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Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations (PAIN-CONTRoLS)
Bayesian Adaptive Comparative Effectiveness Randomized Trial

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IMPORTANCE Cryptogenic sensory polyneuropathy (CSPN) is a common generalized slowly progressive neuropathy, second in prevalence only to diabetic neuropathy. Most patients with CSPN have significant pain. Many medications have been tried for pain reduction in CSPN, including antiepileptics, antidepressants, and sodium channel blockers. There are no comparative studies that identify the most effective medication for pain reduction in CSPN.

OBJECTIVE To determine which medication (pregabalin, duloxetine, nortriptyline, or mexiletine) is most effective for reducing neuropathic pain and best tolerated in patients with CSPN.

DESIGN, SETTING, AND PARTICIPANTS From December 1, 2014, through October 20, 2017, a bayesian adaptive, open-label randomized clinical comparative effectiveness study of pain in 402 participants with CSPN was conducted at 40 neurology care clinics. The trial included response adaptive randomization. Participants were patients with CSPN who were 30 years or older, with a pain score of 4 or greater on a numerical rating scale (range, 0-10, with higher scores indicating a higher level of pain). Participant allocation to 1 of 4 drug groups used the utility function and treatment's sample size for response adaptation randomization. At each interim analysis, a decision was made to continue enrolling (up to 400 participants) or stop the whole trial for success (80% power). Patient engagement was maintained throughout the trial, which helped guide the study and identify ways to communicate and disseminate information. Analysis was performed from December 11, 2015, to January 19, 2018.

INTERVENTIONS Participants were randomized to receive nortriptyline (n = 134), duloxetine (n = 126), pregabalin (n = 73), or mexiletine (n = 69).

MAIN OUTCOMES AND MEASURES The primary outcome was a utility function that was a composite of the efficacy (participant reported pain reduction of ≥50% from baseline to week 12) and quit (participants who discontinued medication) rates.

RESULTS Among the 402 participants (213 men [53.0%]; mean [SD] age, 60.1 [13.4] years; 343 White [85.3%]), the utility function of nortriptyline was 0.81 (95% bayesian credible interval [CrI], 0.69-0.93; 34 of 134 [25.4%] efficacious; and 51 of 134 [38.1%] quit), of duloxetine was 0.80 (95% CrI, 0.68-0.92; 29 of 126 [23.0%] efficacious; and 47 of 126 [37.3%] quit), pregabalin was 0.69 (95% CrI, 0.55-0.84; 11 of 73 [15.1%] efficacious; and 31 of 73 [42.5%] quit), and mexiletine was 0.58 (95% CrI, 0.42-0.75; 14 of 69 [20.3%] efficacious; and 40 of 69 [58.0%] quit). The probability each medication yielded the highest utility was 0.52 for nortriptyline, 0.43 for duloxetine, 0.05 for pregabalin, and 0.00 for mexiletine.

CONCLUSIONS AND RELEVANCE This study found that, although there was no clearly superior medication, nortriptyline and duloxetine outperformed pregabalin and mexiletine when pain reduction and undesirable adverse effects are combined to a single end point.

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Supplemental content

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Many peripheral neuropathies are secondary to disease pathophysiologic conditions such as diabetes and unhealthy alcohol abuse, as well as the use of certain medications. Of the estimated 20 million people with neuropathy in the United States, at least 25% of neuropathies remain idiopathic.[1,2] We refer to these remaining cases as *cryptogenic sensory polyneuropathy* (CSPN).[1-6] Prior reports have used other terms such as *idiopathic neuropathy* or *small fiber sensory peripheral neuropathy*.

Neuropathic pain is a symptom in 70% to 80% of patients with CSPN. Nortriptyline,[7-12] pregabalin,[13,14] and duloxetine[15-18] are considered first-line agents for treating neuropathic pain, while mexiletine[19-24] is listed as a third-line agent. All 4 medications have different mechanisms of actions to reduce pain. The pharmaceutical industry has focused on developing drugs for treating the pain of diabetic sensory polyneuropathy, and 2 drugs are approved by the US Food and Drug Administration (FDA) for the indication (duloxetine and pregabalin). To our knowledge, there have been no efficacy trials of drugs to treat pain in patients with CSPN, there is no information to guide physicians' drug choices for treatment of pain in patients with CSPN, and insurance carriers often reject authorizing prescriptions for some drugs commonly used for diabetic sensory polyneuropathy. The pragmatic nature of the study and patient preference influenced the decision to perform a trial that randomizes patients to receive drugs that are used routinely for neuropathic pain.

