Predictors of Response in Patients With Postherpetic Neuralgia and HIV-Associated Neuropathy Treated With the 8% Capsaicin Patch (Qutenza)

Nathaniel P. Katz, MD, MS, Joy Mou, PhD,* Florence C. Paillard, PhD,* Barry Turnbull, PhD,†‡ Jeremiah Trudeau, PhD,* and Malcolm Stoker, PhD§*

Objectives: Qutenza is a high-dose capsaicin patch used to relieve neuropathic pain from postherpetic neuralgia (PHN) and HIV-associated neuropathy (HIV-AN). In clinical studies, some patients had a dramatic response to the capsaicin patch. Our objective was to determine the baseline characteristics of patients who best benefit from capsaicin patch treatment.

Methods: We conducted a meta-analysis of 6 completed randomized and controlled Qutenza studies by pooling individual patient data. Sustained response was defined as > 50% decrease in the mean pain intensity from baseline to weeks 2 to 12, and Complete Response as an average pain intensity score ≤ 1 during weeks 2 to 12. Logistic regression was used to identify predictors of response and Complete Response, and subgroups of patients who respond best to the capsaicin patch.

Results: Baseline pain intensity score (BPIS) ≤ 4 was a predictor of Sustained and Complete Response in PHN and HIV-AN patients; absence of allodynia and presence of hypoesthesia, and a McGill Pain Questionnaire (MPQ) sensory score < 22 were predictors of Sustained Response in PHN patients; female sex was a predictor of Sustained and Complete Response in HIV-AN patients. Thus, characteristics associated with the highest chance of responding to the capsaicin patch were, for PHN, BPIS ≤ 4, MPQ sensory score ≤ 22, absence of allodynia, and presence of hypoesthesia; for HIV-AN, they were female sex and BPIS ≤ 4. Patients with these characteristics had a statistically significantly greater chance of responding to the capsaicin patch than other patients.

Discussion: We identified subpopulations of PHN and HIV-AN patients likely to benefit from the capsaicin patch.

Key Words: capsaicin patch, postherpetic neuralgia, HIV-associated neuropathy, meta-analysis, predictors of response

(*Clin J Pain* 2015;31:859–866)

Received for publication September 16, 2014; revised January 6, 2015; accepted November 16, 2014.

From the *Analgesic Solutions, Natick; †LLX Solutions, Watertown; ‡Biobridges, Wellesley, MA; and §Astellas Pharma Global Development, Leiderdorp, The Netherlands.

This study was conducted by Analgesic Solutions and was financially supported by Astellas Pharma Global Development, Skokie, IL. N.P.K. is the owner and President of Analgesic Solutions, a for-profit company that provides consultant services to the pharmaceutical industry. As such, N.P.K. has received honorarium from Astellas Pharma. J.M. and J.T. were employees of Analgesic Solutions at the time of the study. F.C.P. is a contractor for Analgesic Solution. M.S. is an employee of Astellas Pharma Global Development. J.M. and J.T. were working at Analgesic Solutions when the study was performed, but no longer work there. B.T. declares no conflict of interest.

Reprints: Nathaniel P. Katz, MD, MS, 232 Pond Street, Natick, MA 01760 (e-mail: nkatz@analgesicsolutions.com).

DOI: 10.1097/AJP.0000000000000186

The challenges in adequately treating neuropathic pain conditions are due to the various etiologies of neuropathic pain syndromes (herpes, human immunodeficiency virus [HIV], diabetes), the various and complex pain mechanisms (central/peripheral, hyperalgesia, allodynia), and the large interindividual variability in pain sensation. For this reason, there is no consensus treatment for each type of neuropathic pain, and clinicians have to try many treatments (or combinations) to find the best possible treatment for each individual patient.

Analysis of clinical trials for analgesic medications in neuropathic pain has identified some patient characteristics that are predictors of a better response to analgesic compounds versus placebo; these predictors include: (1) having had pain for at least 3 months,[1] (2) having moderate pain scores at baseline,[1,2] (3) having low pain intensity variability,[3] (4) having high health-related quality of life,[4] and (5) not being too young.[2] However, these "predictors" were identified by comparing various trials for various analgesic medications in various neuropathic pain indications and; therefore, are not specific to 1 compound and 1 indication. Moreover, because these characteristics predict the ability of certain types of patients to discriminate between the active compound and the placebo, using such characteristics in the clinic may eliminate certain types of patients with a good response to the active treatment on the basis that the same characteristics are associated with a high placebo response.

Herein, we took a different approach, that is, to determine the specific patient characteristics that are predictors of response to Qutenza, a high-concentration (8%) capsaicin patch that has proven effective for the relief of pain associated with postherpetic neuralgia (PHN) or HIV-associated neuropathy (HIV-AN).[5–10] To this end, we conducted meta-analyses of all randomized controlled studies evaluating the capsaicin patch efficacy and used individual patient data from capsaicin patch–treated patients only to identify which types of patients have the greatest response to capsaicin patch treatment.

