

NARRATIVE REVIEW

Neuropathic low back pain in clinical practiceR. Baron¹, A. Binder¹, N. Attal², R. Casale³, A.H. Dickenson⁴, R-D. Treede⁵

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Abstract

Background and objective: Low back pain (LBP) is one of the most common chronic pain conditions. This paper reviews the available literature on the role of neuropathic mechanisms in chronic LBP and discusses implications for its clinical management, with a particular focus on pharmacological treatments.

Databases and data treatment: Literature searches were performed in PubMed, key pain congresses and ProQuest Dialog to identify published evidence on neuropathic back pain and its management. All titles were assessed for relevant literature.

Results: Chronic LBP comprises both nociceptive and neuropathic components, however, the neuropathic component appears under-recognized and undertreated. Neuropathic pain (NP) is challenging to manage. Many patients with chronic LBP have pain that is refractory to existing treatments. Typically, less than half of patients experience clinically meaningful analgesia with oral pharmacotherapies; these are also associated with risks of adverse effects. Paracetamol and NSAIDs, although widely used for LBP, are unlikely to ameliorate the neuropathic component and data on the use of NP medications such as antidepressants and gabapentin/pregabalin are limited. While there is an unmet need for improved treatment options, recent data have shown tapentadol to have efficacy in the neuropathic component of LBP, and studies suggest that the capsaicin 8% patch and lidocaine 5% medicated plaster, topical analgesics available for the treatment of peripheral NP, may be a valuable additional approach for the management of neuropathic LBP.

Conclusions: Chronic LBP often has an under-recognized neuropathic component, which can be challenging to manage, and requires improved understanding and better diagnosis and treatment.

What does this review add?: Increased recognition and improved understanding of the neuropathic component of low back pain raises the potential for the development of mechanism-based therapies.

Open and retrospective studies suggest that agents like tapentadol and topical analgesics — such as the capsaicin 8% patch and the lidocaine 5% medicated plaster — may be effective options for the treatment of neuropathic low back pain in defined patient groups.

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1. Introduction

Low back pain (LBP) – defined as pain and discomfort localized below the costal margins and above the inferior gluteal folds, with or without referred leg pain (Airaksinen et al., 2006) – is one of the most common chronic pain conditions encountered in worldwide clinical practice. Lifetime prevalence of LBP is estimated to be >70% in industrialized countries, with a 1-year prevalence of 15–45% (Kaplan et al., 2013), therefore most individuals will experience LBP at some point during their life. LBP is considered chronic when it persists for 12 weeks or more. It is generally accepted that only a minority of patients report persistent pain after an acute episode. However, a recent systematic review of prospective cohort studies, set in primary care suggests that as many as two-thirds of patients go on to develop chronic LBP (Itz et al., 2013).

Chronic LBP is a disabling and costly condition. Results of the 2010 Global Burden of Disease Study show LBP to be the most common cause of years lived with disability (YLDs) and the sixth leading cause of

disability-adjusted life-years (DALYs) worldwide (Murray et al., 2012; Vos et al., 2012). LBP was estimated to be responsible for 58.2 million YLDs in 1990, increasing to 83.1 million in 2010 (Vos et al., 2012). LBP is frequently associated with comorbid conditions, most notably depression, panic and anxiety disorders, and sleep disturbances (Freynhagen et al., 2006b; Hagen et al., 2006; Freynhagen and Baron, 2009).

Chronic LBP is a complex, heterogeneous condition, where both nociceptive and neuropathic pain mechanisms may be involved. In LBP, nociceptive pain results from activation of nociceptors that innervate ligaments, joints, muscles, fascia and tendons as a response to tissue injury or inflammation and biomechanical stress. Neuropathic back pain describes pain arising from injury or disease directly affecting the nerve roots that innervate the spine and lower limbs, and pathological invasive innervation of the damaged lumbar discs. Chronic LBP is increasingly considered to be a mixed pain syndrome consisting of both nociceptive and neuropathic components (Treede et al., 2008; Freynhagen and Baron, 2009), and it has been suggested that neuropathic components in chronic LBP may be under-recognized and therefore under-treated. This paper reviews the role of neuropathic mechanisms in chronic LBP and discusses implications for clinical management, with particular focus on currently available pharmacological treatment options.