The goal of this study, PAIN-CONTRoLS (Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations) was to engage patients to find the best drug for the treatment for CSPN by determining which medication is most effective and tolerable. Patient advisors encouraged the study based on their priority focus of reducing the amount of time it takes clinicians to find a therapy for pain relief. To address this comparative effectiveness study question, we opted for a bayesian randomized clinical trial using response-adaptive randomization.

Key Points

Question Which of the most commonly prescribed medications (pregabalin, duloxetine, nortriptyline, and mexiletine) is best tolerated and most effective for reducing pain in patients with cryptogenic sensory polyneuropathy?

Findings In a bayesian adaptive randomized clinical trial including 402 patients with cryptogenic sensory polyneuropathy, none of the 4 drugs were clearly superior in performance. However, nortriptyline and duloxetine performed better than pregabalin and mexiletine when efficacy and tolerability were both considered.

Meaning Nortriptyline or duloxetine should be considered first for the treatment of pain among patients with cryptogenic sensory polyneuropathy.

Methods

Trial Design

The PAIN-CONTRoLS trial was a multisite, prospective, open-label comparative effectiveness bayesian adaptive randomized clinical trial conducted from December 1, 2014, through October 20, 2017, that compared 4 drugs for the treatment for CSPN. Response-adaptive randomization trials are often smaller, more powerful, faster to conduct, and place more participants in better-performing groups.[25,26] Measures of pain reduction and tolerability were combined into a single utility function that was used as the primary end point for the trial. Patients were enrolled at 40 different clinical sites (Austin Neuromuscular Center, Austin, Texas; Barrow Neurology, Phoenix, Arizona; Brigham and Women's Hospital, Boston, Massachusetts; Cedars-Sinai Medical Center, Los Angeles, California; Cleveland Clinic, Cleveland, Ohio; Colorado Springs Neurological Associates, Colorado Springs; Columbia University Medical Center, New York, New York; Grand Medical Clinic, Katy, Texas; Henry Ford Hospital, Detroit, Michigan; Hutchinson Clinic, Hutchinson, Kansas; Indiana University, Bloomington; Mercy Medical Center, Des Moines, Iowa; Mt. Sinai Beth Israel, New York, New York; Neurological Services of Orlando Research, Orlando, Florida; NorthShore University Health System, Evanston, Illinois; Norton Neurology Services, Louisville, Kentucky; Oregon Health and Science University, Portland; Pennsylvania State University, Centre County; Phoenix Neurological, Phoenix, Arizona; Saint Louis University, Saint Louis, Missouri; Seton Brain and Spine, Austin, Texas; Spectrum Health, Grand Rapids, Michigan; Texas Neurology, Dallas; The Ohio State University, Columbus; University at Buffalo, Buffalo, New York; University of California-Irvine, Irvine; University of California, San Francisco, San Francisco; University of Cincinnati, Cincinnati, Ohio; University of Colorado-Denver, Denver; University of Florida-Gainesville, Gainesville; University of Florida, Jacksonville, Jacksonville; University of Iowa Hospitals and Clinics, Iowa City; University of Kansas Medical Center, Kansas City; University of Miami, Miami, Florida; University of Michigan, Ann Arbor; University of Minnesota, Minneapolis; University of Nebraska Medical Center, Omaha; University of North Dakota, Grand Forks; University of South Florida-Tampa, Tampa; University of Texas Health Science Center at Houston, Houston; University of Toronto, Toronto, Ontario, Canada; University of Utah, Salt Lake City; University of Vermont, Burlington; University of Virginia, Charlottesville; UT Health Science-San Antonio, San Antonio, Texas; and UT Southwestern Medical Center, Dallas, Texas). Each site's institutional review board approved the trial protocol (Supplement 1). Patients provided written consent prior to enrollment. REDCap was used as the data capture system: a secure, web-based platform to collect and manage study data.[27,28] A data and safety monitoring board made recommendations related to trial continuation. Information on the inclusion and exclusion criteria, interventions, assessments, and study results can be found in the Patient-Centered Outcomes Research Institute Final Research Report.[29] The trial protocol and statistical analysis plan have been published by the Patient-Centered Outcomes Research Institute.[30]

Patients

Before the baseline visit, potential participants were prescreened and confirmed to have CSPN by their physician.

