	Probability (More Expensive vs HCCTS)
HCCTS	\$7,154,818 (\$4,669,691-\$10,231,354)	Reference	Reference
Gabapentin	\$10,538,715 (\$7,267,486-\$14,748,385)	\$3,383,897	93.0%
Duloxetine	\$10,013,104 (\$7,201,040-\$13,871,009)	\$2,858,286	90.0%
Pregabalin	\$12,744,820 (\$8,964,732-\$17,470,254)	\$5,590,002	98.8%
Venlafaxine	\$21,086,287 (\$14,541,92-\$28,877,262)	\$13,931,468	99.8%
Amitriptyline	\$30,221,532 (\$21,133,10-\$42,381,1)	\$23,066,714	99.7%

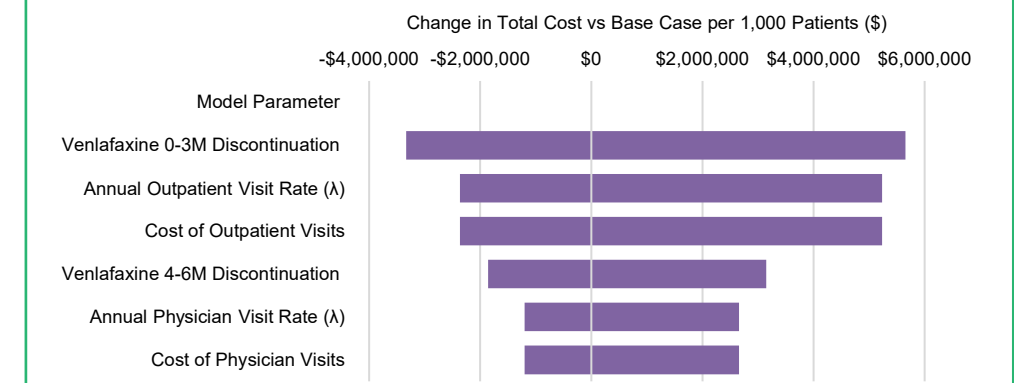
- Oral treatments had higher discontinuation rates (total time off treatment), which led to significant downstream medical costs despite their lower drug acquisition costs, largely driven by outpatient and physician visits (Figure 3).
- Treatment discontinuation magnitude was the dominant driver of cost variation (Figure 4).
- In scenario analyses, total costs for HCCTS remained stable across assumptions, whereas oral therapy costs varied by two- to three-fold depending on discontinuation timing and off-treatment healthcare utilization intensity.

Figure 3. Probabilistic Sensitivity Analysis: Mean Annual Costs by Treatment and Resource Type per 1,000 Patients



\*All outpatient services including hospital.

Figure 4. Sensitivity Analysis: Change in Total Cost of Care by Parameter



## Conclusions

- This analysis established a structured, exposure-driven decision tree model integrating treatment discontinuation to support more accurate economic evaluation of total cost of care among commonly used PDPN treatments.
- Within the model, treatment discontinuation contributed to differences in total 12-month healthcare costs in PDPN, with the greatest persistence observed among patients treated with HCCTS.
- HCCTS treatment persistence minimized time spent in an undertreated state, reduced downstream healthcare utilization, and offset drug acquisition costs, resulting in annual total cost savings of \$2.9M-\$23.1M, mainly attributable to outpatient hospital visits and provider fees, versus oral PDPN therapies for a cohort of 1,000 patients.
- HCCTS was cost-favorable in the base case and across most sensitivity scenarios, with high persistence rates reducing medical resource utilization under varied modeling assumptions.
- These findings highlight the economic importance of treatment persistence when evaluating PDPN therapies from a healthcare payer perspective.

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## Abbreviations

DPN, diabetic peripheral neuropathy; ER, emergency room; FDA, Food and Drug Administration; HCCTS, high-concentration capsaicin (8%) topical system; M, month; PDPN, painful diabetic peripheral neuropathy.