# Low back pain

# Lombociatalgia

Patrick Raymond Nicolas André Ghislain Stump<sup>1</sup>, Ricardo Kobayashi<sup>1</sup>, Alexandre Walter de Campos<sup>2</sup>

DOI 10.5935/1806-0013.20160051

# **ABSTRACT**

**BACKGROUND AND OBJECTIVES:** Neuropathic pain is present in 37 to 55% of cases of low back pain. Neuropathic pain is associated with more intense pain, more severe comorbidities and worse quality of life. In addition, costs are 67% higher when compared to other etiologies. The purpose of this article is to review this issue that has significant impact on quality of life.

CONTENTS: Pain radiating to the lower limb may be radicular or referred pain. Radiation paths of lumbar roots and myofascial trigger points may be very similar, as the root of L5 and gluteus minimus trigger point. Thus, it is essential to use a tool for neuropathic pain assessment, such as: Douleur neuropathique 4 questionnaire, Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale e painDETECT. Clinical history and physical evaluation should formulate diagnostic hypotheses, which should be confirmed with complementary tests when necessary. Guidelines for the treatment of neuropathic pain consider as the first line drugs: anticonvulsants (gabapentin and pregabalin), tricyclic antidepressants (amitriptyline, imipramine, clomipramine and nortriptyline), selective serotonin and norepinephrine reuptake inhibitor (duloxetine and venlafaxine). Second line drugs are: 5% lidocaine patches in localized neuropathic pain and opioids. Surgical treatment of lumbar radiculopathy should be indicated when there is limited or low efficacy of multimodal conservative treatment.

**CONCLUSION**: In low back pain, diagnosis of neuropathic component is critical. Multimodal treatment is imperative, as well as other strategies to rehabilitate and improve the patient's quality of life.

Keywords: Back pain, Low back pain, Neuralgia, Sciatica, Spinal diseases, Trigger points.

# **RESUMO**

JUSTIFICATIVA E OBJETIVOS: A dor neuropática está presente em 37 a 55% dos casos de lombociatalgia, a dor neuropática está relacionada com dor mais intensa, comorbidades mais graves e piora da qualidade de vida. Além disso, os custos são 67% maiores quando comparada a outras etiologias. O objetivo deste artigo foi fazer uma revisão sobre este tema que causa impacto importante na qualidade de vida dos pacientes.

CONTEÚDO: A dor irradiada para o membro inferior pode ser de origem radicular ou referida. Os trajetos de irradiação para o membro inferior de raízes lombares e de pontos-gatilhos miofasciais podem ser muito parecidos, como a raiz L5 e ponto-gatilho do glúteo mínimo. Assim, é essencial a utilização de um instrumento para avaliação da dor neuropática, como: Douleur neuropathique 4 questionnaire, Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale e Pain DETECT. Os dados da anamnese e do exame físico devem formular hipó-

1. Universidade de São Paulo, Faculdade de Medicina, Hospital de Clínicas, Grupo de Dor do Departamento de Neurologia, Instituto de Ortopedia e Traumatologia, São Paulo, SP, Brasil.

NOTE 1. Conflict of interest: none - Sponsoring sources: According to Rule 1595/2000 of the Federal Council of Medicine and Resolution RDC 102/2000 of the Health Surveillance Agency declare that this article was not sponsored and which has already been paid or am by consultancy contracts or fees of the following pharmaceutical companies: Boehringer - Ingelheim Corp., Eli Lilly and Company, Pfizer Inc., Novartis SA, Cristália. NOTE 2. Conflict of interest: none - Sponsoring sources: According to Rule 1595/2000 of the Federal Council of Medicine and Resolution RDC 102/2000 of the Health Surveillance Agency declare that this article was not sponsored and are unpaid or own contract with pharmaceutical companies.

