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**Diagnosis and pharmacologic management of neuropathic pain among patients with chronic low back pain**

Yavuz F *et al.* Neuropathic low back pain

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**Abstract**

Chronic low back pain consists of both nociceptive and neuropathic mechanisms and can be classified as a mixed pain syndrome. Neuropathic component of chronic low back pain has often been under-recognized and under-treated by the physicians. Recent studies have demonstrated that approximately 20%-55% of chronic low back pain patients have neuropathic pain symptoms. An altered peripheral, spinal, and supraspinal processing of pain arising as a result of a lesion affecting the nerves system are the major contributor to neuropathic low back pain. The clinical evaluation is still the gold standard for assessment and diagnosis of neuropathic low back pain. Although diagnosis can be difficult due to the lack of reliable gold standard diagnostic test for neuropathic low back pain, screening tools may help non-specialists, in particular, to identify potential patients with neuropathic low back pain who require further diagnostic evaluation and pain management. Several screening tools for neuropathic pain have been developed and tested with different patient populations. Among the screening tools, the painDETECT questionnaire and the Standardized Evaluation of Pain are validated in patients with low back pain. The Standardized Evaluation of Pain may lead to more effective in discriminating between neuropathic and nociceptive pain in patients with low back pain according to the higher rate of sensitivity and its validity in patients with low back pain. However, the most appropriate approach is still to combine findings on physical and neurologic examinations and patient’s report in distinguishing neuropathic pain from nociceptive pain. The clinical examination including bedside sensory tests is still the best available tool for assessment and diagnosis neuropathic pain among patients with chronic low back pain. Due to the fact that chronic low back pain consists of both nociceptive and neuropathic mechanisms, a multimodal treatment approach is more rational in the management of patients with chronic low back pain. Therefore, combination therapy including drugs with different mechanisms of action should be given to the patients with chronic low back pain.

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**Key words:** Low back pain; Neuropathic; Pharmacotherapy; Screening; Questionnaire

**Core tip:** Neuropathic component of chronic low back pain has often been under-recognized and under-treated by the physicians. Recent studies have demonstrated that approximately 20%-55% of chronic low back pain patients have neuropathic pain symptoms. The clinical examination including bedside sensory tests is still the best available tool for assessment and diagnosis neuropathic pain among patients with chronic low back pain. Combination therapy including drugs with different mechanisms of action should be given to the patients with chronic low back pain.

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**INTRODUCTİON**

Chronic low back pain (LBP) is defined as pain and disability lasting more than 3 mo. In adults, the incidence of chronic LBP is estimated about 6%-15%[1]. Although there are multiple causes of LBP, about 85% of LBP patients have non-specific LBP. If the cause of LBP is not due to a specific pathology such as infection, tumor, osteoporosis, inﬂammatory disorders, disc pathologies, then it can be called non-specific LBP. About 10%-15% of the patients with non-specific LBP will go on to develop chronic, disabling LBP[2,3]. The most common pain generator in chronic LBP is the facet joint (40%), the intervertebral disc (26%) and the sacroiliac joint (2%), respectively[4].

Chronic LBP consists of both nociceptive and neuropathic mechanisms and can be classified as a mixed pain syndrome[5,6]. Non-specific nociceptive pain is caused by an inflammatory response to tissue injury and usually described as a sharp or aching pain, while neuropathic pain is caused by damage to nerve tissues and usually described as a burning or heavy sensation, or numbness along the dermatom of the affected nerve[7,8]. Neuropathic component of chronic LBP has often been under-recognized and under-treated by the physicians. Therefore, recent studies have demonstrated that approximately 20%-55% of chronic LBP patients have neuropathic pain symptoms[6,9-11]. The presence of a neuropathic pain component is associated with more severe pain[6], a greater number of comorbidities[5], reduced quality of life[12] and higher healthcare utilization costs[13].

