



**The Technology
Behind Innovative
Localized
Treatments, for
Relief from Chronic
Neuropathic Pain**

Dr. Alaa Abd-Elseyed

Dr. Amol Soin



Speakers



Alaa Abd-Elseyed MD, MPH

Pain Services University of
Wisconsin – Madison



Amol Soin, MD

Ohio Pain Clinic, Dayton, OH.

Agenda

- Capsaicin 8% topical treatment
- Lidocaine 5% medical plastered
- TENS
- Botulinum Toxin



Localized topical treatments in chronic NP

- Localized neuropathic pain is a prevalent condition associated with a profound impact on quality of life and high burden of care
- In many of these indications, pain is localized (e.g., the area of maximum pain is often characterized by a specific, clearly circumscribed area). The prevalence of localized peripheral neuropathic pain (l-PNP) among chronic pain patients is high and the burden of pain is considerable with a profound impact on quality of life
- Topical treatments have also been suggested as first-line medications for the treatment of l-PNP because of their far better benefit/risk ratios compared with oral medications (OMs), the targeted treatment at the site of the pain and the low systemic exposure and thus a reduced risk of systemic side effects and drug–drug interactions

NEUPSIG Guidelines

GRADE classification	Drugs	Daily dosages and dose regime	Recommendations
STRONG FOR	Gabapentin	1200–3600 mg TID	First-line
	Gabapentin ER/enacarbil	1200–3600 mg BID	First-line
	Pregabalin	300–600 mg BID	First-line
	SNRIs duloxetine/venlafaxine	60–120 mg QD (duloxetine); 150–225 mg QD (venlafaxine ER)	First-line
	TCA's	25–150 mg qd or BID	First-line ¹
WEAK FOR	Capsaicin 8% patches	1–4 patches to the painful area for 30–60 min every 3 months	Second-line (PNP) ²
	Lidocaine patches	1–3 patches to the painful area for up to 12 hours	Second-line (PNP)
	Tramadol	200–400 mg BID (tramadol ER) or TID	Second-line (PNP)
	BTX- A (SC)	50–200 units to the painful area every 3 months	Third-line : specialist use
	Strong opioids	Individual titration	Third line ³
INCONCLUSIVE	Combination therapy Capsaicin cream Carbamazepine Clonidine topical Lacosamide Lamotrigine NMDA antagonists Oxcarbazepine SSRI antidepressants Tapentadol Topiramate Zonisamide		
WEAK AGAINST	Cannabinoids Valproate		
STRONG AGAINST	Levetiracetam Mexiletine		

Therapeutic Algorithm for NP treatment in Adults

French Recommendations 2020

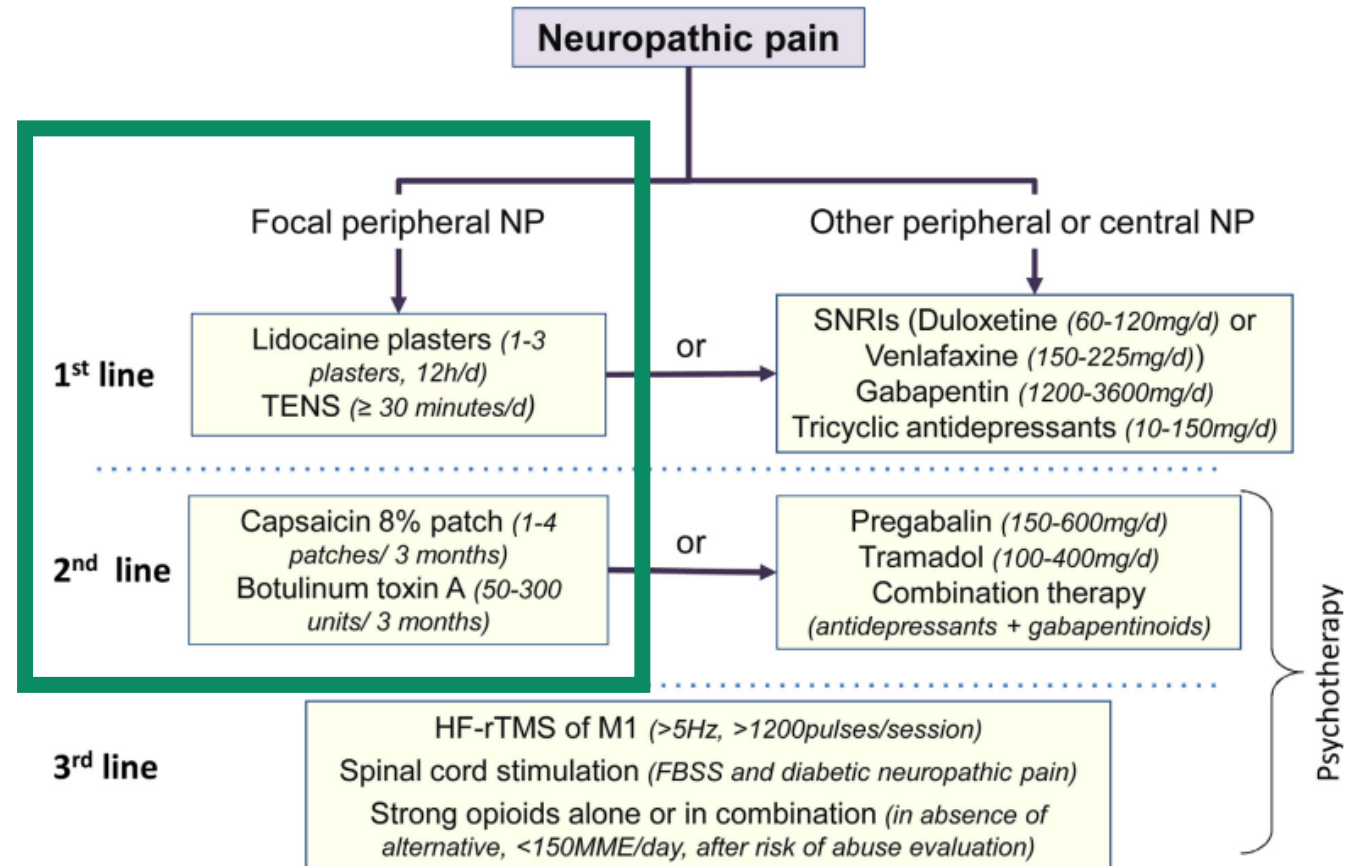


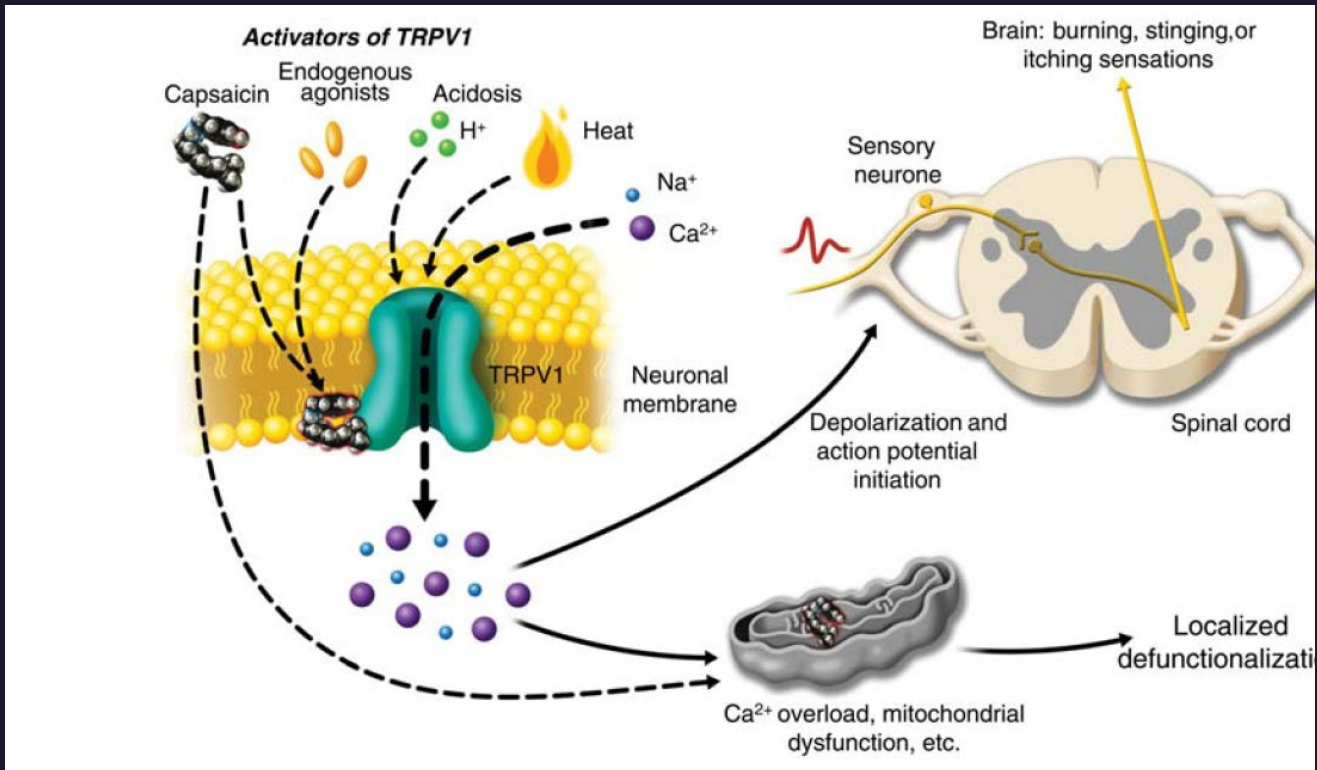
Fig. 2 – Proposed therapeutic algorithm for neuropathic pain treatment in adults. Only treatments available in France in June 2019 were considered. For practical considerations, see Table 4. NP: neuropathic pain; TCAs: tricyclic antidepressants; TENS: transcutaneous electrical nerve stimulation; HF-rTMS: high-frequency repetitive transcranial magnetic stimulation; M1: primary motor cortex; BTX-A: botulinum toxin type A; FBSS: failed back surgery syndrome; MME: mg morphine equivalent.