# Correspondence to:

Patrick Raymond Nicolas André Ghislain Stump R. Alves Guimaráes, 461 AP 94 05410-020 São Paulo,SP, Brasil. E-mail: ptstump@gmail.com

© Sociedade Brasileira para o Estudo da Dor

teses diagnósticas, que devem ser confirmadas com os exames complementares quando necessário. As diretrizes para o tratamento da dor neuropática consideram como primeira linha: anticonvulsivantes (gabapentina e pregabalina), antidepressivos tricíclicos (amitriptilina, imipramina, clomipramina e nortriptilina), inibidores seletivos da receptação de serotonina e de noradrenalina (duloxetina e venlafaxina). As medicações de segunda linha são: emplastros de lidocaína a 5% em dor neuropática localizada e os opioides. O tratamento cirúrgico da radiculopatia lombar deve ser indicado quando existir limitação ou baixa eficácia no tratamento conservador multimodal.

**CONCLUSÃO**: Na lombalgia o diagnóstico do componente neuropático é fundamental. O tratamento multimodal é imperativo, assim como outras estratégias para reabilitar e melhorar a qualidade de vida do paciente.

**Descritores**: Ciática, Doenças da coluna vertebral, Dor lombar, Dor nas costas, Neuralgia, Pontos-gatilho.

#### INTRODUCTION

According to systematic review of 2105, annual prevalence of back pain affects more than 50% of adults and chronic cases may affect between 4.2% and 14.7% of Brazilian population. In addition it is major reason for absenteeism at work<sup>1</sup>.

Low back pain is defined as pain and discomfort localized between the costal margin and inferior gluteal fold, with or without leg pain<sup>2</sup>. In 60% of cases there might be pain irradiated to lower limb and this presentation is called lumbosciatic pain, which may be of radicular (e.g., compression by herniated disc) or referred (e.g., myofacial pain) origin<sup>3</sup>.

Neuropathic pain (NP) is present in 37 to 55% of patients with pain irradiated to lower limb. According to the International Association for the Study of Pain (IASP), it is defined as that appearing as direct consequence of injury of disease affecting the somatosensory system. Neuropathic characteristic is correlated to more severe pain, more severe comorbidities and poorer quality of life (QL). In addition, costs are 67% higher as compared to pain of other etiologies<sup>3-6</sup>.

Many references consider that acute nonspecific low back pain is self-limited, with recovery rate of 90% in the period of 4 to 7 weeks, and chronicity rate of 2 to 7%. However, more recent studies have shown much higher chronicity rate, of 40 to 44%. So, adequate treatment and initial follow up of acute low back pain are extremely important to prevent chronic cases<sup>7</sup>.

# **ETIOLOGIY**

Major lumbosciatic pain etiologies are:

# 1. Disc protrusion

Approximately 90% of lumbosciatic pain cases are related to an inflammatory process on nervous root caused by inflammatory reaction induced by increased intra-disc pressure and intervertebral disc protrusion inside the spinal canal<sup>8</sup>.

# 2. Herniated disc

Condition where, in addition to the inflammatory process on nervous root there is mechanical compression of this root by the intervertebral disc, with prevalence of 5%. Such condition has higher incidence between the third and fourth decades of life. This because in this stage of life, the degenerative process of the intervertebral disc is at a point where there is still pressure inside the nucleus pulposus, however fibrous annulus already has decreased capacity to resist to this internal pressure. With this, there are fibrous annulus ruptures and consequent compression of a nervous root inside the spinal canal or in the intervertebral foramen 9,10.

# 3. Spinal canal stenosis

Condition which may be congenital in a minority of cases, and degenerative in most cases, where spinal canal diameter is between 10 and 12mm, secondary to bone thickening of joint laminae and facets, yellow ligament

<sup>2.</sup> Complexo Hospitalar Heliópolis, Serviço de Neurocirurgia, São Paulo, SP, Brasil.

hypertrophy, posterior longitudinal ligament ossification and hyperlordosis. Such condition is related to mechanical nervous compression and also to vascular insufficiency and relative ischemia<sup>10</sup>.

