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Pharmacological target therapy of neuropathic pain and patient-reported outcomes in patients with chronic low back pain in Korea

Results from the NLBP Outcomes Research

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Abstract

A number of studies have demonstrated an association of neuropathic pain and chronic low back pain (CLBP), but the outcome difference in each medical management is poorly understood. This study is aimed to investigate treatment patterns of neuropathic pain in CLBP patients and to explore patient-reported outcomes (PROs) including quality of life (QoL) and functional disability by treatment patterns.

Data were extracted from the neuropathic low back pain (NLBP) outcomes research. It was a multicenter and cross-sectional study in which 1200 patients were enrolled at 27 general hospitals, from 2014 to 2015. Of total, 478 patients classified as neuropathic pain were used for this subgroup analysis. The patients were divided into 2 groups according to treatment patterns (with vs. without the targeted therapy [TT] of neuropathic pain). Demographic and clinical features were collected by chart reviews and PROs were measured by patient's survey. QoL was assessed by EuroQoL 5-dimension (EQ-5D) questionnaire. Functional disability was measured by the Quebec Back Pain Disability Scale (QBPDS). Multiple linear regression analyses were conducted to compare the PROs between TT group and non-targeted therapy (nTT) group.

Among the NLBP patients (mean age 63years, female 62%), EQ-5D index, EuroQoL-Visual Analog Scale (EQ-VAS), and QBPDS Scores (mean ± standard deviation) were 0.40 ± 0.28, 54.98 ± 19.98, and 46.03 ± 21.24, respectively. Only 142 (29.7%) patients had

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pharmacological TT of neuropathic pain. Univariate analyses revealed no significant mean differences between TT group and nTT group in the EQ-5D index (0.41 ± 0.27 and 0.39 ± 0.28), EQ-VAS (56.43 ± 18.17 and 54.37 ± 20.69), and QBPDS (45.31 ± 21.32 and 46.31 ± 21.24). After adjustment with covariates, TT group had higher scores of EQ-5D index (β = 0.07; $P < 0.01$) and EQ-VAS (β = 4.59; $P < 0.05$) than the nTT group. The TT group's QBPDS score was lower than the nTT group, although its statistical significance still has not been reached (β = −4.13; $P = 0.07$).

We found that considerable proportion of the NLBP patients remains untreated or undertreated. Although TT group had significantly better QoL than nTT group, only 29.7% of NLBP patients had pharmacological TT. Therefore, clinicians should consider using TT for better QoL of neuropathic pain patients.

Abbreviations: CLBP = chronic low back pain, DN4 = Douleur Neuropathique 4, EQ-5D = EuroQoL 5-dimension, EQ-VAS = EuroQoL Visual Analogue Scale, JOABPEQ = Japanese Orthopedic Association Back Pain Evaluation Questionnaire, LBP = low back pain, NLBP = neuropathic low back pain, nTT = non-targeted therapy, OR = outcome research, PRO = patient-reported outcomes, QBPDS = Quebec Back Pain Disability Scale, QoL = quality of life, QTFC-SD = Quebec Task Force Classification for Spinal Disorders, RCTs = randomized controlled trials, SF-36 = Short Form 36, TCAs = tricyclic antidepressants, TT = targeted therapy, VAS = visual analog scale.

Keywords: chronic low back pain, neuropathic pain, pharmacological targeted therapy, quality of life

1. Introduction

Low back pain (LBP) is one of the most common musculoskeletal disorders, resulting in significant personal, social, and economic burden. Mechanical conditions of the spine, including disk disease, disk herniation, spondylosis, spinal stenosis, and fractures, account for up to 98% of LBP cases. Neuropathic pain in chronic LBP was reported to be highly prevalent and neuropathic pain affects the social and psychological well-being of LBP patients.[1–20] A recent systematic review to evaluate prevalence rate of the neuropathic pain in LBP patients has reported prevalence ranging from 29.4 to 73%.[1–20] In addition, the meta-analysis of 20 studies, including a total of 14,269 patients with LBP, found that the pooled prevalence rate of neuropathic low back pain (NLBP) was 47% (40%–54%).[21] Thus, NLBP may require to be considered as an important clinical problem.

