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Equivalency of tricyclic antidepressants in open-label neuropathic pain study

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Objectives – To compare adverse effects, tolerability and efficacy of the tricyclic antidepressants (TCAs) amitriptyline and nortriptyline in management of neuropathic pain due to peripheral neuropathy (PN). *Materials & Methods* – We performed a prospective open-label flexible-dosing comparison of monotherapy or adjuvant therapy using amitriptyline or nortriptyline in PN-associated neuropathic pain. Primary outcomes were quantitative adverse effects and discontinuation rates. Secondary outcomes assessed changes in pain severity, quality of life, disability, sleep efficacy, mood and anxiety, and global improvement. Assessments occurred at 3 and 6 months after initiation. Our hypothesis was that nortriptyline would have better tolerance than amitriptyline. *Results* – A total of 228 PN patients were enrolled approximately equally for monotherapy and adjuvant therapy. Adverse effects and discontinuation rates were similar between amitriptyline and nortriptyline interventions. Weight gain was more common with amitriptyline, while nortriptyline use was associated with greater prevalence of dry mouth. Secondary outcome measures were similar in both groups, demonstrating improvement from baseline. *Conclusions* – Amitriptyline and nortriptyline are equivalent for overall adverse effects and discontinuation rates. Either TCA should be equally considered for use in neuropathic pain due to PN. When used as monotherapy or as part of adjuvant therapy, either TCA can be expected to provide approximately 23–26% visual analog scale pain reduction if tolerated. Discontinuations due to inefficacy or adverse effects can be anticipated in 26–37% of patients initiated on either TCA for PN-associated neuropathic pain.

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Introduction

Due to a lesion or disease of the somatosensory nervous system (1), neuropathic pain affects up to 8% of the general population (2). In patients with peripheral neuropathy (PN), neuropathic pain occurs in up to 50% of cases (3), accompanied by hyperesthesia, allodynia, paresthesias, and motor and coordination deficits. Chronic neuropathic pain due to PN significantly compromises quality of life (4) and frequently requires pharmacotherapy (3).

Tricyclic antidepressants (TCAs) are first-line agents for neuropathic pain treatment in many guidelines (5) with Level B evidence (6). TCAs have strong serotoninergic and noradrenergic reuptake inhibition with additional sodium and calcium channel blockade activity (7). Antihistaminergic and anticholinergic effects likely contribute to their adverse effects including dry eyes and mouth, dizziness, confusion, and urinary retention. The two most commonly studied TCAs are amitriptyline and nortriptyline; amitriptyline is a tertiary amine while nortriptyline is a secondary amine and it is the demethylated metabolite of amitriptyline. Anecdotally, nortriptyline is touted to have fewer adverse effects than amitriptyline (8), possibly due to less anticholinergic activity (7), while retaining similar efficacy. Both amitriptyline (9, 10) and nortriptyline (11) have been studied using randomized controlled studies in forms of neuropathic pain, but outside of a study

examining their use in post-herpetic neuralgia (8), there are no other existing head-to-head comparisons of amitriptyline and nortriptyline in conditions of neuropathic pain.

We hypothesized that nortriptyline would be better tolerated than amitriptyline in the treatment of neuropathic pain associated with PN. We performed a prospective randomized open-label comparison of amitriptyline vs nortriptyline in the treatment of PN-associated neuropathic pain as monotherapy or adjuvant therapy.

Materials and methods

Patient assessment

We prospectively evaluated patients with neuropathic pain related to PN in a tertiary care neuromuscular clinic. Methods of recruitment, assessment, and management have been previously described (12). Ethical approval was received from the Conjoint Health Research Ethics Board at the University of Calgary. Informed consent was obtained from all participants. Patients with PN-associated neuropathic pain were asked, 'Do you have pain or discomfort over your feet and legs on a near-daily basis for more than 6 months'? All patients responding positively with a clinical picture consistent with neuropathic pain and presence of PN were enrolled. The Douleur Neuropathique en 4 questions (DN4) questionnaire, with good sensitivity and specificity, was used to identify clinical likelihood of neuropathic pain presence – only those patients with a score of ≥ 4 were enrolled (13). Severity of PN was assessed using the Toronto Clinical Scoring System (TCSS) as described previously (12) – this scale emphasizes sensory deficits related to PN. Investigations to determine etiology of PN were conducted (12).