Mechanical and chemical pathophysiological mechanisms are thought to be responsible for neuropathic LBP. Mechanical pathomechanism consist of nerve root compression due to spinal stenosis or intervertebral disc herniation and lesions of nociceptive sprouts within the degenerated intervertebral disc. In chemical pathomechanism, chemokines and cytokines originating from the degenerative disc have been elucidated[5,14-16]. In addition, the theoretical consideration of nerve roots as the only cause of neuropathic pain in chronic LBP is incorrect. Regarding the pathogenesis of degenerative and painful discs, it was reported that intervertebral discs have nerve ingrowth into the inner layers of the annulus ﬁbrosis; as such, the intervertebral disc itself can be a source of neuropathic pain in patients with chronic LBP[14]. Some various nerve-damaging mechanisms were shown in generating a neuropathic pain component in patients with chronic LBP[5]. An altered peripheral, spinal, and supraspinal processing of pain arising as a result of a lesion affecting the nerves system are the major contributor to neuropathic LBP[17-20].

**SCREENİNG TOOLS FOR NEUROPATHİC PAİN AMONG PATİENTS WİTH CHRONİC LBP**

Since neuropathic LBP requires specific treatment, favouring the use of drugs with proven efficacy in the treatment of neuropathic pain such as opioids, tricyclic antidepressants and anticonvulsants[21], identifying neuropathic pain from nociceptive pain is important. It is assumed that the treatment directed against the specific cause or particular pain mechanisms will induce better treatment response in the patients. Therefore, physicians should consider chronic LBP not only with nociceptive component but also with neuropathic component. The clinical evaluation is still the gold standard for assessment and diagnosis of neuropathic LBP. The diagnostic work-up should include neurological and psychosocial evaluation. Although diagnosis can be difficult due to the lack of reliable gold standard diagnostic test for neuropathic LBP, screening tools may help to identify neuropathic pain component in patients with chronic LBP[5]. An ideal screening tools should be brief, simple, valid, and sensitive. Several screening tools for neuropathic pain such as the LANSS (Leeds Assessment of Neuropathic Symptoms and Signs)[10], the DN4 (Douleur Neuropathique en 4 questions)[22], the ID-Pain[23], the NPQ (Neuropathic Pain Questionnaire)[24], the StEP (Standardized Evaluation of Pain)[25], and the PD-Q (painDETECT questionnaire)[11] have been developed and tested with different patient populations. These tools contain some weak and strong features, and they are insufficient to diagnose neuropathic pain in 10%-20% of the patients. However, providing immediate information and their ease of use for both clinicians and patients makes these screening tools attractive[26].

Among the screening tools, the PD-Q and the StEP are validated in patients with LBP[11,25]. The PD-Q consists of graduation of pain, pain course pattern and radiating pain. The graduation of pain subscale consists of seven items, and patients are asked to answer each item using a 6-point scale. The PD-Q score is calculated by addition of the each score in the questionnaire, with a maximum score of 38. Scores 19 or greater indicate that neuropathic mechanisms are likely to be involved in the pain; scores between 13 and 18 areuncertain but a neuropathic pain component may be present; scores of ≤ 12 are suggestive of nociceptive pain.Approximately 80% sensitivity and specificity have been found for the PD-Q. The StEP consists of six interview questions and ten physical tests[25]. The StEP achieves higher sensitivity (92%) and specificity (97%) than the PD-Q which consists only interview questions in distinguishing neuropathic pain from nociceptive pain in patients with LBP. Straight-leg-raising test (Lasegue’s sign), a reduced response to cold sensation and a reduced pinprick sensation are the most discriminatory StEP indicators for neuropathic pain[27].

Although the other screening tools except for the PD-Q and the StEP are also used in some clinical studies for distinguishing neuropathic pain from nociceptive pain in patients with LBP[10,28-31], none of themhas been validated in patients with LBP. The LANSS scale[10] and the DN4 questionnaire[22] are another screening tools consist of physical tests such as sensation examination and interview questions. The LANSS comprises a seven-item pain scale, including the sensory descriptors and items for sensory examination, with a maximum score of 24. Scores less than 12 indicate that neuropathic mechanisms are unlikely to be involved in the pain and scores 12 or greater indicate the opposite. The LANSS demonstrated sensitivity of 83% and specificity of 87% in distinguishing neuropathic pain from nociceptive pain. In the DN4 screening tool, three physical tests were using for determining light touch sensation, pinprick sensation and painful response[25]. A score of at least 4/10 in this screening tool is indicative of neuropathic pain, with high sensitivity and speciﬁcity (82.9% and 89.9%, respectively).