Patients were excluded from participating if there was another known cause for polyneuropathy (type 1 or 2 diabetes), if they were unable to give written consent or comply with the study or had any medical condition that would prevent them from taking any of the study drugs. Investigators enrolling patients used the criteria of Wolfe et al[5] with no evidence of "any identifiable metabolic, toxic, infectious, systemic or hereditary disorder known to cause peripheral neuropathy."[5(p546)] Patients with monoclonal gammopathy due to hematologic malignant neoplasms were excluded. Patients 30 years or older were eligible for inclusion if they had a diagnosis of CPSN, were not currently taking the study medications or a similar class of medication for at least 7 days before their baseline visit, and reported a numerical rating pain scale score of 4 or greater (range, 0-10, with higher scores indicating a higher level of pain).[31] To be as pragmatic as possible, inclusion and exclusion criteria for this trial were kept minimal.

Treatment

To start the trial, participants were randomly assigned, in a 1:1:1:1 ratio, to 1 of 4 drugs: 2 drugs (pregabalin and duloxetine) that are FDA approved for painful diabetic peripheral neuropathy and 2 drugs (mexiletine and nortriptyline) that often are used in the United States to treat peripheral neuropathic pain. After the initial allocation for the first 80 enrolled participants, the ratio of assignment to the 4 drugs was updated every 13 weeks. At each interim analysis, the probability that each treatment yielded the highest utility was calculated. These probabilities and the number of patients in each group were used to update the randomization proportion for the next group of patients, with greater weight given to treatment groups that appeared superior and those with less information and greater uncertainty. Randomization was performed from a central, web-based procedure in REDCap.[27,28] The drug was not provided by the study, so all participants received a prescription. Paying for the drug was the responsibility of the participant. The prescribed drug daily doses were as follows: nortriptyline, 75 mg; duloxetine, 60 mg; pregabalin, 300 mg; and mexiletine, 600 mg. Doses were escalated weekly during the first 4 weeks as needed until the target doses were achieved. If the participant could not tolerate the maximum dose, then the dose was titrated down to the previously tolerated dose. Study visits for each participant took place either during a clinic visit or a telephone call at 4, 8, and 12 weeks. Participants who dropped out completed a survey that asked for the reason(s) they discontinued taking the medication and were contacted only for the 30-day safety follow-up call.

Study Outcomes

Patients consistently cited pain as a central study measure, recognizing that their lack of pain relief contributes to poor quality of life and diminishes their abilities to engage in desired daily activities, as well as negatively affects their emotional well-being. We used clinical input to determine the relative weight of pain reduction and medication discontinuation and combined them into a single utility function.

We measured an improvement in pain as the percentage decrease in the numerical rating scale (0-10) scores from baseline to week 12. The percentage decrease was calculated for all participants who took the study drug for all 12 weeks. Any participant who reported at least a 50% reduction in pain was deemed as demonstrating an efficacious result. A 50% decrease in pain is a popular and accepted metric in industry and among patients. The second measure was the observed percentage of participants who quit their treatment drug. Any patient who stopped the study drug for any reason (eg, cost of the medication) or was lost to follow-up was considered to have dropped out. Thus, the final end point of the study is a utility function that reflects a combination of 2 measures: efficacy and dropout rates for each drug. A sensitivity analysis also was performed with the patient's lost to follow-up end point data as null instead of imputed as quit.

To develop a single primary outcome measure, we combined efficacy rates and quit rates into a single utility function. Specifically, the utility function is $U(E, Q) = 0.75E + 1 - Q$, where U is utility and the E and Q terms are numerical proportions between 0 and 1 reflecting the proportion of patients who achieve the 50% reduction in pain or stop the medication, respectively. This utility function was chosen after discussion with clinical experts regarding the relative utility of quit and efficacy.[25]