We prospectively examined and followed 5 cohorts: monotherapy with amitriptyline, monotherapy with nortriptyline, adjuvant therapy with amitriptyline, adjuvant therapy with nortriptyline, and a control group of patients receiving no pharmacological therapy for neuropathic pain by their own choice. Subjects choosing to receive pharmacotherapy were randomized to amitriptyline or nortriptyline via concealed envelope allocation. Once randomized, open-label management was initiated with both patient and investigator aware of allocation. Flexible dosing was permitted to maximize pain relief and tolerability using previously described protocols (12). Our primary endpoint was tolerability based on incidence of the reported adverse events and time to discontinuation of either TCA. Secondary endpoints included changes in pain severity based upon visual analog scale (VAS), quality of life analyzed using EuroQol 5 Domains (EQ-5D), disability examined with the Short Form 36 health survey (SF36), sleep efficiency evaluated by the Medical Outcomes Sleep Study Scale (MOSSS), aspects of pain and function using the modified

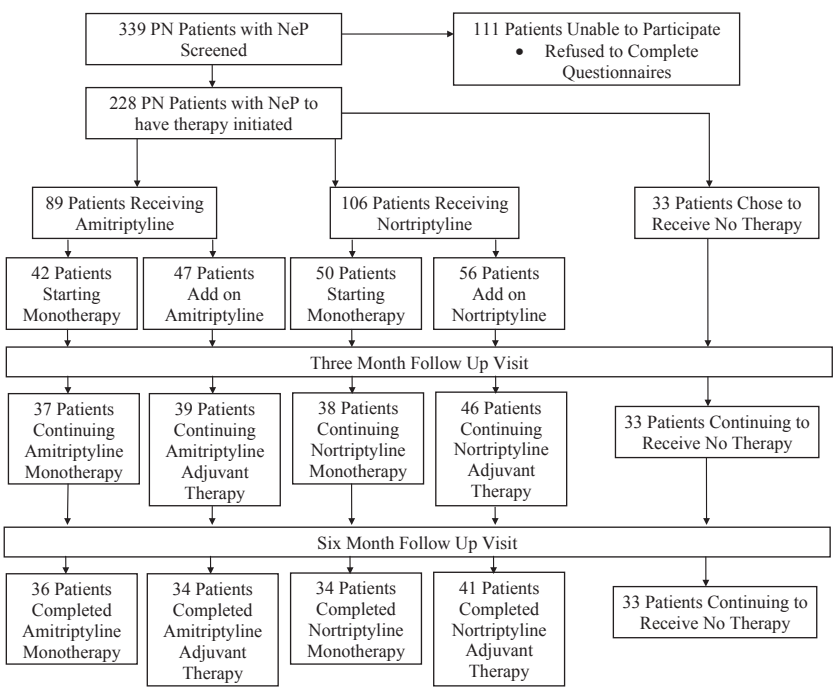

Figure 1. Summary of patient flow during study.

Brief Pain Inventory (BPI) scores, and mood and anxiety analyzed using Hospital Anxiety and Depression Scale (12). All outcomes were established at baseline and after 6 months post-intervention (12), while a 3-month visit determined adverse effects, tolerability, and VAS for pain severity. Patients were weighed and electrocardiograms were performed at the baseline, 3- and 6-month visits. Electrocardiograms were examined for heart rate and corrected QT intervals. An additional telephone call was conducted at 1 week after initiation to examine for adverse

Table 1 Clinical features and baseline characteristics of patient cohorts studied

	Amitriptyline (n = 89)		Nortriptyline (n = 106)		
Clinical features	Monotherapy (n = 42)	Adjuvant Therapy (n = 47)	Monotherapy (n = 50)	Adjuvant Therapy (n = 56)	Control Group (No Pharmacological Therapy) (n = 33)
Age (Mean ± SD)	58 ± 11	56 ± 10	60 ± 9	61 ± 12	61 ± 12
Female sex (%)	26 (62)	30 (64)	30 (60)	32 (57)	19 (58)
Duration of NeP symptoms (months), mean ± SD	17 ± 12	19 ± 15	19 ± 15	20 ± 17	24 ± 19
Age of initiation of NeP (years), mean ± SD	59 ± 10	59 ± 13	61 ± 14	63 ± 15	63 ± 16
Etiology of PN					
Idiopathic	7	8	6	9	5
Diabetes mellitus	10	15	17	15	10
Cobalamin deficiency	8	6	12	8	5
Monoclonal gammopathy of uncertain significance	4	2	2	4	3
Excessive alcohol intake	2	5	3	6	1
Immune-mediated	3	3	3	5	3
Hereditary	2	2	3	3	1
Other	6	6	4	6	5
TCSS	12.6 ± 4.0	12.1 ± 3.7	11.9 ± 3.8	13.0 ± 3.6	12.6 ± 4.6
Pre-existing NeP Therapies, number of patients using and average dose	N/A	Carbamazepine (n = 4), 300 ± 141 mg/d Valproic Acid (n = 3) 650 ± 55 mg/d Phenytoin (n = 4), 300 mg/d Nabilone (n = 6) 1.40 ± 0.46 mg/d Morphine (n = 20) 61 ± 23 mg/d Fentanyl (n = 1) 75 μg/h Oxycodone (n = 12) 43 ± 13 mg/d Acetaminophen (n = 9) 683 ± 185328 mg/d Codeine (n = 2) 125 ± 86 mg/d	N/A	Carbamazepine (n = 7), 420 ± 128 mg/d Venlafaxine (n = 3) 150 mg/d Morphine (n = 23) 56 ± 19 mg/d Fentanyl (n = 2) 63 ± 18 μg/h Oxycodone (n = 18) 33 ± 16 mg/d Acetaminophen (n = 3) 648 ± 166 mg/d Codeine (n = 6) 132 ± 66 mg/d	N/A
Pre-existing side effects of NeP therapies (%)					
Sedation		16 (34)		16 (29)	
Dizziness (Lightheadedness)		12 (26)		19 (34)	
Peripheral edema		2 (4)		4 (7)	
Fatigue		16 (34)		12 (21)	
Dry mouth		8 (17)		8 (14)	
Headache		7 (15)		10 (18)	
Other		19 (40)		24 (43)	
Total responses of adverse effects		80		93	
Number of patients with adverse effects prior to initiation of studied therapies		23 (49)		26 (46)	
Duration of time using NeP therapy prior to initiation of studied therapies (months)		13.9 ± 6.3		14.7 ± 5.8	