Neuropathic pain profoundly decreased the quality of life (QoL).[22] Hiyama et al[18] reported that NLBP patients had significantly higher visual analog scale (VAS) scores and lower the scores of short form 36 (SF-36) and Japanese Orthopedic Association Back Pain Evaluation Questionnaire than LBP patients with nociceptive pain. This result suggests that NLBP affects the physical, social, and psychological well-being compared to nociceptive LBP patients. Hence, it is significant to identify the involvement of neuropathic pain in LBP patients and to effectively manage NLBP.

However, there was no multicenter cohort study not only for the prevalence of NLBP patients but also for the treatment pattern in Korean NLBP patients. Although treatment pattern and outcome could be different in each different country and health care system, it would be valuable to understand relationship between the pattern and the outcome of NLBP treatment.

Pharmacotherapy is the primary clinical approach for managing NLBP. Canadian pain society provided guidelines of pharmacological management of chronic neuropathic pain as follows: first-line treatments were specific antidepressants (tricyclics) and anticonvulsants (gabapentin and pregabalin).[23] Serotonin noradrenaline reuptake inhibitors and topical lidocaine were recommended as second-line therapies. Third-line therapies included tramadol and controlled release opioid analgesics. Recommended forth-line treatments were cannabinoids, methadone, and anticonvulsants. The special interest group of the international association for the study of neuropathic pain recently suggested guidelines of pharmacological management of neuropathic pain.[24] According to their guidelines, tricyclic antidepressants (TCAs), gabapentin, pregabalin, and topical lidocaine were recommended as first-line treatment options and second-line treatments included opioid analgesics and tramadol.

Although these guidelines for neuropathic pain management were provided, there was still a lack of available data on treatment patterns of NLBP patients and outcome by treatment pattern.

Therefore, the purpose of this study was to investigate the treatment patterns of NLBP in Korea and to explore the patient-reported outcomes (PROs) including QoL and functional disability by the treatment patterns.

2. Materials and methods

2.1. Study design and population

This was a subgroup analysis of chronic low back pain (CLBP) patients with neuropathic pain derived from the NLBP outcome research (OR) that was multicentered, cross-sectional study. Data were collected between December 2014 and May 2015 from 27 nationwide general hospitals of South Korea. This study was approved by the all participated centers' Institutional Review Board. We included CLBP patients who have moderate degree of LBP at least (VAS > 4) and received "minimally adequate treatment" with a medication trial lasting at least 4 weeks. Patients judged by physicians to meet the following criteria were included: age 20 years; CLBP at least 3 months; patients diagnosed with LBP owing to herniated disc, stenosis, spondylosis, spondylolysis, spondylolisthesis, or degenerative disc disease, according to magnetic resonance imaging or computed tomography findings; VAS at least 4; pain medication at least 4 weeks before the enrollment; and patients who were able to understand and willing to complete the subject information sheet and informed consent form. If the patients had following criteria, they were excluded: cancer, sprain, infection, fracture, ankylosing spondylitis, myofascial pain, or sacroiliitis; surgery within 3 months; current participation in other interventional studies; or patients with a critical or unstable health condition. The patients were clearly informed about the aim of our study, and their informed consents were obtained.

A target sample size was estimated based on the assumption that the prevalence of NLBP is 37%.[3] With a significance level of 0.05 and an estimated error rate of 2.8%, the required number of