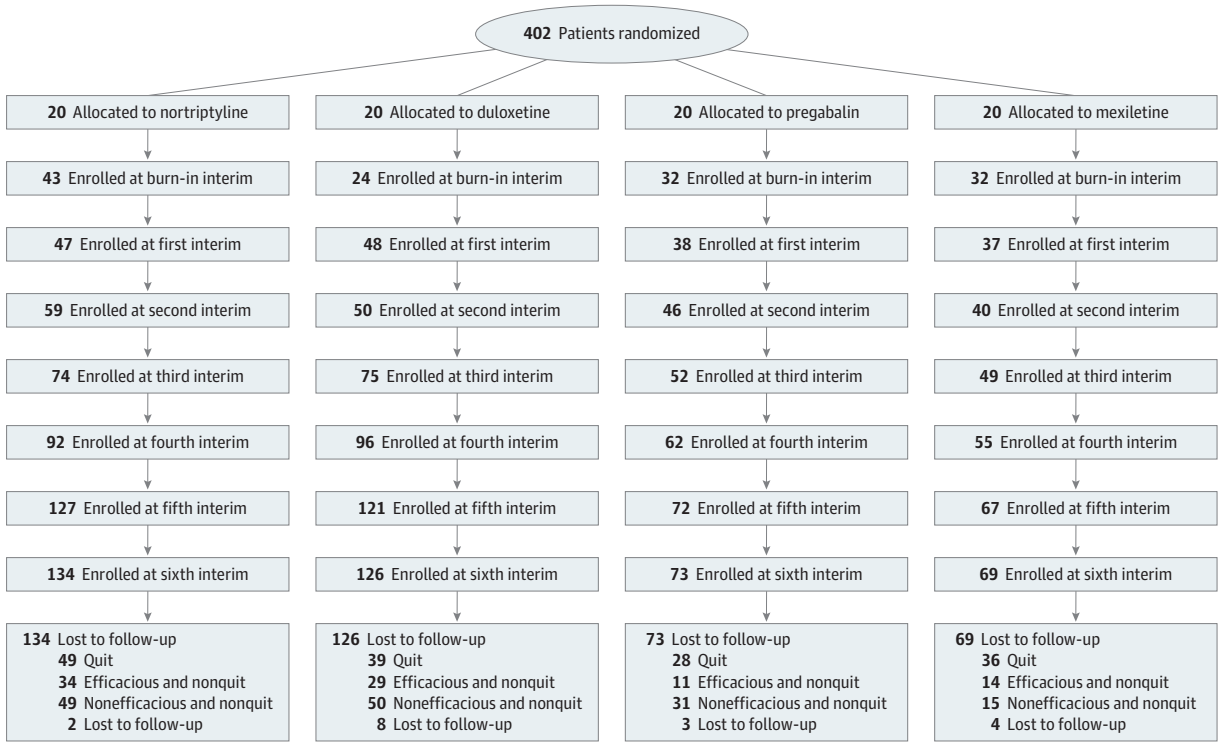
In addition to determining the utility function for each drug, we calculated the probability that a drug was best by comparing utility functions among all drugs. Combining participants' ratings of efficacy with the percentage of participants who stopped taking the drug to which they were assigned provided us with an important single measure for which drug performed best.[30] The best group is referred to as the group of maximum utility. The final analysis determined which of the groups were loser(s), defined as a group that has a probability of being the best group as measured by a combined utility of less than 0.01.

Participants were asked about any adverse effects they experienced at each of the follow-up visits, regardless of whether they chose to maintain use or quit taking the study drug. We conducted qualitative analysis to determine if a meaningful pattern emerged from the ongoing, real-time patient-reported outcomes.

Statistical Analysis

The response adaptive randomization trial design allowed for varying sample size because prespecified rules allowed for the detection of early success, also considered a best-performing group. The utility function, which combines efficacy and quit rates, drove the randomization probabilities, stopping criteria, and final analyses. These 2 rates, along with the number of participants who did not quit but for whom the drug was not efficacious, were modeled as treatment-specific multinomial distributions.[25] The interim analyses were prespecified to test for trial success after end point data were collected for 100 participants. The decision to stop the trial or continue enrolling participants was based on a prespecified calculation of the probability of the maximum utility being larger than 0.925. When enrollment continued, the randomization schedule was updated, and the next interim analysis occurred every 13 weeks until the total sample size was met.