2. Prevalence and burden of neuropathic pain in LBP

Clinical practice guidelines typically suggest that the prevalence of neuropathic pain in LBP is approximately 5%; however, some reports suggest that as many as 16–55% of patients with chronic LBP have possible neuropathic pain components (Hassan et al., 2004; Kaki et al., 2005; Freynhagen et al., 2006a,b; Freynhagen and Baron, 2009; Beith et al., 2011; Fishbain et al., 2014). The wide variation in the reported prevalence of neuropathic pain in LBP is most likely due to differences in methodology between studies, particularly in terms of the definition of neuropathic pain, pain assessment tools and the body area assessed. In a study investigating the neuropathic component of LBP in patients with or without leg pain using the Douleur Neuropathique en 4 Questions (DN4), the relative contribution of neuropathic mechanisms was found to increase with the degree of distal pain radiation (Attal et al.,

2011). The proportion of patients with neuropathic pain as a component ranged from 8% in patients with pain restricted to the lumbar area, to 15% in patients with pain radiating proximally, 39% in patients with pain radiating below the knee without neurological signs and 80% in patients with pain radiating towards the foot in a dermatomal distribution with neurological signs corresponding to typical radiculopathy.

Neuropathic LBP is associated with increased likelihood and severity of medical comorbidities (Freyhagen et al., 2006a; Beith et al., 2011; Mehra et al., 2012), reduced quality of life (QoL) (Beith et al., 2011) and higher health care costs (Berger et al., 2004; Schmidt et al., 2009; Mehra et al., 2012), when compared with low back pain without a neuropathic component. In a study in Germany, health care costs in patients with chronic LBP were 67% higher in those with neuropathic pain than in those with nociceptive pain alone, and approximately 16% of the total costs associated with LBP were estimated to be attributable to neuropathic pain (Schmidt et al., 2009). Furthermore, an analysis of a US claims database found that 90% of patients with chronic LBP have a neuropathic component (Mehra et al., 2012). Total annual direct costs of chronic LBP-related health care resource use were approximately US\$96 million. Chronic LBP with a neuropathic component accounted for 96% of these total costs, with a mean annual per-patient cost of care approximately 160% higher in patients with neuropathic LBP than in those without neuropathic pain (US \$2577 vs. US\$1007, respectively; $p < 0.0001$).

Results from the 2010 Global Burden of Disease Study found that in Germany between 1990 and 2010, LBP caused the loss of 2.1 million DALYs, with only ischaemic heart disease accounting for a greater loss in DALYs. Moreover, the absolute number of DALYs lost as a result of LBP rose by 11% during the study period (Plass et al., 2014). The disproportionately high health care costs in patients with neuropathic LBP suggest a need for more targeted therapeutic interventions to improve patient outcomes and reduce the burden on health care systems.

3. Classification of LBP

Low back pain is classified on the basis of both the clinical characteristics of a patient and the underlying pathophysiology of the condition (Quebec Task Force on Spinal Disorders, 1987; Task Force on Taxonomy of the International Association for the Study

of Pain, 1994; Bogduk, 2009). The Quebec Task Force on Spinal Pain suggested classifying patients with LBP into 11 subgroups, of which the first four were based on pain location and the presence or absence of neurological signs: (i) LBP only; (ii) LBP and pain above the knee; (iii) LBP and pain below the knee and (iv) LBP with pain above and below the knee and signs of nerve root involvement (Quebec Task Force on Spinal Disorders, 1987; Kongsted et al., 2013). Using this classification, patients with LBP and leg pain and signs of nerve root involvement have been shown to be more severely affected and have a worse prognosis than those with LBP alone (Kongsted et al., 2012, 2013). The Oswestry Disability Index is an important tool that researchers and physicians use to classify functional disability as a result of LBP (Fairbank and Pynsent, 2000), and is considered the 'gold standard' of low back functional outcome tools, but does not differentiate between nociceptive and neuropathic components.

Nociceptive LBP is understood to be pain arising from the vertebral column or its adnexa, evoked by noxious stimulation of structures in the lumbar spine, or from the deep soft tissues of the back (muscles and thoracolumbar fascia) (Hoheisel et al., 2013). Noxious stimulation of structures in the lumbar spine can also produce referred pain in addition to back pain. In clinical terms, referred pain is defined as pain perceived as occurring in a region of the body topographically distinct from the region in which the actual source of pain is located. Referred pain arises from central processing of afferent activity in intact nerves; it does not imply an underlying neuropathic mechanism. The mechanism of referred pain (convergence-projection model) consists of convergence of inputs from two tissues onto the same spinal neuron, and projection of the resulting pain sensation into the wrong tissue (i.e. not the one where the injury is located) (Arendt-Nielsen and Svensson, 2001). As the source of spinal referred pain lies in the somatic tissues of the lumbar spine, it is often called somatic referred pain (Bogduk, 2009). Somatic referred pain is generally perceived in regions that share the same segmental innervation as the source. Nociceptive LBP and somatic referred pain do not involve injury or disease of nerves and/or nerve roots.