METHODS

General Methodology

We utilized the Qutenza Clinical Trials Database, which is an individual patient database including all completed randomized controlled clinical trials conducted with the capsaicin patch for neuropathic pain. To identify specific patient characteristics that are predictors of response to the capsaicin patch, the logistic regression analyses focused only on capsaicin patch–treated PHN and HIV-AN patients, and therefore do not address any comparisons between the capsaicin patch and the low-dose control

patch, to represent what clinicians see in practice. There are several reasons for not considering patients treated with the control patch in our approach. First, capsaicin patch clinical trials utilized a low-concentration capsaicin patch as control (control patch) rather than a true placebo patch to mimic the pain associated with the high-dose capsaicin patch application (capsaicin induces a tingling and burning pain) to maintain the blind in the control group. Because low-concentration capsaicin has a certain efficacy,[8] the "placebo response" is relatively high in clinical trials. Second, in a real clinical setting, patients will be treated with the capsaicin patch, not placebo.

A list of candidate predictors of clinical outcome was created, and all variables in the list were subjected to univariate and multivariate analyses to determine their relationship to the response to the capsaicin patch. PHN and HIV-AN populations were analyzed separately. Patients with different predictive characteristics were identified using a multivariate logistic regression model. The response rates for patients treated with the capsaicin patch and the probability of being a responder to the capsaicin patch versus control patch were compared among the subgroups of patients with different predictive characteristics.

Selected Studies, Database Description, and Definitions

All completed randomized, double-blinded, controlled studies performed in neuropathic pain in the Qutenza Clinical Trials Database were included (Table 1). Individual patient data from the selected studies were extracted from the database in SAS format. The population analyzed was the intent-to-treat population (defined as all patients who were randomized in the study and who received study drug), regardless of study completion status, and who had at least 3 days of nonmissing pain intensity scores (past 24 h) on the 0 to 10 numerical rating scale (NRS) for the calculation of baseline average score. For each patient, we calculated the percent change from baseline to weeks 2 to 12 in pain intensity score (primary endpoint). The percent of patients with a Sustained Response (a decrease in pain intensity score from baseline $>50\%$ during weeks 2 to 12) or a Complete Response (an average pain intensity score ≤ 1 on the daily 0 to 10 NRS during weeks 2 to 12) was calculated for PHN and HIV-AN patients.

Univariate and Multivariate Logistic Regression Analyses

The potential predictors of response selected were the baseline patient characteristics that can easily be measured by physicians during office visits and for which data were collected in the trials (Table 2). The univariate logistic regression analysis was performed using the efficacy outcomes of Complete Response or Sustained Response as dependent variables, and using each baseline characteristic as an independent variable. Baseline characteristics with χ^2 P-value ≤ 0.15 were considered as potential predictors of the respective efficacy outcomes.

The multivariate logistic regression analysis was performed using the efficacy outcomes of Complete Response or Sustained Response as dependent variables, and using each potential baseline predictor identified in the univariate logistic regression analysis as an independent variable. Continuous variables were grouped into categories using clinically meaningful cutoffs (Table 2). Baseline variables with a P-value ≤ 0.15 were retained in the model and were considered as significant predictors of Sustained Response or Complete Response after capsaicin patch treatment. This was performed by using the backwards selection method (using the Wald test) to eliminate nonsignificant baseline characteristics: individual parameters that had a P-value > 0.15 were removed from the

TABLE 1. Studies Included in the Meta-analysis

Study No	Phase	Indication	Title	Randomization (Active:Control)	Total No. Patient Enrolled (No. Capsaicin Patch–treated Patient)	Duration of Posttreatment Observations (wk)	Application Time (min)
C108	2/3	PHN	A randomized, double-blind, controlled dose finding study of NGX-4010 for the treatment of PHN	3:1	299 (222)	12 (DB period)	30, 60, 90
C110	2/3	PHN	A randomized, double-blind, controlled study of NGX-4010 for the treatment of PHN	2:1	155 (102)	12	60
C116	3	PHN	A randomized, double-blind, controlled study of NGX-4010 for the treatment of PHN	1:1	402 (206)	12	60
C117	3	PHN	A multicenter randomized, double-blind, controlled study of NGX-4010 for the treatment of PHN studies in patients with HIV-AN	1:1	418 (212)	12	60
C107	2/3	HIV-AN	A randomized, double-blind, controlled dose finding study of NGX-4010 for the treatment of painful HIV-associated distal symmetrical polyneuropathy	3:1	306 (225)	12 (DB period)	30, 60, 90
C119	3	HIV-AN	A multicenter, randomized, double-blind, controlled study of NGX-4010 for the treatment of painful HIV-AN	2:1	494 (332)	12	30, 60
Total capsaicin patch–treated patients					1299		

DB indicates double-blind; HIV-AN, human immunodeficiency virus–associated neuropathy; NGX-4010, Qutenza; PHN, postherpetic neuralgia.