Data are presented as mean ± standard deviation, or as an absolute number.

Numbers in rounded brackets represent prevalence in percentages.

ANOVA tests were performed to compare groups receiving monotherapy as well as the two groups receiving adjuvant therapy.

NeP, neuropathic pain; PN, peripheral neuropathy; TCSS, Toronto Clinical Scoring System.

Table 2 Pharmacotherapy characteristics, associated adverse events, and causes for discontinuation

	Amitriptyline						Nortriptyline					
	Monotherapy ($n = 42$)			Adjuvant Therapy ($n = 47$)			Monotherapy ($n = 50$)			Adjuvant Therapy ($n = 56$)		
	Baseline	3 months	6 months	Baseline	3 months	6 months	Baseline	3 months	6 months	Baseline	3 months	6 months
Initial/maximum dose achieved	29.2 ± 12.7 mg/d	28.3 ± 13.9 mg/d	63.3 ± 31.9 mg/d	24.8 ± 10.6 mg/d	30.6 ± 13.7 mg/d	41.3 ± 27.7 mg/d	51.3 ± 14.3 mg/d	61.2 ± 26.1 mg/d	63.2 ± 27.3 mg/d	30.3 ± 18.1 mg/d	43.1 ± 19.9 mg/d	62.5 ± 29.0 mg/d
Achieved mean and actual doses at each timepoint	10 mg qhs ($n = 5$) 25 mg qhs ($n = 27$) 50 mg qhs ($n = 10$)	10 mg qhs ($n = 7$) 25 mg qhs ($n = 20$) 50 mg qhs ($n = 9$)	10 mg qhs ($n = 2$) 25 mg qhs ($n = 3$) 50 mg qhs ($n = 11$) 100 mg qhs ($n = 10$)	10 mg qhs ($n = 9$) 25 mg qhs ($n = 33$) 50 mg qhs ($n = 5$)	10 mg qhs ($n = 5$) 25 mg qhs ($n = 23$) 50 mg qhs ($n = 12$)	10 mg qhs ($n = 3$) 25 mg qhs ($n = 17$) 50 mg qhs ($n = 9$) 100 mg qhs ($n = 5$)	12.5 mg qhs ($n = 1$) 25 mg qhs ($n = 2$) 50 mg qhs ($n = 44$) 100 mg qhs ($n = 3$)	12.5 mg qhs ($n = 1$) 25 mg qhs ($n = 2$) 50 mg qhs ($n = 24$) 100 mg qhs ($n = 11$)	12.5 mg qhs ($n = 1$) 25 mg qhs ($n = 3$) 50 mg qhs ($n = 21$) 100 mg qhs ($n = 12$)	12.5 mg qhs ($n = 2$) 25 mg qhs ($n = 47$) 50 mg qhs ($n = 4$) 100 mg qhs ($n = 3$)	12.5 mg qhs ($n = 1$) 25 mg qhs ($n = 17$) 50 mg qhs ($n = 24$) 100 mg qhs ($n = 3$)	12.5 mg qhs ($n = 1$) 25 mg qhs ($n = 6$) 50 mg qhs ($n = 20$) 100 mg qhs ($n = 14$)
Number of dropouts		6	16		7	13		12	13		11	15
Side Effects of NeP Mono- and Adjuvant Therapies (Total Number Reported)												
Dry mouth		5	5$^{\delta}$		7	8		7	11$^{\delta}$ [0.12–0.36]		10	12
Sedation		19	22		24	26		20	20		22	23
Dizziness/Lightheadedness		6	6		8	8		8	8		12	12
Fatigue		7	9		6	7		4	6		4	5
Nausea		2	2		4	4		4	4		2	2
Urinary Hesitancy		0	0		0	0		1	1		1	1
Weight gain		9$^{\delta}$ [0.10–0.36]	11$^{\delta}$ [0.13–0.41]		10$^{\delta}$ [0.12–0.40]	12$^{\delta}$ [0.16–0.44]		1	1		4	6
Constipation		1	1		2	2		2	2		2	2
Other		2	4		4	5		2	2		3	5
Total responses of Adverse effects		52	60		65	68		49	55		60	68
Number of patients with adverse effects (%)		22 (52)	25 (58)		27 (57)	29 (62)		29 (58)	31 (62)		31 (55)	35 (63)
Reasons for Discontinuing (Accumulative) (%)												
Sedation		1 (2)	3 (7)		2 (5)	2 (4)		5 (10)	5 (10)		6 (10)	7 (11)
Dizziness/Lightheadedness		1 (2)	1 (2)		1 (2)	1 (2)		3 (6)	3 (6)		2 (3)	2 (3)
Weight gain		1 (2)	3 (7)		2 (5)	4 (10)		0 (0)	1 (2)		0 (0)	3 (5)
Inefficacy		3 (7)	9 (21)		2 (5)	6 (13)		4 (8)	4 (8)		3 (5)	3 (5)

