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Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: informahealthcare.com/journals/icmo20

Pharmacotherapy of low back pain: targeting nociceptive and neuropathic pain components

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To cite this article: Bart Morlion (2011) Pharmacotherapy of low back pain: targeting nociceptive and neuropathic pain components, Current Medical Research and Opinion, 27:1, 11-33, DOI: 10.1185/03007995.2010.534446

To link to this article: https://doi.org/10.1185/03007995.2010.534446

CMRO

Current Medical Research & Opinion Vol. 27, No. 1, 2011, 11–33

0300-7995
doi:10.1185/03007995.2010.534446

Article FT-0105.R1/534446

Review

Pharmacotherapy of low back pain: targeting nociceptive and neuropathic pain components

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Key words:
Low back pain – Neuropathic – Nociceptive – Pharmacotherapy

Accepted: 20 October 2010; published online: 18 November 2010
Citation: Curr Med Res Opin 2011; 27:11–33

Abstract

Aim:
To review pharmacological management of chronic low back pain (LBP), with respect to management of nociceptive and neuropathic components.

Methods:
Studies were identified by a PubMed search of English-language papers from the last 10 years, with additional hand searches of relevant reviews.

Discussion:
Paracetamol, non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors target the nociceptive component of chronic LBP, and do not affect neuropathic pain mechanisms. Antidepressants target the neuropathic component of chronic LBP; however, conflicting efficacy results have been reported. Opioids target both nociceptive and to a lesser extent neuropathic pain. They are effective in chronic LBP, but many patients require higher doses or combination treatment. The long-term efficacy of opioids in chronic LBP has been questioned because of the absence of high-quality data and concerns regarding tolerability and dependence. The topical preparation lidocaine 5% plaster, indicated in post-herpetic neuralgia, is effective in localized neuropathic pain in patients with chronic LBP. Pregabalin is ineffective as monotherapy for chronic LBP but is effective when combined with celecoxib or opioids. Muscle relaxant monotherapy is ineffective in chronic LBP. Combination therapy is often necessary in patients with chronic LBP, in order to manage both nociceptive and neuropathic pain components.

Conclusion:
Chronic LBP often comprises both nociceptive and neuropathic components, therefore a multimodal and individualized treatment approach is necessary. Combining drugs with different mechanisms of action (e.g. an agent with μ-receptor activity plus an agent of a different class) represents a rational approach to management of chronic LBP with both nociceptive and neuropathic components.

Introduction

Chronic pain arises via a number of mechanisms, including peripheral and central sensitization[1–3]. In peripheral sensitization, the sensitivity of peripheral nociceptor terminals is increased as a result of a reduction in the threshold for nociceptor activation and an increase in membrane excitability, and manifests as primary allodynia (sensation arising from an innocuous stimulus) and primary hyperalgesia (sensation arising from a noxious stimulus). Central sensitization, on the other hand, describes an amplification of synaptic strength in nociceptive circuits. In central sensitization, an innocuous stimulus acting on a low-threshold neuron manifests itself as secondary allodynia, while a noxious stimulus acts via a nociceptor to cause secondary hyperalgesia. Central sensitization occurs as a result of synaptic plasticity in the cortex, and involves a number of processes

including: synaptic modulators and excitatory amino acids; changes in ion channels; increased density of ionotopic receptors; and activation of pre-and post-synaptic kinases. The amplification of synaptic strength means that previously sub-threshold inputs are able to activate nociceptive neurons[3].

Multiple processes are responsible for this switch to a state in which even low-intensity input can generate pain[3]. These processes include ectopic nerve impulse generation, facilitation and disinhibition of synaptic transmission, structural changes and neuro-immune interactions. Over time, the contribution of the monoaminergic system increases as inhibitory transmitters fail and the net effect of descending serotonergic input shifts from inhibition to facilitation[3–5]. In parallel, the contribution of the opioidergic pain modulatory system lessens; expression of μ opioid receptors by primary afferents decreases, and dorsal horn neurons become less sensitive to μ-opioid agonist inhibition[3,6].

Manipulation of pain modulatory mechanisms by either non-pharmacological or pharmacological means interferes with pain processing and is therefore useful in the treatment of various pain states[1]. The biopsychosocial model of chronic pain[7] recognizes it as a combination of physical dysfunction, beliefs and coping strategies, distress, illness behaviour and social interactions. Since the introduction of the biopsychosocial model, treatment for chronic pain, such as chronic low back pain (LBP), has become multimodal and multidisciplinary, with the aim of maximizing pain reduction and quality of life, independence and mobility.

LBP is very common; in a national survey in the USA, 26.4% of responders reported LBP on at least one day in the last 3 months[8]. Epidemiological studies indicate that acute and chronic LBP are associated with socioeconomic disadvantage, obesity and depression[8–10]. Chronic LBP is a costly and disabling condition that is associated with increased healthcare utilization and that is often poorly treated[11].

Although there are multiple causes of LBP, in the majority of patients no specific disease aetiology can be identified, so-called non-specific LBP[12,13]. These patients do, nevertheless, require comprehensive clinical assessment and effective management to avoid long-term disability.

Chronic LBP arises from nociceptive and neuropathic mechanisms and can therefore be classified as a mixed pain syndrome[14]. Non-specific nociceptive pain is the result of an inflammatory response to tissue injury[15,16], while neuropathic pain describes somatic referred pain arising from the lumbar spine and/or nerve roots (radicular pain or radiculopathy). The multifactorial nature of chronic LBP has often been under-recognized and under-treated. Thus, recent studies have demonstrated that approximately 20–55% of patients with chronic LBP have a >90% likelihood of a neuropathic pain component[14,17–20], and, in an additional 28% of patients, a neuropathic pain component is suspected[17]. The presence of a neuropathic pain component is associated with more severe pain symptoms[14] and higher healthcare utilization costs[21].

Multiple treatment approaches for chronic LBP exist, both non-pharmacological (e.g. exercise) and pharmacological, making it difficult for clinicians to decide on appropriate management. However, treatment guidelines have recently been developed both in the US, by the American College of Physicians (ACP) and the American Pain Society (APS)[22,23], and in the UK, by the National Institute for Clinical Excellence (NICE)[24,25]. These guidelines advise a multimodal approach to LBP, with pharmacotherapy being the cornerstone of management. Pharmacotherapy will be the focus of the present review.

Despite the existence of treatment guidelines, complete eradication of pain is rare and combined pharmacological agents are increasingly used in an attempt to achieve the best results, particularly in the presence of a neuropathic pain component[26]. However, controversy exists regarding the role of combined pharmacotherapy in these more severely affected individuals, owing to a paucity of available data.

Pharmacotherapy itself presents a challenge in chronic LBP, because of the difficulty in balancing adequate pain relief with acceptable tolerability, and the vicious circle of insufficient efficacy, leading to dose increase, which is followed by unacceptable tolerability, and thus dose reduction, and insufficient efficacy[27]. Adverse drug reactions (ADRs)[28] and lack of efficacy, as well as analgesic tolerance, drive the vicious circle and may contribute to treatment discontinuation. The vicious circle concept applies to opioids in particular, but also to combination therapy[27].

The purpose of this systematic review is to evaluate evidence for the effectiveness of pharmacological monotherapy and combination therapy in chronic LBP, with specific reference to the management of nociceptive and neuropathic pain components. The review will focus principally on non-specific chronic LBP and nociceptive/neuropathic chronic LBP arising from causes that attract conservative pharmacological management (for example, degenerative disc changes with or without radicular pain that does not require surgery).