Radiculopathy and radicular pain are distinct from referred pain. Radiculopathy is defined as objective loss of sensory and/or motor function as a result of damage to the nerve root and can occur with or without associated pain (Task Force on Taxonomy of the International Association for the Study of Pain,

1994). When radiculopathy is associated with pain, this is referred to as painful radiculopathy. According to the proposed neuropathic pain grading system developed by the Special Interest Group on Neuropathic Pain (NeuPSIG), painful radiculopathy fulfils the criteria for definite neuropathic pain when the diagnosis is also based on sensory signs, and the criteria for probable neuropathic pain if it is only based on motor signs (Treede et al., 2008; Haanpää et al., 2011). Painful radiculopathy perceived as arising in a limb or the trunk, with a distribution that is consistent with one or more dermatomes, fulfils the criteria for possible neuropathic pain according to the same grading system. Painful radiculopathy can qualify as being neuropathic, when the underlying neurological lesion or disease is demonstrated by confirmatory tests (as detailed below), when there are sensory signs within the pain distribution, or when both elements are present. Although radiculopathy and radicular pain often coexist, and may be caused by the same lesion, they may also exist in isolation. Typically, painful radiculopathy is associated with direct damage to nerve roots; however, it can occur independently from this, for example, as a result of inflammation affecting the spinal nerves.

Sciatica is a common term used by both doctors and patients to describe a specific pattern of pain in the back of the thigh and sometimes the calf and foot that has radiated along the sciatic nerve. Disc herniation is the most common cause of lumbosacral radicular pain.

Failed back surgery syndrome (FBSS) is the term used to describe chronic back and/or leg pain that persists or occurs after spinal surgery, usually laminectomy. FBSS may or may not also include a neuropathic component (Hussain and Erdek, 2014); and as in other postsurgical pain syndromes, the neuropathic component is likely to contribute to the pain being chronic (Kehlet et al., 2006).

Although radicular pain and radiculopathy are distinct diagnostic entities, a recent systematic review undertaken to assess how radiating leg pain is defined in randomized controlled trials of conservative treatments in primary care found the two terms to be used inconsistently and interchangeably, highlighting the need for further consensus on the classification and definitions of neuropathic back pain (Lin et al., 2014).

4. Mechanisms of neuropathic LBP

A number of pathophysiological mechanisms have been implicated in neuropathic LBP (Fig. 1). In

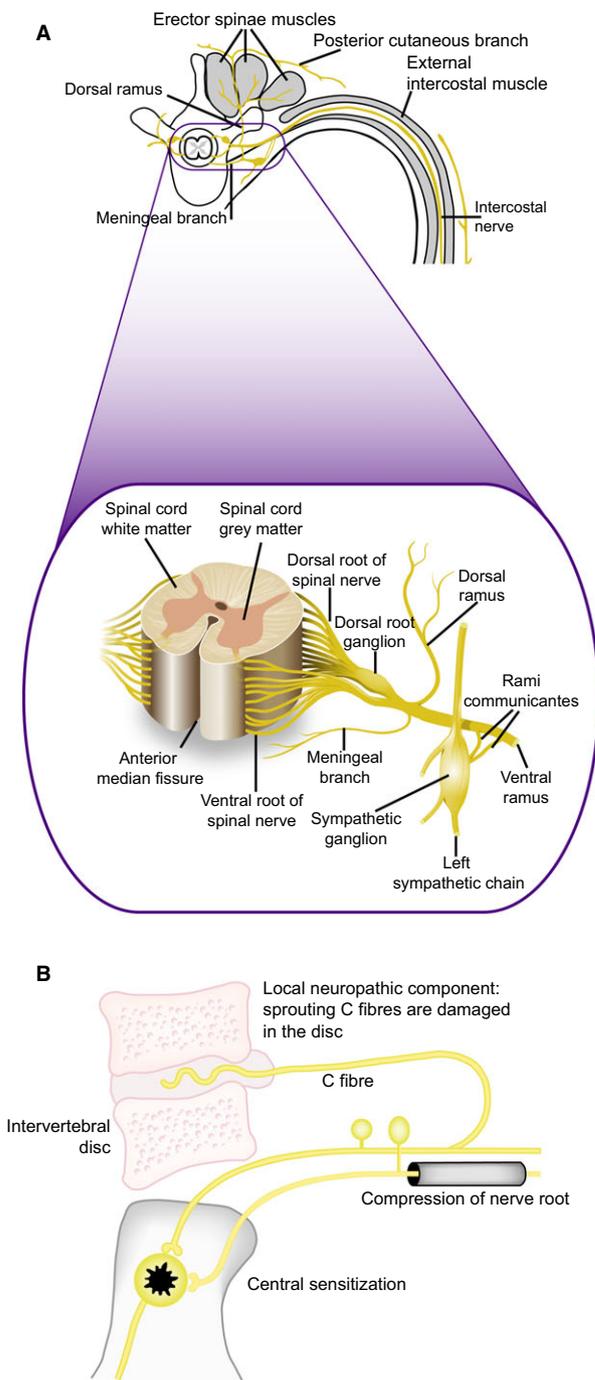


Figure 1 (A) Anatomy of a spinal nerve emerging from the spinal cord. The spinal nerve branches into a dorsal ramus innervating the skin of the lower back and a ventral ramus innervating the leg (via the lumbosacral plexus); (B) Proposed pathophysiological mechanisms in neuropathic back pain (Freyhagen and Baron, 2009). With kind permission from Springer Science+Business Media: *Curr Pain Headache Rep* 2009;13:185–190, Freyhagen R, Baron R, Figure 1.