Figure. CONSORT Diagram



For all 6 interim analyses, some participants had follow-up data observed, but not all had completed the study. Longitudinal modeling was used to estimate participants' 12-week data from data at early time points (4 and 8 weeks). For the final data analysis, all end point data (week 12) were used in the utility function. Based on the prespecified design, this study had 80% power to detect a best treatment drug with approximately 5% type I error.[26]

Results

Between December 1, 2014, and June 14, 2017, 402 patients (213 men [53.0%]; mean [SD] age, 60.1 [13.4] years) with CSPN were enrolled in the study, with the last participant's follow-up occurring October 20, 2017. The overall accrual rate was 3 participants per week. Most patients were recruited from existing populations of patients with neuropathy at each site. Because of the adaptive randomization used, the study resulted in unbalanced treatment groups. The **Figure** provides the treatment accrual across time and shows that the nortriptyline and duloxetine groups have larger sample sizes (nortriptyline, 134; and duloxetine, 162) compared with the pregabalin group (73 participants) and mexiletine group (69 participants). End point data were collected for most of the participants enrolled in the study, with only 17 participants (4.2%) lost to follow-up. All data were included in the final analysis, including those from participants lost to follow-up. The conclusions did not change when the sensitivity analysis with these 17 participants' data was performed.

All 4 medication groups were well matched with respect to baseline characteristics, shown in **Table 1**. At baseline, the primary outcome measure, mean (SD) pain scores, were similar across the 4 groups (nortriptyline, 6.9 [1.5]; duloxetine, 6.7 [1.6]; pregabalin, 6.4 [1.6]; and mexiletine, 6.5 [1.7]).

Outcomes and Utility

Table 2 shows that, at the end of the 12-week follow-up period, nortriptyline and duloxetine had the lowest probability of participants who had quit the study medication (nortriptyline, 51 of 134 [38.1%]; and duloxetine, 47 of 126 [37.3%]). Mexiletine had the highest quit rate (40 of 69 [58.0%]), with many of the participants stopping because of adverse effects. Patient-reported adverse effects were the primary reason for quitting all study drugs.

The percentage decrease in pain scores from baseline to week 12 was calculated for the participants who did not quit (ie, this is a trichotomous response: efficacious, nonefficacious, or quit). At least a 50% reduction in pain score was deemed as efficacious. Pregabalin had the lowest rate of efficacy, with only 15.1% of participants (11 of 73) achieving a 50% reduction in pain (Table 2). All 3 other study medications had similar efficacy rates (nortriptyline, 34 of 134 [25.4%]; duloxetine, 29 of 126 [23.0%]; and mexiletine, 14 of 69 [20.3%]).

Using the utility function framework that combines the quit rate and the efficacy rates, the utility function of nortriptyline was 0.81 (95% credible interval [CrI], 0.69-0.93; 34 of 134 [25.4%] efficacious; and 51 of 134 [38.1%] quit), of duloxetine was 0.80 (95% CrI, 0.68-0.92; 29 of 126 [23.0%] efficacious; and 47 of 126 [37.3%] quit), pregabalin was 0.69 (95% CrI, 0.55-

Table 1. Demographic and Baseline Characteristics for Participants[a]

Characteristic	Nortriptyline (n = 134)	Duloxetine (n = 126)	Pregabalin (n = 73)	Mexiletine (n = 69)	Total (N = 402)
Age, mean (SD), y	60.3 (12.7)	59.9 (14.0)	59.5 (13.6)	60.7 (13.7)	60.1 (13.4)
Sex, No. (%)					
Female	59 (44.0)	68 (54.0)	34 (46.6)	28 (40.6)	189 (47.0)
Male	75 (56.0)	58 (46.0)	39 (53.4)	41 (59.4)	213 (53.0)
Hispanic or Latino ethnicity (self-report), No. (%)					
No	126 (94.0)	119 (94.4)	68 (93.2)	66 (95.7)	379 (94.3)
Yes	8 (6.0)	6 (4.8)	4 (5.5)	3 (4.3)	21 (5.2)
Unknown	0	1 (0.8)	1 (1.4)	0	2 (0.5)
Race (self-report), No. (%)					
White	113 (84.3)	104 (82.5)	62 (84.9)	64 (92.8)	343 (85.3)
Black or African American	10 (7.5)	11 (8.7)	4 (5.5)	1 (1.4)	26 (6.5)
American Indian or Alaska Native	1 (0.7)	0	0	0	1 (0.2)
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Asian	6 (4.5)	4 (3.2)	4 (5.5)	3 (4.3)	17 (4.2)
Other	4 (3.0)	5 (4.0)	3 (4.1)	1 (1.4)	13 (3.2)
Unknown	0	2 (1.6)	0	0	2 (0.5)
Likert pain visual analog scale score, mean (SD)[b]	6.9 (1.5)	6.7 (1.6)	6.4 (1.6)	6.5 (1.7)	6.7 (1.6)
PROMIS pain interference T-score, mean (SD)[c]	63.1 (7.0)	62.4 (6.8)	63.3 (5.5)	60.9 (7.9)	62.5 (6.9)
PROMIS fatigue T-score, mean (SD)[c]	59.6 (3.4)	59.7 (3.3)	59.1 (3.73)	59.7 (3.2)	59.6 (3.4)
PROMIS sleep disturbance T-score, mean (SD)[c]	59.1 (9.8)	60.6 (8.3)	59.8 (8.7)	57.0 (11.4)	59.3 (9.5)
SF-12 Health composite scores, mean (SD)[d]					
Physical	38.0 (9.3)	38.5 (9.3)	37.9 (9.1)	41.1 (10.1)	38.7 (9.4)
Mental	48.0 (10.4)	46.7 (10.1)	46.8 (11.3)	47.2 (11.1)	47.2 (10.6)