Methods for literature search

Studies were identified by means of a PubMed search using the following terms to identify articles published over the last 10 years investigating pharmacological treatments for

chronic LBP and including terms relating to the neuropathic component of back pain:

((“Back Pain”[Mesh] OR “Low Back Pain”[Mesh] OR “back pain”[All fields] OR “lumbago”[All fields] OR “lumbar”[All fields]) AND (“neuropathic”[All fields] OR “neuropathy”[All fields] OR “neurogenic”[All fields] OR “neuralgia”[All fields] OR “neuralgic”[All fields] OR “radicular”[All fields] OR “radiculopathy”[All fields] OR “nociceptive”[All fields] OR “myofascial”[All fields]) NOT “acute”[All fields] NOT (“Behavior Therapy”[Mesh] OR “Cognitive Therapy”[Mesh] OR “Surgical Procedures, Operative”[Mesh] OR “surgery”[Subheading] OR “Acupuncture Therapy”[Mesh]) AND (“2000/04/14”[PDAT]: “2010/04/13”[PDAT]) AND “humans”[MeSH Terms]) AND (“Review”[Publication Type] OR “Randomized Controlled Trial”[Publication Type] OR “Meta-Analysis”[Publication Type])

Non-English language papers were excluded, unless pertinent data could be gleaned from an English abstract.

This strategy identified 273 articles, the abstracts of which were hand searched to identify a subset with the specific focus of pharmacological treatment of chronic LBP of relevance to the current review. Nineteen studies on pharmacological management of chronic LBP (irrespective of the cause) were identified as relevant and were included in this review. A further 28 papers were identified from searching review reference lists and from the author’s own experience. The most frequently investigated agents were opioids (13 publications evaluating monotherapy and six publications evaluating combination therapy). According to the reported inclusion and exclusion criteria an assessment was made of the likely pain components studied. Seven publications examined principally nociceptive pain, 11 publications examined principally neuropathic pain and 29 publications examined pain due to both nociceptive and neuropathic components.

Causes of chronic low back pain

Differential diagnosis

Overall, 80–90% of patients with LBP are thought to experience pain arising from a nociceptive mechanical cause. In the majority of these patients (65–70%) the cause is unknown but assumed to arise from muscle strain or ligamentous injury, whereas in other patients there may be evidence of degenerative disc or joint disease, or vertebral fracture[13,29]. Pure neuropathic causes are thought to account for 5–15% of LBP, and include herniated intravertebral disc and spinal stenosis. However, note that this percentage is higher in the presence of a neuropathic pain component when chronic LBP is considered[14]. Non-mechanical spinal conditions such as cancer, infection and inflammatory arthritis account for a further 1–2%. The remaining cases are accounted for by referred visceral pain (e.g. gastrointestinal or renal disease; 1–2%) and other causes such as fibromyalgia (2–4%)[29].

Pain subtypes in non-specific chronic LBP

Chronic LBP arises from nociceptive and neuropathic mechanisms. Chronic LBP can therefore be classified as a mixed pain syndrome[14]. Nociceptive pain arises because of tissue damage or tissue-damaging stimuli, which leads to an inflammatory response[15,16]. In quality, it manifests itself as aching, dull or throbbing[30]. Examples of nociceptive pain include arthritis, exercise/sports injury, mechanical LBP and post-operative pain[15]. Nociceptive pain is usually an adaptive, short-lived response that resolves once the injury has healed[16].

Neuropathic pain, on the other hand, is defined as ‘pain arising as a direct consequence of a lesion or disease affecting the somatosensory system’[31]. Neuropathic pain quality can be paroxysmal (e.g. shooting, stabbing or electrical shock like pain), dysaesthetic (e.g. numbness) or associated with abnormal thermal sensations (e.g. burning or extreme cold). It may occur spontaneously, or in response to non-painful stimuli such as light touch, and moderate heat or cold (allodynia), or as an exaggerated response to painful stimuli (hyperalgesia)[14]. However, it is important to note that some features of neuropathic pain also occur in inflammatory nociceptive pain, such as inflammatory hyperalgesia[32]. In chronic LBP, the processes causing neuropathic pain include: mechanical nerve root compression from a herniated intravertebral disc (mechanical neuropathic root pain), damage to local nerve fibres within a degenerated disc (local neuropathic pain); and the effect of inflammatory mediators arising from a degenerated disc on nerve fibres (inflammatory neuropathic root pain)[14]. Unlike nociceptive pain, neuropathic pain tends to be maladaptive and chronic in nature[16]. However, there is evidence that repeated nociceptive stimuli can result in peripheral and/or central sensitization resulting in the transition from predominantly acute nociceptive to chronic pain with both nociceptive and neuropathic pain components[33].

Several screening questionnaires have been developed to attempt to identify patients with chronic LBP who may have a neuropathic component (reviewed in Cruccu and Truini[34]). These include the *Neuropathic Pain Questionnaire*[35], ID Pain[36], *PainDETECT questionnaire* (PD-Q)[17], the *Leeds Assessment of Neuropathic Symptoms and Signs* (LANSS) pain scale[20], the *Douleur Neuropathique en 4 Questions*[37] and the *Standardized Evaluation of Pain*[34]. PD-Q is the only questionnaire to be validated in patients with LBP. It rates graduation of pain, pain course pattern and radiating pain according to a 6-point scale, and has

demonstrated high sensitivity, specificity and accuracy in patients with chronic LBP. A score of ≥19 is strongly suggestive of a neuropathic pain component; a score between 13 and 18 is ambiguous but a neuropathic pain component may be present; and a score of ≤12 is suggestive of nociceptive pain[17]. However, despite the development of these assessment tools, distinguishing nociceptive from neuropathic pain in clinical practice remains difficult.

Estimates of the proportion of patients with a neuropathic component to their chronic LBP vary; the reported prevalence has been shown to range from 20% to as high as 55%[14,17–20]. The presence of a neuropathic pain component is associated with a higher pain intensity[17], a greater number and greater severity of comorbidities[17], reduced quality of life[38] and higher healthcare costs[21]. Indeed, one study estimated that healthcare costs in patients with chronic LBP were 67% higher in those with neuropathic pain versus those with nociceptive pain only[21]. These costs were attributable to a combination of high medical costs, together with loss of ability to work and, in some cases, the need for institutionalization[38].

Management of chronic low back pain

The management of chronic LBP comprises a combination of pharmacotherapy, physical therapy, and multidisciplinary approaches[24,39,40], but complete pain relief is rarely achievable. Therefore, pain management aims to reduce dysfunction and improve quality of life by reducing pain whilst minimizing associated ADRs[41].

Brief overview of non-pharmacological management of LBP

Whilst the focus of this review is not to consider non-pharmacological interventions in detail because these have been addressed in other recent publications[23], a brief summary will be provided to set the pharmacological management of chronic LBP within a holistic therapeutic context. Several non-pharmacological strategies are recommended in published guidelines for chronic LBP. Both NICE and ACP/APS guidelines emphasize the benefit of staying physically active[24,40]. NICE guidelines suggest a structured exercise programme, including aerobic activity, movement instruction, muscle strengthening, and postural control and stretching, for up to 12 weeks. NICE guidelines also recommend manual therapy (including spinal manipulation) and acupuncture for up to 12 weeks[24]. A combined physical and psychological treatment programme should be considered for patients in psychological distress who have received at least one less intensive treatment[24]. Similar recommendations have been made in the ACP/APS guidelines for chronic LBP: spinal manipulation, exercise therapy, massage, acupuncture, yoga, cognitive-behavioural therapy, progressive relaxation and intensive interdisciplinary rehabilitation[23].

However, most of the published data on these non-pharmacological interventions comes from studies in acute LBP; therefore it is difficult to draw conclusions on their benefit in the chronic setting. Evidence from Cochrane reviews suggests that exercise therapy relieves pain and improves function in chronic LBP[42], and post-treatment exercise may be of some benefit for preventing recurrence of LBP[43]. Moderate evidence suggests that, in the short- and intermediate-term, back schools (educating patients about the nature of their condition and how best to manage it) in an occupational setting are associated with pain reduction, improved function and improved return-to-work status[44–46].