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TABLE 2. Potential Predictors Analyzed in the Models

Predictors	Categories and Cutoffs
Race	White, black, other
Sex	Male, female
Age	HIV: ≤40, >40 PHN: <65, 65-80, >80
BMI	≤25, 25-30, >30
Average baseline pain intensity	<4, 4-7, >7
Concomitant analgesic usage	0, 1, 2, or >2
Size of treatment area	<280 cm^2, 280-560, >560
SF-36-MCS	Median split (≤48 vs. >48)
SF-36-PCS	Median split (≤38 vs. >38)
MPQ sensory score	≥22 (ie, an average of "moderate" or worse on the 11 items)
MPQ affective score	≥8 (ie, an average of "moderate" or worse on the 4 items)
Pain sensory assessment of light brush	3 categories: low (absent; diminished), normal (normal; increased but not paresthetic, dysesthetic, or painful), high (increased and abnormal; increased and painful)
Pain sensory assessment of pin prick	3 categories: low, normal, high (as above)
Neurosensory quality of pain	>40 on each 0-100 VAS

BMI indicates Body mass index; HIV-AN, human immunodeficiency virus–associated neuropathy; MPQ, McGill Pain Questionnaire; PHN, postherpetic neuralgia; SF-36-MCS, SF-36 mental component summary; SF-36-PCS, SF-36 physical component summary; VAS, visual analog scale.

model; once a parameter was removed from the model, it remained excluded. The process was repeated until no other parameter in the model met the specified level for removal. When baseline pain and SF-36 were both significant predictors in the univariate analysis, only baseline pain was included in the multivariate analysis because the model was not stable when these 2 highly correlated predictors (SF-36 has a pain subscale that measures pain intensity) were both included.

Analysis of Outcome for Patients With the "Best" and "Worst" Predictors

Patient subgroups were created based on the significant predictors identified in the multivariate logistic regression model. The subgroups were defined as the "Best Predictive Group" (patients who combined all predictors of Sustained Response), the "Worst Predictive Group" (patients who had the worst combination of predictors), and all other patients. The percent change from baseline in pain intensity scores was calculated for each subgroup. The probability of having a Sustained Response when treated with the capsaicin patch was calculated and compared among the subgroups of patients with different predictive characteristics. The relative risk ratio (RR) and 95% confidence intervals (CIs) were utilized to compare the probability of being a responder between patients with the best predictive characteristics and those with the worst predictive characteristics, and between patients with the best predictive characteristics and all other patients. Finally, the relative RRs and 95% CIs of being a responder to the capsaicin patch versus control patch were compared among these subgroups using the Qutenza Clinical Trial Database for both capsaicin patch–treated and control patch–treated patients.

RESULTS

Source Studies

The Qutenza Clinical Trials Database includes 7 completed RCTs. Study C102 was excluded because the study was only 4 weeks, whereas all others were 12 weeks. Thus, 6 source studies (Table 1) were included in this meta-analysis, 4 PHN studies and 2 HIV-AN studies. Conducting meta-analyses of these studies was made possible by the fact that: (1) all studies utilized the 8% capsaicin patch as active treatment and the low-concentration capsaicin patch as control; (2) studies were of similar design (including having a 12-week endpoint); (3) studies collected the same primary endpoint data; and (4) patient selection criteria were similar (within the same indication).

Patient Baseline Characteristics

Only capsaicin patch–treated patients were selected for the logistic regression analyses. Of the 1299 capsaicin patch–treated patients, 1014 (485 PHN, 529 HIV-AN) had sufficient data to be included in the meta-analysis. For PHN patients the male/female ratio was 45%/55%; the majority (91%) of patients were white; the mean age was 71 years; the mean body mass index (BMI) was 28; and the mean ± SD baseline pain intensity was 5.7 ± 1.7 on 0 to 10 NRS (Table 3). In HIV-AN patients, the male/female ratio was 89%/11%; the majority of patients were white (63%) but blacks represented 27%; the mean age was 49 years; the mean BMI was 27; and the mean ± SD baseline pain intensity was 6.0 ± 1.6 (Table 3).

Candidate Predictors

The potential predictors of response selected were the baseline patient characteristics that can easily be measured by physicians during office visits and for which data were collected in the trials (Table 2). Continuous variables were grouped into categories using clinically meaningful cutoffs (Table 2).

Univariate Analysis

Univariate analysis results are presented in Table 4. Mild baseline pain intensity was associated with better outcome across disease and efficacy response categories than moderate or severe pain. Absence of allodynia on examination was associated with better outcome in the PHN-Sustained Response group; absence of allodynia and presence of hypoesthesia on examination, and absence of allodynia and presence of hypoesthesia on the Neurological/Sensory Assessment (NSA; a questionnaire), was associated with better outcome in the PHN Complete Response group. MPQ sensory scores were associated with better outcome for PHN patients. Better physical and mental health (SF-36) was associated with better outcome across disease and efficacy response categories.