Parameters measured for mono- and adjuvant tricyclic antidepressant therapy groups at baseline, 3 and 6 months after initiation of treatment. Initial doses are provided for baseline timepoints. Maximum maintained doses provided are those achieved during the duration of time studied if continued until the 3- or 6-month timepoint.

Data are presented as mean ± standard deviation; when rounded brackets are placed, this is to present prevalence data as a percentage.

Square brackets indicate binomial confidence intervals for integer variables.

ANOVA tests were performed to compare groups receiving monotherapy at the same timepoints.

qhs refers to 'at bedtime' administration.

$^{\delta}$A significant difference with ANOVA testing between amitryptyline and nortriptyline cohorts ($P < 0.05$).

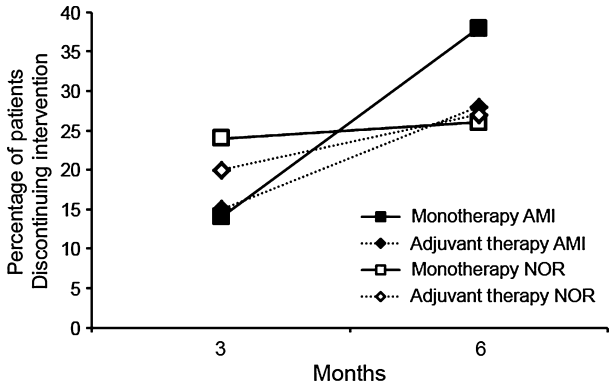

Figure 2. The time to discontinue study medication for both monotherapy and adjuvant therapy was not statistically significant between cohorts receiving amitriptyline (AMI) or nortriptyline (NOR). Values shown are the percentage of patients discontinuing each intervention after follow-up visits of 3 and 6 months.

effects. To gauge global improvement, the patient global impression of change scale (PGIC) was administered at the 6 month endpoint visit.

Adverse events

An adverse event was defined as a noxious, unintended, or unexpected response with suspected causal relationship to the medication started. Identification of tolerable/intolerable adverse effects occurred at each follow-up point. A serious adverse event was defined as any life-threatening reaction to medication requiring hospitalization, additional urgent physician assessment, or resulting in persistent or significant disability. We treated adverse effects and intolerability as accumulative throughout the study. For those patients receiving adjuvant therapy, baseline adverse effects were recorded in order to ensure that adverse effects reported at follow-ups represented those experienced due to new adjuvant pharmacotherapy.

Data analysis

Sample size estimates were performed assuming a 2-sided comparison with tolerance for type I error set to be $\alpha = 0.05$. We estimated a difference in number of adverse events reported of 20% between the two treatments. A sample size of 36 subjects per cohort would provide 80% power; assuming a dropout rate of 15%, meaning that a required group size of 42 total subjects in each cohort would be recruited.

Continuous data (separated for mono- and adjuvant therapy) were analyzed using unmatched