Capsaicin 8% Topical System

Indicated in adults for the treatment of neuropathic pain associated with postherpetic neuralgia (PHN) and for neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet.

Mechanism of action

- Capsaicin is a highly selective agonist for the transient receptor potential vanilloid-1 receptor (TRPV1) preferentially expressed on sensory (nociceptive) nerve fibers – mainly C and A δ fibers.

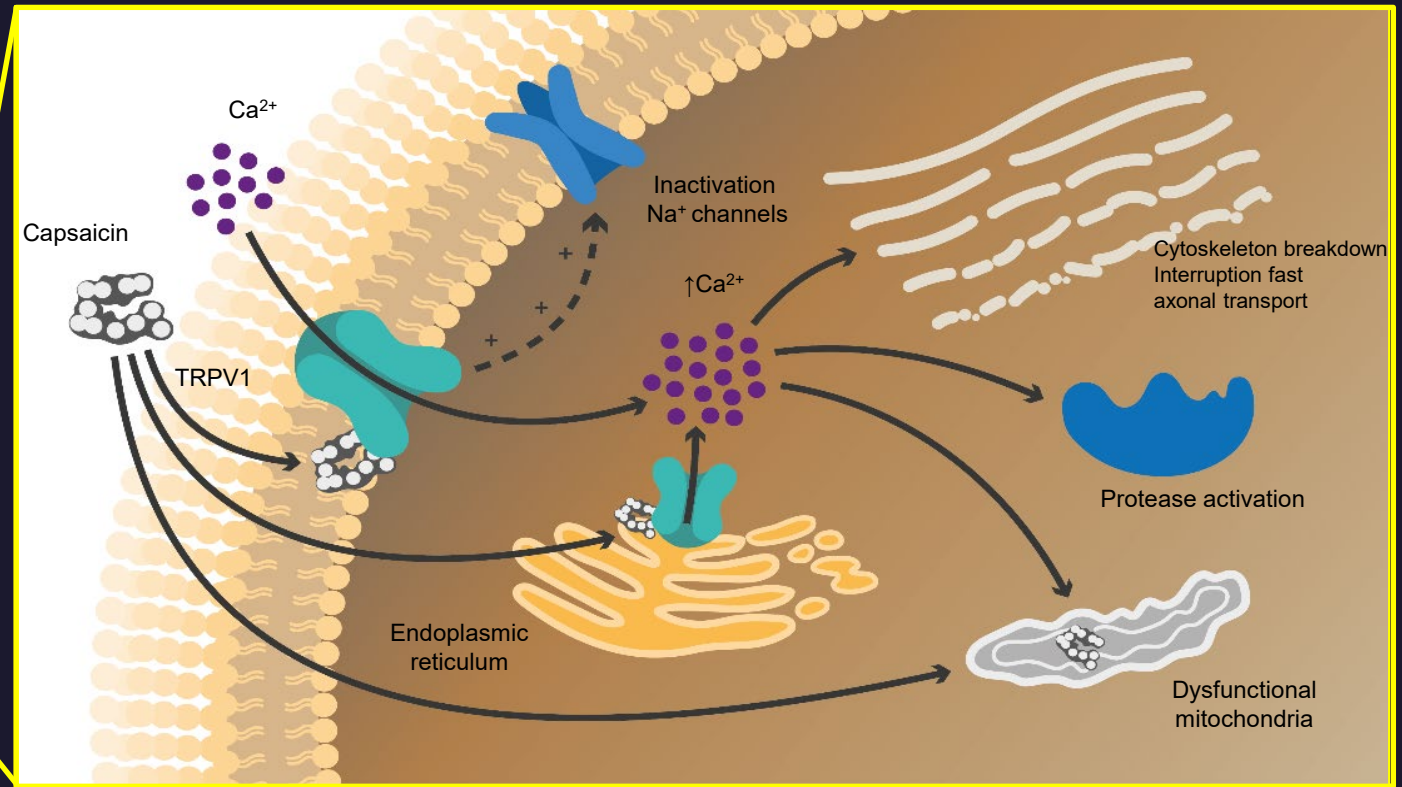
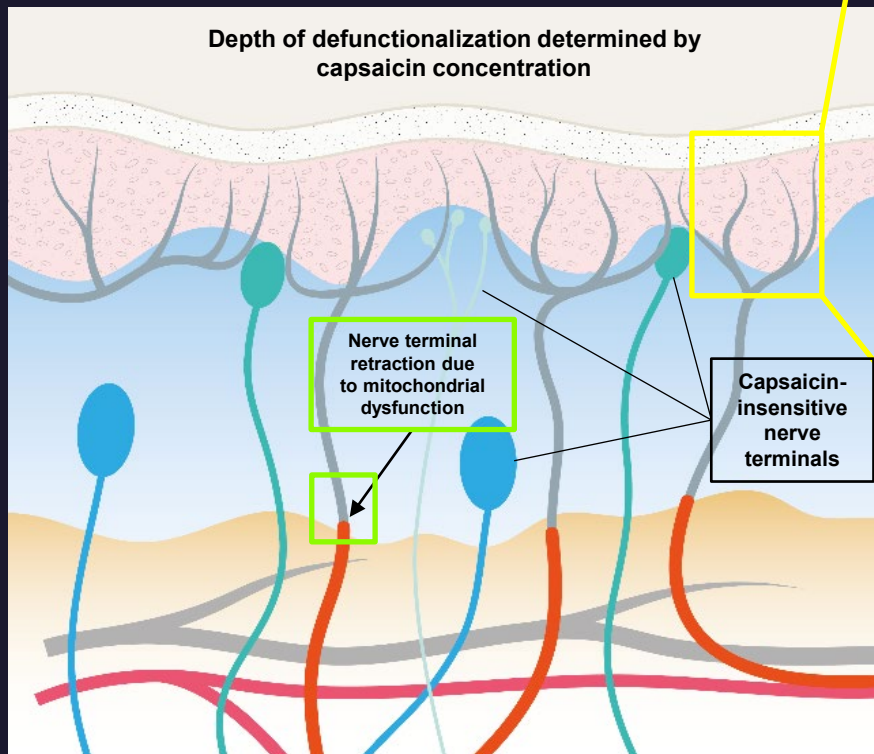


- Activation of TRPV1 by capsaicin results in sensory neuronal depolarization, and can induce local sensitization to activation by heat, acidosis, and endogenous agonists.

- Topical exposure to capsaicin leads to the sensations of heat, burning, stinging, or itching.

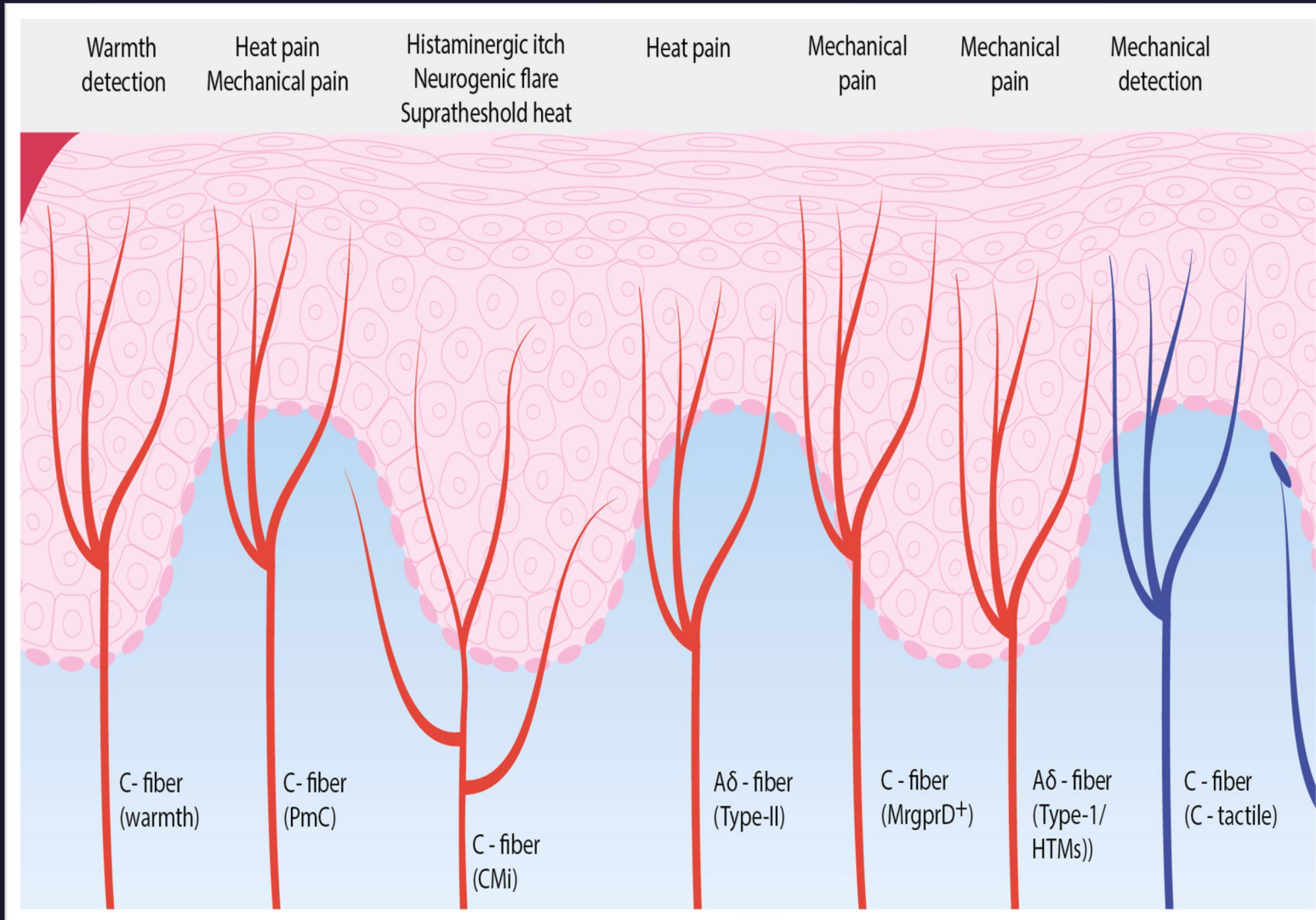
Mitochondrial Dysfunction is Key Contributor

Multiple mechanisms underlie capsaicin-induced defunctionalization²



- High concentrations of capsaicin or repeated applications can produce a persistent local effect on cutaneous nociceptors, which is best described as defunctionalization and constituted by reduced spontaneous activity and a loss of responsiveness to a wide range of sensory stimuli.