Female sex and absence of use of concomitant analgesics were associated with better outcome in HIV-AN patients. Higher BMI was associated with better outcome in PHN patients. Decreased sensation on the baseline sensory examination was associated with better outcome in PHN patients. Increased pain to touch on the baseline sensory

TABLE 3. Summary of Demographic Characteristics

Patient Characteristics	PHN (N = 485)*	HIV-AN (N = 529)*
Race (n [%])		
White	442 (91.1)	333 (62.9)
Black	12 (2.5)	141 (26.7)
Other	31 (6.4)	55 (10.4)
Sex (n [%])		
Male	219 (45.2)	471 (89.0)
Female	266 (54.8)	58 (11.0)
Age		
Mean ± SD (N)	71.1 ± 11.6 (485)	49.1 ± 8.4 (529)
Median (min, max)	73.0 (21.0, 94.0)	48.0 (26.0, 74.0)
BMI		
Mean ± SD (N)	28.3 ± 5.8 (480)	26.5 ± 5.4 (525)
Median (min, max)	28.0 (17.0, 55.0)	25.0 (14.0, 57.0)
Average baseline pain intensity		
Mean ± SD (N)	5.7 ± 1.7 (485)	6.0 ± 1.6 (529)
Median (min, max)	5.7 (1.2, 9.5)	6.1 (2.2, 9.8)

*Denominators are patients who were treated with Qutenza and had at least 70% of baseline pain diary completed.

BMI indicates body mass index; PHN, postherpetic neuralgia; HIV-AN, human immunodeficiency virus–associated neuropathy; Min, minimum; Max, maximum.

examination was associated with worse outcome in PHN patients.

Multivariate Analysis

Multivariate analysis results are presented in Table 5. Mild baseline pain intensity (NRS score $\leq$4/10) was associated with better outcome than high baseline pain intensity (NRS score > 7) in all analyses (when removing SF-36 from the model—see Methods). Absence of allodynia on light brush examination was associated with better outcome than presence of allodynia in the PHN-Sustained Response group. Lower MPQ sensory scores (< 22) were consistently associated with better outcomes in PHN patients. A high rating of numbness ($\geq$ 40) on the NSA was associated with better outcome in the PHN Complete Response group. Female sex was associated with better outcome in HIV patients.

Outcome of Patients With "Best" Versus "Worst" Predictive Characteristics

On the basis of the final multivariate logistic regression model, subgroups of patients with the "best" and "worst" combination of predictive characteristics (termed Best and Worst Predictive Groups, respectively) for a Sustained Response were defined. For PHN patients, the Best Predictive Group was composed of patients with baseline average pain intensity $\leq$4, MPQ sensory score $\leq$22, and absent or diminished pain sensation to light brush, whereas the Worst Predictive Group was composed of patients with baseline average pain intensity > 7, MPQ sensory score > 22, and painful/increased pain sensation to light brush. For HIV-AN patients, the Best Predictive Group was composed of female patients with baseline average pain intensity $\leq$4, and the Worst Predictive Group composed of male patients with baseline average pain intensity > 7. "Other patients"

TABLE 4. Predictors of Sustained Response and Complete Response in the Univariate Analysis

	PHN				HIV-AN			
	Sustained Response		Complete Response		Sustained Response		Complete Response	
Patients' Characteristics	Parameter Estimate	*P**	Parameter Estimate	*P**	Parameter Estimate	*P**	Parameter Estimate	*P**
Baseline pain intensity†	−0.2386	0.0001	−0.4509	< 0.0001	−0.2046	0.0018	−0.2684	0.0217
Allodynia/hypoesthesia‡	−0.3727	0.0065	−0.4849	0.0128	NC	NC	NC	NC
MPQ sensory§	−0.0415	0.0073	−0.0540	0.0246	−0.0026	0.8668	−0.0177	0.5182
SF-36-MCS/MPQ-A‖	0.0342	0.0075	0.0419	0.0365	0.0282	0.0409	−0.0162	0.5013
SF-36-PCS‖	0.0406	0.0025	0.0543	0.0088	0.0350	0.0314	0.0124	0.6754
Sex¶	−0.1593	0.4340	−0.2349	0.4401	−0.7318	0.0122	−0.8543	0.0580
Taking concomitant analgesics#	−0.1171	0.2243	−0.2021	0.1630	−0.2560	0.0046	−0.1211	0.4465
BMI**	0.0311	0.0671	0.0479	0.0389	0.0214	0.2402	0.0219	0.4796
Neurosensory: numbness††	0.0044	0.5461	0.0181	0.0355	NC	NC	NC	NC
Neurosensory: increased pain to touch‡‡	−0.0261	0.5121	−0.0976	0.1207	NC	NC	NC	NC

†Milder pain was associated with better outcome across disease and efficacy response categories

‡Absence of allodynia on examination was associated with better outcome in the PHN-Sustained Response analysis; absence of allodynia and presence of hypoesthesia on examination, and absence of allodynia and presence of hypoesthesia on the NSA was associated with better outcome in the PHN Complete Response group. Absence of allodynia was determined by the absence or diminished response on light brush or pin prick stimulus.

§Milder pain based on rating of severity of pain sensory qualities was associated with better outcome for PHN patients.

‖Better physical and mental health was associated with better outcome across disease and efficacy response categories.