Table 3 Results of outcome measures

	Amitriptyline						Nortriptyline					
	Monotherapy ($n = 42$)			Adjuvant Therapy ($n = 47$)			Monotherapy ($n = 50$)			Adjuvant Therapy ($n = 56$)		
	Baseline	3 months	6 months	Baseline	3 months	6 months	Baseline	3 months	6 months	Baseline	3 months	6 months
MOSSS Sleep Problems Index	34.8 ± 10.7 [31.5–38.1]		26.8 ± 10.2* [23.7–29.9]	37.4 ± 11.6 [33.8–40.9]		26.2 ± 9.3* [23.3–29.1]	33.5 ± 11.0 [30.4–36.6]		24.8 ± 10.6* [21.8–27.8]	38.8 ± 11.8 [35.4–42.3]		28.7 ± 11.0* [25.5–31.9]
HADS (Total)	16.7 ± 9.3 [13.8–19.6]		11.7 ± 6.8* [9.6–13.8]	19.2 ± 9.0 [16.4–22.0]		13.4 ± 7.8* [11.0–15.8]	14.1 ± 8.7 [13.8–19.6]		11.5 ± 5.2 [9.8–13.2]	19.8 ± 10.5 [17.1–22.5]		14.6 ± 8.9* [12.3–16.9]
Change in weight (kg)		0.5 ± 0.9	1.2 ± 1.4		0.2 ± 0.7	0.4 ± 0.8		0.4 ± 0.7	0.9 ± 1.1		0.2 ± 0.6	0.4 ± 0.9
Heart rate (/min)	72.7 ± 5.8	74.1 ± 6.2	74.2 ± 7.6	73.9 ± 6.3	75.6 ± 8.0	76.1 ± 10.2	74.1 ± 6.5	75.0 ± 5.9	75.3 ± 7.2	73.7 ± 6.7	75.4 ± 7.3	76.0 ± 9.4
QT_c (ms)	388.2 ± 7.3	399.5 ± 8.4	403.5 ± 9.9*	384.6 ± 7.9	392.7 ± 9.1	398.1 ± 10.4	386.5 ± 7.8	395.7 ± 9.2	400.6 ± 9.4*	386.5 ± 8.0	393.6 ± 9.2	396.8 ± 9.5

Outcome measures for mono- and adjuvant tricyclic antidepressant therapy groups at baseline, 3 and 6 months after initiation of treatment.
Data are presented as mean ± standard deviation; when rounded brackets are placed, this is to present prevalence data as a percentage. Square brackets indicate confidence intervals.
ANOVA tests were performed to compare groups receiving monotherapy at the same timepoints.
For significant values, binomial confidence intervals are presented in square brackets for integer variables.
For continuous variables, the 95% confidence intervals are presented in square brackets.
*A significant difference with ANOVA testing when the timepoint data are compared with baseline data ($P < 0.05$).

ANOVA testing between intervention groups and between timepoints using an intention to treat analysis with the last observations carried forward in the case of loss to follow-up or discontinuation. PGIC scores were analyzed using modified ridit transformation with the Cochran–Mantel–Haenszel procedure following adjustment for center. Kaplan–Meier survival analysis was performed to assess discontinuation rates. Statistical significance was set to be $\alpha = 0.05$ in each case.

Results

A total of 228 PN patients were enrolled; 178 patients completed 6 months of participation (Fig. 1). Exclusion of patients occurred during prescreening if prior TCA use had occurred for 46 patients; causes for exclusion after enrollment other than lack of completion of questionnaires were not present. Baseline characteristics between each monotherapy and adjuvant therapy group were comparable (Table 1). Overall quantitative adverse event occurrence and discontinuation rates were similar between amitriptyline and nortriptyline for both monotherapy and adjuvant therapy cohorts (Table 2), although there were trends in differences between profiles of adverse events. Amitriptyline use was more likely to produce symptoms of weight gain while nortriptyline use produced more reports of dry mouth for monotherapy treatment. There were non-significant increases in weight gain and heart rate in all cohorts without statistical difference between cohorts. Overall, discontinuations due to intolerability or inefficacy were witnessed in 26–37% of patients receiving monotherapy or adjuvant therapy. The time to discontinuation of intervention was not different between cohorts (Fig. 2). No serious adverse events occurred. The corrected QT interval lengthened in each monotherapy (but not adjuvant therapy) cohort at the 6-month visit relative to baseline but without significant difference between cohorts (Table 3).

Visual analog scale scores showed significant improvement for both amitriptyline and nortriptyline treatments for both monotherapy and adjuvant therapy groups (Fig. 3) as compared to the control cohort without significant difference between the two treatments. The percentage improvement in the VAS was 23–26% in each cohort. As well, sleep efficacy, anxiety and depression subscores, and some of the subdomains of the SF-36 [obtained through the method of summated ratings (14)] (Fig. 4) and of the modified BPI short-form (Fig. 5) scales significantly improved in treatment cohorts. There were

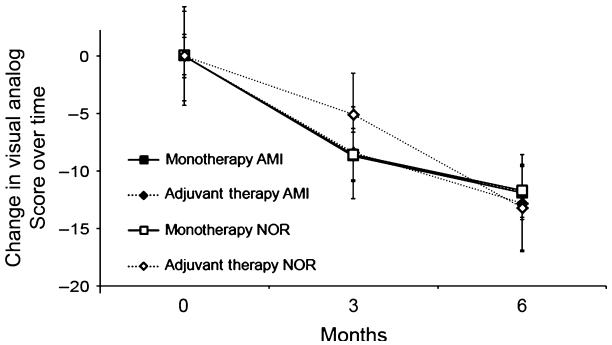

Figure 3. Pain relief for both monotherapy and adjuvant therapy was not statistically significant between cohorts receiving amitriptyline (AMI) or nortriptyline (NOR). Negative values indicate lower visual analog scores. At each of 3 and 6 months, significant improvements in pain scores for all cohorts were observed when compared with the control cohort receiving no pharmacotherapy. Values shown are the changes in visual analog pain scores with averages ± standard errors with follow-up visits of 3 and 6 months as compared to baseline values.