Abbreviations: PROMIS, Patient-Reported Outcome Measurement Information System; SF-12, 12-item Short Form Survey.

[a] Percentages may not sum to 100 because of rounding. There were no significant differences between the treatment groups with respect to the baseline characteristics.

[b] Scores on the Likert visual analog scale ranged from 0 to 10, with higher scores indicating a more severe level of pain.

[c] T-score metric: 50 is the mean of a relevant reference population and 10 is the SD of that population. Higher scores represent worse outcome (ie, more pain interference).

[d] Scores are calibrated so that 50 is the mean score or norm with an SD equal to 10. Higher scores indicated better health for both physical and mental component scores.

0.84; 11 of 73 [15.1%] efficacious; and 31 of 73 [42.5%] quit), and mexiletine was 0.58 (95% CrI, 0.42-0.75; 14 of 69 [20.3%] efficacious; and 40 of 69 [58.0%] quit) (Table 2). The probability that the treatment has the best utility was 0.52 for nortriptyline, 0.43 for duloxetine, 0.05 for pregabalin, and 0.00 for mexiletine. Nortriptyline and duloxetine performed better, resulting in more participants receiving those medications. However, neither of these 2 drugs can be defined as the best, but mexiletine can be defined as a loser because the probability it is the best treatment is less than 0.01. Mexiletine has a higher observed efficacy rate compared with pregabalin, but the 95% CrIs that drive the utility probabilities have substantial overlap. The quit rate for mexiletine is much higher compared with pregabalin, providing the lower utility. Pregabalin's low probability is owing to a combination of higher quit rates and low efficacy rates, relative to nortriptyline and duloxetine.

Safety Outcomes

The second aim of the study was to determine which treatment had the fewest and most adverse effects. Adverse effects were reported from all participants in the study, regardless of whether they continued to take the study drug or quit. Participants could report adverse effects at any of the 3 follow-up visits or when they quit. **Table 3** summarizes adverse events for each medication. There were no serious adverse events during the trial. Nortriptyline had the highest proportion of participants who reported adverse effects: of the 134 participants assigned to receive nortriptyline, 75 (56.0%) reported experiencing 1 or more adverse effects even though only 38.1% quit. The most frequent adverse effect reported by the participants was dry mouth. Mexiletine and pregabalin had very similar proportions (mexiletine, 27 of 69 [39.1%]; pregabalin, 29 of 73 [39.7%]) of participants reporting 1 or more adverse effects. Nausea (n = 11) and insomnia (n = 12) were the most common adverse effects reported among participants taking duloxetine (59 of 126 [46.8%] reported ≥1 adverse effects).

Discussion

To our knowledge, this is the first prospective comparative effectiveness study using 4 drugs with different mechanisms of action in a large group of patients with CSPN. Given the symptom of chronic pain, patient engagement efforts confirmed the need to identify effective treatments as early as possible in the patient's course after receiving a diagnosis of CSPN. Clinicians have little evidence on which to make an initial medi-