¶Female sex was associated with better outcome for HIV patients.

#Absence of use of concomitant analgesics was associated with better outcome for HIV-AN patients.

**Higher BMI was associated with better outcome for PHN patients.

††Increased numbness during baseline neurosensory examination associated with better outcome for PHN patients.

‡‡Increased pain to touch during baseline neurosensory examination associated with worse outcome for PHN patients.

BMI indicates body mass index; HIV-AN, human immunodeficiency virus–associated neuropathy; MPQ, McGill Pain Questionnaire; NC, not collected; PHN, postherpetic neuralgia; SF-36-MCS, SF-36 mental component summary; SF-36-PCS, SF-36 physical component summary.

*χ^2 *P*-value for parameters in the univariate logistic regression. Parameters with *P*-value $\leq$0.15 were considered potential predictors. Only statistically significant *P*-values are shown in the table

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TABLE 5. Predictors of Sustained Response and Complete Response in the Multivariate Analysis

	PHN				HIV-AN			
	Sustained Response		Complete Response		Sustained Response		Complete Response	
Patients' Characteristics	*P**	Odds Ratio† (95% CI)	*P**	Odds Ratio† (95% CI)	*P**	Odds Ratio† (95% CI)	*P**	Odds Ratio† (95% CI)
Mean baseline pain intensity: (A) 4-7 vs. (B) ≤4	0.6898	0.65 (0.38, 1.13)	0.1985	0.64 (0.22, 1.86)	0.5234	0.54 (0.30, 0.95)	0.4660	0.43 (0.18, 1.04)
Mean baseline pain intensity: (A) >7 vs. (B) ≤4	**0.0079**	0.35 (0.17, 0.73)	**0.0285**	0.08 (0.01, 0.71)	**0.0114**	0.38 (0.20, 0.74)	**0.1109**	0.32 (0.11, 0.93)
Pain sensory light brush: (A) normal vs. (B) low	0.7683	0.74 (0.38, 1.43)	X	X	NC	NC	NC	NC
Pain sensory light brush: (A) high vs. (B) low	**0.0116**	0.47 (0.24, 0.90)	X	X	NC	NC	NC	NC
MPQ sensory score: (A) ≥22 vs. (B) <22	**0.0164**	0.37 (0.17, 0.84)	X	X	X	X	X	X
Baseline neurosensory: numbness (A) ≥40 vs. (B) <40	X	X	**0.0541**	4.11 (0.98, 17.30)	NC	NC	NC	NC
Sex: (A) male vs. (B) female	X	X	X	X	**0.0059**	0.44 (0.24, 0.79)	**0.0412**	0.39 (0.16, 0.96)

†For a patient's characteristics "A vs. B," an odds ratio > 1 favors A, whereas an odds ratio < 1 favors B.

HIV-AN indicates human immunodeficiency virus–associated neuropathy; High, increased and abnormal, increased and painful; Low, absent or diminished; MPQ, McGill Pain Questionnaire; NC, not collected; Normal, Normal, increased but not paresthetic, dysesthetic, or painful; PHN, postherpetic neuralgia; X, not significant.

*Backward model selection with a significance level of *P*-value≤0.15 to retain variables in the model. The parameters presented are significant predictors. Statistically significant *P*-values are shown in bold.

were patients not in the Best or the Worst Predictive Group.

The average percent change in pain intensity from baseline to weeks 2 to 12 was calculated in capsaicin patch–treated patients for the Best Predictive Group, the Worst Predictive Group, and other patients (Fig. 1). In PHN patients, the Best Predictive Group had a 48% (95% CI: 32.7%, 63.1%) reduction in pain intensity from baseline to weeks 2 to 12, whereas the Worst Predictive Group only had a 21% (95% CI: 8.2%, 33.7%) decrease, and other patients a 31% (95% CI: 28.2%, 34.7%) decrease in pain intensity.

In HIV-AN patients, the decrease in pain intensity from baseline to weeks 2 to 12 was 48% (95% CI: 12.0%,