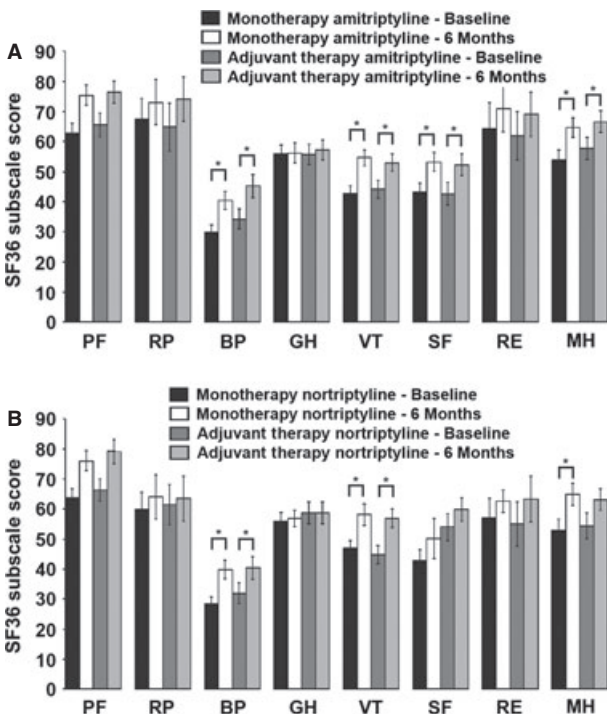

Figure 4. Some, but not all, of the subdomains of the SF-36 Short-Form health survey demonstrated improvement after 6 months receiving amitriptyline as monotherapy or adjuvant therapy (A). Aspects of physical health, including physical functioning (PF), role physical (RP), bodily pain (BP), and general health (GH) as well as measures of mental health including vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH) were studied. Significant improvements in BP, VT, SF, and MH occurred with either amitriptyline intervention. For nortriptyline interventions, improvements in BP, VT, and MH (for monotherapy only) were evident after 6 months (B). Values shown were obtained using transformation of scores derived from the method of summated ratings, with bars representing standard errors. * represents $P < 0.05$ (unmatched ANOVA).

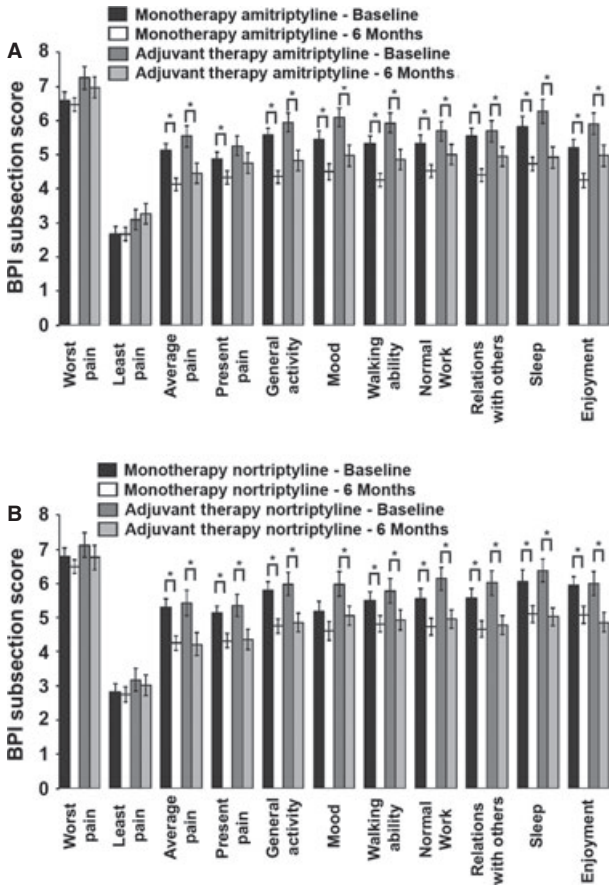

Figure 5. Most, but not all, of the subscales for the modified Brief Pain Inventory (BPI) short form showed evidence for improvement with amitriptyline provided as monotherapy or adjuvant therapy for 6 months (A). Overall, similar results were seen for nortriptyline used as monotherapy or adjuvant therapy at final timepoint (B). Values shown are averaged values with bars representing standard errors. * represents $P < 0.05$ (unmatched ANOVA).