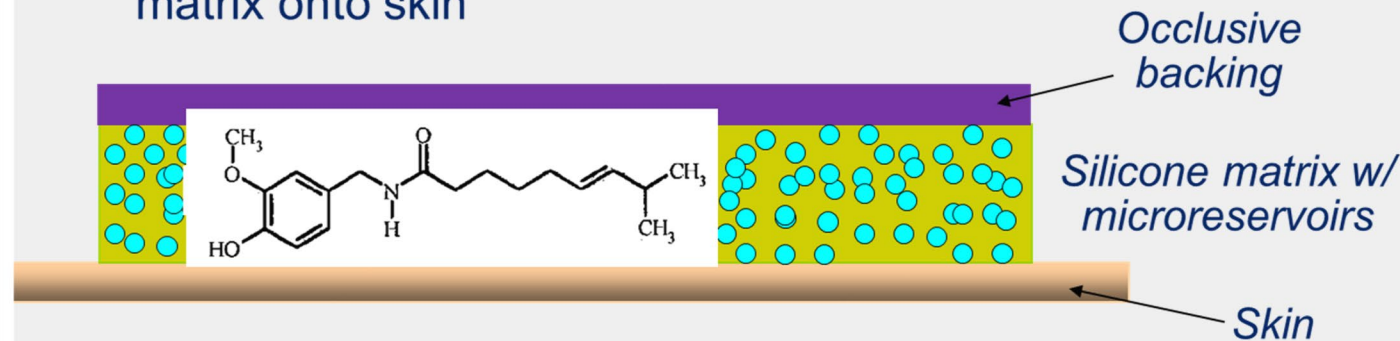
Defunctionalization of afferent fiber subpopulations



- Schematic model of primary afferent fiber subpopulations thought to be robustly defunctionalized by the 8% capsaicin treatment (shown in **red**).

Capsaicin 8% Topical System

- Capsaicin fully solubilized in Transcutol (DGME)
- Capsaicin and DGME diffuse through silicone adhesive matrix onto skin



- Occlusion potentiates delivery and limits contamination
- Capsaicin released: $\sim 2.5\%$ of $640 \mu\text{g}/\text{cm}^2$, or $\sim 16 \mu\text{g}/\text{cm}^2/\text{hr}$
- Capsaicin absorbed: $\sim 1.1\%$, or $7 \mu\text{g}/\text{cm}^2$ skin

Effect on epidermal nerve fiber density

Capsaicin 8% topical system in healthy volunteers

1 week after use: significant reduction in ENF density versus unexposed skin sites² and placebo patch³ Increase in tactile thresholds.² Decrease in sharp mechanical pain²

12 weeks after use: evidence of ENF regeneration²

24 weeks after use: nearly full (93%) recovery of ENF²

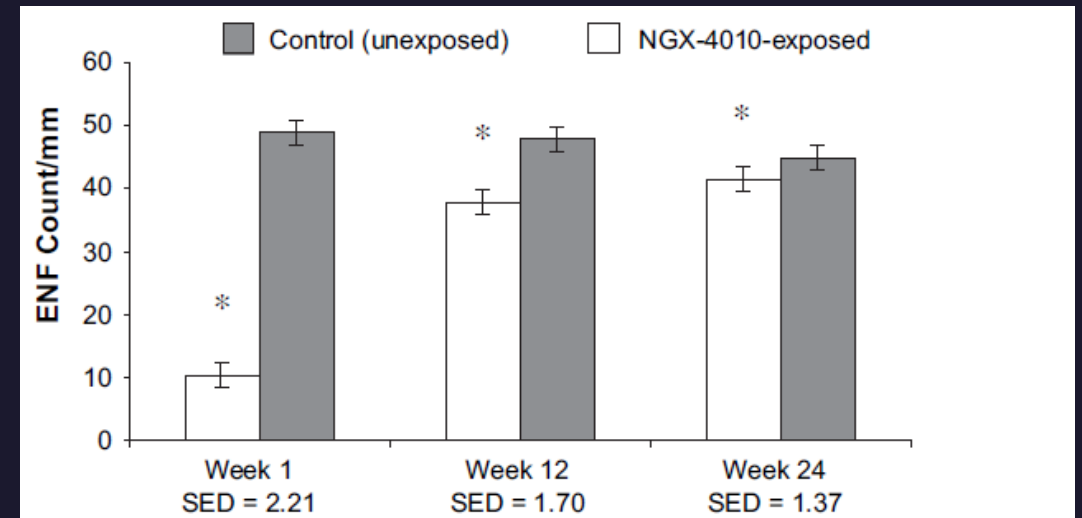
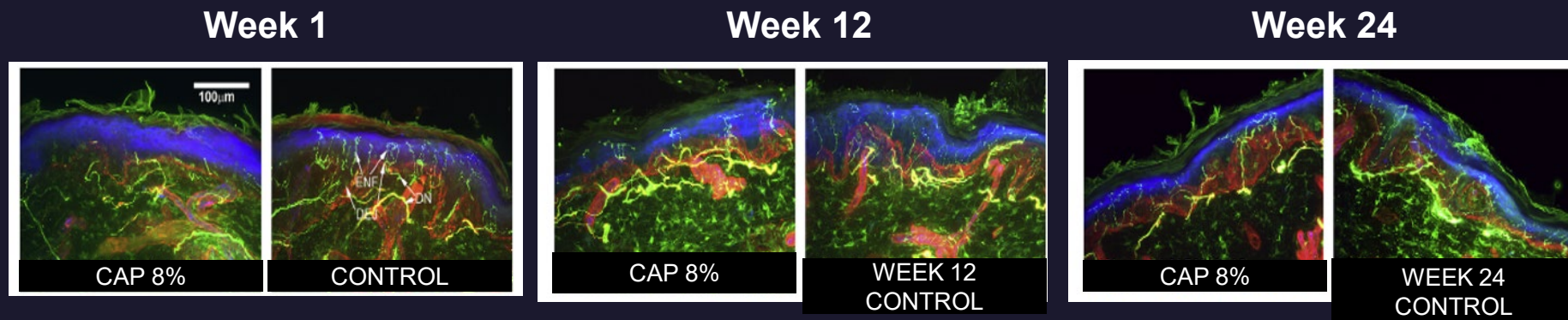


Figure 4. Mean reductions in epidermal nerve fiber (ENF) density at 1, 12 and 24 weeks after a single NGX-4010 patch application. Number of subjects is 36 for weeks 1 and 12, and 35 for week 24. Values represent least square means and error bars indicate standard errors of the means. *indicates $P < .05$ relative to control. SED = Standard error of difference between NGX-4010 and Control.

Reversible Reduction of Nerve Fiber Density

Visualization of the reduction of epidermal nerve fibers (ENF) following single capsaicin 8% application to the thighs of healthy volunteers:



ENF reduction (80%)

Partial ENF regeneration

ENF recovery (93%)

Scale bar = 100 μm.

Immunostaining at time point indicated:

ENF and dermal nerves = **yellow** or **green**

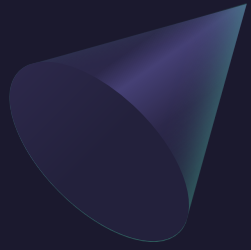
Basement membrane at the dermal-epidermal junction and around blood vessels = **red**

Epidermis = **blue**



Pharmacokinetics at glance

- Capsaicin is the primary capsaicinoid causing the spicy flavor of chili pepper fruit.
- Lipophilic water-insoluble compound that penetrates the epidermis (keratinocyte layer), with low transdermal penetration.
- Capsaicin is not soluble in plasma and is not absorbed into the microvasculature.
- Each 280 cm² patch contains 179 mg of capsaicin (640 µg capsaicin/cm²).
- After 60-minute application of the 8% capsaicin patch, plasma concentrations are very low (C_{\max} =1.38 ng/mL; T_{\max} =1.46 hours).⁵⁷
- Capsaicin absorption is affected by duration, site and total area of application.
- Capsaicin is metabolized by various cytochrome P450 enzymes in human liver, and it is unlikely that its metabolites act on transient receptor potential vanilloid 1 receptor (TRPV1).⁵⁹
- In healthy volunteers, elimination half-life of capsaicin after dermal application is 1.64 hours, and drug plasma levels decline very rapidly after patch removal.⁵⁷
- Capsaicin is mainly excreted as metabolites by the kidneys and in a small untransformed proportion in feces and urine.⁶⁰



Capsaicin 8% topical system

Clinical data on PDPN of the feet



STEP

In this Phase 3 study, 369 DPN patients were randomized 1:1 to receive either a Capsaicin 8% topical system or placebo 30-min. patch application to painful areas of the feet, with daily NPRS reports and other evaluations over for 12 weeks: areas of the feet

Key inclusion criteria:

- Aged ≥ 18 years with a diagnosis of PDPN for at least 1 year
- HbA1c $\leq 11\%$ at screening and 3–6 months
- Stable doses of pain medication >4 weeks before screening*
- Average NPRS score over the last 24 hours of ≥ 4 during the screening period

n=369

12 days before treatment:
baseline NPRS score

n=186

Randomization
(1:1 ratio)

n=183

8% capsaicin topical
system
30 min application

Placebo patch
30 min application

(all patients could use opioid rescue
medication up to 5 days after; no topical
pain medications)