# 4. Post-laminectomy syndrome

Approximately 10 to 40% of patients submitted to lumbar spine surgery for pain relief, regardless of the surgical technique, evolve with chronic neuropathic pain in lower limb which is responsible for poorer quality of life. Such condition is multifactorial and is related to pre, intra and post-surgery events<sup>11,12</sup>.

### 5. Piriformis syndrome

Approximately 6% of lumbosciatic pain cases may be related to piriformis syndrome<sup>13</sup>. Such condition is related to sciatic nerve compression by piriformis muscle or even by the tendon of this muscle in pelvic floor. This happens when there is muscle hypertrophy, inflammation or anatomic variation<sup>14</sup>.

### **CLINICAL PRESENTATION**

Accurate diagnosis of pain pattern is essential for a good therapeutic result, since the drug has to be specific for each type of pain: nociceptive, neuropathic or mixed. The identification of the neuropathic component depends on thorough history and physical evaluation, in addition to complementary exams<sup>15</sup>

NP is spontaneous and may have specific clinic characteristics, such:

- Hyperalgesia: exaggerated pain (disproportionate) to a normally painful stimulus;
- Hyperpathia: exaggerated reaction to severe or repetitive pain stimuli applied to hypoesthesic regions;
- Allodynia: pain to a normally painless stimulus<sup>16</sup>.

Physical evaluation should include static and dynamic inspection, gait, special provocative maneuvers, palpation (bony parts and soft parts), in addition to the evaluation of myofascial trigger-points (TP). TP are present in 85% of patients evaluated in pain centers and are major causes of chronic pain<sup>17</sup>.

Neurological exam shall evaluate mobility, sensitivity (tactile, painful, thermal and vibratory) and deep tendinous reflexes in patellar (L4) and Achilles (S1) tendon. Most commonly used provocative maneuver is the extended leg raising test, which is considered positive for sciatic nerve involvement when reproducing radicular symptoms at a height between 35° and 70° 18.19.

# **NEUROPATHIC PAIN EVALUATION TOOLS**

Irradiation pathways of lumbar roots and TP to lower limb are very similar (e.g., root L5 and gluteus minimum TP). So, it is critical to use an NP evaluation tool to evaluate the type of pain.

Table 1 shows the incidence of neuropathic component in lumbosciatic pain, in addition to the score considered positive and maximum score of major tools: *Douleur neuropathique 4* questionnaire (DN-4)<sup>5</sup>, Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS)<sup>4</sup> e Pain DETECT <sup>6</sup>.

**Table 1.** Major neuropathic pain evaluation tools showing its incidence in lumbosciatic pain, positive score for neuropathic pain and maximum score of the tool

Tools	Incidence of neuropathic pain in lumbosciatic pain	Positive score for neuropathic pain	Maximum score of the tool
DN-4	44%	≥ 4	10
LANSS	55%	≥ 12	24
PainDETECT	37%	≥ 19	38

# **COMPLEMENTARY EXAMS**

History and physical evaluation data should formulate diagnostic hypotheses, which are to be confirmed by complementary exams, when needed. Red flags are indicators of investigation with imaging exams and should be considered to try to rule out cases of fractures, infections, tumors and cauda equina syndrome<sup>20</sup>.

Currently, complementary exams are widely used to justify patients' pain,

however, altered exams not always are related to pain etiology, since degenerative alterations are common even in asymptomatic patients. However, they should be indicated according to history/physical evaluation and be appreciated when compatible with clinical presentation<sup>17</sup>.

# 1. Disc protrusion and herniated disc

Computerized tomography (CT) may show intervertebral disc protrusion to inside the spinal canal, however the golden standard is nuclear magnetic resonance (MRI) which shows intervertebral disc degeneration process, in addition to fibrous annulus ruptures and migrated nucleus pulposus fragments<sup>10</sup>.

#### 2. Spinal canal stenosis

Spine X-rays and CT show bone hypertrophy. They also show spinal canal narrowing. MRI, in turn, adds information related to soft tissues, such as ligamentous hypertrophy<sup>10</sup>.

