Lower systemic analgesic use in patients with painful diabetic peripheral neuropathy (PDPN) of the feet treated with high-concentration capsaicin topical system (HCCTS) in a real-world clinical setting

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Objective

- To evaluate the impact of repeated HCCTS treatments on analgesic concomitant medication use in patients with PDPN of the feet who have a history of polypharmacy.

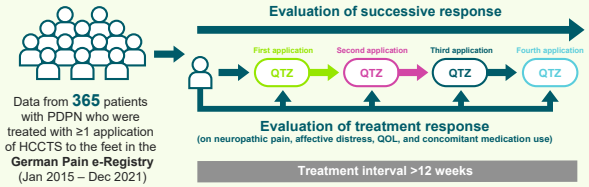
Introduction

- Diabetic peripheral neuropathy (DPN) is a widespread, debilitating, and difficult-to-treat complication, impacting up to 50% of individuals with diabetes.[1,2]
- The most commonly prescribed first-line therapies for managing painful PDPN are oral agents, principally pregabalin, gabapentin, amitriptyline, or duloxetine.[3]
  - Oral opioids are also used, but they are not recommended by most professional societies including the American Society of Pain and Neuroscience (ASPN) and the American Academy of Neurology (AAN) due to risk of addiction and side effects.[4,5]
- Oral therapies often fail to provide adequate pain relief: it is estimated that only 10–25% of patients achieve a clinically meaningful response to oral therapies vs placebo.[6]
- Oral therapies are also limited by systemic side effects; for example, somnolence, dizziness, nausea, fatigue, and gastrointestinal issues.[7]
- For these reasons, patients with PDPN of the feet often cycle through multiple oral treatments. In a survey of 506 patients, 70% reported trying two or more pain medications, while 33% had tried three or more since their diagnosis.[8]
- Combination therapy is required in an estimated 90% of patients,[6] and this can entail a significant pill burden and risk of drug–drug interactions, which can lead to side effects and serious health complications.[9]
- Polypharmacy, side effects, and health complications lead to low persistence: one US study in patients with DPN (n=12,074) found that, at 1 year, 64.4%, 71.7%, and 76.7% of patients had discontinued duloxetine, gabapentin, and pregabalin, respectively.[3]
- There is currently a significant need for additional treatment strategies in this complex and polypharmacy patient population with unresolved pain.
- In a survey of 506 patients with PDPN of the feet, 58% were not satisfied with their current treatment.[8]
  - Additionally, one-third of patients reported that they did not want to add to their pill burden[8] (which may include medications for metabolic control of diabetes as well as management of diabetes-related complications, including pain).
- One alternative to oral treatments is topical therapy. The high-concentration capsaicin (8%) topical system (HCCTS; Qutenza®) is approved by the US Food and Drug Administration for the treatment of neuropathic pain associated with DPN of the feet and postherpetic neuralgia.[10]
- Real-world evidence suggests that HCCTS helps patients with non-diabetic peripheral neuropathic pain reduce their use of oral therapies, including opioids.[11] Therefore, we analyzed data from the CASPAR study to determine if similar effects were observed in patients with PDPN of the feet.

Methods and materials

- CASPAR (registry number: EUPAS 1000000106) was a retrospective, non-interventional cohort study conducted using data from the German Pain e-Registry.[12]
- The study included 365 patients with PDPN of the feet who received 1–4 HCCTS treatments at approximately 3-month intervals, followed for 12 months (**Figure 1**).
- Data were analyzed from patients who had received ≥1 HCCTS treatment, had ≥12 months of follow-up data, and recorded ≥1 post-baseline/post-HCCTS measure within the evaluation period.
- This analysis focuses on the following outcomes:
  - 24-hour average pain intensity (API) using the visual analog scale (VAS) from 0 (no pain) to 100 (worst pain conceivable).
  - The use of concomitant pain medication measured by the percentage of patients receiving analgesic co-medication, including antiepileptics (most common: pregabalin, gabapentin, carbamazepine), antidepressants (most common: amitriptyline, duloxetine, citalopram), mild opioids (codeine, dihydrocodeine, tilidine, tramadol), and strong opioids (morphine, hydromorphone, oxycodone, buprenorphine, fentanyl, methadone, tapentadol, others).