NPRS completed daily
Study visits at weeks
indicated

2

4

8

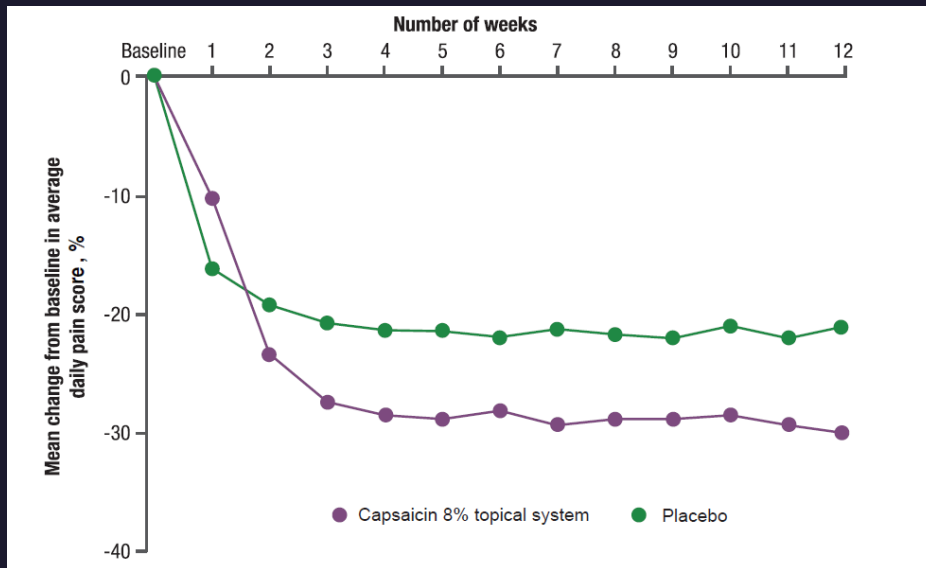
12

Weeks

STEP

Efficacy Results: Average Change in Pain from Baseline to Week 12

Mean percentage change in average weekly NPRS score:



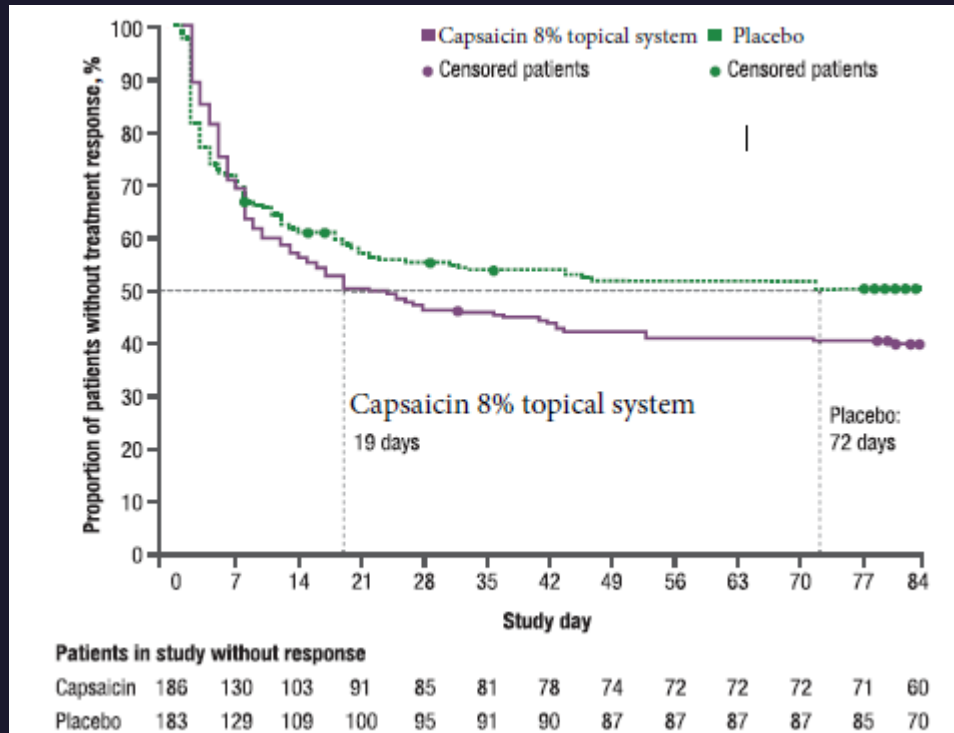
Percent change in average pain from baseline to Week 12 was higher -30% ($\pm 3\%$) in the Capsaicin 8% group compared to the Placebo group -22% ($\pm 3\%$)

Adapted from: Simpson DM *et al.* J Pain. 2017;18:42–53

CI, confidence interval; NPRS, Numeric Pain Rating Scale; PBO, placebo; PDPN, painful diabetic peripheral neuropathy

STEP Study

Efficacy Results: Time to Treatment Response



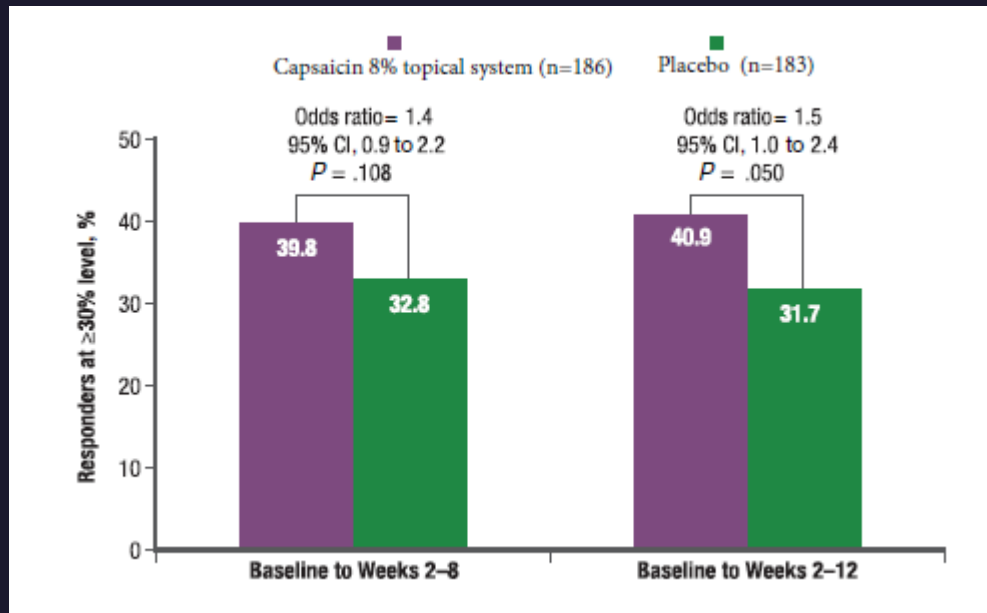
Kaplan–Meier curves for median time to treatment response (≥30% reduction in average daily pain; safety analysis set).

- The median time to treatment response was shorter with Capsaicin 8% topical system versus placebo.
- 50% of patients achieving at least a 30% reduction in average daily pain after:
 - 19 days in the Capsaicin 8% topical system group (95% CI for median, 12.0–37.0)
 - 72 days in the placebo group (95% CI for median, 19.0–not calculable)

STEP Study

Efficacy Results: Responder Rate

Proportion of patients achieving $\geq 30\%$ reduction in pain from baseline



More patients achieved a $\geq 30\%$ reduction in pain from baseline to 2-12 weeks on the Capsaicin 8% topical system vs PBO

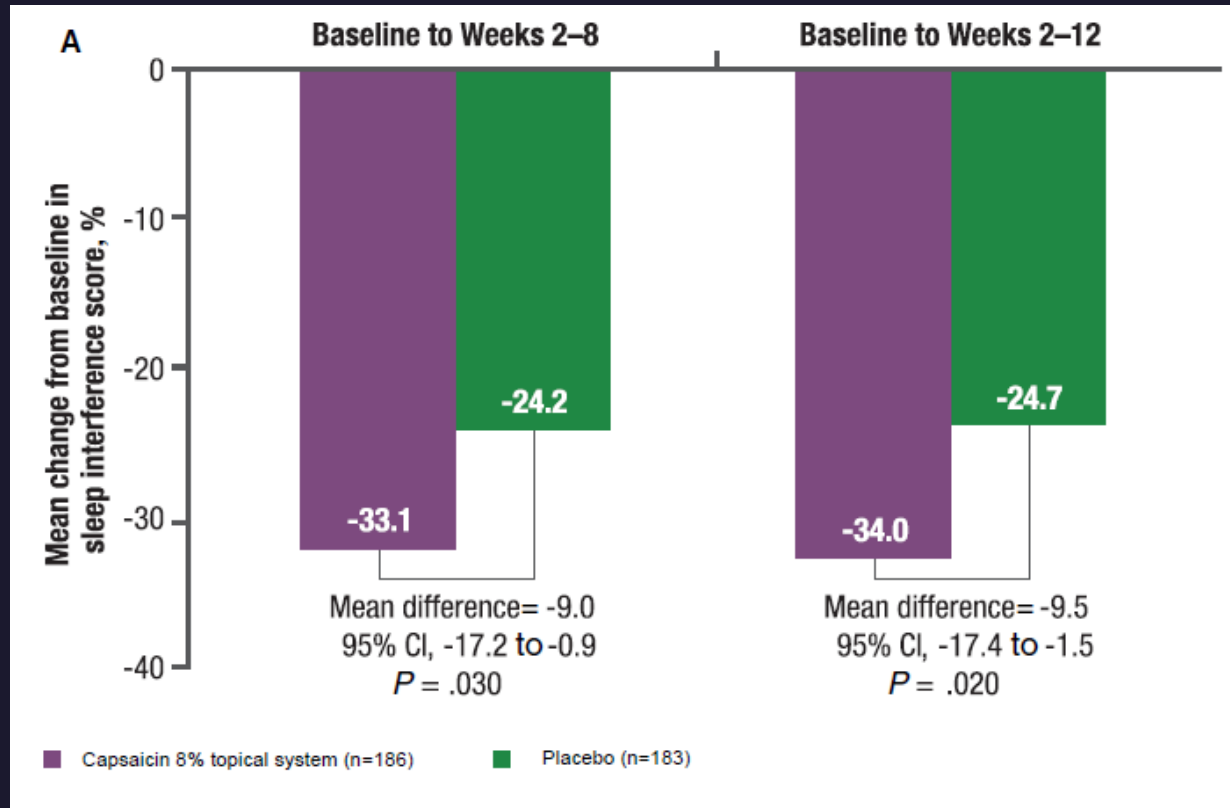
Proportion of patients who achieved a $\geq 30\%$ reduction in average pain score from baseline to between weeks 2 through 8 and weeks 2 through 12 (baseline or last observation carried forward; ITT).