Table 2. Study Outcomes

Outcome	Nortriptyline (n = 134)	Duloxetine (n = 126)	Pregabalin (n = 73)	Mexiletine (n = 69)	Total (N = 402)
Week 12 outcome, No. (%)[a]					
Efficacious and nonquit	34 (25.4)	29 (23.0)	11 (15.1)	14 (20.3)	88 (21.9)
Nonefficacious and nonquit	49 (36.6)	50 (39.7)	31 (42.5)	15 (21.7)	145 (36.1)
Quit	51 (38.1)	47 (37.3)	31 (42.5)	40 (58.0)	169 (42.0)
Reason for quit, No. (%)					
Loss to follow-up	2 (1.5)	8 (6.3)	3 (4.1)	4 (5.8)	17 (4.2)
Denied by insurance[b]	0 (0.0)	5 (4.0)	6 (8.2)	3 (4.3)	14 (3.5)
Due to adverse events	34 (25.4)	27 (21.4)	10 (13.7)	18 (26.1)	89 (22.1)
Cost[b]	0 (0.0)	1 (0.1)	7 (9.6)	2 (2.9)	10 (2.5)
Lack of efficacy	8 (7.0)	2 (1.6)	3 (4.1)	6 (8.7)	19 (4.7)
Physician's decision	3 (2.2)	3 (2.4)	0	4 (5.8)	10 (2.5)
Other	4 (3.0)	1 (0.1)	2 (2.7)	3 (4.3)	10 (2.5)
Week 12 outcome,[c] posterior mean (95% bayesian credible interval)					
Efficacious and nonquit	0.25 (0.18-0.33)	0.23 (0.16-0.31)	0.15 (0.08-0.24)	0.20 (0.12-0.31)	NA
Nonefficacious and nonquit	0.36 (0.29-0.45)	0.40 (0.31-0.48)	0.42 (0.31-0.54)	0.22 (0.13-0.32)	NA
Quit	0.38 (0.30-0.46)	0.37 (0.29-0.46)	0.42 (0.31-0.54)	0.58 (0.46-0.69)	NA
Utility (95% bayesian credible interval)[d]	0.81 (0.69-0.93)	0.80 (0.68-0.92)	0.69 (0.55-0.84)	0.58 (0.42-0.75)	NA
Probability that the treatment is best	0.52	0.43	0.05	0.00	NA

Abbreviation: NA, not applicable.

[a] A patient's outcome was deemed efficacious and nonquit when they continued the drug and observed a 50% or more decrease from baseline to week 12 in the Likert pain visual analog scale score. A patient who continued the study drug but did not observe a 50% decrease in pain was considered to have a nonefficacious and nonquit outcome. A patient who quit the study drug for any reason or was lost to follow up before week 12 was considered to have a quit outcome.

[b] Patients were not provided the study drug to keep owing to the pragmatic nature of the study.

[c] A patient's outcome was deemed efficacious and nonquit when they continued the drug and observed a 50% or more decrease from baseline to week 12 in the Likert pain visual analog scale score. A patient who continued study drug but did not observe a 50% decrease in pain was considered to have a nonefficacious and nonquit outcome. A patient who quit the study drug for any reason or was lost to follow-up before week 12 was considered to have a quit outcome.

[d] The highest possible utility value for the treatment is 1.75 and lowest is 0.

Table 3. Safety Outcomes[a]

Outcome	Nortriptyline (n = 134)	Duloxetine (n = 126)	Pregabalin (n = 73)	Mexiletine (n = 69)	Total (N = 402)
Patients with no adverse events, No. (%)	59 (44.0)	67 (53.2)	44 (60.3)	42 (60.9)	212 (52.7)
Patients with ≥1 adverse events, No. (%)	75 (56.0)	59 (46.8)	29 (39.7)	27 (39.1)	190 (47.3)
Patients with ≥1 serious adverse events, No. (%)[b]	0	0	0	0	0
Most common adverse events, No.[c]					
Dry mouth	27	3	1	3	34
Drowsiness or sleepiness	16	7	8	3	34
Nausea	3	11	1	6	21
Insomnia	5	12	1	2	20
Fatigue	7	8	3	1	19
Bloating or constipation	10	3	1	2	16
Headache	4	2	2	1	9

[a] Adverse event reporting was captured at all follow-ups.

[b] There were no serious adverse events reported for the duration of the trial or the follow-up period.