The ID-Pain[23] and the NPQ[24] rely only on interview questions, and they don’t include physical examinations. The ID-Pain is a six-item screening tool, scores ranged from 1 to 5, with a higher score indicative of pain that contains a neuropathic component.The NPQ consists a 12-item questionnaire form, and this scale demonstrated sensitivity of 66.6% and specificity of 74.4% in distinguishing neuropathic pain from nociceptive pain.

Based on the above mentioned clinical studies, it seems plausible that the StEP may lead to more effective in discriminating between neuropathic and nociceptive pain in patients with LBP according to the higher rate of sensitivity and its validity in patients with LBP. However, the most appropriate approach is still to combine findings on physical and neurologic examinations and patient’s report in distinguishing neuropathic pain from nociceptive pain.

**BEDSIDE SENSORY TESTS**

The Neuropathic Pain Special Interest Group of the International Association for the Study of Pain recommend the sensory bedside examination which consists of touch, pinprick, pressure, cold, heat, and vibration sensations for patients presenting with possible neuropathic pain[32]. In order to demonstrate sensory abnormalities in patients with chronic LBP, sensory symptoms and signs should be investigated carefully in the affected dermatome. Thus, these tests will help to physicians confirming or denying the presence of neuropathic pain. A piece of cotton wool can be used in touch sensation examination. Thermal sensation can be assessed by warm and cold objects. Vibration sense can be assessed by a 128-Hz tuning fork[5,33]. The ﬁndings in the painful area should be compared with the ﬁndings in the non-painful area in contralateral side. The reported responses of the patient are recorded as the same, increased, or decreased, as compared with the normal area. Temporal summation, hypoalgesia to pinprick, allodynia to brush and cold, and hypoesthesia to light touch are discriminant findings for the neuropathic pain. The bedside sensory tests were also found more sensitive than quantitative sensory testing[34,35]. In order to show a lesion of the somatosensory system suggesting possible neuropathic pain, careful clinical examination should be made. However, there is no gold standard finding to label a speciﬁc pain within an area of sensory abnormalities as neuropathic pain.

**PHARMACOLOGİC MANAGEMENT OF NEUROPATHİC PAİN AMONG PATİENTS WİTH CHRONİC LBP**

In the treatment of neuropathic pain among patients with chronic LBP, there are many treatments consist of non-pharmacological and pharmacological. Thus, it is difficult for physicians to decide on convenient treatment method. In recently, some treatment guidelines which suggest a multimodal approach for the treatment of neuropathic pain have been developed[36-40]. In the present review, we will only focus on pharmacological treatment of neuropathic pain among patients with chronic LBP. First-line medications recommended for neuropathic pain include tricyclic antidepressants, anticonvulsants, and opioid analgesics.

***Antidepressants***

Tricyclic antidepressants (TCAs) show their analgesic effect *via* some mechanisms in the central and peripheral nervous systems, including: reuptake inhibition of noradrenaline and serotonin neurotransmission; actions on opioid, adrenergic, serotonin, gamma-aminobutyric acid and N-methyl-D-aspartate receptors; and activation some ion channels[41]. Their analgesic effects are independent of their antidepressant effect. TCAs are recommended in the NICE guidelines for patients with chronic LBP who showed inadequate treatment response to other drugs[42]. TCAs have several side-eﬀects such as sedation, dry mouth, blurred vision, and urinary retention. All of these side-effects are often due to their anticholinergic properties. Especially, elderly patients may be more susceptible to some of these effects. Therefore, TCAs should be used carefully in elderly patients[43]. Data on the efficacy of antidepressants other than TCAs such as serotonin noradrenaline reuptake inhibitors (SNRIs)–duloxetine and venlafaxine- and selective serotonin reuptake inhibitors (SSRIs)in chronic LBP are conflicting[44-48].

