World Journal of Rheumatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5499/wjr.v4.i3.54

World J Rheumatol 2014 November 12; 4(3): 54-61
ISSN 2220-3214 (online)

REVIEW

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

Ferdi Yavuz, Umut Guzelkucuk

Ferdi Yavuz, The Clinic of Physical Medicine and Rehabilitation, Military Hospital of Etimesgut, 06790 Ankara, Turkey
Umut Guzelkucuk, Department of Physical Medicine and Rehabilitation, TAF Rehabilitation Centre, Gulhane Military Medical Academy, 06790 Ankara, Turkey
Author contributions: Guzelkucuk U performed the review of literature; Yavuz F written and revised the article.
Correspondence to: Ferdi Yavuz, MD, The Clinic of Physical Medicine and Rehabilitation, Military Hospital of Etimesgut, The Street of Erler, 06790 Ankara, Turkey. ferdiyavuz@yahoo.com
Telephone: +90-312-3461311 Fax: +90-312-2911009
Received: June 1, 2014 Revised: September 28, 2014
Accepted: October 14, 2014
Published online: November 12, 2014

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.

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.

Yavuz F, Guzelkucuk U. Diagnosis and pharmacologic management of neuropathic pain among patients with chronic low back pain. *World J Rheumatol* 2014; 4(3): 54-61 Available from: URL: http://www.wjgnet.com/2220-3214/full/v4/i3/54.htm DOI: http://dx.doi.org/10.5499/wjr.v4.i3.54

INTRODUCTION

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 underrecognized 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].

SCREENING TOOLS FOR NEUROPATHIC PAİN AMONG PATIENTS WİTH CHRONIC 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 workup 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 Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)[10], the Douleur Neuropathique en 4 questions (DN4)[22], the ID-Pain[23], the Neuropathic Pain Questionnaire (NPQ)[24], the Standardized Evaluation of Pain (StEP)[25], and the painDETECT questionnaire (PD-Q)[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 are uncertain but a neuropathic pain component may be present; scores of $\leqslant$ 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 them has 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.

PHARMACOLOGIC MANAGEMENT OF NEUROPATHIC PAIN AMONG PATIENTS WITH CHRONIC 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-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 or 60 mg and placebo. Although duloxetine 120 mg showed significant effect on reduc-

ing 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 up titrated 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 and placebo 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 controlled release (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.

COMBINATION 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.

CONCLUSION

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.