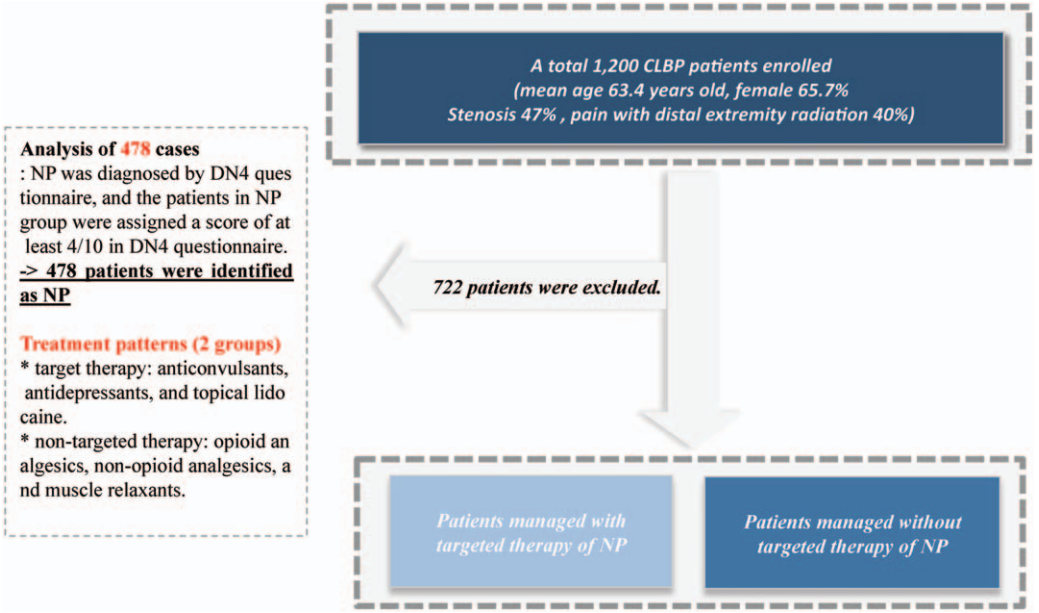


Figure 1. Study design of this study. Among the total 1200 patients enrolled in neuropathic low back pain outcome research, neuropathic low back pain patients whose scores were at least 4/10 in DN4 questionnaire were included in this subgroup analysis. CLBP = chronic low back pain, NP = neuropathic pain.

patients to be enrolled was calculated to be approximately 1200:

$$n = z^2_{1-\alpha/2}P(1-P)/d^2[15](P = 0.37; z^2_{1-\alpha/2} = 1.96^2, when\ \alpha\ is\ 0.05; d = 0.028).$$

Among the total 1200 patients enrolled in NLBP OR, NLBP patients whose scores were at least 4/10 in Douleur Neuropathique 4 (DN4) questionnaire were included in this subgroup analysis (Fig. 1).

2.2. Study data

2.2.1. Baseline variables. Demographic and clinical features were obtained through reviews of medical records and PRO (QoL and functional disability) were measured by the patient's survey. Age, sex, height, and body weight were included in demographic information. Clinical variables contained diagnosis of LBP, comorbidities, symptom period, pain VAS scores, DN4 score, Quebec Task Force Classification for Spinal Disorders (QTFC-SD), and pain control state (pharmacotherapy and surgery). As one of clinical characteristics, QTFC-SD was used to categorize patients' spinal disorders on the basis of clinical examination and pain localization.[25]

2.2.2. Treatment group. Treatment patterns were divided into 2 groups according to whether patients received targeted therapy (TT) of neuropathic pain or not. The TT group included anticonvulsants, TCAs, and topical lidocaine, whereas non-targeted therapy (nTT) group included opioid analgesics, nonopioid analgesics, and muscle relaxants.[26,27]

2.2.3. Outcomes. QoL was assessed by generic EuroQoL 5-dimension (EQ-5D) questionnaire. EQ-5D is made up of 2 parts: a descriptive system, which could be converted into a single index, and a EuroQoL Visual Analogue Scale (EQ-VAS). The descriptive measurement consists of 5 dimensions: "mobility," "self-care," "usual activities," "pain/discomfort," and "anxiety/depression." Each dimension has 3 levels: no problems, some problems, and severe problems, coded as numbers of 1, 2, and 3 in order. These scores, measured by descriptive part, were converted into scores of a single index (EQ-5D index) with a range from −0.229 to 1 point by applying the equation as follows:

Final EQ-5D index's score[28] = 1 − (0.165 + 0.003 × M2 + 0.274 × M3 + 0.058 × SC2 + 0.078 × SC3 + 0.045 × UA2 + 0.133 × UA3 + 0.048 × PD2 + 0.130 × PD3 + 0.043 × AD2 + 0.103 × AD3 + 0.347 × N3 + 0.014 × I2sq)

The EQ-VAS with a range from 0 to 100 points was used for subjective evaluation of patient's current health state. The ends of the scale were marked "best imaginable health state" and "worst imaginable health." In these 2 measurements, a higher score means a higher QoL.