CI, confidence interval.

Adapted from: Simpson DM et al. J Pain. 2017;18:42-53

STEP Study

Secondary Endpoint: Effect on Sleep Interference

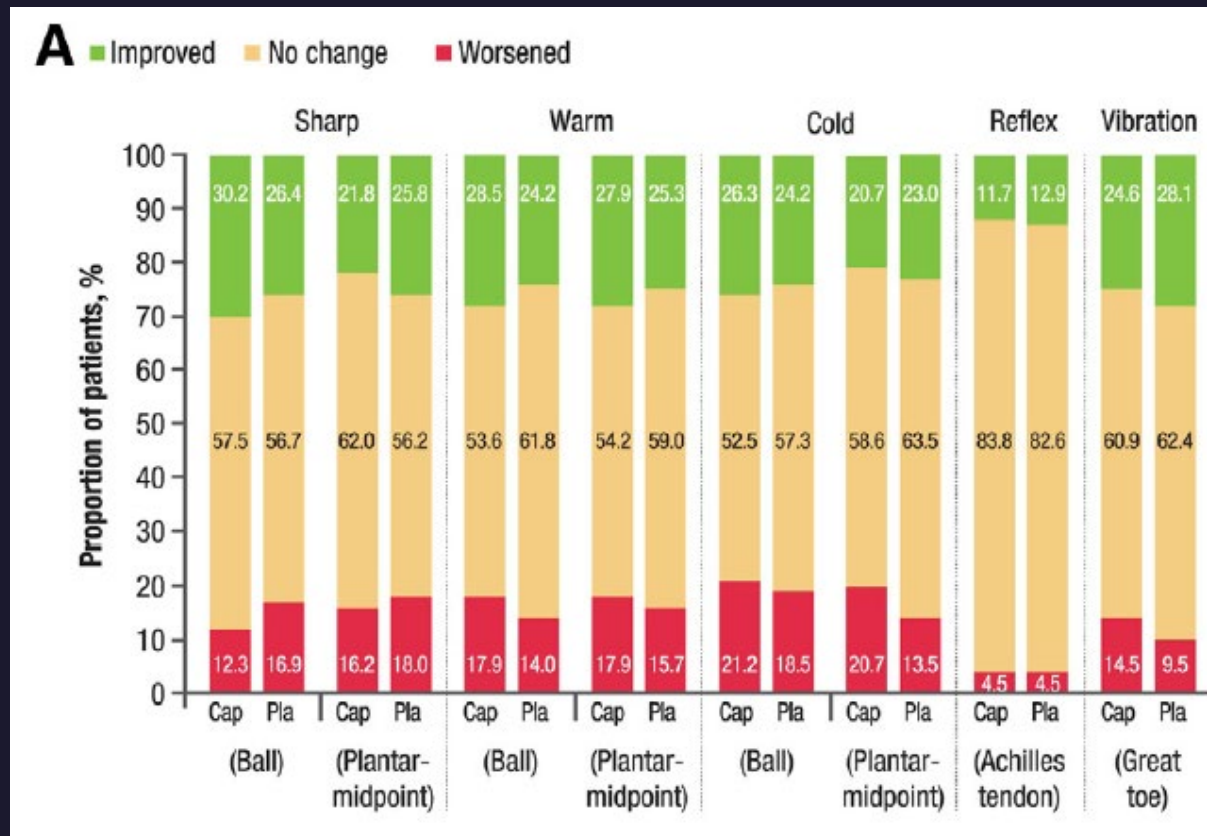


- A reduction in sleep interference score was observed with Capsaicin 8% topical system vs Placebo
- Capsaicin 8% topical system provides a holistic benefit to patients, including relief of pain and associated Quality of Life (QoL) reducing symptoms such as poor sleep quality

Adapted from: Simpson DM *et al.* J Pain. 2017;18:42-53

STEP Study

Secondary Endpoint: Changes in Sensory Perception and Reflex Testing



- Most patients either had **no change (52.5% to 83.8% across tests)** or **improved (12% to 30% across tests)** in the capsaicin and placebo groups
- Overall, worsened sensation was reported by a lower proportion of patients (4.5% to 21.2% across tests) and a numerically similar proportion in both groups at EoS compared with baseline

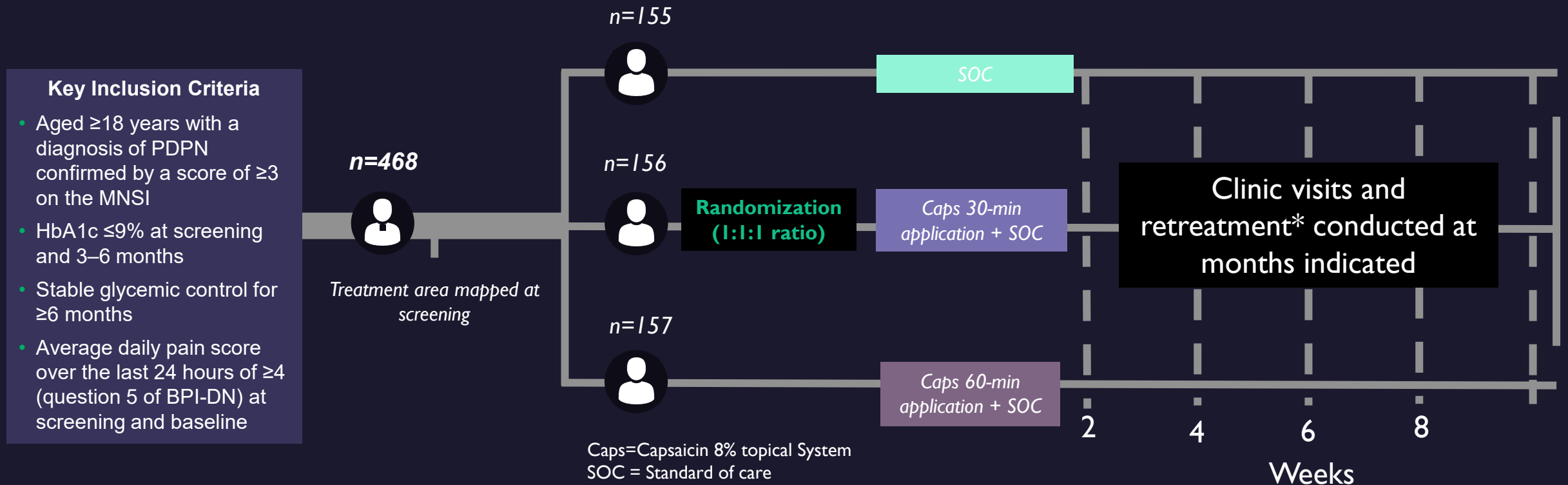
Proportion of patients who reported improved, remained the same, or worsened sensory or reflex function by EoS (safety analysis set; SAS).
Abbreviations: Cap, capsaicin 8% topical system ; Pla, placebo.

PACE Study Design

Phase III, open-label, long-term safety study –

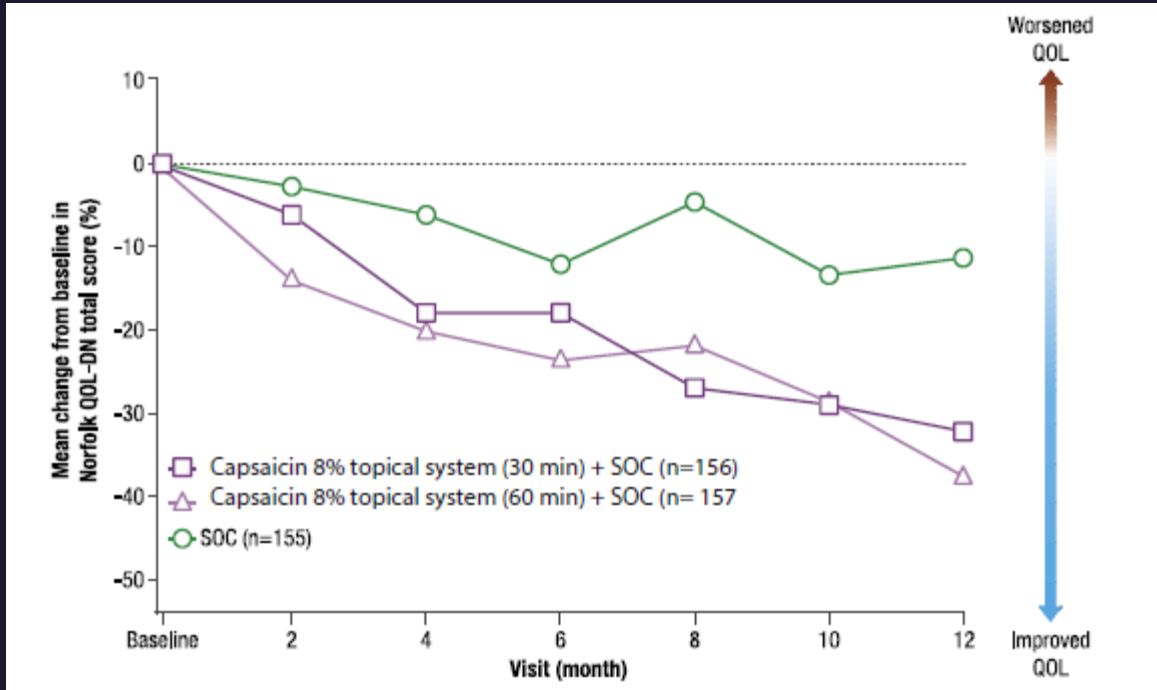
Capsaicin 8% topical system (30- or 60 minute repeated applications* to feet only) + SOC vs SOC alone; 52-week follow-up

The primary objective was the evaluation of safety, in particular with regard to effects on sensory function in diabetic patients



PACE study

Mean Percentage Change in Norfolk QOL-DN total score from baseline to EoS (SAS)