Overview of pharmacological agents

For some patients, chronic LBP can be adequately managed with single-agent therapy. However, because as many as 55% of patients with chronic LBP have a neuropathic pain component, combination pharmacotherapy may be necessary[26].

Pharmacological agents available for the management of chronic LBP include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, antidepressants, anticonvulsants, topical treatments and others (e.g. muscle relaxants). Clinical data with these agents will be reviewed below.

Monotherapy

Paracetamol

Paracetamol (acetaminophen) possesses analgesic and anti-pyretic activity but not anti-inflammatory activity. It is thought to inhibit prostaglandin synthesis by acting on the cyclo-oxygenase (COX) enzymes[47]. In addition, paracetamol reinforces descending inhibitory pain pathways[48]. Paracetamol is recommended in both the NICE[24] and ACP/APS guidelines[40] as first-line treatment for chronic LBP. It is not recommended in guidelines for neuropathic pain[15].

No new data on the use of paracetamol as monotherapy in chronic LBP were identified by the literature search.

NSAIDs

NSAIDs target nociceptive pain, as inflammation is a prominent cause of nociception[15]. They are suitable for many patients with chronic LBP and are recommended in the NICE and ACP/ACS guidelines for patients in whom paracetamol has not been successful, provided the risk of ADRs is taken into consideration and managed appropriately[24,40]. However, NSAIDs are ineffective in

pain arising from neuropathic causes, and are therefore not recommended in neuropathic pain guidelines[15].

NSAIDs act on the COX-1 and COX-2 enzymes, inhibiting prostaglandin synthesis[49]. COX-2 inhibition blocks production of pro-inflammatory prostaglandins, while COX-1 inhibition blocks production of gastroprotective prostaglandins. Traditional NSAIDs inhibit both COX-1 and COX-2, while selective COX-2 agents inhibit COX-2 only[49]. Traditional NSAIDs are therefore associated with dyspepsia, ulcers and subepithelial haemorrhage[50] and are thus unsuitable for patients at risk of gastric complications, such as the elderly. For patients ≥45 years, NICE guidelines for non-specific LBP recommend an oral NSAID or a COX-2 inhibitor with co-prescription of a proton pump inhibitor (the latter for gastroprotection). Patients taking NSAIDs are also at risk of renal effects, most commonly peripheral oedema, which occurs as a result of salt retention[51]. Acute renal failure is observed in a small proportion of NSAID users[51]. It should be noted that NSAIDs are associated with a 42% relative increase in the incidence of serious cardiovascular events[52]. Indeed, the COX-2 inhibitor rofecoxib was withdrawn after an increased risk of cardiovascular events was observed in a chemoprevention trial in patients with a history of colorectal adenomas[53]. Naproxen has a relatively favourable cardiovascular risk profile and is therefore the most appropriate NSAID for patients at increased cardiovascular risk[52,54]. However, a recent review warned that all NSAIDs appear to be associated with some degree of gastrointestinal, cardiovascular and renal ADR risk[55]. Caution is therefore advised when prescribing NSAIDs to patients with pre-existing gastrointestinal or cardiovascular conditions[55].

The broad range of ADRs and estimated 16,000 NSAID-related deaths occurring annually[56] limit the use of NSAIDs in the chronic LBP setting. In light of the significant toxicities associated with NSAID use, the American Geriatric Society (AGS) has issued new guidelines for pain management in the elderly, which recommend that NSAIDs are used rarely, with extreme caution and in highly selected individuals[57]. Where used, they should be given at the lowest effective dose and for the shortest possible duration[57].

In the last 10 years, there have been only two original published research papers on the use of NSAIDs in chronic LBP, and both have been with selective COX-2 inhibitors.

In two 4-week, randomized, double-blind studies in 690 patients with chronic LBP, significant reductions in LBP intensity were observed with rofecoxib 25 mg using a visual analogue scale (VAS) from 0–100 mm (−13.50 mm relative to placebo; $p<0.001$) and rofecoxib 50 mg (−13.81 mm relative to placebo; $p<0.001$). The 50 mg dose of rofecoxib yielded no significant advantage over the 25 mg dose in terms of efficacy, and was associated with a slightly less favourable tolerability profile than the 25 mg dose[58]. Among the patients who achieved a meaningful analgesia (defined as ≥50% reduction in VAS pain intensity), the median time to onset was 2 days, and onset of perceptible ('a little') pain relief was 2 hours[59].

In contrast, 4 weeks' treatment with celecoxib 3–6 mg/kg failed to produce significant pain relief in patients with chronic LBP ($n=36$). However, a significant improvement was observed only in patients with a LANSS scale score of <12[60], suggesting that these agents may only be effective for nociceptive chronic LBP.

A meta-analysis by the Cochrane collaboration examined the use of NSAIDs in both acute and chronic LBP[61]. Sixty-five trials and a total of 11,237 patients were included in the analysis. NSAIDs were shown to be effective in chronic LBP without sciatica (i.e. patients without a neuropathic component), although the effect sizes were small. No differences in efficacy between NSAIDs were observed, but selective COX-2 inhibitors were associated with a reduced proportion of patients experiencing gastrointestinal side effects[61]. However, despite the reduced gastrointestinal risk, many COX-2 inhibitors have now been discontinued secondary to increased cardiovascular risk, and one of the few remaining drugs in this class, celecoxib, has relatively poor analgesic efficacy. Thus, the number needed to treat for the relief of acute pain at the recommended celecoxib dose of 200 mg was 4.2[62] versus 3.5 for paracetamol 500 mg[63].

Table 1 summarizes the included studies examining monotherapy of chronic LBP with the non-opioid analgesics paracetamol and NSAIDs.

Opioids

Opioids bind to opioid receptors in the central nervous system, modulating the pathways involved in the generation, transmission, and modulation of pain impulses and the experience of pain[39]. They are considered to be effective in nociceptive pain and moderately effective in neuropathic pain[64,65]. Tolerability issues with opioids limit their usefulness in clinical practice; ADRs are well known and a meta-analysis of 34 randomized controlled trials ($n=5546$) of opioid treatment in chronic non-malignant pain indicate that the commonest ADRs include dry mouth (25% of patients), nausea (21%), constipation (15%), dizziness (14%), drowsiness (14%), pruritis (13%) and vomiting (10%)[66]. In addition, older adults, who have more extensive degenerative LBP, are also more prone to experience ADRs such as constipation (30%), nausea (28%) and dizziness (22%) than younger adults[67].

The use of opioids in chronic non-malignant pain management remains controversial because of concerns surrounding development of analgesic tolerance and dependence in susceptible patients[68]. In addition, while the efficacy of opioids in the short-term management of

Table 1. Summary of identified studies examining monotherapy of chronic low back pain with non-opioid analgesics.