### 3. Post-laminectomy syndrome

Post-surgery X-rays, CT and MRI may not show abnormalities. Possible abnormalities: insufficient decompression, hematomas, infection, vertebral instability, inadequate positioning of orthoses and vertebral fractures<sup>21</sup>.

### 4. Piriformis syndrome

Pelvic MRI shows piriformis muscle and its relation with the sciatic nerve<sup>22</sup>.

#### **CONSERVATIVE TREATMENT**

The objective of chronic pain treatment is to rehabilitate patients, improve QL and promote social reintegration, since complete pain elimination is not always feasible. Satisfactory results depend on accurate diagnosis and tailored treatment, in addition to patients' adhesion to proposed therapies<sup>17</sup>.

Most studies of pharmacological neuropathic pain treatments were performed with models of diabetic polyneuropathy and post-herpetic neuralgia. Pharmacological treatment is still the most important therapy to treat chronic neuropathic pain (chronicity is defined as persistent pain for more than 3 months). Different classes of drugs are used to treat neuropathic pain. The choice of the right drug for each case still has some difficulties due to the inefficacy of some drugs or to adverse effects associated to effective drugs in recommended doses. Many patients need more than one drug, but the correct choice of the drug to be associated, as well as the sequential order of its introduction is still not clear<sup>23</sup>.

Guidelines to treat neuropathic pain consider as first line treatments with efficacy proven by best consistency experimental or observational studies (level A) These drugs are:

- • Voltage-gated calcium channels  $\alpha$  28 subunits modulator anticonvulsants: gabapentin and pregabalin;
- Tricyclic antidepressants (TAD): amitriptyline, imipramine, clomipramine and nortriptyline;
- $\bullet$  Selective serotonin and norepine phrine reuptake inhibitors (SSNRI): duloxetine and venla faxine  $^{23}.$

Second line drugs are:

- 5% lidocaine plasters as a function of their localized action. These have precise indication for post-herpetic neuralgia<sup>23</sup>. This presentation may be mistaken by lumbosciatic pain when lumbar or sacral ganglia are involved;
- Opioids due to risk of addiction<sup>23-25</sup>. In addition, there are evidences of cognitive disorders in patients with chronic lumbosciatic pain under opioids for a long period<sup>26</sup>.

Aiming at acting in different pain mechanisms, as well as in comorbidities present in chronic lumbosciatic pain patients, such as sleep and mood disorders. The association of drugs with pharmacokinetics and pharmacodynamics of synergistic potency may benefit patients' QL<sup>27</sup>. The association of gabapentin and tricyclics or opioids was more effective than the use of isolated treatment and allows decreasing the dose of each molecule<sup>27-29</sup>. In addition to analgesia, pregabalin is effective to improve sleep quality and anxiety disorder<sup>30</sup>. All TAD have proven efficacy to treat depression and anxiety, however, in higher doses than that used to treat pain, amitriptyline may also improve sleep. Dual receptors are effective to treat anxiety and depression<sup>25</sup>. The efficacy of tramadol, even in association with paracetamol, was shown in sensory polyneuropathies (level A)<sup>31-33</sup> (Table 2).

# 1st stage

Start treatment with one or more first line drugs:

- $\bullet$   $\alpha$   $2\delta$  ligants (gabapentin, pregabalin);
- SSNRI (duloxetine, venlafaxine);
- TAD (amitriptyline, nortriptyline).