REFERENCES

1 **Manchikanti L**. Epidemiology of low back pain. *Pain Physician* 2000; **3**: 167-192 [PMID: 16906196]
2 **Deyo RA**, Phillips WR. Low back pain. A primary care challenge. *Spine* (Phila Pa 1976) 1996; **21**: 2826-2832 [PMID: 9112706]
3 **Carey TS**, Garrett JM, Jackman AM. Beyond the good prognosis. Examination of an inception cohort of patients with chronic low back pain. *Spine* (Phila Pa 1976) 2000; **25**: 115-120 [PMID: 10647169]
4 **Manchikanti L**, Singh V, Pampati V, Damron KS, Barnhill RC, Beyer C, Cash KA. Evaluation of the relative contributions of various structures in chronic low back pain. *Pain Physician* 2001; **4**: 308-316 [PMID: 16902676]
5 **Freynhagen R**, Baron R. The evaluation of neuropathic components in low back pain. *Curr Pain Headache Rep* 2009; **13**: 185-190 [PMID: 19457278 DOI: 10.1007/s11916-009-0032-y]
6 **Romanò CL**, Romanò D, Lacerenza M. Antineuropathic and antinociceptive drugs combination in patients with chronic low back pain: a systematic review. *Pain Res Treat* 2012; **2012**: 154781 [PMID: 22619711 DOI: 10.1155/2012/154781]
7 **Forde G**. Adjuvant analgesics for the treatment of neuropathic pain: evaluating efficacy and safety profiles. *J Fam Pract* 2007; **56**: 3-12 [PMID: 17270113]
8 **Woolf CJ**. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004; **140**: 441-451 [PMID: 15023710]
9 **Beith ID**, Kemp A, Kenyon J, Prout M, Chestnut TJ. Identifying neuropathic back and leg pain: a cross-sectional study. *Pain* 2011; **152**: 1511-1516 [PMID: 21396774 DOI: 10.1016/j.pain.2011.02.033]
10 **Kaki AM**, El-Yaski AZ, Youseif E. Identifying neuropathic pain among patients with chronic low-back pain: use of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale. *Reg Anesth Pain Med* 2005; **30**: 422-428 [PMID: 16135345]
11 **Freynhagen R**, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* 2006; **22**: 1911-1920 [PMID: 17022849 DOI: 10.1185/030079906X132488]
12 **O'Connor AB**. Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. *Pharmacoeconomics* 2009; **27**: 95-112 [PMID: 19254044 DOI: 10.2165/00019053-200927020-00002]
13 **Schmidt CO**, Schweikert B, Wenig CM, Schmidt U, Gockel U, Freynhagen R, Tölle TR, Baron R, Kohlmann T. Modelling the prevalence and cost of back pain with neuropathic components in the general population. *Eur J Pain* 2009; **13**: 1030-1035 [PMID: 19201230 DOI: 10.1016/j.ejpain.2008.12.003]
14 **Coppes MH**, Marani E, Thomeer RT, Groen GJ. Innervation of "painful" lumbar discs. *Spine* (Phila Pa 1976) 1997; **22**:

2342-2349; discussion 2349-2350 [PMID: 9355214]
15 **Peng B**, Hou S, Wu W, Zhang C, Yang Y. The pathogenesis and clinical significance of a high-intensity zone (HIZ) of lumbar intervertebral disc on MR imaging in the patient with discogenic low back pain. *Eur Spine J* 2006; **15**: 583-587 [PMID: 16047210 DOI: 10.1007/s00586-005-0892-8]
16 **Peng B**, Wu W, Hou S, Li P, Zhang C, Yang Y. The pathogenesis of discogenic low back pain. *J Bone Joint Surg Br* 2005; **87**: 62-67 [PMID: 15686239]
17 **Wu G**, Ringkamp M, Murinson BB, Pogatzki EM, Hartke TV, Weerahandi HM, Campbell JN, Griffin JW, Meyer RA. Degeneration of myelinated efferent fibers induces spontaneous activity in uninjured C-fiber afferents. *J Neurosci* 2002; **22**: 7746-7753 [PMID: 12196598]
18 **Amir R**, Kocsis JD, Devor M. Multiple interacting sites of ectopic spike electrogenesis in primary sensory neurons. *J Neurosci* 2005; **25**: 2576-2585 [PMID: 15758167 DOI: 10.1523/JNEUROSCI.4118-04.2005]
19 **Finnerup NB**, Jensen TS. Mechanisms of disease: mechanism-based classification of neuropathic pain-a critical analysis. *Nat Clin Pract Neurol* 2006; **2**: 107-115 [PMID: 16932532]
20 **Baron R**. Mechanisms of disease: neuropathic pain--a clinical perspective. *Nat Clin Pract Neurol* 2006; **2**: 95-106 [PMID: 16932531]
21 **Finnerup NB**, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain* 2005; **118**: 289-305 [PMID: 16213659]
22 **Bouhassira D**, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lantéri-Minet M, Laurent B, Mick G, Serrie A, Valade D, Vicaut E. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 2005; **114**: 29-36 [PMID: 15733628 DOI: 10.1016/j.pain.2004.12.010]
23 **Portenoy R**. Development and testing of a neuropathic pain screening questionnaire: ID Pain. *Curr Med Res Opin* 2006; **22**: 1555-1565 [PMID: 16870080 DOI: 10.1185/030079906X115702]
24 **Krause SJ**, Backonja MM. Development of a neuropathic pain questionnaire. *Clin J Pain* 2003; **19**: 306-314 [PMID: 12966256 DOI: 10.1097/00002508-200309000-00004]
25 **Scholz J**, Mannion RJ, Hord DE, Griffin RS, Rawal B, Zheng H, Scoffings D, Phillips A, Guo J, Laing RJ, Abdi S, Decosterd I, Woolf CJ. A novel tool for the assessment of pain: validation in low back pain. *PLoS Med* 2009; **6**: e1000047 [PMID: 19360087 DOI: 10.1371/journal.pmed.1000047]
26 **Baron R**, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol* 2010; **9**: 807-819 [PMID: 20650402 DOI: 10.1016/S1474-4422(10)70143-5]
27 **Cruccu G**, Truini A. Tools for assessing neuropathic pain. *PLoS Med* 2009; **6**: e1000045 [PMID: 19360134 DOI: 10.1371/journal.pmed.1000045]
28 **Enthoven WT**, Scheele J, Bierma-Zeinstra SM, Bueving HJ, Bohnen AM, Peul WC, van Tulder MW, Berger MY, Koes BW, Luijsterburg PA. Back complaints in older adults: prevalence of neuropathic pain and its characteristics. *Pain Med* 2013; **14**: 1664-1672 [PMID: 24118796 DOI: 10.1111/pme.12232]
29 **El Sissi W**, Arnaout A, Chaarani MW, Fouad M, El Assuity W, Zalzala M, Dershaby YE, Youseif E. Prevalence of neuropathic pain among patients with chronic low-back pain in the Arabian Gulf Region assessed using the leeds assessment of neuropathic symptoms and signs pain scale. *J Int Med Res* 2010; **38**: 2135-2145 [PMID: 21227019 DOI: 10.1177/147323001003800629]
30 **Attal N**, Perrot S, Fermanian J, Bouhassira D. The neuropathic components of chronic low back pain: a prospective multicenter study using the DN4 Questionnaire. *J Pain* 2011; **12**: 1080-1087 [PMID: 21783428 DOI: 10.1016/j.jpain.2011.05.006. Epub]
31 **Walsh J**, Rabey MI, Hall TM. Agreement and correlation between the self-report leeds assessment of neuropathic symptoms and signs and Douleur Neuropathique 4 Questions neuropathic pain screening tools in subjects with low back-related leg pain. *J Manipulative Physiol Ther* 2012; **35**: 196-202 [PMID: 22397741 DOI: 10.1016/j.jmpt.2012.02.001]
32 **O'Connor AB**, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. *Am J Med* 2009; **122**: S22-S32 [PMID: 19801049 DOI: 10.1016/j.amjmed.2009.04.007]
33 **Cruccu G**, Anand P, Attal N, Garcia-Larrea L, Haanpää M, Jørum E, Serra J, Jensen TS. EFNS guidelines on neuropathic pain assessment. *Eur J Neurol* 2004; **11**: 153-162 [PMID: 15009162 DOI: 10.1111/j.1468-1331.2004.00791.x]
34 **Haanpää M**, Attal N, Backonja M, Baron R, Bennett M, Bouhassira D, Cruccu G, Hansson P, Haythornthwaite JA, Iannetti GD, Jensen TS, Kauppila T, Nurmikko TJ, Rice AS, Rowbotham M, Serra J, Sommer C, Smith BH, Treede RD. NeuPSIG guidelines on neuropathic pain assessment. *Pain* 2011; **152**: 14-27 [PMID: 20851519 DOI: 10.1016/j.pain.2010.07.031]
35 **Baron R**. Neuropathic pain: clinical, vol 5. In: Basbaum AI, Kaneko A, Shepherd GM, et al (eds). The Senses: a Comprehensive Reference. Amsterdam: Elsevier, 2008: 865-900
36 **Moulin DE**, Clark AJ, Gilron I, Ware MA, Watson CP, Sessle BJ, Coderre T, Morley-Forster PK, Stinson J, Boulanger A, Peng P, Finley GA, Taenzer P, Squire P, Dion D, Cholkan A, Gilani A, Gordon A, Henry J, Jovey R, Lynch M, Mailis-Gagnon A, Panju A, Rollman GB, Velly A. Pharmacological management of chronic neuropathic pain - consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manag* 2007; **12**: 13-21 [PMID: 17372630]
37 **Dworkin RH**, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007; **132**: 237-251 [PMID: 17920770]
38 **Jensen TS**, Madsen CS, Finnerup NB. Pharmacology and treatment of neuropathic pains. *Curr Opin Neurol* 2009; **22**: 467-474 [PMID: 19741531 DOI: 10.1097/WCO.0b013e3283311e13]
39 **Dworkin RH**, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, Kent JL, Krane EJ, Lebel AA, Levy RM, Mackey SC, Mayer J, Miaskowski C, Raja SN, Rice AS, Schmader KE, Stacey B, Stanos S, Treede RD, Turk DC, Walco GA, Wells CD. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc* 2010; **85**: S3-S14 [PMID: 20194146 DOI: 10.4065/mcp.2009.0649]
40 **Attal N**, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, Nurmikko T. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010; **17**: 1113-1e88 [PMID: 20402746 DOI: 10.1111/j.1468-1331.2010.02999.x]
41 **Verdu B**, Decosterd I, Buclin T, Stiefel F, Berney A. Antidepressants for the treatment of chronic pain. *Drugs* 2008; **68**: 2611-2632 [PMID: 19093703 DOI: 10.2165/0003495-200868180-00007]
42 **National Collaborating Centre for Primary Care (UK).** Low Back Pain: Early Management of Persistent Non-specific Low Back Pain [Internet]. London: Royal College of General Practitioners (UK), 2009: May. Available from: URL: http://www.ncbi.nlm.nih.gov/books/NBK11702/
43 **Amann U**, Schmedt N, Garbe E. Prescribing of potentially inappropriate medications for the elderly: an analysis based on the PRISCUS list. *Dtsch Arztebl Int* 2012; **109**: 69-75 [PMID: 22368709 DOI: 10.3238/arztebl.2012.0069]
44 **Skljarevski V**, Ossanna M, Liu-Seifert H, Zhang Q, Chappell