Quebec Back Pain Disability Scale (QBPDS) was used for measuring functional disability. The QBPDS consists of 20 questions and has a scale of 0 to 5 for each question with a range from 0 to 100 points. A higher score of this tool indicates a more severe disability of function.

2.3. Study ethics

This investigation was designed as multicenter cross-sectional observational study of LBP patients. The patients (or their legal representatives) were provided with all study-related information, and they signed an informed consent form. All participating medical institutions obtained approval from their respective institutional review boards.

2.4. Statistical analysis

Patient's demographic and clinical characteristics were summarized as mean ± standard deviation (SD) for continuous variables or frequency (percentage) for categorical variables. Comparisons of patient's characteristics between the TT group and nTT group

Table 1

Demographic and clinical variables of patients with neuropathic chronic low back pain (n = 478).

Variables	Total N = 478	TT N (%) = 142 (29.7)	nTT N = 336 (70.3)	P*
Age, y, mean ± SD	62.96 ± 13.40	63.65 ± 12.74	62.68 ± 13.67	.4689
Sex, n (%)				.7830
Female	294 (61.5)	86 (60.6)	208 (61.9)	
Male	184 (38.5)	56 (39.4)	128 (38.1)	
Comorbid disease, n (%)				.6944
Yes	283 (59.2)	86 (60.6)	197 (58.6)	
No	195 (40.8)	56 (39.4)	139 (41.4)	
Pain VAS (scores), mean ± SD	6.40 ± 1.70	6.45 ± 1.54	6.37 ± 1.77	.6506
Pain duration, mo†, mean ± SD	52.45 ± 68.67	50.15 ± 76.54	53.42 ± 65.15	.7631
LBP period, mo†, mean ± SD	15.44 ± 23.60	18.30 ± 22.62	14.03 ± 23.99	<.0001
Detailed diagnosis‡, n (%)				
Herniated disc	183 (38.3)	65 (45.8)	118 (35.1)	
Stenosis	314 (65.7)	99 (69.7)	215 (64.0)	
Spondylosis	39 (8.2)	17 (12.0)	22 (6.5)	
Spondylolysis	12 (2.5)	3 (2.1)	9 (2.7)	
Spondylolisthesis	74 (15.5)	19 (13.4)	55 (16.4)	
Degenerative disc disease	48 (10.0)	10 (7.0)	38 (11.3)	
QTFC-SD, n (%)				<.0001
Pain without radiation	27 (5.7)	10 (7.1)	17 (5.1)	
Pain with proximal extremity radiation	68 (14.2)	9 (6.3)	59 (17.6)	
Pain with distal extremity radiation	238 (49.8)	70 (49.3)	168 (50.0)	
Pain with radiation and neurologic finding	47 (9.8)	9 (6.3)	38 (11.3)	
Spinal nerve root compression	41 (8.6)	21 (14.8)	20 (5.9)	
Spinal stenosis	57 (11.9)	23 (16.2)	34 (10.1)	
Nonpharmacological treatment, n (%)				<.0001
Yes	37 (7.7)	4 (2.8)	33 (9.8)	
No	441 (92.3)	138 (97.2)	303 (90.2)	
Surgical intervention, n (%)				<.0001
No surgery	268 (56.1)	73 (51.4)	195 (58.0)	
Patients having surgery plan	82 (17.1)	19 (13.4)	63 (18.8)	
Patients undergoing surgery 3 mo ago	128 (26.8)	50 (35.2)	78 (23.2)	

LBP = low back pain, nTT = non-targeted therapy, QTFC-SD = Quebec Task Force Classification for Spinal Disorders, SD = standard deviation, TT = targeted therapy, VAS = visual analogue scale.

* *P* values are from 2 independent sample *t* test or χ^2 test as appropriate

† A logarithmic transformed values were used for the independent *t* test to compare TT and nTT groups.

‡ Multiple responses item.