In a systematic review by Staiger *et al*[49], TCAs were found to produce moderate pain reductions for patients with chronic LBP while SSRIs were not found effective in pain reducing in patients with chronic LBP. In addition, conflicting results were found about the antidepressants whether they improve functional status of patients with chronic LBP. In the Cochrane review of 10 placebo-controlled clinical trials including antidepressants, the authors conclude that “there is no clear evidence that antidepressants are more effective than placebo in the management of patients with chronic LBP’’[50]. In randomized placebo controlled trial involving duloxetine, the reduction in weekly mean pain observed with duloxetine was significantly greater at higher doses (120 mg) than with placebo. However, there were no differences between duloxetine 20 mg or 60 mg and placebo. Although duloxetine 120 mg showed significant effect on reducing pain level, adverse reactions were found significantly higher than placebo[44]. In contrast to this study, further clinical studies showed that duloxetine 60 mg provided significantly greater pain reductionsthan placebo in patients with chronic LBP[45,46].

***Anticonvulsants***

Anticonvulsant agents such as pregabalin and gabapentin show their analgesic effects by binding to the α2-γ subunit of N-type voltage-gated calcium channels which leads to decreased release of neurotransmitters[51]. Gabapentin is initiated at 300 mg/d and uptitrated in 300-mg increments every 3-7 d according to tolerability, to a target dose of 1800-3600 mg/d in three divided doses. Pregabalin is initiated at 150 mg/d in two divided doses. After 7 d, the dose was elevated to target dose of 300-600 mg/d. The main side effects of these drugs include somnolence, dizziness and peripheral oedema, and caution is advised in patients with renal insufficiency[37].

To date, there is no systematic reviews of anticonvulsants for chronic LBP. However, there are two clinical trials of gabapentin for chronic LBP[52,53]. As the result of these studies, gabapentin showed small improvements in pain scores compared with placebo. There was no difference between gabapentin andplacebo in according to the rates of adverse reactions. In the treatment of chronic LBP, there is no evidence to support the use of pregabalin. In two randomized trials, there were no significant difference between pregabalin and placebo groups in according to the reduction in weekly mean pain score. In addition, when the patients with treatment-refractory neuropathic pain, including those with chronic LBP had taken pregabalin as a monotherapy, pain relief and improvement in quality of life were found significantly lower than those patients with either oxycodone CR alone or the combination of oxycodone CR and pregabalin[54,55].

***Opioid analgesics***

These drugs show their analgesic effect with binding to opioid receptors in the central nervous system, thus they regulate the pathways involved in the generation, transmission, and modulation of pain impulses[56]. In clinical practice, the most important factors for the restriction of an opioid using are drug tolerability issues and adverse reactions. The most common adverse reactions are dry mouth, nausea, constipation, dizziness, drowsiness, pruritis and vomiting[57]. In addition, the other concerns about opioids using in chronic non-malignant pain management are development of analgesic tolerance and dependence in susceptible patients. However, the short-term using of opioids is recommended in those patients with nociceptive and neuropathic pain who have unresponsive to first-line treatment and in those patients who have moderate to severe pain[58]. Due to the absence of high-quality published trials, there are few meta-analyses and systematic reviews investigating opioids in the chronic pain setting.

In higher-quality trial, sustained-release oxymorphone or sustained-release oxycodone was found to be superior than placebo in the treatment of chronic LBP [59]. In another study conducted by Schnitzer *et al*[60] tramadol was found more effective than placebo for short-term pain relief in the patients with chronic LBP. Two other trials of tramadol found that there were no significant differencesin beneﬁts or harms between sustained-release and immediate-release tramadol for chronic LBP[61,62]. There is no trial comparing tramadol with acetaminophen or opioid monotherapy, or with other NSAIDs. Another open-label, randomized multicenter study showed that transdermal fentanyl and sustained-release oral morphine provided similar pain relief in patients with chronic LBP[63]. The meta-analysis investigating the use of opioids in chronic non-cancer pain, including chronic LBP reported that opioids were more effective than placebo for both nociceptive and neuropathic pain[64]. Controversy exists as to whether opioids are effective for neuropathic component of chronic LBP.