A, Iyengar S, Detke M, Backonja M. A double-blind, randomized trial of duloxetine versus placebo in the management of chronic low back pain. *Eur J Neurol* 2009; **16**: 1041-1048 [PMID: 19469829 DOI: 10.1111/j.1468-1331.2009.02648.x]

45 **Skljarevski V**, Zhang S, Desaiah D, Alaka KJ, Palacios S, Miazgowski T, Patrick K. Duloxetine versus placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. *J Pain* 2010; **11**: 1282-1290 [PMID: 20472510 DOI: 10.1016/j.jpain.2010.03.002]

46 **Skljarevski V**, Desaiah D, Liu-Seifert H, Zhang Q, Chappell AS, Detke MJ, Iyengar S, Atkinson JH, Backonja M. Efficacy and safety of duloxetine in patients with chronic low back pain. *Spine* (Phila Pa 1976) 2010; **35**: E578-E585 [PMID: 20461028 DOI: 10.1097/BRS.0b013e3181d3cef6]

47 **Skljarevski V**, Zhang S, Chappell AS, Walker DJ, Murray I, Backonja M. Maintenance of effect of duloxetine in patients with chronic low back pain: a 41-week uncontrolled, dose-blinded study. *Pain Med* 2010; **11**: 648-657 [PMID: 20546509 DOI: 10.1111/j.1526-4637.2010.00836.x]