chronic LBP, neuropathic pain may be caused by lesions of nociceptive sprouts within a degenerated disc (local neuropathic pain), by mechanical com-

pression of the nerve root (mechanical neuropathic root pain), or by the effects of inflammatory mediators arising from a degenerative disc that results in inflammation and damage to the nerve roots (Freyenhagen and Baron, 2009; Cohen and Mao, 2014).

Various preclinical models have been developed that attempt to mimic aspects of pathophysiological mechanisms that contribute to chronic LBP. These include application of nucleus pulposus material near the lumbar dorsal root ganglia (DRG), chronic compression of the DRG or localized inflammation of the DRG, and nerve growth factor injections into the multifidus muscle (Hoheisel et al., 2013; Strong et al., 2013). These models, which are primarily developed in rats, have many common features including behavioural hypersensitivity of the hind paw, enhanced excitability and spontaneous activity of sensory neurons, and locally elevated levels of inflammatory mediators including cytokines. However, some drugs shown to be effective in preclinical models of neuropathic pain fail in clinical studies, either due to lack of tolerability or testing in heterogeneous groups of patients, highlighting the need for careful selection of patient subgroups in trials of potential neuropathic pain drug therapies.

5. Diagnosis of neuropathic LBP

Differentiating between nociceptive and neuropathic pain in LBP is clinically important. These components require different pain management strategies directed at peripheral and central processes, but there is currently no gold-standard approach for the diagnosis of neuropathic LBP (Freyenhagen and Baron, 2009; Haanpää et al., 2011). A focused clinical examination, following a full patient history, should be the first step in the differential diagnosis of any suspected neuropathic pain condition in order to document the distribution of the pain, any associated sensory or motor signs within that distribution, as well as any evidence for an underlying neurological lesion or disease (Treede et al., 2008; Haanpää et al., 2011; Nijs et al., 2015). However, one recent study revealed that as many as 43% of patient visits for LBP did not involve any form of direct physical examination and nearly 20% did not even involve palpation (i.e. no sensory examination) (Press et al., 2013). The substantial lack of a routine approach to the diagnosis of pain is further highlighted by the results of a recent study undertaken in a rehabilitation setting, where LBP is a major clinical problem (Casale et al., 2012).

Painful signs and symptoms arising in an area of altered sensation are the hallmarks of neuropathic pain; however, signs and symptoms of neuropathic pain can vary between patients and even within individual patients over time. Cardinal features include spontaneous pain (i.e. arising without stimulus), abnormal response to nonpainful stimuli such as light touch and moderate heat or cold (allodynia), or an exaggerated response to painful stimuli (hyperalgesia). Spontaneous pain can be paroxysmal (e.g. shooting, stabbing or electric shock-like), dysaesthetic (unpleasant abnormal sensations of touch, for example prickling, pins and needles or crawling) or associated with abnormal thermal sensations (e.g. burning or ice cold). These signs and symptoms can coexist in an area with a loss of afferent sensations (numbness). Signs of neuropathic pain can be assessed using bedside sensory tests when they are due to root compression or inflammation, but not when they result from a lesion that affects nerve sprouts that are pathologically innervating the spinal disc.

Clinical examination of a patient with LBP in which a neuropathic component is suspected should focus on identifying possible sites of an underlying somatosensory lesion, which is consistent with the anatomical distribution and type of symptoms described by the patient (Cohen et al., 2008; Treede et al., 2008; Haanpää et al., 2011; Nijs et al., 2015). Therefore, careful assessment of the patient's sensory, motor and autonomic systems should be done, in conjunction with musculoskeletal examination and palpation of their spine, in order to identify any neurological dysfunction or structural abnormality. Because clinical examination of these patients is rarely, if ever, definitive in isolation it will often be used to guide further laboratory investigation, and rule out other potentially causative pathologies as part of a differential diagnosis (Haanpää et al., 2011).

Several screening tools have been developed to facilitate identification of a neuropathic pain component in patients with chronic LBP (Bennett et al., 2007; Cruccu and Truini, 2009; Haanpää et al., 2011). These tools are generally based on elicitation of verbal pain descriptors, although some also include bedside testing; sensitivity and specificity typically range from 80% to 90% (Table S1). However, these tools are not a substitute for the clinical examination of the patient.