Figure 1 – Design of CASPAR



Data from **365** patients with PDPN who were treated with ≥1 application of HCCTS to the feet in the **German Pain e-Registry** (Jan 2015 – Dec 2021)

HCCTS, high-concentration capsaicin topical system; PDPN, painful diabetic peripheral neuropathy; QOL, quality of life; QTZ, Qutenza®.

Conclusions

- In this cohort of patients with a history of polypharmacy, HCCTS led to decreases in use of concomitant pain medications and had an opioid-sparing effect.
- In all cohorts, the use of concomitant pain medications decreased following repeated HCCTS treatments. In the cohorts that discontinued HCCTS treatment, concomitant medication use tended to increase following discontinuation.
- The cohort that received four HCCTS treatments demonstrated the greatest reduction in the proportion of patients taking concomitant medications.
- Approximately one-third of patients who received four HCCTS treatments were able to discontinue concomitant pain medication entirely by month 12.
- These results show the real-world value of HCCTS in providing effective pain relief and decreasing the significant medication burden in patients with PDPN, who often struggle with high levels of polypharmacy and are exposed to the risk of systemic side effects.

Results

Baseline characteristics

- Baseline characteristics are summarized in **Table 1**.
- All patients were taking concomitant medications for neuropathic pain at baseline.

Table 1 – Baseline characteristics

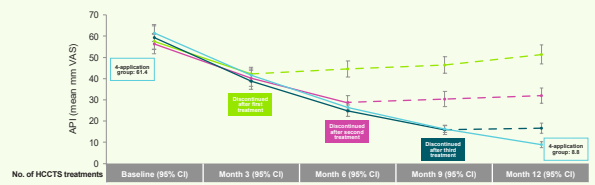
Baseline characteristic	Patients (n=365)
Sex, female, n (%)	185 (50.7)
Age, years, mean ± SD	66.1 ± 13.3
Body mass index, kg/m², mean ± SD	31.5 ± 7.2
Pain duration, years, mean ± SD	4.6 ± 3.6
24-hour API, mm VAS, mean ± SD (95% CI)	58.7 ± 18.8 (56.5–60.9)
mPDI sum score, mm VAS, mean ± SD (95% CI)	65.4 ± 19.1 (63.1–67.6)
Number of current systemic neuropathic pain medications, mean ± SD (95% CI)	4.1 ± 1.6 (3.9–4.2)
Number of previous neuropathic pain or adjuvant medications, mean ± SD (95% CI)	7.7 ± 2.4 (7.4–8.0)
Patients with previous neuropathic pain or adjuvant medications,* n (%)	
Mild opioid analgesic*	285 (78.1)
Strong opioid analgesic†	259 (71.0)
Antiepileptic	246 (67.4)
Antidepressant	338 (92.6)

VAS ranges from 0 (no pain) to 100 (worst pain conceivable).
*Codeine, dihydrocodeine, tilidine, tramadol, †Morphine, hydromorphone, oxycodone, buprenorphine, fentanyl, methadone, tapentadol, others.
API, average pain intensity; CI, confidence interval; mPDI, modified Pain Disability Index; SD, standard deviation; VAS, visual analog scale.

Pain intensity

- There were significant reductions in the mean 24-hour API (measured by VAS) at month 3, following one HCCTS treatment (VAS; p<0.001 vs baseline) (**Figure 2**).
- Patients who received four HCCTS treatments had a reduction in mean 24-hour API from 61.4 at baseline to 8.8 at month 12 (VAS; p<0.001).
- Patients who discontinued HCCTS treatment experienced an increase in mean API over time after discontinuation.