Table 2. IASP recommended drugs to treat neuropathic pain and available in Brazil<sup>23</sup>

	Total daily dose	Recommendation		
Strongly recommended				
Gabapentin	1200 to 3600mg, divided in 3 $\times$ a day	1 <sup>st</sup> line		
Pregabalin	300 to 600mg, divided in 2 x a day	1 <sup>st</sup> line		
Dual serotonin ndnorepine- phrine reup- takers	60 to 120mg, 1 x a day (Duloxetin) 150 to 225mg, 1 x a day (exten- ded action venlafaxine)	1 <sup>st</sup> line		
Tricyclic anti- depressants	25 to 150mg in 1 or 2 x a day	1 <sup>st</sup> line		
Weak recommendation				
5% lidocaine plaster	1 to 3 plasters in the painful área during 12h with interval of 12hs	2 <sup>nd</sup> line Peripheral neuropathy		
Tramadol	200 to 400mg, 2 x in slow release formulation or 3 x a day	2 <sup>nd</sup> line		
Botulinum toxin	50 to 200 units in painful area every 3 months	3 <sup>rd</sup> line Peripheral neuropathy		
Strong opioids	Individual titration according to opioid	3 <sup>rd</sup> line		

Dworkin et al. have proposed in 2010 an evidence-based algorithm (level A), for the introduction and association of drugs to treat neuropathic pain<sup>34</sup>

# 2nd stage

- If there is partial pain relief, add another first line drug;
- If there is inadequate or no pain relief, replace by different first line drug.

# 3rd stage

- If first line drugs, alone or in combination, fail, consider second line drugs (opioids, tramadol);
- Or refer to a pain specialist<sup>34</sup>.

# **SURGICAL TREATMENT**

Surgical treatment of lumbar radiculopathy should be indicated when there is limitation or low efficacy of multimodal conservative treatment. In this sense, one may divide surgical treatment to be indicated in: acute phase, up to 12 weeks after symptoms onset and chronic lumbar radicu-

Surgical treatment may also be divided in antalgic treatment, in situations when there is motor neurological and deep reflexes preservation and surgical treatment aiming at maintaing spinal nerve integrity.

# 1. Acute lumbar radiculopathy with motor preservation

a) Foraminal infiltration with steroid

It may be indicated for pain relief in patients with insatisfactory response to systemic pharmacological therapy and physiotherapy<sup>35,36</sup>.

# 2. Chronic lumbar radiculopathy with motor preservation

a) Application of pulsed radiofrequency in dorsal root ganglion of affected spinal nerve

Outpatient procedure under aseptic conditions with local anesthesia and in operating center with the aid of radioscopy. Dorsolateral percutaneus access is performed to reach intervertebral foramen corresponding to the affected dermatome. When the upper third of the intervertebral foramen is reached, impedance is checked, which should be less than 400 ohms. Sensory stimulation is performed to 50 hertz with up to 0.5 volts to obtain referred paresthesia to the dermatome to be treated. Motor stimulation with 2 hertz to 5 hertz should be obtained with at least twice the voltage obtained to get this sensory response.

Pulsed radiofrequency is applied with temperature limitation at 42° Celsius and exposure time of at least 120 seconds<sup>37,38</sup>.

b) Spinal cord stimulation

In patients with pharmacological treatment limitation and insatisfactory

response to percutaneous interventionist treatment, the surgical option is spinal electrode implant to stimulate spinal cord above the conus. Permanent implant is conditioned to an initial test phase with external pulse

Spinal electrode implant may be percutaneous for cylindrical electrodes or by microlaminectomy for plate electrodes. Risk of electrode migration is higher for cylindrical electrode. After electrode implant, a pulse generator is implanted in subcutaneous pouch. This pulse generator creates an electric field on spinal cord dorsal region which acts to relieve NP. The conformation of this electric field is based on the combination of stimulus frequency, electromagnetic wave length and electric field potency, parameters which are established by the assistant physician.

This is a well established therapy with evidence level I, which improves QL and functional capacity<sup>39-41</sup>.

# 3. Acute lumbar radiculopathy with loss of deep reflexes and/or motor defficiency in patients without previous surgical treatment

- a) Nerve decompression
- a.1. Open discectomy

This treatment modality is indicated for herniated lumbar disc with nerve compression inducing dermatomeric symptoms compatible with affected nervous root and when conservative treatment fails<sup>42</sup>.

### a.2. Laminectomy

Indicated in clinical neurogenic lameness conditions when there is spinal canal stenosis evidenced by complementary exams.

a.3. Foraminotomy

When there is intervertebral foramen narrowing.