Reference	Main inclusion/exclusion criteria	Pain type	Trial design	Intervention(s) and dose	Principle outcome
Paracetamol					
No studies examining paracetamol monotherapy were identified					
NSAIDs					
Katz *et al.*, 2003[58]	18–75 years Chronic LBP Taking daily analgesics Patients with Quebec Task Force System Class 1[a] and Class 2[b] were eligible Chronic LBP due to known secondary cause excluded	Nociceptive	2 × 4-week, randomized, double-blind studies	Rofecoxib 25 mg ($n = 233$) OR Rofecoxib 50 mg ($n = 229$) OR Placebo ($n = 228$)	Significant reductions in LBP intensity scores (assessed using 0–100 mm VAS) were observed in both rofecoxib groups ($p < 0.05$); reductions were significantly greater than with placebo ($p < 0.001$)
Katz *et al.*, 2004[59]	As for Katz *et al.*, 2003[58]	Nociceptive	Assessment of onset of efficacy using data from Katz *et al.*, 2003[58]	As for Katz *et al.*, 2003[58]	Rates of meaningful pain relief (time to confirmed 50% reduction in pain and time to confirmed 'slightly' or 'not at all' bothersome pain) were significantly higher with rofecoxib 25 mg (60.4%) and rofecoxib 50 mg (58.4%) than with placebo (34.7%; $p < 0.001$)
Roelofs *et al.*, 2008[61]	Randomized controlled trials and double-blind studies of NSAIDs in non-specific LBP with or without sciatica	Mixed	Meta-analysis by Cochrane collaboration	65 trials ($n = 11,237$)	NSAIDs are effective for short-term symptomatic relief in chronic LBP without sciatica; however, effect sizes are small There is no evidence that one NSAID is more effective than another

LBP = low back pain; Mixed = mixed nociceptive and neuropathic pain; NSAIDs = non-steroidal anti-inflammatory drugs; VAS = visual analogue scale.
[a]Quebec Task Force system Class 1: pain without radiation to an extremity and without neurological signs.
[b]Quebec Task Force system Class 2: pain with radiation to an extremity, but not below the knee and without neurological signs.

nociceptive and neuropathic pain states is well established, their efficacy in pain states without a clear pathology, such as chronic LBP, is less certain, and studies are often of insufficient duration to establish long-term benefit[69,70]. Furthermore, meta-analyses and systematic reviews examining opioids in the chronic pain setting are limited by the absence of high-quality published trials.

Despite these limitations, opioids can be both effective and safe if used appropriately[71]. Thorough patient assessment, including medical and psychosocial history, and accurate diagnosis and analysis of comorbidity, are important components for identifying which patients will benefit most from opioid therapy. Careful consideration should also be given to which opioid is prescribed, as well as route of administration, dosing and monitoring[71]. A short-term trial is often necessary to establish whether opioid therapy is effective and safe in a specific patient, and recent studies have set out to identify the predictors of response to opioid therapy. In a secondary analysis using data from the Fentanyl International-26 study, a 13-month trial comparing transdermal fentanyl with sustained-release oral morphine, employment status and high doses of opioids were identified as the most influential factors affecting response (defined as ≥30% reduction in pain from baseline), with chi-squared values of 11.06 and 3.04, respectively[72]. After 1 month of treatment, lack of response was predictive of non-response, indicating that a 1-month trial may be sufficient to identify non-responders and to establish tolerability. Neuropathic pain components should not rule out a response to strong opioids, but may be useful for identifying patients who may have a poorer response to treatment[72]. Patients without a response after the 1-month trial may be eligible for higher doses or combination therapy.

Another determinant of poor response to opioids is the presence of psychopathology; in patients with discogenic LBP, analgesia with intravenous morphine was shown to be 37–63% lower in patients with high *versus* low psychopathology[73]. In a further analysis from this study, placebo response rates were significantly higher in patients with moderate (23.4%) or high (23.5%) levels of psychopathology than in those with low psychopathology (7.7%; $p<0.05$)[74].

Regarding specific studies examining opioid monotherapy of chronic LBP, two enriched-enrolment, placebo-controlled, randomized-withdrawal design trials examining oxymorphone extended release (ER) were identified, together with a retrospective pooled analysis of these same two trials. A further two placebo-controlled trials comparing oxymorphone ER and oxycodone controlled release (CR) and an open-label study comparing transdermal fentanyl and sustained-release oral morphine were also identified.

The first enriched-enrolment, placebo-controlled, randomized-withdrawal design study of oxymorphone ER was performed in opioid-experienced patients ($n=250$) with moderate to severe nociceptive chronic LBP; patients with radiculopathy were specifically excluded[75]. Patients were first stabilized on oxymorphone ER until average VAS pain intensity was reduced to <40 mm. Stabilized patients ($n=143$) were then randomized to switch to placebo or to continue with oxymorphone ER. A significantly greater increase in pain intensity was observed in patients switched to placebo (+31.6 mm) than in those continuing with oxymorphone ER (8.7 mm; $p<0.0001$ for difference *versus* placebo). In addition, patients switched to placebo were eight times more likely to discontinue treatment due to lack of efficacy than patients switched to oxymorphone ER ($p<0.001$). The rate of discontinuation due to adverse events (AEs) was similar between treatment groups (oxymorphone ER: 11%; placebo: 10%)[75]. The second study employed a similar design but was performed in opioid-naïve patients with mixed nociceptive and neuropathic presentations ($n=205$)[76]. After stabilization on oxymorphone ER a 46.7 mm reduction in pain intensity was observed. A significantly greater increase in pain intensity was observed in patients switched to placebo (+26.9 mm) than in those continuing with oxymorphone ER (10 mm; $p<0.0001$ for difference *versus* placebo). Patients in the placebo group discontinued due to lack of efficacy significantly sooner than those in the opioid group. Discontinuation rates due to AEs were approximately 8% in each treatment group, and no unexpected ADRs were reported[76].

These findings were confirmed in a retrospective pooled analysis of the Hale *et al.* (2007) and Katz *et al.* (2007) trials in a total of 347 patients with moderate to severe chronic LBP who received oxymorphone ER titrated to a stable, tolerable effective dose[77]. Significant differences between oxymorphone ER and placebo were observed for VAS pain scores ($p<0.001$), which were not affected by age, gender or prior opioid use. The rate of discontinuation due to lack of efficacy was significantly higher with placebo than with oxymorphone ER ($p<0.001$), and was similar between oxymorphone ER-treated opioid-naïve and opioid-experienced patients. AEs were significantly more frequent with oxymorphone ER than with placebo ($p=0.03$) and were typical of opioid therapy[77].

Two studies have conducted head-to-head comparisons between opioids in patients with chronic LBP comparing 10 to 110 mg of oxymorphone extended release (ER) with 20 to 220 mg of oxycodone controlled release. In the first study of patients with moderate to severe chronic nociceptive LBP ($n=213$), the reduction in VAS pain intensity was significantly greater with both oxymorphone ER and oxycodone CR than with placebo ($p=0.0001$), and both active treatments were considered to be safe[78]. The second study was a large ($n=680$) open-label, randomized multicentre study in patients with chronic LBP who were naïve to strong opioids. Patients received transdermal fentanyl (25 μg/hour every 72 hours) or sustained-release oral

morphine (30 mg every 12 hours) for 13 months. The study did not exclude patients with radiculopathy, therefore, the recruited sample is likely to be comprised of patients with both nociceptive and neuropathic pain. The two agents provided similar pain relief but constipation was significantly more frequent with morphine than with fentanyl treatment[79].

Controversy exists as to whether opioids are effective for neuropathic chronic LBP in addition to nociceptive pain because very few studies have specifically examined subpopulations of patients. Indeed a recent Cochrane review was unable to perform such sub-analyses owing to insufficient data[70]. A prior meta-analysis examining the use of opioids in chronic non-cancer pain, in which 80% of patients had nociceptive pain from osteoarthritis, rheumatoid arthritis or back pain and 12% had neuropathic pain from post-herpetic neuralgia, diabetic neuropathy or phantom limb, reported that opioids were more effective than placebo for both nociceptive and neuropathic pain[65]. However, it may not be valid to extrapolate opioid effectiveness in neuropathic pain from other causes to effectiveness in radiculopathy. The only study specifically examining opioid effectiveness (oral morphine) in patients with radicular pain was small ($n = 55$), experienced a very high dropout rate (number completing = 28) and failed to demonstrate any significant difference compared with placebo on ratings of leg pain[80]. Further large-scale randomized controlled trials will be required to resolve this issue.