Doleur Neuropathique en 4 Questions, PainDETECT (PD-Q) and the Standardized Evaluation of Pain (STEP) are the only screening tools to have been specifically validated in patients with LBP (Freyenhagen et al.,

2006a; Scholz et al., 2009; Attal et al., 2011). The DN4 comprises both interview questions and physical tests, and has been shown to have high sensitivity and specificity for the detection of neuropathic pain components in patients with LBP (Attal et al., 2011). The PD-Q questionnaire screens for typical signs and symptoms of neuropathic pain, pain course pattern and the presence of radiating pain (Freynhagen et al., 2006a). It is easy to administer, even in primary care settings, and has demonstrated high sensitivity, specificity and accuracy in patients with chronic LBP. A score of ≥ 19 is considered strongly suggestive of a neuropathic pain component, with a score of 13–18 indicating that a neuropathic pain component may be present. However, it appears that further research is required to establish whether the PD-Q score can be used to predict treatment response (Morsø et al., 2011). StEP includes six interview questions and ten physical tests, and has been shown to distinguish between radicular pain and non-neuropathic low back pain with high sensitivity and specificity (Scholz et al., 2009).

More detailed radiological and neurological assessments may be indicated in some patients, including quantitative sensory testing (QST). QST is used to reveal pathological signs of neuropathic pain and is recognized to be a useful additional diagnostic tool (Freynhagen and Baron, 2009; Schäfer et al., 2014). Additionally, neurophysiological investigations utilizing electroneuromyography (i.e. nerve conduction studies) may be useful in helping to differentiate peripheral lesions from suspected LBP with a neuropathic component, but only when considered in conjunction with a detailed patient history and careful clinical examination (Cruccu and Truini, 2009; Haanpää et al., 2011). Conventional electrophysiological techniques can also be used to document radiculopathy, albeit not painful radiculopathy, while nociceptive sensory deficit can be documented objectively using laser evoked potentials (Quante et al., 2010). Radiological imaging studies, primarily MRI, may help when conducting a differential diagnosis in patients with neuropathic LBP, but need to be interpreted with caution as there is a high prevalence of asymptomatic degenerative disorders in older adults and areas of abnormal MRI signal do not necessarily imply tissue damage or dysfunction (Cohen et al., 2008; Haanpää et al., 2011). Currently, there is an unmet need for a dedicated diagnostic algorithm for the clinical assessment of patients with LBP with a suspected neuropathic component. Such an algorithm would help guide rational treatment choices.

6. Treatment options

The goal of treatment of chronic LBP is to reduce pain, maintain function and prevent future exacerbation. Numerous evidence-based clinical practice guidelines for the management of chronic LBP have been published (Chou et al., 2007; National Institute for Health and Clinical Excellence, 2009; Koes et al., 2010; German Medical Association, National Association of Statutory Health Insurance Physicians, and Association of Scientific Medical Societies, 2013). Available guidelines typically advise a multimodal approach to the management of chronic LBP, combining pharmacological therapies for symptomatic relief with nonpharmacological approaches, such as physical activity and psychosocial/behavioural interventions. Choice of treatment should be individualized according to the nature and severity of symptoms, the presence of comorbid conditions (e.g. depression or sleep disorders), potential for adverse effects and drug interactions, risks of misuse and abuse, and cost. However, these guidelines typically do not include specific recommendations for the treatment of neuropathic components of chronic LBP.

Clinical practice guidelines are also available for the treatment of neuropathic pain (Attal et al., 2010; Dworkin et al., 2013; National Institute for Health and Clinical Excellence, 2013; Finnerup, Attal et al., 2015). However, the definitions used by these guidelines do not typically include all forms of neuropathic LBP, for example, the most recent update of the NeuPSIG guidelines only covers back pain with radiculopathy (Finnerup, Attal et al., 2015). Most randomized controlled trials of drug therapies for neuropathic pain have been undertaken in patients with postherpetic neuralgia (PHN) or painful diabetic peripheral neuropathy (PDN), and the extent to which results of these studies can be extrapolated to other neuropathic conditions, such as chronic LBP, is unknown. Typically, no more than half of patients experience clinically meaningful pain relief with currently available oral pharmacotherapy, and all oral agents are associated with a risk of significant adverse effects which can have a serious impact on patients' quality of life. Furthermore, studies undertaken to date are typically short term (<3 months' duration) and evidence of effectiveness and risks associated with long-term treatment is limited. In addition, few head-to-head trials comparing different treatments have been undertaken, so direct comparisons of efficacy and tolerability are generally not possible. In one recent study undertaken to assess adherence of French general practitioners to chronic

neuropathic pain clinical guidelines, typical radicular pain was correctly identified in most cases (90.7%). In contrast, very few respondents (5.2%) were able to identify all the recommended first-line drugs (pregabalin, gabapentin, tricyclic antidepressants and duloxetine), and only 44.3% would have prescribed one of these agents (Martinez et al., 2014).