- a.4. The combination of above-described procedures depends on complementary imaging exams results (CT or MRI).
- a.5. Endoscopic microdiscectomy

Transmuscular percutaneous minimally invasive treatment modality using optic system. It is indicated for symptomatic herniated disc, however its results are not better than open discectomy and it is more expensive 42,43.

# CONCLUSION

For chronic back pain patients, the diagnosis of the neuropathic component and of comorbidities (sleep disorder, anxiety, depression) is critical. Therapeutic strategy with the association of more than one drug is mandatory, as well as the use of all tools (physical medicine, cognitive therapy, etc.) to improve QL of patients in its highest biopsychosocial spectrum.

# **REFERENCES**

- Nascimento PR, Costa LO. [Low back pain prevalence in Brazil: a systematic review]. Cad Saude Publica. 2015;31(6):1141-56. English, Portuguese.
- Andersson JA. Problems of classification of low-back pain. Rheumatol Rehabil. 1977;16(1):34-6.
- Konstantinou K, Dunn KM, Ogollah R, Vogel S, Hay EM. Characteristics of patients with low back and leg pain seeking treatment in primary care: baseline results from the ATLAS cohort study. BMC Musculoskelet Disord. 2015;16:332.
- Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with
- neuropathic characteristics in the general population. Pain. 2008;136(3):380-7.

  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(10):1080-7.
- 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(10):1911-20. Itz CJ, Geurts JW, van Kleef M, Nelemans P. Clinical course of non-specific low back pain: a syste-
- matic review of prospective cohort studies set in primary care. Eur J Pain. 2013;17(1):5
- Valat JP, Genevay S, Marty M, Rozenberg S, Koes B. Sciatica. Best Pract Res Clin Rheumatol. 2010;24(2):241-52.
- Kramer J. Intervertebral Disc Disease; Causes, Diagnosis, Treatment and Prophylaxis, 2nd ed. New York: Thieme Medical; 1990.
- Youmans neurological surgery, 5th ed. 2004.293.
- 11. Wilkinson HA: The Failed Back Syndrome: Etiology and Therapy. 2nd ed. Philadelphia: Harper & Row: 1991.
- North RB, Kidd D, Shipley J, Taylor RS. Spinal cord stimulation versus reoperation for failed back surgery syndrome: a cost effectiveness and cost utility analysis based on a randomized controlled trial. Neurosurgery. 2007;61(2):361-9.
- Parziale JR, Hudgins TH, Fishman LM. The piriformis syndrome. Am J Orthop. 1996;25(12): 819-23.
- Silver JK, Leadbetter WB. Piriformis syndrome: assessment of current practice and literature review. Orthopedics. 1998;21(10):1133-5.
- Santos JG, Brito JO, de Andrade DC, Kaziyama VM, Ferreira KA, Souza I, et al. Translation to Portuguese and validation of the Douleur Neuropathique 4 questionnaire. J Pain. 2010;11(5):484-90. Yeng LT, Mattar Júnior R, Kobayashi R, Cantara MG, Teixeira MJ. Síndrome complexa de dor
- regional. In: Bispo Júnior RZ, Mello Júnior CF. Ortopedia básica. Rio de Janeiro: Revinter; 2014.
- Yeng LT, Kobayashi R, Kobayashi CBC, Rossi Junior J, Loduca A, Muller BM, et al. Avaliação funcional do doente com dor crônica, in: Martins MA, Carrilho FI, Alves VAF, Castilho EA, Cerri