48 **Dickens C**, Jayson M, Sutton C, Creed F. The relationship between pain and depression in a trial using paroxetine in sufferers of chronic low back pain. *Psychosomatics* 2000; **41**: 490-499 [PMID: 11110112 DOI: 10.1176/appi.psy.41.6.490]

49 **Staiger TO**, Gaster B, Sullivan MD, Deyo RA. Systematic review of antidepressants in the treatment of chronic low back pain. *Spine* (Phila Pa 1976) 2003; **28**: 2540-2545 [PMID: 14624092]

50 **Urquhart DM**, Hoving JL, Assendelft WW, Roland M, van Tulder MW. Antidepressants for non-specific low back pain. *Cochrane Database Syst Rev* 2008; **(1)**: CD001703 [PMID: 18253994 DOI: 10.1002/14651858.CD001703.pub3]

51 **Sills GJ**. The mechanisms of action of gabapentin and pregabalin. *Curr Opin Pharmacol* 2006; **6**: 108-113 [PMID: 16376147]

52 McCleane GJ. Does gabapentin have an analgesic effect on background, movement and referred pain? A randomised, double-blind, placebo controlled study. *Pain Clinic* 2001; **13**: 103-107 [DOI: 10.1163/156856901753420945]

53 **Yildirim K**, Sisecioglu M, Karatay S, Erdal A, Levent A, Ugur M. The effectiveness of gabapentin in patients with chronic radiculopathy. *The Pain Clinic* 2003; **15**: 213-218 [DOI: 10.1163/156856903767650718]

54 **Remmers AE**, Sharma U, Lamoreaux L. Pregabalin treatment of patients with chronic low back pain. Abstract 660. Proceedings of the 19th Annual Meeting of the American Pain Society 2000. Atlanta, Georgia, 2000

55 **Gatti A**, Sabato AF, Occhioni R, Colini Baldeschi G, Reale C. Controlled-release oxycodone and pregabalin in the treatment of neuropathic pain: results of a multicenter Italian study. *Eur Neurol* 2009; **61**: 129-137 [PMID: 19092248 DOI: 10.1159/000186502]

56 **Grabois M**. Management of chronic low back pain. *Am J Phys Med Rehabil* 2005; **84**: S29-S41 [PMID: 15722781]

57 **Moore RA**, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther* 2005; **7**: R1046-R1051 [PMID: 16207320]

58 **Deshpande A**, Furlan A, Mailis-Gagnon A, Atlas S, Turk D. Opioids for chronic low-back pain. *Cochrane Database Syst Rev* 2007; **(3)**: CD004959 [PMID: 17636781]

59 **Hale ME**, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. *J Pain* 2005; **6**: 21-28 [PMID: 15629415 DOI: 10.1016/j.jpain.2004.09.005]

60 **Schnitzer TJ**, Gray WL, Paster RZ, Kamin M. Efficacy of tramadol in treatment of chronic low back pain. *J Rheumatol* 2000; **27**: 772-778 [PMID: 10743823]

61 **Raber M**, Hofmann S, Junge K, Momberger H, Kuhn D. Analgesic efficacy and tolerability of tramadol 100mg sustained-release capsules in patients with moderate to severe low back pain. *Clin Drug Investig* 1999; **17**: 415-423 [DOI: 10.2165/00044011-199917060-00001]

62 **Sorge J**, Stadler T. Comparison of the analgesic efficacy and tolerability of tramadol 100mg sustained-release tablets and tramadol 50mg capsules for the treatment of chronic low back pain. *Clin Drug Investig* 1997; **14**: 157-164 [DOI: 10.2165/00044011-199714030-00001]

63 **Allan L**, Richarz U, Simpson K, Slappendel R. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naïve patients with chronic low back pain. *Spine* (Phila Pa 1976) 2005; **30**: 2484-2490 [PMID: 16284584]

64 **Furlan AD**, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ* 2006; **174**: 1589-1594 [PMID: 16717269 DOI: 10.1503/cmaj.051528]