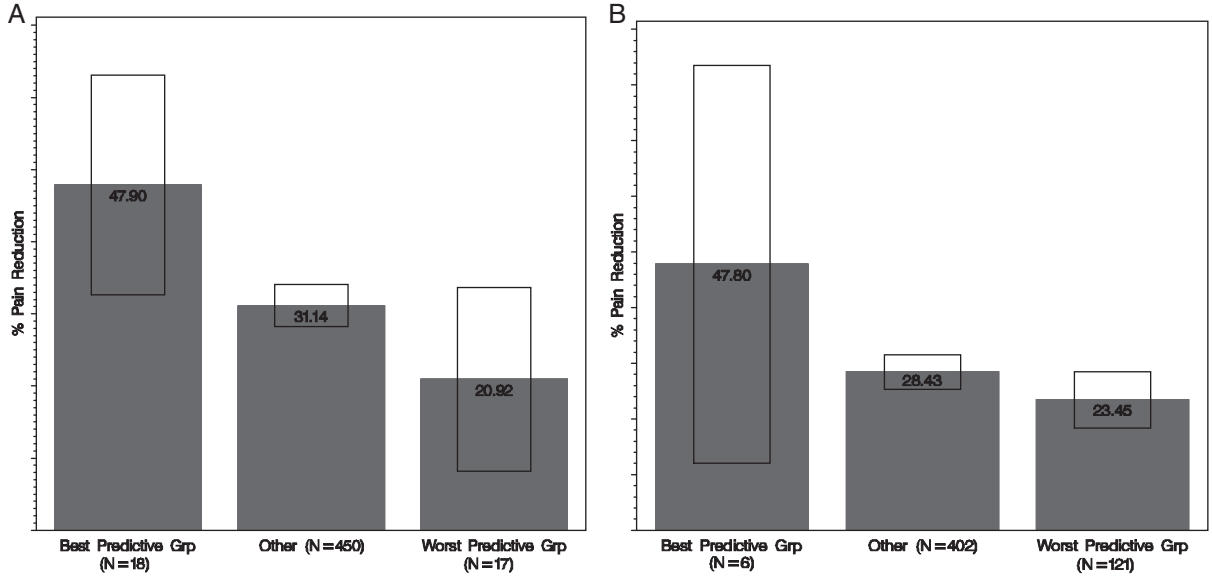

FIGURE 1. Percentage of pain intensity reduction over weeks 2 to 12 by groups of predictive characteristics. A, Postherpetic neuralgia patients. Best Predictive Group, patients with baseline average pain intensity≤4, MPQ sensory score≤22, and absent or diminished pain sensation to light brush; Worst Predictive Group, patients with baseline average pain intensity>7, MPQ sensory score>22, and painful/increased pain sensation to light brush (based on results of multivariate logistic regression for 50% responders); Other, other patients. B, HIV-associated neuropathy patients. Best Predictive Group, female patients with baseline average pain intensity≤4; Worst Predictive Group, male patients with baseline average pain intensity>7 (based on results of multivariate logistic regression for 50% responders); Other, other patients. The error bar represents the 95% confidence interval. Grp indicates group; MPQ, McGill Pain Questionnaire.

83.6%) in the Best Predictive Group, but only 23% (95% CI: 18.4%, 28.5%) in the Worst Predictive Group, and 28% (95% CI: 25.3%, 31.5%) in all other patients.

The probability of having a Sustained Response to the capsaicin patch was compared among the subgroups (Fig. 2). In both PHN and HIV-AN patients, patients in the Best Predictive Group had a statistically significantly greater chance of having a Sustained Response to the capsaicin patch than patients in the Worst Predictive Group or other patients. Indeed, in PHN patients, the Best Predictive Groups was 8.50 (95% CI: 1.20, 60.15) times and 1.77 (95% CI: 1.09, 2.88) times more likely to have a Sustained Response to the capsaicin patch than the Worst Predictive Group and other patients, respectively (Fig. 2). In HIV-AN patients, the RRs were 4.03 (95% CI: 2.01, 8.07) and 2.55 (95% CI: 1.42, 4.60) for Best versus Worst and Best versus other patients, respectively (Fig. 2).

The probability of having a Sustained Response to the capsaicin patch versus the control patch was compared among the subgroups (Fig. 3). For PHN patients in the Best Predictive Group, the probability of having a Sustained Response after capsaicin patch treatment was 1.75 (95% CI: 0.68, 4.52) times higher than that after control patch treatment. In the Worst Predictive Group, patients tended to respond better to the control patch than to the capsaicin patch (RR = 0.47 [95% CI: 0.05, 4.70]). For HIV-AN patients, the RR of Sustained Response for the capsaicin patch versus control patch was 1.33 (95% CI: 0.30, 5.96) in the Best Predictive Group and 1.13 (95% CI: 0.51, 2.50) in the Worst Predictive Group.