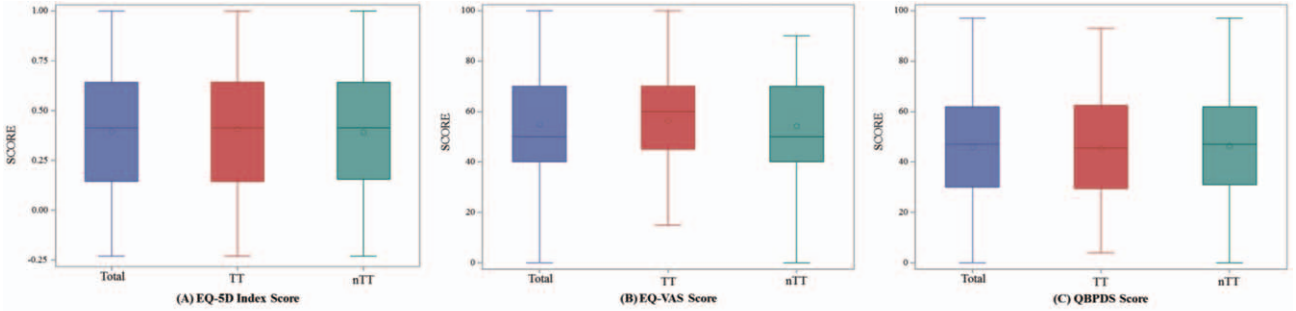
were made by Student 2 independent sample t test or χ^2 test, as appropriate. Mean differences of patient's QoL measured by EQ-5D index and EQ-VAS scores as well as their functional disability measured by QBPDS were also examined using the independent *t* test. An appropriateness of a use of the test was examined by histogram and normal probability plot for each of numerical variables. For variables with positively skewed data, a logarithmic transformation was performed before the *t* test. Multiple linear regression analyses were performed to compare scores of EQ-5D index, EQ-VAS, and QBPDS between 2 groups after adjusting potential confounders. Variables with $P < .1$ from bivariate analyses were selected as the potential confounders. Degree of performance of the regression model was measured by its coefficient of determination (R^2). Collinearity among explanatory variables has also been checked, and no noticeable problem found in the multiple regression models used in this study. All statistical analyses were performed using the SAS software, version 9.4 (SAS Institute Inc., Cary, NC), and a 2-tailed *P* value $<.05$ was considered as statistically significant.

3. Results

3.1. Characteristics of the NLBP patients

Demographic and clinical features of NLBP patients are presented in Table 1. Of a total 478 patients with NLBP, 294 (61.5%) patients were females and mean age was 62.96 ± 13.40 years. The most common type of spinal disease was stenosis (65.7%), followed by herniated disc (38.3%) and spondylolisthesis (15.5%). By the QTFC-SD category, the pain with distal extremity radiation was the most (49.8%). Only 142 (29.7%) patients had pharmacological TT of neuropathic pain. There were not significantly difference between the TT group and the nTT group in terms of age, sex ratio, comorbid diseases, pain VAS, and pain duration. LBP period of TT group (18.30 ± 22.62 months) was significantly longer than the nTT group (14.03 ± 23.99 months). The QTFC-SD items showed significant difference among the groups ($P < .0001$). In the TT group, the most frequent pain type was pain with distal extremity radiation (49.3%) followed by spinal stenosis (16.2%) and spinal nerve root compression (14.8%). pain with distal extremity radiation (50.0%) showed the highest proportion in the nTT group as in the TT group. However, unlike the TT group, pain with proximal extremity radiation (17.6%) was the secondly highest, followed by pain with radiation and neurologic finding (11.3%).

Our data also showed that the subject's severity of LBP measured by QBPDS was associated with their anxiety/depression which was the fifth dimension of EQ-5D index measured as "none," "some/moderate," and "extreme." Specifically, patient having more severe anxiety/depression showed significantly higher mean QBPDS score ($P < .0001$).



		Total	TT	nTT	*P* value
EQ-5D Index	N	470	141	329	0.5489
	mean±SD	0.40±0.28	0.41±0.27	0.39±0.28	
EQ-VAS	N	478	142	336	0.3041
	mean±SD	54.98± 19.98	56.43±18.17	54.37±20.69	
QBPDS	N	453	128	325	0.6540
	mean±SD	46.03±21.24	45.31±21.32	46.31±21.24	

Figure 2. Patient-reported outcome scores in patients with neuropathic chronic low back pain. There were no differences in the EQ-5D index, EQ-VAS and QBPDS between two groups (TT and nTT) in the student t-tests. However, the multiple linear regression analysis showed that EQ-5D index scores and EQ-VAS scores were significantly higher in the patients managed by the TT ($\beta = 0.07$; $P < 0.01, \beta = 4.59$; $P < 0.05$ respectively) than the nTT group. The patients who received TT tended to have lower QBPDS scores ($\beta = -4.13$; $P = 0.07$), compared to the nTT group. EQ-5D = EuroQoL 5-dimension, EQ-VAS = EuroQoL Visual Analogue Scale, nTT = non-targeted therapy, QBPDS = Quebec Back Pain Disability Scale, SD = standard deviation, TT = targeted therapy, VAS = visual analogue scale.