- GG. Clínica Médica do HCFMUSP. Barueri: Manole; 2015. 38-44p.
- Delfino HLA. Coluna Lombar. In: Barros Filho TEP, Lech O. Exame físico em ortopedia. S\u00e3o Paulo: Sarvier; 2001. 37p.
- van der Windt DA, Simons E, Riphagen II, Ammendolia C, Verhagen AP, Laslett M, et al. Physical examination for lumbar radiculopathy due to disc herniation in patients with low-back pain. Cochrane Database Syst Rev. 2010;17;(2):CD007431.
- van Tulder M, Becker A, Bekkering T, Breen A, del Real MT, Hutchinson A, et al. Chapter 3. European guidelines for the management of acute nonspecific low back pain in primary care. Eur Spine J. 2006;15(Suppl 2):S169-91.
- Bordoni B, Marelli F. Failed back surgery syndrome: review and new hypothesis, J Pain Res. 2016;9:17-22.
- Arooj S, Azeemuddin M, Pirirformis syndrome a rare cause of extraspinal sciatica. J Pak Med Assoc. 2014:64(8):949-51.
- Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015;14(2):162-73.
- Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010;17(9):1113-e88.
- Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007;132(3):237-51.
   Shiltenwolf M, Akbar M, Hug A, Pfüller U, Gantz S, Neubauer E, et al. Evidence of specific cogniti-
- Shiltenwolf M, Akbar M, Hug A, Pfüller U, Gantz S, Neubauer E, et al. Evidence of specific cognitive deficits in patients with chronic low back pain under long-term substitution treatment of opioids. Pain Physician. 2014;17(1):9-20.
- Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double- blind, randomised controlled crossover trial. Lancet, 2009;374(9697):1252-61.
- Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med. 2005;352(13):1324-34.
- Gilron I, Jensen TS, Dickenson AH. Combination pharmacotherapy for management of chronic pain: from bench to bedside. Lancet Neurol. 2013;12(11):1084-95.
   Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabe-
- Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain. 2004;110(3):628-38.
- Hollingshead J, Dühmke RM, Cornblath DR. Tramadol for neuropathic pain. Cochrane Database Syst Rev. 2006;3:CD003726.

- Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. JAMA. 2005;293(24):3043-52.
- Freeman R, Raskin P, Hewitt DJ, Vorsanger GJ, Jordan DM, Xiang J, et al. Randomized study of tramadol/acetoaminophen versus placebo in painful diabetic peripheral neuropathy. Curr Med Res Opin. 2007;23(1):147-61.
- Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc. 2010;85(3 Suppl):S3-14.
- Manchikanti L, Buenaventura RM, Manchikanti KN, Ruan X, Gupta S, Smith HS, et al. Effectiveness of therapeutic lumbar transforaminal epidural steroid injections in managing lumbar spinal pain. Pain Physician. 2012;15(3):E199-245.
- van Helvoirt H, Apeldoorn AT, Ostelo RW, Knol DL, Arts MP, Kamper SJ, et al. Transforaminal
  epidural steroid injections followed by mechanical diagnosis and therapy to prevent surgery for
  lumbar disc herniation. Pain Med. 2014;15(7):1100-8.
- Koh W, Choi SS, Karm MH, Suh JH, Leem JG, Lee JD, et al. Treatment of chronic lumbosacral radicular pain using adjuvant pulsed radiofrequency: a randomized controlled study. Pain Med. 2015;16(3):432-41.
- Van Boxem K, Cheng J, Patijn J, van Kleef M, Lataster A, Mekhail N, et al. Lumbosacral radicular pain. Pain Pract. 2010;10(4):339-58.
- Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicenter randomised controlled trial in patients with failed back surgery syndrome. Pain. 2007;132(1-2):179-88.
- Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, et al. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24 month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. Neurosurgery. 2008;63(4):762-70.
- Grider JS, Manchikanti L, Carayannopoulos A, Sharma ML, Balog CC, Michael E. et al. Effectiveness of spinal cord stimulation in chronic spinal pain: a systematic review, Pain Physician. 2016;19(1):E33-54
- Gibson JN, Waddell G.) Surgical interventions for lumbar disc prolapse. Cochrane Database Syst Rev. 2007;2:CD001350
- Smith N, Masters J, Jensesn C, Khan A, Sprowson A. Systematic review of microendoscopic discectomy for lumbar disc herniation, Eur Spine J. 2013;22(11):2458-65.