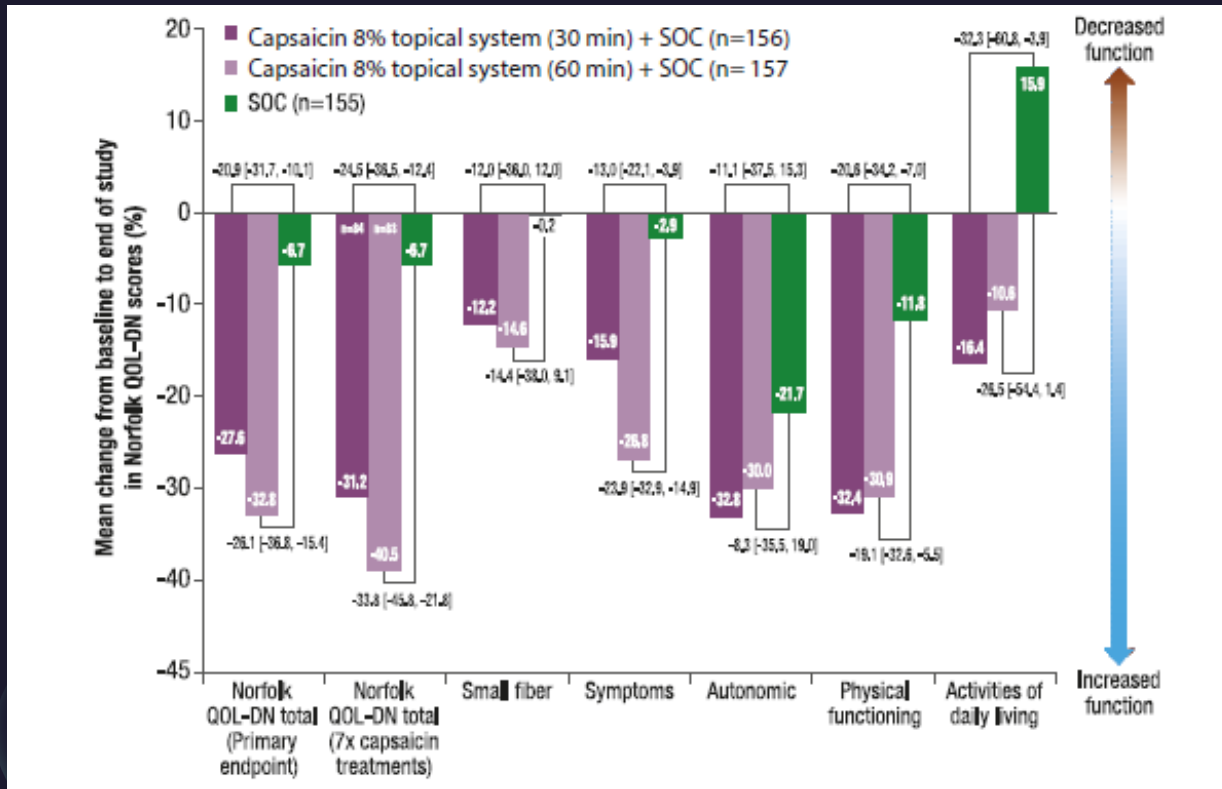


Mean percentage change in Norfolk QOL-DN total score from baseline during the study (SAS) in patients who received a capsaicin treatment at Month 12 and had an end of study visit at Month 14, mean [SD] change in Norfolk total score by Month 14 was: 30 min, -36.1% [51.6] (n = 79); 60 min, -40.2% [39.4] (n = 76). SAS safety analysis set, SOC standard of care

- Patients treated with Capsaicin experienced no deterioration in mean Norfolk QOL-DN total score from baseline to end of study
- Similar improvements were observed across Norfolk subscale scores: 1,2
 - Small fiber
 - Symptoms
 - Autonomic
 - Physical function
 - Activities of daily living

PACE study

Mean change in UENS total and subscale scores from baseline to study end



- The mean change in UENS total score from baseline to EoS showed improvements in the Capsaicin group compared with SOC alone.
- Improvements in the sharp sensation subscale were greater in the Capsaicin group compared with SOC alone
- The UENS total score did not deteriorate in patients who received up to 7 repeated Capsaicin treatments

Mean percentage change from baseline to end of study in Norfolk QOL-DN scores (LOCF) (SAS)
 Treatment group comparisons are least squares mean difference [90% CI]. CI confidence interval, LOCF last observation carried forward, SAS safety analysis set, SOC standard of care

PACE Study

Use of concomitant medications at baseline and end of study

Neuropathic pain medications at baseline and EoS

Table 5. Neuropathic pain medication at baseline and EoS.

	QUTENZA (30 min) + SOC (N = 156)	QUTENZA (60 min) + SOC (N = 157)	SOC alone (N = 155)
Baseline	156	157	155
Antidepressants	17 (10.9)	8 (5.1)	12 (7.7)
Antiepileptic drugs	44 (28.2)	49 (31.2)	50 (32.3)
Opioids	17 (10.9)	9 (5.7)	13 (8.4)
End of study	146	147	146
Antidepressants	16 (11.0)	10 (6.8)	22 (15.1)
Antiepileptic drugs	43 (29.5)	53 (36.1)	63 (43.2)
Opioids	16 (11.0)	12 (8.2)	17 (11.6)

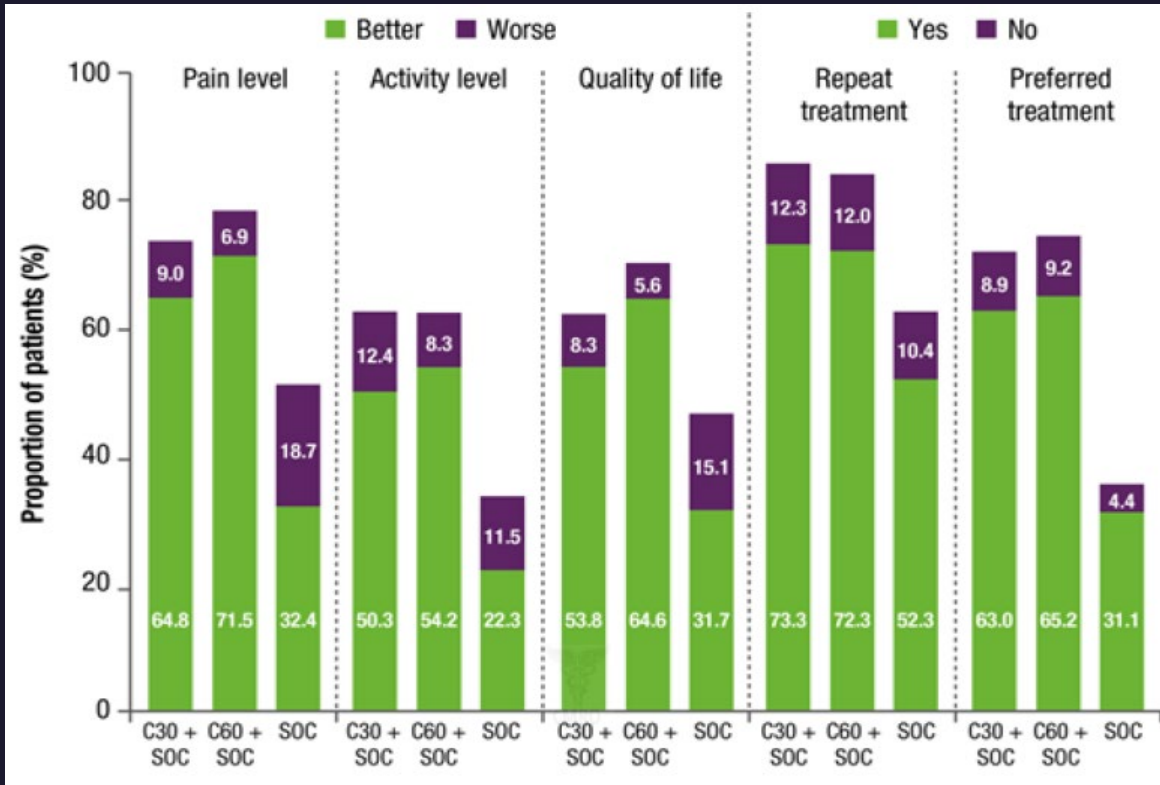
The medication was summarized on the day before baseline visit and on the day before the end of study visit,
N: Number of patients; n: Number of patients in the sample; SOC Standard of care

Overall use of systemic pain medications at end of study – antidepressants, antiepileptics, opioids:

- Did not increase in patients treated with Capsaicin
- Increased in the SOC alone group

PACE Study

Patient self-assessment of treatment at EoS (LOCF; SAS)