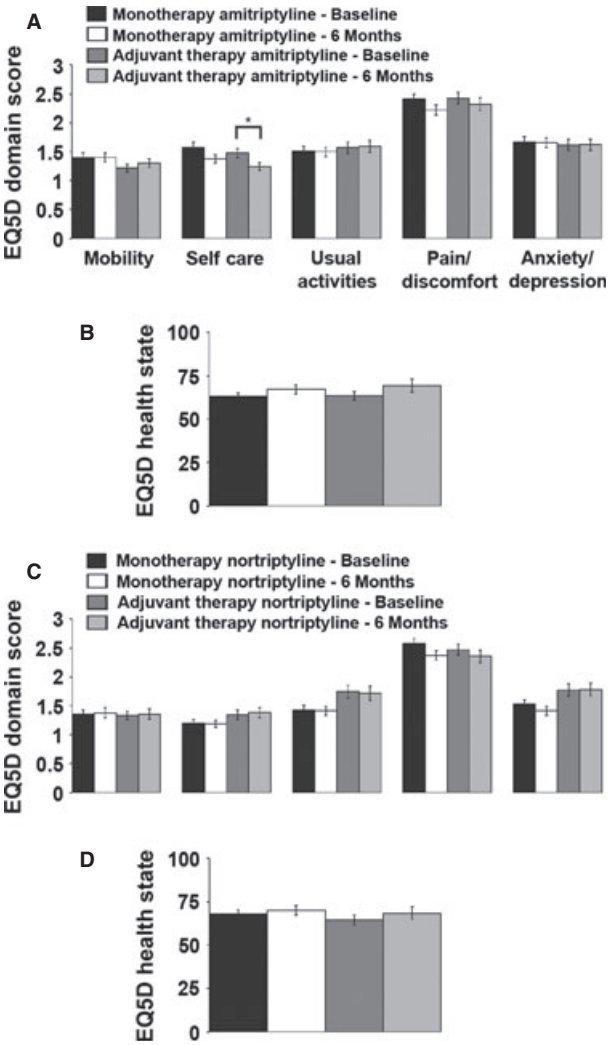

Figure 6. Nearly, all domains of the EuroQol 5 Domains (EQ-5D) instrument showed no evidence for statistical improvement with amitriptyline given as monotherapy or adjuvant therapy (A) (except for the self-care domain with adjuvant amitriptyline therapy). Similarly, there was no significant improvement in the self-rated health score visual analog scale (B). There were analogous results using nortriptyline either as monotherapy or adjuvant therapy (C, D). Values shown are averaged values with bars representing standard errors. * represents $P < 0.05$ (unmatched ANOVA).

no significant changes witnessed for other secondary outcomes, including the EQ-5D (Fig. 6) and without differences between interventions for PGIC outcomes (Fig. 7).

Patients receiving no pharmacotherapy had a baseline VAS of 32.6 ± 10.8, with scores of 31.7 ± 11.3 and 31.4 ± 11.0 at 3 and 6 months of follow-up, respectively. These patients had no change with time for outcome measures including the EQ-5D subdomains or health index score, BPI or SF-36 subdomains, or with the PGIC (Fig. 7).

Discussion

Our prospective comparison of amitriptyline and nortriptyline showed equivalence for tolerability and efficacy when used for management of neuropathic pain in PN. It is possible that weight gain may occur more commonly with amitriptyline, and that dry mouth is more prevalent with nortriptyline. Discontinuations were not statistically different between the cohorts suggesting equal tolerability either with mono- or adjuvant therapy. It is interesting to note that in the monotherapy cohort, the dose of nortriptyline did not vary much from baseline to 6 months – this was largely in response to discontinuations of nortriptyline that was started at doses of ≥50 mg/day. There were no other significant differences in outcome measures between intervention cohorts, suggesting that efficacy and tolerability of both TCA medications were similar.