Figure 2 – Change in 24-hour API from baseline measured by VAS



No. of HCCTS treatments	Baseline (95% CI)	Month 3 (95% CI)	Month 6 (95% CI)	Month 9 (95% CI)	Month 12 (95% CI)
One (n=94)	57.5 (53.7–61.4)	42.2 (39.0–45.3), p<0.001	44.5 (40.7–48.3), p<0.001	46.4 (42.4–50.3), p<0.001	51.4 (46.9–55.8), p=0.020
Two (n=88)	56.3 (51.8–60.8)	40.1 (36.4–43.9), p<0.001	28.6 (25.3–31.9), p<0.001	30.4 (26.9–33.9), p<0.001	31.9 (28.3–35.5), p<0.001
Three (n=75)	59.3 (53.8–64.7)	38.7 (35.0–42.4), p<0.001	24.9 (22.3–27.6), p<0.001	15.8 (13.6–18.0), p<0.001	16.7 (14.3–19.1), p<0.001
Four (n=108)	61.4 (57.4–65.4)	41.6 (38.5–44.6), p<0.001	26.5 (24.5–28.5), p<0.001	16.2 (14.6–17.9), p<0.001	8.8 (7.4–10.2), p<0.001

Error bars show 95% CI.
VAS ranges from 0 (no pain) to 100 (worst pain conceivable).
API, average pain intensity; CI, confidence interval; HCCTS, high-concentration capsaicin topical system; VAS, visual analog scale.