As well as focusing on pain *intensity* with analgesic medication, recently there has been a great deal of interest in the use of pain *quality* as a measure of treatment efficacy. A secondary analysis of a clinical trial in 140 patients with chronic LBP reported that different opioids affect different pain qualities[81]. Patients were switched from opioid therapy to an equivalent dose of oxymorphone ER, which was then titrated to a stable dose. Oxymorphone ER was shown to have the greatest impact on the intense, unpleasant, deep, aching and sharp items of the *Pain Quality Assessment Scale* (PQAS), as well as the PQAS Paroxysmal and Deep scales. These results suggest that pain treatment can be targeted according to the type of pain experienced by the patient[81].

High rates of discontinuation among patients receiving opioids are reported in the literature, limiting clinical utility. One meta-analysis reported a dropout rate of 33%, despite a mean treatment duration of just 5 weeks[65]. In a meta-analysis of 26 studies investigating opioid therapy in chronic non-cancer pain, discontinuation due to AEs was reported in 22.9%, 12.1% and 8.9% of patients receiving oral, transdermal and intrathecal opioid therapy, respectively, and discontinuation due to insufficient pain relief was reported in 10.3%, 7.6% and 5.8% of patients, respectively[82]. For those who do continue long-term opioid therapy, evidence suggests these agents do provide clinically significant pain relief. The benefit of opioids for improving quality of life, however, remains to be established[82].

Tramadol is a centrally acting analgesic that activates the μ-opioid receptor and inhibits serotonin and noradrenaline reuptake[83,84]. Tramadol is a step II opioid for moderate to severe pain, according to the World Health Organization pain relief ladder[85]. Evidence suggests that tramadol reduces not only nociceptive, but also neuropathic pain[86]. The most commonly reported ADRs with tramadol are nausea, headache, somnolence and dizziness[87].

An enriched-enrolment, placebo-controlled, randomized-withdrawal design study examined the rate of therapeutic failure ('inadequate pain relief') among patients with chronic LBP ($n = 254$) receiving tramadol 200–400 mg/day or placebo[87]. The exclusion criteria were a history of back surgery within 5 years, neurologic deficits in the lower extremities, severe pain in a location other than the low back, disk herniation, spondylolisthesis and spinal stenosis. It is likely, therefore, that the selected patients were largely experiencing nociceptive pain. The Kaplan–Meier cumulative discontinuation rate at day 28 was significantly lower with tramadol (20.7%) than with placebo (51.3%, $p \leq 0.0001$), and <5% of patients discontinued due to an AE. At the end of treatment, the following parameters were significantly lower ($p < 0.05$) with tramadol than with placebo: VAS pain score; sensory *Short-Form McGill Pain Questionnaire* (SF-MPQ) score; affective SF-MPQ score; total SF-MPQ score; *Roland Disability Questionnaire* (RDQ) score; and the proportion of patients with a poor outcome[87].

No further data on the use of other opioids with additional mechanisms of action as monotherapy for chronic LBP were identified by the literature search.

Table 2 summarizes the included studies examining monotherapy of chronic LBP with opioid analgesics.

Antidepressants

Antidepressants target the neuropathic component of chronic LBP. Their analgesic properties are independent of their antidepressant properties and arise through a number of mechanisms in the central and peripheral nervous systems, including: noradrenaline and serotonin neurotransmission by reuptake inhibition; actions on opioid, adrenergic, serotonin, gamma-aminobutyric acid and N-methyl-D-aspartate receptors; ion channel activation; and effects on inflammatory cytokines[88]. Historically, studies investigating the utility of antidepressants in chronic LBP have mainly used the tricyclic antidepressants (TCAs), although in recent years other agents have also been investigated. ADRs typically observed with TCAs are linked to their anti-cholinergic actions and include sedation, dry mouth, blurred vision, weight gain and urinary retention[88].

Table 2. Summary of identified studies examining monotherapy of chronic low back pain with opioid analgesics.

Reference	Main inclusion/exclusion criteria	Pain type	Trial design	Intervention(s) and dose	Principle outcome
Opioids					
Allan *et al.*, 2005[79]	Adults with chronic LBP requiring strong opioid treatment	Mixed	Fentanyl International-26 study: 13-month, open-label, randomized, parallel group study	Transdermal fentanyl patch delivering 25 μg/hour, with patches replaced every 72 hours ($n=338$) OR Sustained-release morphine 30 mg every 12 hours ($n=342$) Doses were titrated according to the pain	Transdermal fentanyl and sustained-release morphine provided similar levels of pain relief (assessed using 0–100 mm VAS), however transdermal fentanyl was associated with a lower incidence of constipation
Kalso *et al.*, 2007[72]	Adults with chronic LBP requiring strong opioid treatment	Mixed	Secondary analysis using data from the Fentanyl International-26 study[79]	Transdermal fentanyl patch delivering 25 μg/hour, with patches replaced every 72 hours ($n=338$) OR Sustained-release morphine 30 mg every 12 hours ($n=342$) Doses were titrated according to the pain	Neither baseline pain type and severity, nor patient characteristics, can be used to identify responders to opioid treatment For most patients, a 1-month trial is adequate to determine response and tolerability
Hale *et al.*, 2005[78]	18–75 years Moderate to severe chronic LBP Treated with stable dose of opioids for ≥3 consecutive days before screening Patients achieving a stable dose of oxymorphone ER or oxycodone CR during titration period eligible for treatment period	Mixed	Multi-centre, randomized trial: 7–14-day double-blind titration period, 18-day treatment period	*Titration period* Oxymorphone ER 10–110 mg ($n=166$) OR Oxycodone CR 20–220 mg ($n=164$) *Treatment period* Current treatment at stable dose (oxymorphone ER: $n=80$; oxycodone CR: $n=80$) OR Placebo ($n=75$)	Patients were rapidly titrated and stabilized (oxymorphone ER: 40 mg/12 hours; oxycodone CR: 80 mg/12 hours, suggesting a 2:1 potency ratio for oxymorphone ER: oxycodone CR) Reductions in pain intensity (assessed using 0–100 mm VAS) were significantly greater with oxymorphone ER than with placebo ($p=0.0001$) No significant difference in efficacy was observed between oxymorphone ER and oxycodone CR
Katz *et al.*, 2007[76]	≥18 years Moderate to severe chronic LBP Opioid-naïve Pain intensity score ≥50 mm (0–100 mm VAS)	Mixed	EERW (open-label titration period) followed by 12-week double-blind treatment period	*Titration period* Oxymorphone ER titrated to stable tolerable dose ($n=205$) *Treatment period* Current treatment at stable dose ($n=105$) OR Placebo ($n=100$)	Mean pain intensity (0–100 mm VAS) decreased from 69.4 mm pre-titration to 22.7 mm post-titration ($p<0.0001$) Rates of discontinuation due to lack of efficacy were significantly higher with placebo than with oxymorphone ER ($p<0.0001$) Pain intensity increased significantly more with placebo (+26.9) than with oxymorphone ER (+10.0; $p<0.0001$)

(*continued*)

Table 2. Continued.