6.1 Nonpharmacological management

Nonpharmacological options for the management of chronic LBP are often applied in the context of multimodal and multidisciplinary pain therapy, with specialist physiotherapy input and cognitive-behavioural therapies making important contributions. Other options may also include noninvasive approaches, such as transcutaneous electrical nerve stimulation (TENS), and invasive procedures, including epidural steroid injections (ESIs) and spinal cord stimulation (SCS). These approaches have been reviewed in detail elsewhere (Kumar et al., 2012; Morlion, 2013). TENS is often used as a therapeutic adjunct in the management of LBP. It is a relatively safe, non-invasive and easy-to-use modality that can be conveniently self-administered by patients at home, making it an attractive treatment option. However, a Cochrane review found conflicting evidence regarding the benefits of TENS for chronic LBP (Khadilkar et al., 2008). ESI is a common approach in patients with radiculopathy; however, recent systematic reviews suggest only modest evidence of short-term benefits (≤ 3 months) (Cohen et al., 2013; Dworkin et al., 2013). A number of studies support the efficacy and cost-effectiveness of SCS for the treatment of FBSS (Kumar et al., 2012; Kumar and Rizvi, 2013; Hussain and Erdek, 2014; Kapural, 2014).

6.2 Pharmacotherapy

Pharmacological agents available for the management of chronic LBP include paracetamol (acetaminophen), nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, anticonvulsants, opioids, tapentadol and topical treatments (Table 1). Oral agents are recommended as first-line therapy. Paracetamol and NSAIDs target the nociceptive component of LBP and have no effect against neuropathic pain components, while currently available neuropathic pain medications generally show only modest evidence of efficacy in patients with chronic LBP. This may be because studies undertaken to assess these agents in this setting generally have not specifically selected patients with a significant neuropathic component. Response rate

with neuropathic pain medications is typically only around 30–50% in patients with classical neuropathic conditions, and may be lower in patients with chronic LBP.

First-line and long-term treatment with opioids is generally not recommended due to concerns regarding tolerability and dependence. Despite this, a recent study in the UK found high use of opioid analgesics as first-line treatment (either as monotherapy or in combination with other therapies) in 64% of patients with neuropathic LBP (Hall et al., 2013). A recent systematic review found evidence of moderate short-term efficacy for opioids in chronic LBP compared with placebo; however, the few trials that compared opioids with NSAIDs or antidepressants did not show any differences in treatment outcome (Chaparro et al., 2013). Results of another meta-analysis also fail to support the use of opioids alone for the treatment of chronic non-cancer pain (Reinecke et al., 2015).

Extended-release tramadol may also be considered for the treatment of chronic LBP. Tramadol is a weak μ -opioid receptor agonist, which also appears to inhibit serotonin and noradrenaline reuptake. It is generally considered to have a lower sedative effect and risk of abuse compared with other opioids. However, there are only limited data to support the use of tramadol in this setting (Vorsanger et al., 2008).

Tapentadol, a dual μ -opioid receptor agonist and noradrenaline reuptake inhibitor, has been shown to be as effective as oxycodone for the treatment of chronic LBP. It was effective in patients with nociceptive and neuropathic low back pain (Steigerwald et al., 2012; Gálvez et al., 2013), with better gastrointestinal tolerability and improved treatment adherence compared with oxycodone alone (Pergolizzi et al., 2011). In a recent Phase IIIb study, tapentadol monotherapy was found to be as effective as combination therapy with tapentadol and pregabalin in patients with severe, chronic LBP with a neuropathic component (Baron et al., 2015). Neuropathic pain and QoL measures improved significantly in both groups; however, the incidence of dizziness and/or somnolence was significantly lower in patients who received tapentadol alone.

Antidepressants are often used in patients with neuropathic pain, particularly those with comorbid depression or anxiety; their analgesic properties are mediated through their effects on noradrenergic and serotonergic neurotransmission. Systematic reviews show tricyclic antidepressants, for example, amitriptyline, and dual serotonin, and norepinephrine

Table 1 Overview of pharmacological agents that can be used for the treatment of chronic LBP