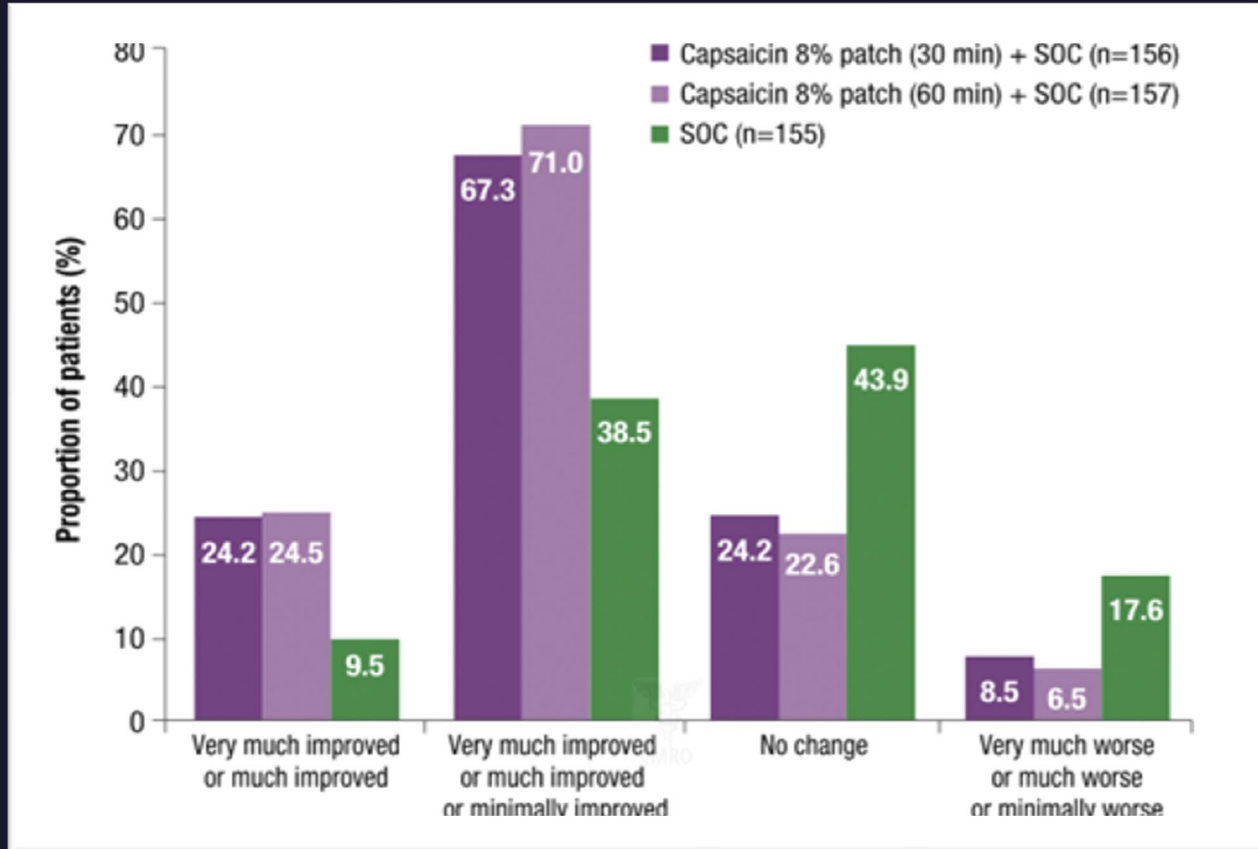
LOCF, last observation carried forward; SAS, safety analysis set

- At EoS, a greater proportion of patients in both capsaicin plus SOC groups versus SOC alone reported improvements in pain level, activity level, and QoL.
- A greater proportion of capsaicin 8% topical system treated patients also indicated their willingness to undergo treatment again, and also preferred capsaicin treatment over their previous treatment

PACE Study

Patient Global Impression of Change

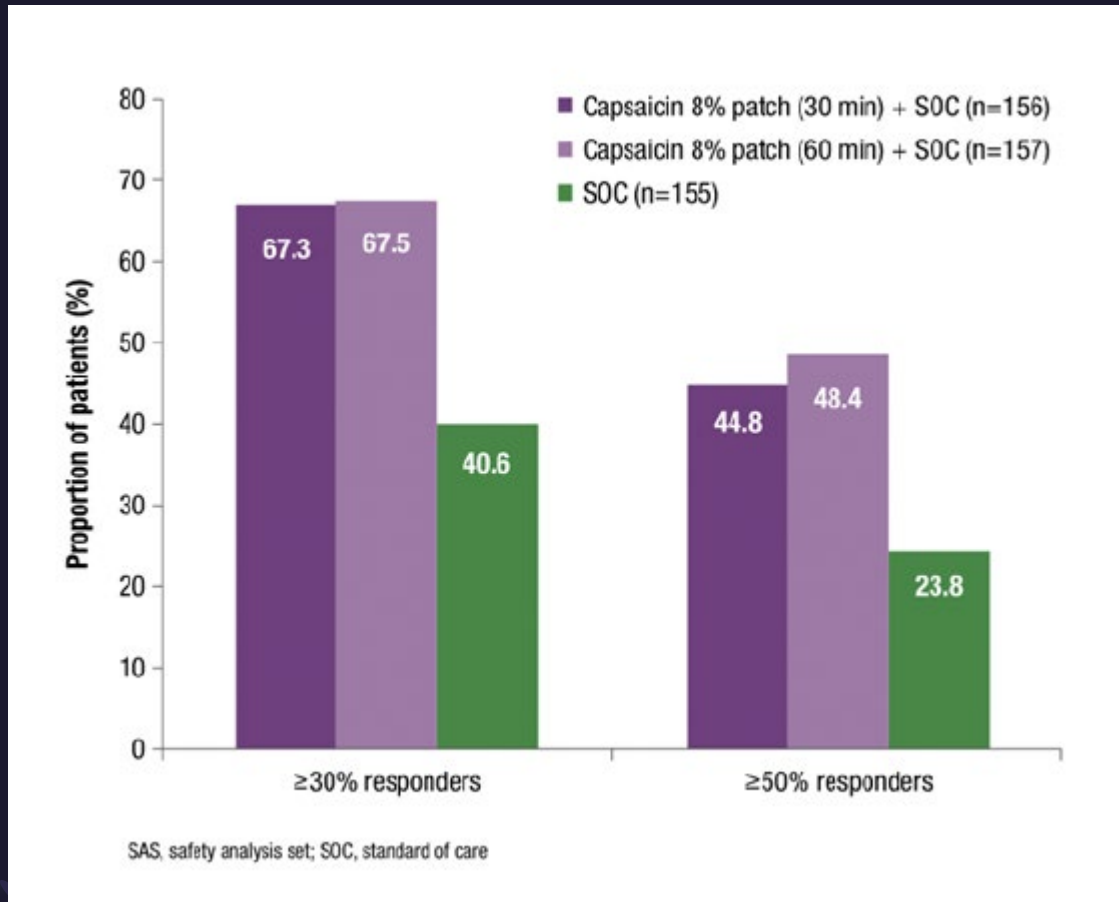
Patient global impression of change, 52-week clinical study



- Substantially more patients in the Capsaicin group reported very much or much improvement by EoS
- Greater proportion of patients in the Capsaicin group reported improvement in QoL, compared with SOC alone

PACE Study

Proportion of 30% and 50% average pain responders during the study (SAS).

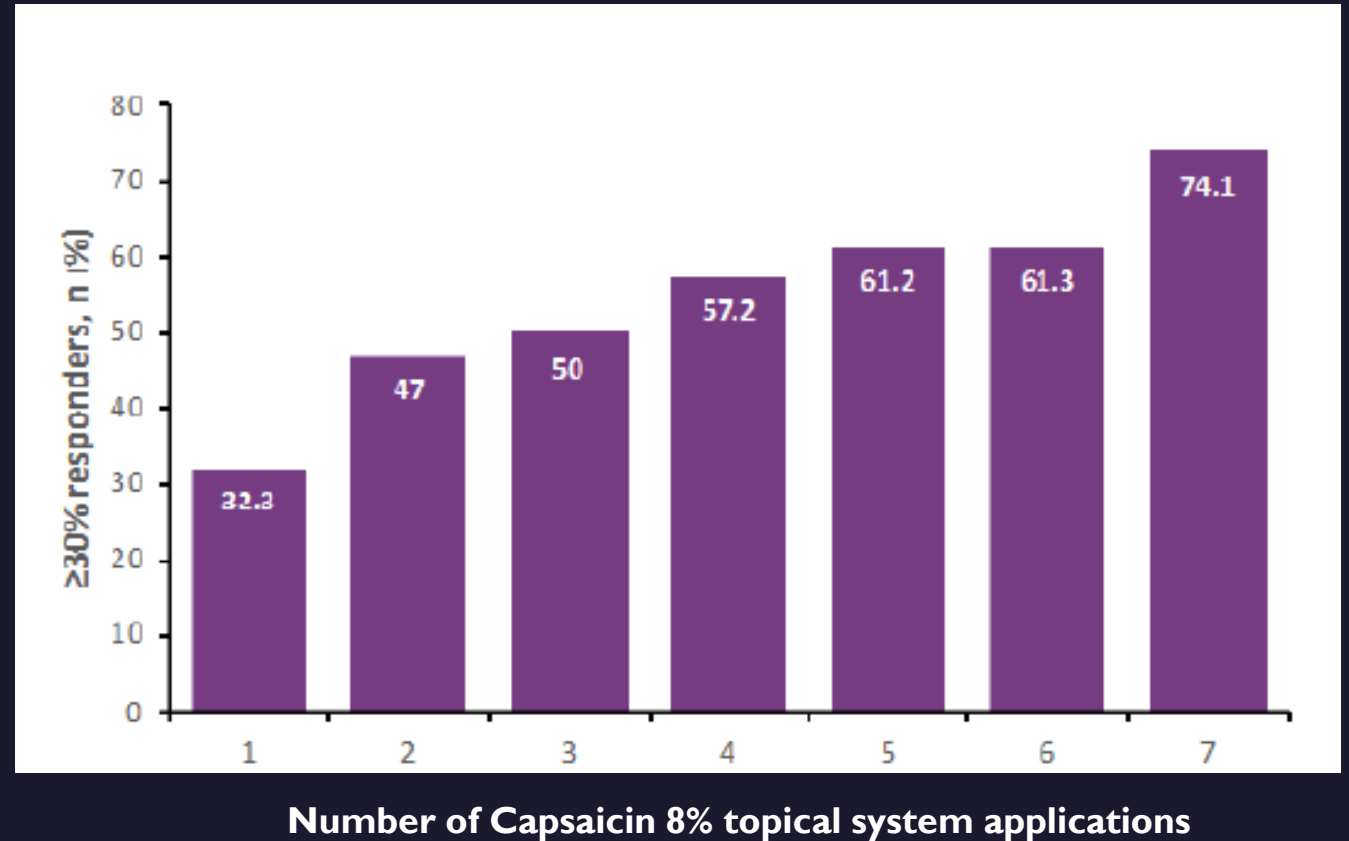


- A greater proportion of patients in the capsaicin plus SOC groups had 30% reduction in average pain (30 min, 67.3%; 60-min, 67.5%), compared with SOC alone (40.6%)
- These trends were similar for the proportion of patients with 50% reduction in average pain (30-min, 44.8%; 60-min, 48.4%; SOC, 23.8%)

PACE Study

- Proportion of patients with 30% reduction from baseline in average daily pain (Numeric Pain Rating Scale score) who received seven applications of capsaicin 8% topical system