65 **Tzschentke TM**, Jahnel U, Kogel B, Christoph T, Englberger W, De Vry J, Schiene K, Okamoto A, Upmalis D, Weber H, Lange C, Stegmann JU, Kleinert R. Tapentadol hydrochloride: a next-generation, centrally acting analgesic with two mechanisms of action in a single molecule. *Drugs Today* (Barc) 2009; **45**: 483-496 [PMID: 19834626 DOI: 10.1358/dot.2009.45.7.1395291]

66 **Buynak R**, Shapiro DY, Okamoto A, Van Hove I, Rauschkolb C, Steup A, Lange B, Lange C, Etropolski M. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. *Expert Opin Pharmacother* 2010; **11**: 1787-1804 [PMID: 20578811 DOI: 10.1517/14656566.2010.497720]

67 **Steigerwald I**, Müller M, Davies A, Samper D, Sabatowski R, Baron R, Rozenberg S, Szczepanska-Szerej A, Gatti A, Kress HG. Effectiveness and safety of tapentadol prolonged release for severe, chronic low back pain with or without a neuropathic pain component: results of an open-label, phase 3b study. *Curr Med Res Opin* 2012; **28**: 911-936 [PMID: 22443293 DOI: 10.1185/03007995.2012.679254]

68 **Lange B**, Kuperwasser B, Okamoto A, Steup A, Häufel T, Ashworth J, Etropolski M. Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. *Adv Ther* 2010; **27**: 381-399 [PMID: 20556560 DOI: 10.1007/s12325-010-0036-3]

69 **Baron R**, Martin-Mola E, Müller M, Dubois C, Falke D, Steigerwald I. Effectiveness and Safety of Tapentadol Prolonged Release (PR) Versus a Combination of Tapentadol PR and Pregabalin for the Management of Severe, Chronic Low Back Pain With a Neuropathic Component: A Randomized, Double-blind, Phase 3b Study. *Pain Pract* 2014 Apr 17; Epub ahead of print] [PMID: 24738609 DOI: 10.1111/papr.12200]

70 **Kim HK**, Park SK, Zhou JL, Taglialatela G, Chung K, Coggeshall RE, Chung JM. Reactive oxygen species (ROS) play an important role in a rat model of neuropathic pain. *Pain* 2004; **111**: 116-124 [PMID: 15327815 DOI: 10.1016/j.pain.2004.06.008]

71 **Romanò CL**, Romanò D, Bonora C, Mineo G. Pregabalin, celecoxib, and their combination for treatment of chronic low-back pain. *J Orthop Traumatol* 2009; **10**: 185-191 [PMID: 19921480 DOI: 10.1007/s10195-009-0077-z]

72 **Chaparro LE**, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev* 2012; **7**: CD008943 [PMID: 22786518 DOI: 10.1002/14651858.CD008943.pub2]

73 **Pota V**, Maisto M, Pace MC. Association of buprenorphine TDS and pregabalin in the treatment of low back pain. *Eur J Pain* 2007; **11**: S83 [DOI: 10.1016/j.ejpain.2007.03.206]

74 **Ruoff GE**, Rosenthal N, Jordan D, Karim R, Kamin M. Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: a multicenter, randomized, double-blind, placebo-controlled outpatient study. *Clin*

Ther 2003; **25**: 1123-1141 [PMID: 12809961 DOI: 10.1016/S0149-2918(03)80071-1]

75 **Peloso PM**, Fortin L, Beaulieu A, Kamin M, Rosenthal N. Analgesic efficacy and safety of tramadol/ acetaminophen combination tablets (Ultracet) in treatment of chronic low back pain: a multicenter, outpatient, randomized, double blind, placebo controlled trial. *J Rheumatol* 2004; **31**: 2454-2463 [PMID: 15570651]

P- Reviewer: Beales DJ, Schencking M, Tangtrakulwanich B
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com