Drug class	Mode of action	Comments
Tricyclic antidepressants (e.g., amitriptyline, nortriptyline)	Inhibit presynaptic reuptake of serotonin and noradrenaline	Effective against comorbid depression Risk of anticholinergic adverse effects
SNRIs (e.g., duloxetine, venlafaxine)	Serotonin/noradrenaline reuptake inhibition	More effective than SSRIs for the treatment of neuropathic pain Effective against comorbid depression and anxiety Adverse effects include nausea, sleep disturbances and sexual dysfunction
Anticonvulsants (e.g., pregabalin, gabapentin)	Alpha-2-delta calcium channel modulators	Approved for the treatment of neuropathic pain Effective against pain, depression, anxiety and sleep disturbance, but limited evidence of efficacy in chronic LBP Adverse effects include sedation, dizziness and peripheral oedema
Opioids (e.g., morphine, oxycodone)	μ -opioid receptor agonism	Moderate evidence of efficacy in chronic LBP Risk of gastrointestinal side effects, tolerance and abuse First-line and/or long-term treatment generally not recommended in clinical practice guidelines
Tramadol	Weak μ -opioid receptor agonism and serotonin/noradrenaline reuptake inhibition	Lower potential for abuse compared with older opioids
Tapentadol	μ -opioid receptor agonism and selective noradrenaline reuptake inhibition	Lower potential for gastrointestinal side effects, tolerance and abuse compared with older opioids
High-concentration 8% capsaicin patches	Selective agonist of TRPV1 channels	Topical agent, limited risk of systemic adverse effects and drug–drug interactions May be combined with oral therapies Treatment option for patients unable to tolerate oral medications
5% Lidocaine plasters	Sodium channel blocker	Topical agent, limited risk of systemic adverse effects and drug interactions May be combined with oral therapies Treatment option for patients unable to tolerate oral medications

LBP, low back pain; SNRI, serotonin noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TRPV1, transient receptor potential vanilloid 1.

reuptake inhibitors, for example, duloxetine and venlafaxine, to have efficacy for the treatment of neuropathic pain (Saarto and Wiffen, 2007; Dharmshaktu et al., 2012; Finnerup, Attal et al., 2015). In contrast, the analgesic effects of selective serotonin reuptake inhibitors – such as fluoxetine, paroxetine and citalopram – appear limited and inconsistent (Saarto and Wiffen, 2007; Dharmshaktu et al., 2012). However, robust data to support the use of antidepressants for the treatment of neuropathic LBP are lacking. Indeed, a Cochrane review of randomized, controlled trials comparing antidepressants with placebo in patients with nonspecific LBP, which included patients with neuropathic pain components, failed to reveal clear evidence of efficacy for antidepressants in this setting (Urquhart et al., 2008).

The anticonvulsants gabapentin and pregabalin are also frequently used in the treatment of neuropathic pain; these agents are calcium channel alpha-2-delta ligands. For other types of neuropathic pain, such as spinal cord injury, it was found that these agents reduce pain as well as comorbid depression, anxiety and sleep disturbances, and improve QoL (Mehta

et al., 2014). However, robust data are lacking to support the use of these agents for the treatment of neuropathic LBP (Chung et al., 2013). In one study specifically undertaken to assess the efficacy and safety of pregabalin for the treatment of neuropathic pain in patients with chronic lumbosacral radiculopathy, most patients responded to pregabalin therapy; however, time to loss of response (the primary study endpoint) did not significantly differ between pregabalin and placebo (Baron et al., 2010). Results of another small, prospective randomized study in patients with chronic LBP suggest that pregabalin may be most effective when used in combination with celecoxib (Romanò et al., 2009). A large double-blind, randomized, placebo-controlled study has recently been initiated to assess the efficacy of pregabalin in addition to usual care for the treatment of sciatica (Mathieson et al., 2013). Future studies of potential drug therapies for use in this setting should aim to carefully select patients with well-defined neuropathic pain components using appropriate screening and diagnostic tools. Two topical analgesics – the capsaicin 8% patch and the lidocaine 5% med-

icated plaster – are available for the treatment of peripheral neuropathic pain. Currently the 8% capsaicin patch is licensed for use in the treatment of peripheral neuropathic pain in adults, while the lidocaine 5% medicated plaster is only indicated for use in PHN (Astellas Pharma Europe B.V., 2015). Emerging data suggest that these agents may also be effective for the treatment of patients with chronic neuropathic LBP. Although both treatments are topical they are applied in different ways, the capsaicin 8% patch is applied once every 3 months, under physician supervision, for either 30 or 60 min, whereas the lidocaine 5% medicated plaster is applied by the patient and worn daily, for up to 12 h a day.

Capsaicin is a selective agonist of the transient receptor potential vanilloid 1 (TRPV1) channel, which is highly expressed on nociceptors. The capsaicin 8% patch was found to be well tolerated and effective for the treatment of peripheral neuropathic pain (Backonja et al., 2008; Simpson et al., 2008; Maihöfner and Heskamp, 2013). In a prospective, noninterventional study involving over 1000 patients with a variety of neuropathic pain conditions, including patients with radiculopathy, the proportions of patients achieving a 30% and 50% decrease in pain at 3 months were 43% and 24%, respectively, following a single treatment (Maihöfner and Heskamp, 2013). Highest treatment response rates were observed in patients with pre-existing pain for <6 months when compared with patients whose duration of pain was 6 months to 2 years (30% and 50% decreases in pain score in 62% and 39% of patients, respectively, in the former group, vs. 41% and 23% of patients in the latter group), suggesting that early initiation of treatment may be beneficial (Maihöfner and Heskamp, 2014). A retrospective analysis of patients with peripheral neuropathic pain of varying aetiologies, including radiculopathy and FBSS, treated in a clinical setting found that the capsaicin 8% patch provided rapid and sustained pain relief, with a significant reduction in prescribed concomitant pain medications (Wagner et al., 2013). In this study, 67% and 33% of patients with radiculopathy and FBSS achieved reductions in pain score of $\geq 30\%$ and $\geq 50\%$, respectively; however, these results should be interpreted with caution due to the small number of patients studied ($n = 6$).