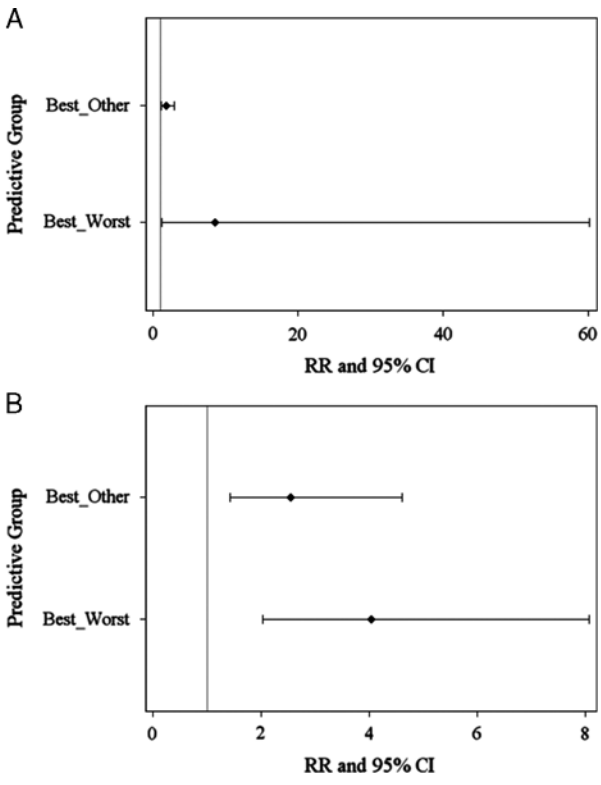

FIGURE 2. Comparison of the different subgroups for the probability of being a responder to the capsaicin patch. Data presented are the risk ratio (RR) and 95% confidence interval (CI) of Best versus Worst Predictive Groups and Best Predictive Group versus other patients. A, Postherpetic neuralgias patients. "Best" = Best Predictive Group, patients with baseline average pain intensity ≤ 4, MPQ sensory score ≤ 22, and absent or diminished pain sensation to light brush; "Worst" = Worst Predictive Group, patients with baseline average pain intensity > 7, MPQ sensory score > 22, and painful/increased pain sensation to light brush (based on results of multivariate logistic regression for 50% responders); "Other," other patients. B, HIV-associated neuropathy patients. "Best" = Best Predictive Group, female patients with baseline average pain intensity ≤ 4; "Worst" = Worst Predictive Group, male patients with baseline average pain intensity > 7 (based on results of multivariate logistic regression for 50% responders); "Other," other patients. MPQ indicates McGill Pain Questionnaire.

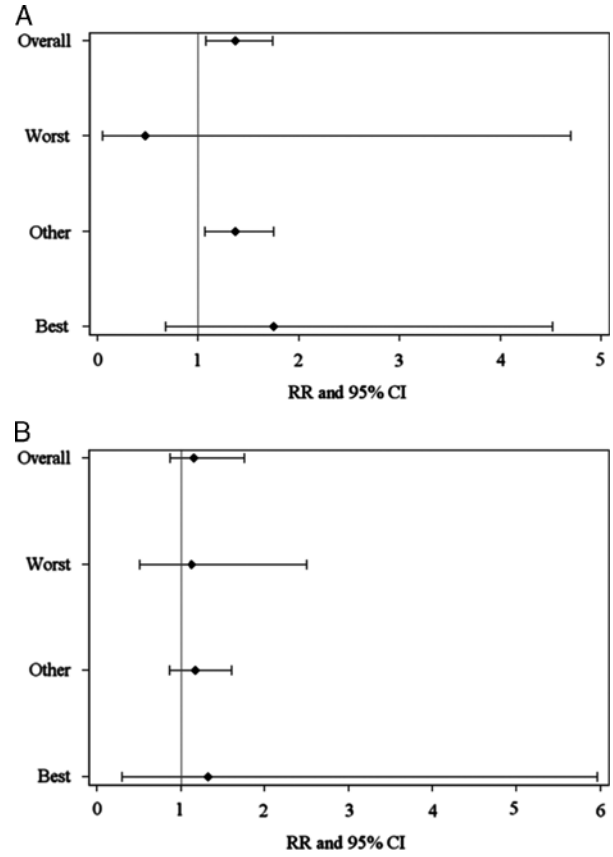

FIGURE 3. Probability (RR) of having a Sustained Response to the capsaicin patch versus control patch in the different subgroups. A, Postherpetic neuralgias patients. "Overall," all patients; "Best" = Best Predictive Group, patients with baseline average pain intensity ≤ 4, MPQ sensory score ≤ 22, and absent or diminished pain sensation to light brush; "Worst" = Worst Predictive Group, patients with baseline average pain intensity > 7, MPQ sensory score > 22, and painful/increased pain sensation to light brush (based on results of multivariate logistic regression for 50% responders); "Other," other patients. B, HIV-associated neuropathy patients. "Overall," all patients; "Best" = Best Predictive Group, female patients with baseline average pain intensity ≤ 4; "Worst" = Worst Predictive Group, male patients with baseline average pain intensity > 7 (based on results of multivariate logistic regression for 50% responders); "Other," other patients. CI indicates confidence interval; MPQ, McGill Pain Questionnaire; RR, risk ratio.

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DISCUSSION

Clinicians who treat patients with neuropathic pain have no information regarding the prognostic factors that are associated with positive treatment outcomes with various interventions. Therefore, we attempted to assess prognostic factors (patient baseline characteristics) associated with the effectiveness of capsaicin patch treatment in patients with neuropathic pain by conducting a meta-analysis of 6 clinical trials.

We found that baseline pain intensity was a consistent predictor of response: patients with mild baseline pain intensity ($\leq$4/10) fared consistently better than patients with higher pain in all analyses. In a study by Edwards et al,[11] baseline pain was found to be a predictor of response to pharmacotherapy (oral opioids) in PHN but in the opposite way: in that study, a higher baseline pain score was related to greater pain reduction upon opioid treatment, but not upon treatment with placebo or tricyclic antidepressants. The discrepancy between Edwards' findings and our results may simply be due to the difference in mechanisms of analgesia between oral opioids (in Edwards's study) and topical analgesic (in the present study). A lower overall MPQ sensory score, which reflects a lower score of all types of pain broken down by sensory qualities, was consistently associated with better outcomes, consistent with the results for baseline pain intensity.