3.2. PRO in the NLBP patients

In NLBP patients, mean scores of EQ-5D index, EQ-VAS, and QBPDS were 0.40 ± 0.28, 54.98 ± 19.98, and 46.03 ± 21.24, respectively (Fig. 2). In the student *t* tests, performed to identify differences of PRO among 2 groups (TT and nTT), there were no differences in the EQ-5D index (0.41 ± 0.27 and 0.39 ± 0.28), EQ-VAS (56.43 ± 18.17 and 54.37 ± 20.69), and QBPDS (45.31 ± 21.32 and 46.31 ± 21.24) (Fig. 2).

In the multiple linear regression analyses adjusting with potential confounders (age, sex, duration of LBP, QTFC-SD category, comorbidities, scores of DN4, and scores of pain VAS), the patients managed by the TT showed higher scores of EQ-5D index ($\beta = 0.07$; $P < .01$) (Table 2) and EQ-VAS scores ($\beta = 4.59$; $P < .05$) (Table 3) than the nTT group. The patients who received TT tended to have lower QBPDS scores ($\beta = -4.13$; $P = .07$) (Table 4), compared to the nTT group.

4. Discussion

This study showed the mismatch between diagnosis and treatment pattern of NLBP patients. Although 39.8% of LBP patients met the DN4 criteria for neuropathic pain, only 29.7% were receiving pharmacological treatment with proven efficacy in neuropathic pain. The literature reveals that *neuropathic pain* is often *undertreated* or treated with ineffective or untested modalities.

Table 2

Effect of targeted therapy on patient's quality of life measured by EuroQol-5dimensions index score after adjusting potential confounders with multiple linear regression analysis.

Variables	Coeff.	SE	Std. Coeff.	*P*
NP patients, TT group	0.0707	0.0269	0.1208	.0088
Age, y	−0.0023	0.0010	−0.1057	.0288
Sex, male	0.0621	0.0259	0.1100	.0169
LBP duration after diagnosis, mo	−0.0007	0.0006	−0.0588	.2126
QTFC-SD				
Pain with proximal extremity radiation	0.0460	0.0719	0.0552	.5228
Pain with distal extremity radiation	−0.0259	0.0641	−0.0469	.6864
Pain with radiation and neurologic finding	−0.0542	0.0755	−0.0563	.4737
Spinal nerve root compression	−0.0195	0.0740	−0.0208	.7922
Spinal stenosis	−0.0046	0.0710	−0.0056	.9484
Comorbidities, yes	0.0136	0.0264	0.0242	.6065
DN4 (Scores)	−0.0307	0.0090	−0.1609	.0007
Pain VAS (scores)	−0.0755	0.0075	−0.4719	<.0001

Coeff. = coefficient, DN4 = Douleur Neuropathique 4, LBP = low back pain, NP = neuropathic pain, QTFC-SD = Quebec Task Force Classification for Spinal Disorders, SE = standard error, Std. Coeff. = standardized coefficient, TT = targeted therapy, VAS = visual analogue scale. Reference category: NP patients (non-targeted therapy group), sex (female), QTFC-SD (pain without radiation), comorbidities (no). Model $R^2 = 33.9\%$.

Table 3

Effect of targeted therapy on patient's quality of life measured by EuroQol-visual analogue scale after adjusting potential confounders with multiple linear regression analysis.