Reference	Main inclusion/exclusion criteria	Pain type	Trial design	Intervention(s) and dose	Principle outcome
Hale *et al.*, 2007[75]	>18 years Moderate to severe chronic LBP Receiving stable around-the-clock opioid pain medication (equivalent to ≥60 mg/day of oral morphine) for 2 weeks before screening Patients with radiculopathy excluded	Nociceptive	EERW study (open-label titration period) followed by a 12-week double-blind treatment period	*Titration period* Patients were switched to equianalgesic dose of oxymorphone ER and up-titrated to a stable tolerable dose ($n=250$) *Treatment period* Stabilized patients were randomized to: Oxymorphone ER ($n=70$) OR Placebo ($n=73$)	Increase in mean pain intensity (assessed using 0–100 mm VAS) was significantly greater with placebo (31.6 mm) than oxymorphone ER (8.7 mm; $p<0.0001$) Rates of discontinuation due to lack of efficacy were 8 times greater with placebo than oxymorphone ER ($p<0.001$)
Peniston and Gould, 2009[77]	Retrospective pooled analysis of Hale *et al.*, 2007[75] and Katz *et al.*, 2007[76]	Mixed	2 × EERW (open-label titration period) followed by 12-week titration period	Interventions as for Hale *et al.*, 2007[75] and Katz *et al.*, 2007[76] Pooled study population: $n=347$	Least-squares mean difference in pain intensity (assessed using 0–100 mm VAS) was significantly different between oxymorphone ER and placebo at study completion ($p<0.001$) Differences were not affected by age, gender or prior opioid use
Gould *et al.*, 2009[81]	Opioid-experienced patients with chronic LBP enrolled in Hale *et al.*, 2007[75]	Nociceptive	Secondary analysis using data from Hale *et al.*, 2007, a 12-week, double-blind, randomized study[75]	*Titration period* Patients were switched to an equianalgesic dose of oxymorphone ER, up-titrated by 10 mg/12 hours every 3 days to a stable tolerable dose ($n=140$) *Treatment period* Patients were randomized to oxymorphone ER or placebo for 12 weeks ($n=65$; *n* numbers for treatment groups separately not given)	Oxymorphone ER has the greatest effect on intense, unpleasant, deep, aching and sharp items on the Pain Quality Assessment Scale Pain descriptor measures can be used to evaluate effects of treatment on different pain qualities, enabling pain treatment to be targeted according to the type of pain
Wasan *et al.*, 2005[73]	21–70 years Chronic discogenic back pain (≥6 months), with or without radicular pain Pain intensity ≥4 (0–10 VAS) No back surgery in previous year Patients stratified according to presence of psychopathology: low ($n=20$), moderate ($n=20$) or high ($n=20$)	Mixed	Double-blind, 2-way crossover study	Single intravenous infusion of morphine 4–6 mg dosed by ideal body weight AND Placebo ($n=60$; *n* numbers by treatment group not given)	Rates of total pain relief (assessed using 0–10 Numerical Rating Scale of Pain Relief) during morphine analgesia were significantly lower in patients with high (41.0%) than low (65.1%) psychopathology ($p=0.026$) Rates of total pain relief during placebo analgesia were significantly higher in patients with high (23.5%) than low (7.7%) psychopathology ($p=0.03$) High levels of psychopathology were thus associated with reduced opioid analgesia
Wasan *et al.*, 2006[74]	As for Wasan *et al.*, 2005[73]	Mixed	Analysis of placebo analgesia using data from Wasan *et al.*, 2005[73], a double-blind 2-way crossover study	As for Wasan *et al.*, 2005[73]	High and moderate levels of psychopathology were associated with increased placebo analgesia

Furlan *et al.*, 2006[65]	Randomized trials of chronic non-cancer pain (>6 months) investigating any opioid (oral, transdermal routes or rectal suppositories)	Mixed (nociceptive pain: 80% of patients; neuropathic pain: 12%; fibromyalgia: 7%; mixed pain: 1%)	Meta-analysis	41 trials included ($n = 6019$)	Weak and strong opioids are more effective than placebo in chronic non-cancer pain Other agents provide better functional outcomes Strong opioids provide better pain relief than other agents Discontinuation from opioid therapy is common
Deshpande *et al.*, 2007[70]	Randomized controlled trials assessing use of opioids (monotherapy or combination therapy) for ≥4 weeks in adults with chronic LBP with or without radiating symptoms to the legs and without failed back surgery syndrome Studies included if they compared non-injectable opioids to other treatments Patients with cancer, infections, inflammatory arthritic conditions and compression fractures excluded. Comparisons between opioids excluded	Mixed	Meta-analysis by Cochrane collaboration	4 studies included (placebo-controlled trials [3 studies]: $n = 908$; active comparator trials [1 study]: $n = 36$)	Few high-quality studies on use of long-term opioids in chronic LBP exist Benefit of opioids in chronic LBP remains questionable
Noble *et al.*, 2010[82]	Prospective, randomized controlled trials and pre-post case series (>10 patients) investigating efficacy of opioid treatment (≥6 months) for chronic non-cancer pain	Mixed	Meta-analysis by Cochrane collaboration	26 studies with 27 treatment groups ($n = 4893$)	Discontinuation due to AEs or insufficient pain relief is common during long-term opioid therapy Patients who continue opioid therapy long-term experience clinically significant pain relief
Opioids with more than one mechanism of action					
Schnitzer *et al.*, 2000[87]	25–75 years Chronic LBP Open-label period: pain score ≥4 cm (1–10 cm VAS) Double-blind period: patients who reported experiencing enough pain relief to consider taking their medication Protocol was amended to allow inclusion of patients with successful back surgery >5 years previously Patients with neurological deficits in extremities, severe pain in a location other than the back, disk herniation, spondylolisthesis or spinal stenosis excluded	Mixed	EERW (3-week open-label, titration phase) followed by 4-week randomized, double-blind treatment period	*Open-label period* Tramadol 50 mg (with up-titration to stable tolerable dose [max 400 mg]) ($n = 380$) *Double-blind period* Tramadol 200–400 mg/day ($n = 127$) OR Placebo ($n = 127$)	Time to therapeutic failure (inadequate pain relief) was significantly longer with tramadol than placebo Cumulative discontinuation rate due to therapeutic failure was significantly lower with tramadol (20.7%) than with placebo (51.3%; $p \leq 0.0001$) Mean pain scores (10 cm scale) were significantly lower with tramadol (3.5 cm) than with placebo (5.1 cm; $p \leq 0.0001$)

AE = adverse event; CR = controlled release; EERW = enriched-enrolment randomized-withdrawal; ER = extended release; LBP = low back pain; Mixed = mixed nociceptive and neuropathic pain; VAS = visual analogue scale.

Several meta-analyses and systematic reviews have reported small benefits for antidepressants, and thus TCAs are recommended in the NICE guidelines for patients with chronic LBP who have experienced insufficient pain relief with other agents[24]. A meta-analysis by Salerno *et al.* (2002) examined nine randomized controlled trials (RCTs) considered to be of moderate quality in the treatment of chronic back pain, which also included neck pain as well as LBP ($n = 504$). Antidepressants significantly reduced pain compared with placebo although the benefit was small (standardized mean difference: 0.41; 95% confidence interval [CI]: 0.22–0.61), but without effect on functional status[89]. In a systematic review by Staiger *et al.* (2003), a mild to moderate reduction in pain relief was noted for antidepressants that inhibit noradrenaline reuptake (amitriptyline, imipramine, nortriptyline, maprotiline), but not for those that do not (trazodone, paroxetine)[90]. No impact on functional status was observed[90]. A subsequent Cochrane review of 10 placebo-controlled antidepressant trials, however, reported that "there is no clear evidence that antidepressants are more effective than placebo in the management of patients with chronic LBP"[91].

The majority of original research papers published in the last 10 years have failed to show a benefit for antidepressants in chronic LBP. In a comparison of morphine, nortriptyline and their combination, nortriptyline was shown to be ineffective for reduction of leg pain scores in patients with sciatica ($n = 55$), a surprising finding given the efficacy of TCAs in other neuropathic syndromes, including painful diabetic neuropathy and postherpetic neuralgia[80]. Overall, 68% of nortriptyline patients reported an AE, most commonly dry mouth or constipation[80]. A sustained-release formulation of the noradrenaline and dopamine reuptake inhibitor bupropion failed to show any benefit over placebo in patients with chronic LBP, although the majority of patients (41/44) had pain of a non-neuropathic origin in this study[92].