***Other drugs***

Tapentadol is a centrally acting analgesic used to treat moderate to severe acute pain. This drug show its analgesic effect *via* acting as μ-opioid receptor agonist and providing noradrenaline re-uptake inhibition[65]. In phase 3 studies, patients with chronic LBP showed good clinical results to tapentadol prolonged release (PR)[66,67]. In these studies, tapentadol PR demonstrated similar analgesic efﬁcacy compared with oxycodone CR. Gastrointestinal tolerability and the incidence of drug discontinuations were lower in patients using tapentadol PR than those patients using oxycodone CR[68,69]. In another phase 3b study, the effectiveness and safety of tapentadol PR *vs* a combination of tapentadol PR and pregabalin were compared for the management of severe, chronic LBP with a neuropathic component. The authors found that tapentadol PR showed comparable improvements in pain intensity and quality-of-life measures to combination of tapentadol PR and pregabalin, with improved drug tolerability[69]. Ascorbic acid (Vitamin C) is an anti-oxidant. This means it lowers the amount of free radicals produced from oxidation, like the reactive oxygen species (ROS). ROS are critically involved in the development and maintenance of neuropathic pain. So, free radical scavengers like ascorbic acid could be useful for treatment of neuropathic pain[70]. However, there is no clinical study investigating tilidine and ascorbic acid in the management of neuropathic pain among patients with chronic LBP.

**COMBİNATİON THERAPY**

Since chronic LBP consists of both nociceptive and neuropathic mechanisms, combination therapy such as antidepressants and/or anticonvulsants plus opioids or NSAIIs might be rational in the treatment of chronic LBP[71]. Treatment guidelines also recommend combination therapy in the treatment of neuropathic pain due to different causes as an option for patients who are unresponsive to the monotherapy[7,36]. However, combination therapy is associated with some limitations consisting of adverse reactions and drug interactions[39,72].

In the literature, the number of clinical studies investigating the effect of combination therapy for neuropathic pain component in patients with chronic LBP is very few. Although most of the available clinical studies have investigated combinations of an opioid plus another drugs, there is only one study investigating the efficacy of celecoxib plus pregabalin combination drug therapy in a mixed population of patients including chronic LBP[71]. In this study, the authors showed that combination therapy showed significantly greater reductions in LBP, and a similar frequency of adverse reactions, compared with either celecoxib or pregabalin alone. In the literature, there were two studies investigating the benefit of an opioid plus pregabalin. In the first study, the combination of oxycodone CR plus pregabalin was compared with either oxycodone CR or pregabalin alone in 409 patients with treatment-refractory neuropathic pain (most commonly due to radiculopathy). The authors found that LBP relief was faster and more substantial in the patients with combination therapy than in those patients with pregabalin monotherapy. The patients with combination therapy showed significantly greater improvements in quality of life than patients with either oxycodone CR or pregabalin using. Combination therapy also showed a superior safety profile to both monotherapies[55]. In the second study, the authors investigated the benefit of combination of buprenorphine plus pregabalin in patients with chronic LBP. Pain reduction was found significantly greater in patients with combination therapy than in patients with buprenorphine monotherapy[73]. There were also 2 studies examining the benefit of tramadol plus paracetamol in a combination therapy for the patients with chronic LBP. In these studies, significantly greater improvements in LBP severity were determined in patients with combination therapy than in patients with placebo. Adverse reactions were found more common with the combination therapy than with placebo[74,75].

To sum up, combination therapy of pregabalin plus other analgesic drugs such as celecoxib, oxycodone CR and buprenorphine appears to be more effective in reducing neuropathic pain component whereas pregabalin monotherapy seems to be ineffective. Tramadol alone and in combination with paracetamol also appeared to be effective.

**CONCLUSİON**

Presently, there is no available gold standard test for determining a neuropathic pain component in chronic LBP. Neurophysiological testing and screening tools have some limitations in the differentiation of a neuropathic component in chronic LBP patients. So that, bedside sensory tests is the still best available tool for assessment and diagnosis neuropathic pain among patients with chronic LBP. Due to the fact that chronic LBP consists of both nociceptive and neuropathic mechanisms, a multimodal approach to medication probably is more rational in the management of patients with chronic LBP. Therefore, combination therapy including drugs with different mechanisms of action should be given to the patients with chronic LBP. In the literature there is no clear evidence that antidepressants and opioids are effective in the management of neuropathic pain among patients with chronic LBP. In addition, there is no evidence to support the use of anti-convulsant drugs. In order to improve level of evidence in diagnosing and treating neuropathic LBP, further well-designed clinical studies investigating pharmacologic management in neuropathic pain among patients with chronic LBP are needed.

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