Variables	Coeff.	SE	Std. Coeff.	*P*
NP patients, TT group	4.5933	2.3117	0.1063	.0477
Age, y	−0.0658	0.0900	−0.0410	.4649
Sex, male	1.4553	2.2285	0.0349	.5142
LBP duration after diagnosis, mo	−0.0214	0.0472	−0.0248	.6510
QTFC-SD				
Pain with proximal extremity radiation	0.2700	6.2248	0.0044	.9654
Pain with distal extremity radiation	6.0399	5.5478	0.1486	.2771
Pain with radiation and neurologic finding	9.6431	6.4856	0.1389	.1380
Spinal nerve root compression	−0.3866	6.4094	−0.0056	.9519
Spinal stenosis	4.2575	6.1546	0.0703	.4896
Comorbidities, Yes	−0.7273	2.2648	−0.0176	.7483
DN4 (Scores)	0.8215	0.7765	0.0583	.2909
Pain VAS (scores)	−2.8657	0.6446	−0.2432	<.0001

Coeff. = coefficient, DN4 = Douleur Neuropathique 4, LBP = low back pain, NP = neuropathic pain, QTFC-SD = Quebec Task Force Classification for Spinal Disorders, SE = standard error, Std. Coeff. = standardized coefficient, TT = targeted therapy, VAS = visual analogue scale. Reference category: NP patients (non-targeted therapy group), sex (female), QTFC-SD (pain without radiation), comorbidities (no). Model $R^2 = 8.\%$

A reason for the low proportion of patients having TT would be difficulty in distinguishing the certain clinical difference between NLBP and nociceptive LBP. Identifying the underlying mechanism of chronic pain allows the use of pharmacological agents targeting specific pain mechanisms.[29] NLBP results from a primary lesion or a malfunction within the somatosensory system, whereas nociceptive LBP is caused by tissue injury and/or inflammatory process.[30] The general clinical diagnosis of neuropathic pain was based on the evidence of a lesion or a disease of the nervous system, which was ascertained by interviewing the patients and performing clinical examinations. However, it is complex and difficult methods to detect neuropathic pain in LBP patients.

Some clinicians used screening tools of neuropathic pain as a simpler means. However, there were various standardized screening measurements incurring wide variation in diagnosis of neuropathic pain and no consensus on the diagnosis of neuropathic pain.

In addition, although there were many evidence-based guidelines in the pharmacological management of neuropathic pain due to the attempts for developing a therapeutic approach of related societies, neuropathic pain treatment guideline for LBP was absent.

Canadian pain society provided guidelines of pharmacological management of chronic neuropathic pain as follows: first-line treatments were specific antidepressants (tricyclics) and anticonvulsants (gabapentin and pregabalin).[23] Serotonin noradrenaline reuptake inhibitors and topical lidocaine were recommended as second-line therapies. Third-line therapies included tramadol and controlled release opioid analgesics. Recommended forth-line treatments were cannabinoids, methadone, and anticonvulsants. The special interest group of the international association for the study of neuropathic pain recently suggested guidelines of pharmacological management of neuropathic pain.[24] According to their guidelines, TCAs, gabapentin, pregabalin, and topical lidocaine were recommended as first-line treatment options and second-line treatments included opioid analgesics and tramadol.

We defined the TT and nTT based on these 2 references. Target therapy included TCAs, gabapentin, pregabalin, and topical

Table 4

Effect of targeted therapy on patient's functional disability measured by Quebec Back Pain Disability Scale score after adjusting potential confounders with multiple linear regression analysis.

Variables	Coeff.	SE	Std. Coeff.	*P*
NP patients, TT group	−4.1342	2.2776	−0.0888	.0704
Age, y	0.3089	0.0874	0.1812	.0005
Sex, male	−8.7176	2.1589	−0.1969	<.0001
LBP duration after diagnosis, mo	0.0712	0.0453	0.0786	.1167
QTFC-SD				
Pain with proximal extremity radiation	−4.2244	6.1035	−0.0639	.4894
Pain with distal extremity radiation	0.8659	5.4153	0.0200	.8731
Pain with radiation and neurologic finding	1.7938	6.3971	0.0235	.7793
Spinal nerve root compression	−1.9055	6.2397	−0.0257	.7603
Spinal stenosis	1.2947	5.9710	0.0202	.8285
Co-morbidities, Yes	−0.5652	2.2022	−0.0128	.7976
DN4 (Scores)	1.5182	0.7559	0.1005	.0454
Pain VAS (scores)	4.8950	0.6154	0.3956	<.0001