Lidocaine blocks voltage-gated sodium-channels and hence action potential conduction of nociceptors at the level at which it is applied (Mick and Corra-Illanes, 2012). In two uncontrolled, open-label studies that included patients with moderate-to-severe

LBP, treatment with the lidocaine 5% plaster for 6 weeks significantly reduced both the intensity of the pain and its impact on the patients' QoL (Galer et al., 2004; Gimbel et al., 2005). A retrospective case series also reported marked reductions in pain intensity in patients with neuropathic pain after disc herniation during long-term treatment with the lidocaine 5% plaster (mean treatment duration 7.6 months) (Likar et al., 2012). In a more recent study, add-on therapy with the lidocaine 5% plaster was associated with a clinically meaningful reduction in pain scores after 3 months of treatment in 24 patients experiencing LBP with a neuropathic component (Casale et al., 2014).

Both types of topical treatment are applied directly to the most painful skin area, either on the back or more peripherally in the corresponding dermatome and multiple patches/plasters may be used to cover the affected region if needed. Applications may be repeated if warranted by the persistence or return of pain. These topical approaches are generally well tolerated; application-site reactions are the most common adverse event. Risks of systemic adverse events and pharmacokinetic interactions with concomitant oral medications are minimal owing to low systemic exposure, making them attractive options for use in combination with other pharmacological approaches for chronic LBP.

7. Unmet needs and future perspectives

Neuropathic pain is challenging to manage, and many patients with chronic LBP have pain that is refractory to existing treatments. There remains a clear need for improved treatment options for the management of the neuropathic component of chronic LBP. As chronic LBP is often characterized by both nociceptive and neuropathic components, combination therapy with drugs with different mechanisms of action would appear to be an attractive treatment option; however, clinical studies to support this approach are limited (Romanò et al., 2012). Combining oral agents also raises the potential for drug–drug interactions and increased adverse effects. The positive results from trials with tapentadol may reflect the benefit of a single molecule that possesses two mechanisms of action, thereby modulating both nociceptive and neuropathic elements.

Emerging data suggest that it may be possible to profile patients with chronic LBP according to the sensory abnormalities they experience, possibly reflecting differences in underlying pathophysiological mechanisms (Mahn et al., 2011; Förster et al.,

2013). Analysis of epidemiological and clinical data for 2094 patients with painful radiculopathy showed touch-evoked allodynia and thermal hyperalgesia to be relatively uncommon in radiculopathy compared with classical neuropathic pain syndromes, such as PDN and PHN (Mahn et al., 2011). This difference may be related to the fact that the site of the nerve lesion in radiculopathy is often located proximally to the dorsal root ganglion. A distinct sensory profile was identified in patients with radiculopathy, namely severe painful attacks and pressure-induced pain in combination with mild spontaneous pain, mild mechanical allodynia and thermal hyperalgesia. The painful attacks in these patients might be explained by compression-induced ectopic discharges from a dorsal root and not necessarily by nerve damage. Such differences in sensory phenotype between different neuropathic pain conditions may explain, at least in part, why many therapeutic approaches shown to be effective in PDN and PHN have failed to demonstrate efficacy in chronic LBP. Sensory phenotyping of patients with chronic LBP is a promising technique that may enable individualized treatment, potentially leading to improved patient outcomes, and could assist in the development of more targeted drug therapies.

8. Conclusion

Chronic LBP often has an associated neuropathic pain component. Neuropathic pain is challenging to manage and is frequently refractory to current treatments. It represents a serious burden both in terms of the health of the individual patients and the costs to society as a whole. Treatment recommendations in current guidelines for LBP and for neuropathic pain differ substantially, which can leave clinicians at a loss as to which guidelines to follow when a patient has LBP with an associated neuropathic component. To resolve this issue, increased recognition and improved understanding of the neuropathic component of LBP is needed, together with the development of dedicated evidence-based diagnostic and therapeutic algorithms. This may lead to the development of individualized mechanism-based treatment regimens, which can be expected to result in improved patient outcomes.

Author contribution

All authors have made substantial contributions to drafting or revising this paper and have read and approved the final version to be published.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Overview of screening tools for detection of neuropathic components in chronic LBP (Bennett et al., 2007; Cruccu and Truini, 2009).