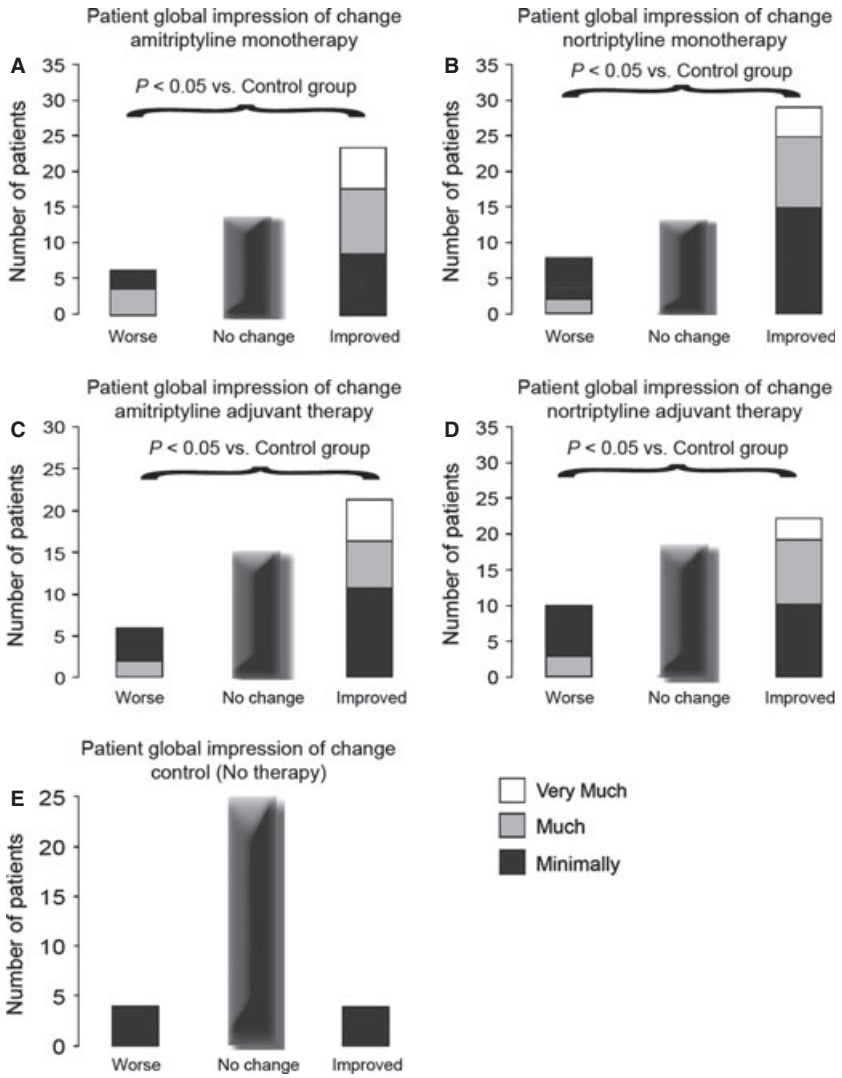

Figure 7. Patient global impressions of change (PGIC) were analyzed using a Cochran–Mantel–Haenszel procedure, adjusting for center in each case. There was a rightward shift from center indicating global perceived improvement as compared to baseline for each of amitriptyline monotherapy (A), amitriptyline adjuvant therapy (B), nortriptyline monotherapy (C), and nortriptyline adjuvant therapy (D). As compared to patients receiving no pharmacotherapies (E), there were significant improvements in each intervention cohort. However, there were no significant differences between intervention cohorts.

Previous comparisons of amitriptyline and nortriptyline, or other TCA medications, are uncommon and smaller in scope. In patients with fibromyalgia, comparison between receipt of amitriptyline, nortriptyline, or placebo showed general improvement for all three treated cohorts, but only the amitriptyline cohort improved more than the placebo cohort with respect to patient-reported global improvement (15); in this study, nortriptyline dosing was possibly associated with greater numbers of tolerable adverse effects. In post-herpetic neuralgia, a randomized, double-blinded crossover study comparing amitriptyline and nortriptyline identified equal efficacy and patient preference, while intolerable adverse effects leading to discontinuation were possibly more frequent with amitriptyline (8). An older TCA, maprotiline, is less efficacious in management of post-herpetic neuralgia pain when compared with amitriptyline (16). Meanwhile, desipramine has similar efficacy as amitriptyline in diabetic neuropathic pain management (9). A systematic review comparing amitriptyline with other TCA medications (17) identified greater efficacy for treatment of depression with amitriptyline, but with greater prevalence of adverse effects; of the four studies providing comparison with nortriptyline, there were no significant differences in responder rates or dropouts, but adverse effects were more limited with nortriptyline.

There are limitations associated with our results. This was an open-label study with randomization but not blinding; interviewer and measurement bias may have occurred as both clinician and patient were aware of allocation after randomization envelopes were opened. Further, dosing was unstructured but flexible to simulate real-world management, contributing to variability in side effect profiles and perhaps pain efficacy outcomes. We did not formally study for cognitive impairment, a common adverse effect for these medications. The use of concomitant medications varied between patients in the adjuvant cohorts, limiting determination regarding contribution of the intervening TCA medications. Control cohorts were comprised of patients self-selecting no pharmacological therapy; these patients had lower VAS scores, which may suggest fewer requirements for pharmacological therapy.

Our data suggest equal tolerability as well as efficacy for nortriptyline and amitriptyline either in mono- or adjuvant therapy for neuropathic pain associated with PN. With considerations of the limitations of this open-label study, we advocate for the use of both amitriptyline and nortriptyline for management of neuropathic pain in patients with PN. In clinical situations where TCAs are ineffective or intolerable, other oral pharmacotherapies or topical agents, such as lidocaine-medicated plaster (18), should be considered. Clinicians should anticipate discontinuations due to adverse effects or inefficacy in 26–37% of patients receiving these TCAs, while patients with PN-associated neuropathic pain tolerating these TCAs typically receive a VAS pain reduction estimated to be 25% either with mono- or adjuvant therapy.

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Author contributor

Dr. Liu performed analysis and interpretation of the data and constructed the first draft of the manuscript. Dr. Kanungo performed analysis and interpretation of the data and edited the manuscript. Dr. Toth conceptualized the study, obtained ethical approval, performed most of the patient visits with acquisition of data, assisted with final analyses and interpretations, revised the manuscript, and supervised the study.

Disclosures and conflict of interest

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