[c] These were the most common reported adverse events for patients who maintained on the drug or quit the drug. Patients who quit the drug were no longer followed up.

cation selection for chronic pain in patients with CSPN, giving rise to individual bias, inefficient processes, and lack of effective pain management. In this real-world situation comparative effectiveness study, many variables were involved in whether a drug was determined to be a winner or loser in helping reduce pain among patients with CSPN. This study went beyond whether the drug reduced pain to also focus on adverse effects. As the first study of its kind, to our knowledge, to compare nortriptyline, duloxetine, pregabalin, and mexiletine in a real-life setting, the results add to the body of evidence available for effective management and support the need for newer and more effective drugs for neuropathic pain in

patients with peripheral neuropathy. Using both efficacy and quit rates to arrive at the best therapeutic choice is of interest to clinicians who care for patients with CSPN. This novel approach may be difficult to grasp, but it is reflective of a real practice decision-making situation. For example, patients who withdrew from this study include those randomized to receive a drug that they chose not to take because of cost or insurance coverage denial. This situation happens daily in real medical practice, affecting patient adherence and compromising disease management.

The pragmatic design we used is like one proposed more than decade ago.[32] We used a Likert-like pain scale similar to one desired by people with pain.[33] These prior studies suggested significant health and economic benefits by reducing chronic pain to levels equivalent to no worse than mild pain (less than 3 of 10 on a numerical rating scale).

We used a 50% decrease in pain as our efficacy cutoff; while this cutoff may be a high performance bar, it is popular in pharmaceutical, drug-labeling indication studies as well as corroborated as being meaningful to patients.[13-15] The efficacy rate for the 4 medications ranged from 15% to 25%, which is much lower than rates described in prior studies of the individual drugs. For neuropathic pain, the percentage of patients who reached 50% improvement in the pivotal duloxetine and pregabalin diabetic neuropathy studies was 50% and 36%, respectively.[33,34] The placebo effect in these studies was 30% and 18%, respectively. However, our study is a real-life situational trial, and we believe these findings more accurately reflect real decisional situations in practice, which needs to be kept in mind by patients and physicians when prescribing these drugs. When the drug did not reach our 50% pain reduction criterion, it does not imply that the drug was completely ineffective in reducing pain. This is one of the limitations of the study.

Our findings could affect how these 4 drugs are used by all physicians who treat patients with neuropathy. Findings support duloxetine and nortriptyline as better-performing drug choices in this population with neuropathic pain, suggesting that they should be prescribed before pregabalin or mexiletine are considered. However, this study also supports a finding that all 4 drugs helped improve pain in at least some patients, so each could be tried if others failed.

These findings support the conclusions of prior systematic reviews. A Cochrane review on nortriptyline in neuropathic pain and earlier literature stated that the drug has a role in pain management, even though it is not FDA approved for that indication.[35] The evidence-based guideline for the treatment of painful diabetic neuropathy showed strong recommendations for the use of nortriptyline, duloxetine, and pregabalin, while providing a strong recommendation against using mexiletine based on the Grade classification. Furthermore, it had been established in many prior studies that tricyclic antidepressants are more effective in relieving pain and often more effective than selective serotonin reuptake inhibitors.[36]

Limitations

The trial has some limitations. The study was not placebo-controlled and it was open label, so patients and physicians knew which drug participants were taking. We did not repeat the testing to look for other causes of neuropathy; however, we allowed the investigators determine the cause. There is a small possibility that patients may have another underlying cause of neuropathy; however, owing to the large number of patients enrolled in the study, we do not suspect this possibility would affect the study. Patients could enroll in the study if they had been prescribed and taken 1 of the 4 drugs in the past, which may have introduced explicit or implicit bias toward the randomized drug they received. Our definition of quit could be biased, as it included the limitation of whether insurance would not pay or if the drug was considered too expensive to purchase by patients. Specifically, the 4 medications used vary significantly in cost and copayment requirements. Because quit rate is an outcome, patients may have chosen not to titrate the drug to the full recommended dose to save money, or to quit the drug because they thought that the pain relief was good, but not good enough, to merit paying out of pocket.

Conclusions

There was no clearly superior performing drug in the study; however, of the 4 medications, nortriptyline and duloxetine performed better when efficacy and dropouts were both considered. Therefore, we recommend that either nortriptyline or duloxetine be considered before selecting pregabalin or mexiletine for the treatment of pain among patients with CSPN.

We recognize that several other nonnarcotic drugs are used to treat painful peripheral neuropathy. These include gabapentin, venlafaxine, tricyclic antidepressants, other sodium channel inhibitors such as lacosamide, topiramate, and carbamazepine. Additional comparative effectiveness research studies can be performed on those drugs, so physicians can have a library of data on all these drugs for CPSN.

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