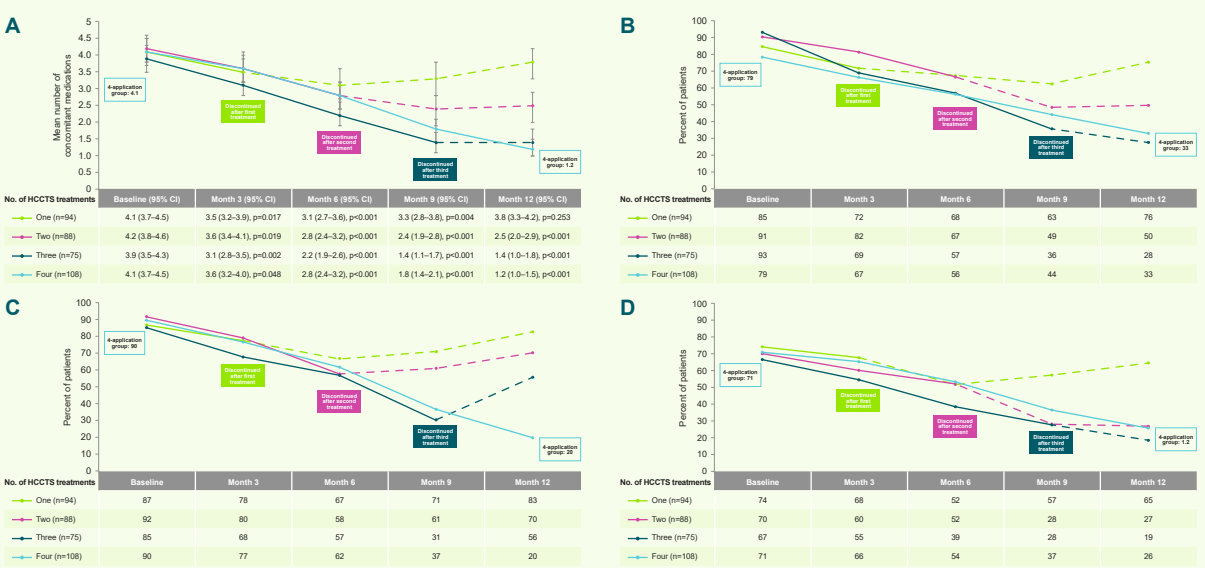
Concomitant pain medication use

- In the cohort of patients who received four HCCTS treatments, there was a reduction in the mean (95% confidence CI) number of total analgesic concomitant medications from 4.1 (3.9–4.2) at baseline to 1.2 (1.0–1.5) at month 12 (p<0.001) (**Figure 3A**).
- In the cohort of patients who received >1 HCCTS treatment, each HCCTS treatment led to a statistically significant reduction in the mean number of concomitant medications vs baseline (**Figure 3A**) and led to a numeric reduction in the percentage of patients receiving any opioid (**Figure 3B**), antidepressant (**Figure 3C**), or antiepileptic (**Figure 3D**).
  - The cohort of patients who received four HCCTS treatments had the greatest reductions compared with baseline in use of all classes of concomitant medication.
  - Discontinuation of HCCTS was generally accompanied by an increase in co-medication use. Among patients who discontinued after one HCCTS treatment, there was a numeric increase compared with baseline in the total number of concomitant medications from month 6 onward, as well as in the percentages of patients receiving each class of medication.
  - Among patients receiving ≥3 HCCTS treatments, there was a reduction in concomitant opioid use compared with baseline.
- In the cohort that received four HCCTS treatments, 34% of patients were able to discontinue concomitant pain medication entirely.

Tolerability

- The most common adverse events were transient, consisting of local application-site reactions.

Figure 3 – Use of concomitant analgesic medications. A) Mean number of total concomitant analgesic medications. B) Percentage of patients receiving any opioid. C) Percentage of patients receiving antidepressants. D) Percentage of patients receiving antiepileptics.



A: No. of HCCTS treatments	Baseline (95% CI)	Month 3 (95% CI)	Month 6 (95% CI)	Month 9 (95% CI)	Month 12 (95% CI)
One (n=94)	4.1 (3.7–4.5)	3.5 (3.2–3.9), p=0.017	3.1 (2.7–3.6), p<0.001	3.3 (2.8–3.8), p=0.004	3.8 (3.3–4.2), p=0.253
Two (n=88)	4.2 (3.8–4.6)	3.6 (3.4–4.1), p=0.019	2.8 (2.4–3.2), p<0.001	2.4 (1.9–2.8), p<0.001	2.5 (2.0–2.9), p<0.001
Three (n=75)	3.9 (3.5–4.3)	3.1 (2.8–3.5), p=0.002	2.2 (1.9–2.6), p<0.001	1.4 (1.1–1.7), p<0.001	1.4 (1.0–1.8), p<0.001
Four (n=108)	4.1 (3.7–4.5)	3.6 (3.2–4.0), p=0.048	2.8 (2.4–3.2), p<0.001	1.8 (1.4–2.1), p<0.001	1.2 (1.0–1.5), p<0.001

B: No. of HCCTS treatments	Baseline	Month 3	Month 6	Month 9	Month 12
One (n=94)	85	72	68	63	76
Two (n=88)	91	82	67	49	50
Three (n=75)	93	69	57	36	28
Four (n=108)	79	67	56	44	33

C: No. of HCCTS treatments	Baseline	Month 3	Month 6	Month 9	Month 12
One (n=94)	87	78	67	71	83
Two (n=88)	92	80	58	61	70
Three (n=75)	85	68	57	31	56
Four (n=108)	90	77	62	37	20

D: No. of HCCTS treatments	Baseline	Month 3	Month 6	Month 9	Month 12
One (n=94)	74	68	52	57	65
Two (n=88)	70	60	52	28	27
Three (n=75)	67	55	39	28	19
Four (n=108)	71	66	54	37	26

Error bars show 95% CI. All p-values show significance vs baseline. CI, confidence interval; HCCTS, high-concentration capsaicin topical system.

Limitations

- The study is limited by its retrospective, non-randomized, observational design.
- The non-interventional nature may have introduced selection bias as patients were prescribed HCCTS based on their clinical profile and personal preferences, rather than randomly assigned to this therapy.
- The lack of a control group limits the interpretation as no comparison is possible.
- Causality cannot be established from the results of this study, and reverse causality (patients who received the most benefit being those who persisted) cannot be ruled out.

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Disclosures

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