Data on the efficacy of the serotonin and noradrenaline reuptake inhibitor duloxetine in chronic LBP are conflicting. In a placebo-controlled study ($n = 404$), the reduction in average weekly pain (measured on a 0–10 Likert scale) was significantly greater with duloxetine at doses of 60 mg than with placebo from weeks 3–11 ($p < 0.05$), but this difference was not maintained through to study endpoint (week 13)[93]. Significant improvements in several pain scales were also observed, including the *Patient Global Impression of Improvement* (PGI-I), *Roland Morris Disability Questionnaire* (RMDQ-24), *Brief Pain Inventory* (BPI)-average pain and BPI-average interference. The proportion of patients experiencing ≥30% reduction in average weekly pain was significantly greater with duloxetine 120 mg (57.8%) than with placebo (43.4%; $p = 0.033$), although no differences were observed between duloxetine 20 mg (41.1%) or 60 mg (53.6%) and placebo. No significant differences were observed in the proportion of patients achieving ≥50% reduction in average weekly pain. The proportion of patients discontinuing due to AEs was significantly higher with duloxetine 120 mg (24.1%) than with placebo (8.5%)[93]. These findings contrast with two further placebo-controlled studies, in which duloxetine 60 mg was associated with significantly greater reductions in BPI average pain scale score than placebo after 12[94] and 13[95] weeks' treatment. They also contrast with findings from an extension study ($n = 181$), in which the effect of duloxetine on pain reduction was maintained (and reduced further) during the 41-week follow-up period[96].

In a placebo-controlled trial of patients with chronic LBP and depressive symptoms ($n = 92$), 56 days' treatment with the selective serotonin reuptake inhibitor paroxetine 20 mg did not significantly improve depression, pain or disability compared with placebo[97]. In addition, no direct relationship between pain and depression was observed in this study; associations were entirely mediated by disability and illness attitudes and were lost when these factors were controlled[97]. It should be noted that SSRI use is limited by ADRs, including sexual dysfunction, weight gain and sleep disturbance as reviewed by Ferguson[98].

Anticonvulsants

The newer anticonvulsant agents pregabalin and gabapentin target the neuropathic component of chronic LBP. They exert their analgesic effects by binding to the α2-δ subunit of N-type voltage-gated calcium channels[99] thereby modulating pathologically enhanced neurotransmission in the central terminals of primary afferent neurons. The main ADRs with these agents include somnolence, dizziness, weight gain and peripheral oedema, and caution is advised in patients with renal insufficiency[41]. Gabapentin also demonstrates a complicated titration scheme; typically, treatment is initiated at 100–300 mg/day and uptitrated in 100–300-mg increments every 3–7 days according to tolerability, to a target dose of 1800–3600 mg/day as three divided doses[15]. An adequate trial of gabapentin comprises 6–8 weeks to enable titration and a further 1–2 weeks at the maximum tolerated dose[15].

There is no evidence to support the use of pregabalin as a monotherapy for treatment of chronic LBP. In two randomized trials, the reduction in weekly mean pain score (as measured by a patient daily pain diary) observed with pregabalin was not significantly greater than that observed with placebo[100]. Furthermore, when administered as a monotherapy to patients with treatment-refractory neuropathic pain, including those with chronic LBP (mostly due to spinal stenosis, failed back surgery or radiculopathy), pregabalin provided significantly less pain relief and a poorer quality of life when compared with either

oxycodone CR alone or the combination of oxycodone CR and pregabalin[101].

Results from a pilot study ($n = 55$) with gabapentin suggested this agent may be of some value in patients with lumbar spinal stenosis[102]. Significantly greater improvements in walking distance, pain scores and recovery of sensory deficit were observed with gabapentin (900–2400 mg) than with standard treatment (therapeutic exercises, lumbosacral corset with steel bracing and NSAIDs)[102]. Gabapentin also demonstrated efficacy in the treatment of neuropathic pain in patients with spinal cord injury[103]. Patients received gabapentin at doses of 900–3600 mg for 4 weeks. Significant improvements from baseline were observed with gabapentin with respect to: VAS pain intensity; all pain descriptors except the itchy, sensitive, dull and cold types; and quality of life. Gabapentin was also significantly more effective than placebo for all of these outcomes.

Promising efficacy results were reported for topiramate (50–400 mg) in patients ($n = 42$) with chronic lumbar radicular pain. However, 11 patients (10 of which were in the topiramate group) discontinued from the study due to AEs, including sacral paraesthesias, nausea and anorexia, sedation and amnesia, depression and anxiety, and rash[104]. On the basis of a relatively poor benefit–risk ratio in chronic lumbar radiculopathy, the authors advised that topiramate is at best marginally effective in patients who can tolerate it, and should only be considered as a second-line treatment for patients in whom other agents have not been effective[104].

Topical preparations

Topical preparations such as the lidocaine 5% plaster are recommended for management of localized peripheral neuropathic pain such as post-herpetic neuralgia and diabetic polyneuropathy[41]. However, it is of note that the only registered indication for the lidocaine 5% plaster is post-herpetic neuralgia. The analgesic effects of the lidocaine plaster are thought to arise via a reduction of aberrant firing of sodium channels in damaged pain fibres situated directly under the plaster with the quantity of lidocaine absorbed being small enough (<5%) to avoid systemic effects or local anaesthesia[105]. Mild skin reactions are the most common AE observed with the lidocaine plaster[106].

The efficacy of lidocaine 5% plaster in patients with chronic LBP was examined in a study of 40 patients. Overall, 63% of patients reported a significant clinical effect of lidocaine plaster. In particular, lidocaine plaster decreased the neuropathic characteristics of pain, an effect that was maintained after finishing treatment[107]. In a second study, add-on therapy with the lidocaine 5% patch (up to 4 patches daily for 2 weeks) significantly ($p < 0.001$) improved pain intensity and relief (as measured by the BPI) in patients with LBP of non-radicular origin (LBP was chronic in 109/131 patients)[108]. Significant improvements in the BPI composite score for pain interference with quality of life and Beck Depression Inventory Score were also observed ($p < 0.0001$)[108]. It should be noted that the use of the lidocaine plaster in chronic LBP is not indicated in the summary of product characteristics; however, given the efficacy reported in the above two studies, this off-label indication warrants further investigation.

Another topical preparation, containing capsicum, has also demonstrated efficacy in chronic LBP. In 154 patients with chronic non-specific LBP, response rates (≥30% reduction in pain) after 3 weeks were significantly higher in the capsicum plaster group (60.8%) than in the placebo group (42.1%; $p = 0.0219$)[109]. However, improvements in total movement and disability were small and not significantly greater than with placebo[109]. Given, the relative lack of systemic side effects with these topical agents, further studies investigating their use as first-line treatments are required.

Other agents

Muscle relaxants include benzodiazepines, non-benzodiazepines and anti-spasticity agents. A Cochrane review concluded that muscle relaxants were effective for alleviating symptoms in chronic LBP, but that drowsiness, dizziness and other AEs were frequent[110]. The risk of long-term dependence is also a concern[110]. While muscle relaxants are recommended in the acute setting, their use is not recommended for the management of chronic LBP[40].

Several other agents have been investigated in chronic LBP, all of which have been studied in patients with lumbar spinal stenosis. The efficacy of the vasodilatory prostaglandin E1 derivative limaprost for improving quality of life was examined in a randomized controlled trial in 79 patients with symptomatic lumbar spinal stenosis, in which relative ischaemia of neural tissue is thought to occur[111]. Improvements in the Short Form 36 items Physical Functioning, Role Physical, Bodily Pain, Vitality and Mental Health were significantly greater with limaprost than with the comparator, the NSAID etodolac. Limaprost appeared to be most effective in patients with mild symptoms. No serious AEs were reported[111]. In a second randomized controlled trial in lumbar spinal stenosis, a nasal preparation of salmon calcitonin failed to show any significant benefit over placebo in terms of the *Oswestry Disability Index* score, VAS for leg pain, and walking distance[112]. In patients with degenerative lumbar spinal stenosis ($n = 152$), methylcobalamin (a form of vitamin B12) 0.5 mg three times daily plus conventional management did not yield any additional improvement in pain or in neurological signs compared with conventional management alone (with the exception of neurogenic

claudication, which was significantly improved in the active treatment group)[113].