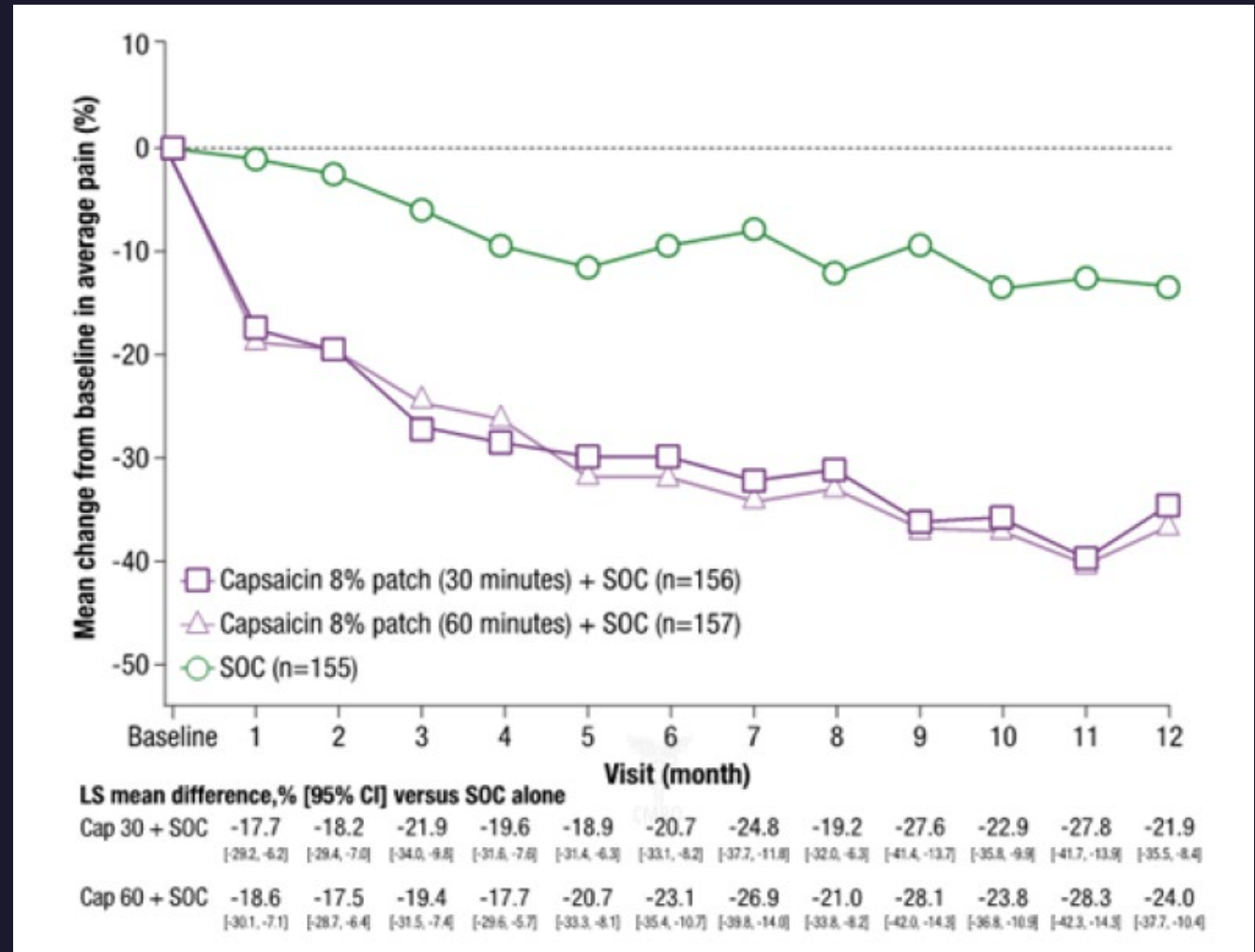
In a post-hoc analysis of all subjects who received seven applications of capsaicin 8% topical system (n=167), the 30% responder rate increased steadily with each application from 32.3% to 47.0%, 50.0%, and finally to 74.1%, 2 months after the first, second, third, and seventh (i.e. last application), respectively



PACE Study

Mean percentage change from baseline in average pain during the study (SAS).

- Greater mean percentage reductions in average pain were seen, versus SOC alone, with both capsaicin plus SOC groups throughout the study period from Month 1, and this difference was maintained and increased by Month 12



STEP and PACE Study Safety and Tolerability

STEP

TEAEs occurring in ≥1% of patients in overall population

TEAEs	Capsaicin 8% 30 minutes (N = 186) %	Control 30 minutes (N = 183) %
Application site burning sensation	14	3
Application site pain	10	2
Application site erythema	2	0
Excoriation	2	0
Pain in extremity	11	6
Headache	3	2
Upper respiratory infection	4	<1
Cough	2	<1
Hypertension	2	<1
Less common adverse reactions (<1%) with QUTENZA observed during DPN clinical trials included: dizziness, dysesthesia, blister.		

DPN, painful diabetic peripheral neuropathy;
TEAE, treatment-emergent adverse event.

PACE

TEAEs occurring in ≥5% of patients in any treatment group

n (%)	Capsaicin 8% 30 minutes (N = 156) %
≥1 TEAE	104 (66.7)
Application site reactions	60 (38.5)
Application site pain	44 (28.2)
Burning sensation	14 (9.0)
Application site erythema	12 (7.7)
Pain in extremity	6 (3.8)
TEAE leading to permanent discontinuation	7 (4.5)
Drug-related TEAE	62 (39.7)

Safety Summary

- Mostly anticipated application site reactions (burning sensation, pain in extremity, application site pain)

Tolerability, safety and toxicity

- Optimal systemic safety profile of topical capsaicin, thanks to its low systemic exposure and its rapid elimination half-life after dermal application.
- Dose adjustment is not required in patients with renal or hepatic impairment.⁵⁷
- Due to its low plasma concentrations, it is unlikely that capsaicin alters the systemic metabolism of concomitant medications by inhibiting or inducing CYP enzymes.⁵⁷
- No additive effects of topical 8% capsaicin patch on oral medication were found in patients with PHN.⁶¹
- The principal adverse effects are transitory localized skin reactions such as burning, itching and erythema, caused by the release of substance P and subsequent stimulation of afferent C-fibers.

The PDPN Meta-Analysis shows that patients who use Capsaicin 8% topical system achieve similar pain relief to first line oral agents, but with less safety or tolerability risks.

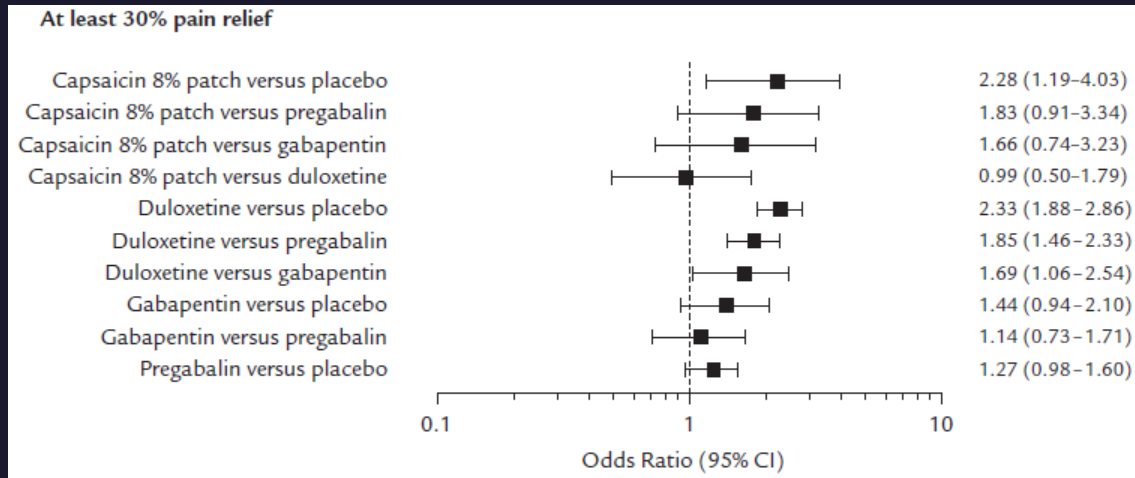


Table III. Network meta-analysis: Cumulative ranking for efficacy and tolerability outcomes.

Outcome	Mean Surface Under the Cumulative Curve, %*				
	Capsaicin 8% Patch	Pregabalin	Gabapentin	Duloxetine	Amitriptyline
Efficacy outcomes					
≥ 30% pain reduction	81.2	33.0	44.6	89.2	-
≥ 50% pain reduction	54.9	38.2	73.5	81.5	-
Tolerability outcomes					
Somnolence	-	40.2	48.1	6.1	0.6
Dizziness	-	35.0	36.3	74.7	4.0
Nausea	-	65.5	42.1	0.4	-
Headache	10.6	83.3	60.4	28.8	-
Fatigue	-	61.4	22.3	29.1	-
Constipation	-	41.1	49.9	86.9	1.0
Diarrhea	-	67.9	60.1	2.8	-
Discontinuation due to adverse events	-	46.2	34.3	19.5	-

*A larger surface under the cumulative ranking curve indicates a greater probability that the drug will be ranked as the best treatment.

Meta-analysis of clinical studies versus SoC options has shown that Capsaicin 8% topical System achieves similar pain relief to other commonly prescribed PDPN treatments



Summary

In the phase III STEP study, Capsaicin 8% topical system was shown to provide significant improvements in pain relief and sleep quality compared with placebo over 12 weeks

In patients with PDPN, Capsaicin 8% topical System repeat treatment plus SOC over 52 weeks was well tolerated, had no negative functional or neurological effects and raised no new safety concerns compared with SOC therapy

A network analysis showed Capsaicin 8% offers efficacy comparable to that of oral agents but with systemic tolerability benefits

Summary

- Localized Neuropathic Pain (LNP) accounts for 60 % of neuropathic pain syndromes.
- There is no single etiology of LNP. The diagnostic approach is similar to that for other neuropathic pain conditions.
- So far, there are no specific guidelines for the management of LNP; for this reason, guidelines for general neuropathic pain are used.
- Topical treatments are included as part of second-line strategies in the NEUPSIG guidelines.
- Despite the lack of guidelines, 5 % lidocaine patches and 8 % capsaicin topical system have been proven effective in LNP models.

Thank You