Coeff. = coefficient, DN4 = Douleur Neuropathique 4, LBP = low back pain, NP = neuropathic pain, QTFC-SD = Quebec Task Force Classification for Spinal Disorders, SE = standard error, Std. Coeff. = standardized coefficient, TT = targeted therapy, VAS = visual analogue scale. Reference category: NP patients (non-targeted therapy group), sex (female), QTFC-SD (pain without radiation), comorbidities (no). Model $R^2 = 28.4\%$.

lidocaine, which are recommended as first- or second-line medical treatment because their efficacy in neuropathic pain has been established in multiple randomized controlled trials (RCTs).

Neuropathic pain patients had severe and chronic symptoms that impaired their QoL.[31,32] QoL measured by EQ-5D scores of patients with neuropathic pain (0.40 ± 0.28) was considerably lower in this study than those of other chronic diseases reported in the previous study (hypertension: 0.81,[33] 0.87–0.89;[34] cardiovascular disease: 0.74,[33] 0.62–0.72;[35] diabetes: 0.82,[33] 0.83;[36] cancer: 0.86;[36] chronic kidney disease: 0.885;[37] rheumatoid arthritis: 0.83,[36] 0.67–0.73[38]), which showed the negative impact of the neuropathic pain in CLBP patients. After adjustment with covariates, the patients managed by pharmacological TT showed higher EQ-5D index and EQ-VAS scores than the nTT group, which suggested that the neuropathic pain patients who received the TT showed significantly better outcome in terms of pain control and QoL than the nTT group. In many RCTs, medications included in TT group of our study were proven in terms of efficacy of neuropathic pain therapy. Two studies of antidepressants in neuropathic pain reported that TCAs provided the identical efficacy in the neuropathic pain management.[39,40] Gabapentin and pregabalin have shown the efficacy in the studies on comparison between anticonvulsants and placebo in patients with several neuropathic pain conditions.[41,42] The 5% lidocaine patch has shown excellent efficacy and tolerability in allodynia patients due to various types of peripheral neuropathic pain.[41,42]

This study has several limitations. First, some of the well-known risk factors for NLBP include advanced age, female sex, and diabetes with or without hypertension, obesity, smoking, and psychological factors such as depression. Although these data demonstrated that neuropathic LBP and depression are significantly correlated with each other, the relationship between neuropathic LBP and other risk factors was not examined in this study because the aim of this study was to investigate treatment patterns of NLBP patients and to explore PRO including QoL and functional disability by treatment patterns.

Second limitation of this study stems from the differential diagnosis of neuropathic pain. This study used DN4 questionnaire to diagnose a neuropathic pain in LBP patients based on a more reliable identification and qualification of a neuropathic pain. Despite the good sensitivity and specificity of the DN4 questionnaire, the question remains whether the distinction between neuropathic and nociceptive symptom profiles truly represents the biological background of pain, or whether it may be an artificial effect. Moreover, these categories of pain overlap to some degree. Although screening tools may give guidance to clinicians by selecting patients that need further diagnostic evaluation and pain management by specialists, they clearly do not replace clinical judgment. In this regard, the evaluation method using the questionnaire that was employed in this study is also a limitation.

In addition, it should be noted that because other pain measures were not part of the study, no comparisons can be made between the DN4 questionnaire and other neuropathic pain screening scales.

The third limitation of this study results from the subject population because it was mostly performed at a tertiary care university hospital. The spectrum of presenting patients obviously differs between primary care clinics and community hospitals. Fourth, this subgroup analysis has the limitation on the sample size, not calculated to investigate this subgroup. Thus, it is difficult to generalize the study results. Lastly, we could use only measured variables in this study as the potential confounders.

Despite these limitations, there have been no other similar studies to compare the treatment outcome between TT and nTT in the NLBP population and this study showed that TT could be associated with a better QoL of NLBP patients. There were, however, relatively low numbers of patients having pharmacological TT of neuropathic pain in this study. These results could suggest that in cases with neuropathic pain, appropriate pharmacological treatments for the neuropathic component should be considered to have better QoL. Further studies are required to explore effects of TT on the improvement of QoL and functional ability in larger population with NLBP.

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