Evaluation of allodynia and hyper/hypoesthesia was performed for PHN patients only, based on a structured physical examination and on patient self-report (NSA). Patients without allodynia and with hypoesthesia, on both the physical examination and the NSA, had better outcomes. This seems to be a robust finding as it is consistent across clinical examination and patient self-report methods of capturing these phenomena. Although it is opposite to what would be expected clinically, it is similar to the findings from Wasner et al[12] showing that patients with impairment of nociceptor function (as measured by quantitative sensory testing) had significantly greater pain reduction under lidocaine versus placebo. From our data, however, it is unclear whether the absence of allodynia and presence of hypoesthesia predict benefits from the capsaicin patch or are disease markers with a more favorable natural history. Nonetheless, these variables predict favorable outcome among patients treated with 2 topical analgesics that presumably work through different mechanisms: capsaicin patch and topical lidocaine. Preliminary, unpublished evidence from some data series generated in everyday practice may indicate otherwise and that more evaluations are required to truly comprehend the patient profile with regard to sensory testing. More evidence that neurosensory characteristics are associated with treatment outcome is provided by Edwards[11] who found that patients with relatively higher heat pain thresholds at baseline had a greater reduction in pain intensity during treatment with opioids. Bouhassira et al[13] also found that neuropathic pain sensory profiles influenced response to treatment.

Female sex appeared to predict better outcomes in patients with HIV-AN, but not PHN. This could be an artifact because there is an important sex imbalance in HIV-AN patients (most patients are males). Sex may also be a confounding variable with mood or general health: when we excluded the SF-36 Mental Component Summary (that includes some mood-related items) from the analysis, the *P*-value for sex as a predictor dropped substantially. Nevertheless, sex has been shown to be an important predictor of analgesic response, with females responding better than males.[14] For instance, Ross and colleagues found that, in patients with tumor-related neuropathic pain, females respond to gabapentin better than men.[15]

Some results from the regression analyses were more consistent than others. For example, baseline pain intensity was a good predictor throughout but low MPQ sensory findings were predictive in PHN only, suggesting that baseline pain is a robust predictor. In general, however, data were inconsistent. Some predictors in PHN patients were not predictors in HIV-AN patients.

We used these predictive factors to determine what the outcome of capsaicin patch treatment would be in patients harboring all of the favorable baseline characteristics (Best Predictive Group). We found that patients with the best predictive characteristics (baseline pain intensity $\leq$4, MPQ sensory score $\leq$22, and no allodynia and presence of hypoesthesia for PHN patients; female patients with baseline average pain intensity $\leq$4 for HIV-AN patients) had a statistically significantly greater chance of having a Sustained Response than patients with the worst predictive characteristics or the other patients. In fact, PHN patients with the best characteristics had a 48% average decrease in pain intensity from baseline through weeks 2 to 12, compared with 20% for patients with the worst characteristics, and 31% for all others. In HIV-AN patients, these values were 48%, 23%, and 28%, respectively.

We then analyzed whether these predictive factors impacted the response to capsaicin patch treatment versus control patch, a piece of information that could be useful when conducting clinical trials with the capsaicin patch or in clinical practice. In both PHN and HIV-AN patients, the response to the capsaicin patch was not statistically different from that with the control patch in patients with the best or the worst predictive characteristics. This was essentially because the RR had large CIs (including 1), due to the small size of some of these subgroups.

A limitation of our study, as with all studies using regression analyses, is that variables may "carry" confounding factors. For example, sex characteristics could have been confounded with something else (eg, general health, mood, or socioeconomic status). In addition, the HIV-AN findings were based on only 2 studies that were composed predominantly of males.

No studies have identified predictors of treatment response in HIV-AN patients. In PHN patients, a few studies, which were discussed above, have identified predictors of response in PHN patients, such as high baseline pain score, impairment of nociceptor function, and certain sensory phenotypes.[11,12,13] Another study found that the presence of comorbid sleep disturbance predicted, in part, response to pregabalin treatment.[16] The fact that these studies evaluated oral treatments while the present study evaluated a topical analgesic may limit the relevance of comparisons. Although different types of analgesic may share similar predictors of response, ultimately, each type of analgesic may have its own specific predictors for response, which would need to be identified.

Our analysis provides preliminary evidence that certain patients may derive more of a benefit from capsaicin patch treatment, particularly in patients with PHN. Although it is unclear whether these predictors reflect the mechanism of action of the capsaicin patch (eg, capsaicin-related pain pathways) or whether they are general prognostic factors, PHN patients with baseline average pain intensity $\leq$4, MPQ sensory score $\leq$22, and absent or diminished pain sensation to light brush had greater

improvements than other patients when treated with the capsaicin patch. When counseling patients on the relative risk-benefit of potential options for PHN, clinicians can use this information to help determine the potential options.

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