Table 3 summarizes the included studies examining monotherapy of chronic LBP with antidepressants, anticonvulsants, topical preparations and other agents.

Combination therapy

Chronic LBP is thought to arise as a result of both nociceptive and neuropathic mechanisms[114]. Therefore, targeting the different mechanisms of pain by combining agents with different mechanisms of action is a rational approach to management of chronic LBP.

Guidelines recommend combination therapy for the general management of neuropathic pain arising from a number of different causes as an option for patients in whom monotherapy has failed[15,41]. As well as improving analgesia, combination therapy has also been shown to reduce drug consumption of the single drug[60,101]. Fixed-dose combinations are likely to be associated with greater adherence than free combinations.

However, combination therapy is associated with some limitations. One such limitation is ADRs, which help to drive the vicious circle outlined in the Introduction[27]. These can, to some extent, be overcome by initiating treatment at low doses and slowly escalating the dose to maximum analgesia or intolerable ADRs[15]. Other considerations with combination therapy include the potential for drug interactions; specific combinations of agents must, therefore, be evaluated empirically[26]. A further limitation relates to free combinations of analgesics and the difficulty in maintaining the dose ratio within the ideal range for balanced efficacy and tolerability[115]. Fixed-dose combinations can overcome this limitation.

Very few studies are available investigating the value of combination therapy for neuropathic pain components specifically in patients with chronic LBP. Most of the available studies have investigated combinations comprising an opioid plus another agent.

The only study to examine a non-opioid combination investigated the efficacy of a free combination of celecoxib plus pregabalin in a mixed population of patients with chronic LBP ($n = 36$)[60]. Combination therapy was associated with significantly greater reductions in pain, and a similar frequency of AEs, compared with either celecoxib or pregabalin alone ($p \leq 0.001$). Mean drug consumption of the single drugs was significantly lower with combination therapy than with pregabalin ($p < 0.05$)[60].

Gatti *et al.* (2009) examined the efficacy of a fixed-dose combination of an opioid plus paracetamol in patients with multimodal, chronic non-malignant pain. In this prospective observational study, the efficacy of 6 weeks' treatment with low-dose oxycodone plus paracetamol was evaluated using the *Pain Management Index*[116]. Patients were stratified according to the presence of prevalent osteoarticular pain ($n = 78$) or prevalent neuropathic pain ($n = 72$). Combination therapy was associated with an improvement in pain in the majority of compliant patients, although its benefit in patients with neuropathic pain was less marked[116].

One study has investigated a free opioid–antidepressant combination. In 61 patients with sciatica, the combination of morphine and nortriptyline failed to reduce average leg pain scores or any other leg or back pain scores, and 89% of patients receiving combination treatment reported an AE, most commonly constipation[80].

Two studies have examined the benefit of an opioid plus pregabalin. In the first study, 409 patients with treatment-refractory neuropathic pain (most commonly due to radiculopathy) received CR oxycodone plus pregabalin in free combination for 90 days[101]. Treatment was initiated at the doses recommended for their condition and up-titrated to achieve the optimal analgesia–tolerability ratio. Pain relief was faster and more substantial with combination therapy than with pregabalin monotherapy. Improvements in quality of life (as measured by the BPI) were significantly greater with combination therapy than with the respective monotherapies ($p = 0.0009$). Combination therapy displayed a superior safety profile to both monotherapies and was associated with a 22% reduction in CR oxycodone dose. The rate of discontinuation due to AEs was lower with combination therapy (5.9%) than with CR oxycodone monotherapy (10.4%) or with pregabalin monotherapy (19.0%). The proportion of patients reporting no AEs was 45.1%, 42.2% and 34.8%, respectively. Constipation was the most common AE with combination therapy[101]. The second study, investigating the benefit of a free combination of buprenorphine plus pregabalin in patients with chronic LBP, demonstrated that combination therapy yielded significantly greater reductions in 0–100 mm VAS scores than buprenorphine monotherapy ($p < 0.01$)[117].

Finally, two studies have examined the benefit of tramadol plus paracetamol in a fixed combination in chronic LBP. In the first study ($n = 318$), 3 months' treatment with tramadol 37.5 mg/paracetamol 325 mg yielded significantly greater improvements in pain VAS score ($p = 0.015$) and Pain Relief Rating Scale score ($p < 0.001$) than placebo[118]. Significant improvements were also observed for RDQ scores, several of the SF-MPQ items, and the Role-Physical, Bodily Pain, Role-Emotional, Mental Health, Reported Health Transition and Mental Component items of the *Short Form 36* (SF 36; all $p < 0.05$). The rates of discontinuation due to insufficient pain relief were significantly lower with tramadol plus paracetamol (22.1%) than for placebo (41.0%; $p < 0.001$) and the proportion of patients and investigators rating treatment as 'good' or 'very good' was higher with combination therapy than with placebo ($p < 0.001$ for patients; $p = 0.002$ for investigators). AEs were, however,

Table 3. Summary of identified studies examining monotherapy of chronic low back pain with antidepressants, anticonvulsants, topical preparations and other agents.

Reference	Main inclusion/exclusion criteria	Pain type	Trial design	Intervention(s) and dose	Principle outcome
Antidepressants					
Katz *et al.*, 2005[92]	≥18 years Chronic LBP Patients who had received prior antidepressant treatment (except for single trial of 1 antidepressant medication for chronic LBP) were excluded	Mixed (non-neuropathic pain: $n=41$; neuropathic pain: $n=3$)	16-week single-centre randomized, 2-way crossover study	Bupropion SR (150 mg od for 3 days, 150 mg bid until end of sixth week, 150 mg od for seventh week) (bupropion first: $n=26$) AND Placebo (placebo first: $n=28$)	No significant difference between bupropion SR and placebo were observed for daily and weekly pain scores (assessed using 0–10 numerical rating scale), MPQ Present Pain Intensity scale ratings and pain relief ratings
Dickens *et al.*, 2000[97]	18–65 years Chronic LBP (majority of patients had simple non-specific LBP) Significant depressive symptoms (Montgomery Asberg Depression Rating Scale score ≥16) Significant disability in daily tasks (Oswestry Disability Index ≥30%)	Mixed	56-day placebo-controlled study	Paroxetine 20 mg ($n=44$) OR Placebo ($n=48$)	Significant improvements in depression, pain and disability were not observed with paroxetine compared with placebo Patients taking paroxetine were more likely to reduce concomitant analgesic medication No direct relationship between pain and depression was observed
Skljarevski *et al.*, 2010[94]	Adults with chronic non-neuropathic LBP Pain intensity ≥4 BPI score	Nociceptive	12-week randomized, double-blind study	Duloxetine 60 mg OR Placebo ($n=401$; n numbers by treatment group not given)	Significantly greater reductions in BPI mean pain scores were observed with duloxetine compared with placebo ($p \leq 0.001$)
Skljarevski *et al.*, 2008[95]	Adults with non-neuropathic chronic LBP (>6 months) Mean weekly 24-hour pain score ≥4 (0–10 scale) No major depressive disorder	Nociceptive	13-week randomized study	Duloxetine 60 mg (increased to 120 mg in patients with <30% pain reduction at week 7) OR Placebo (n numbers not given)	Duloxetine-treated patients reported a significantly greater reduction in BPI 24-hour mean pain scores than placebo-treated patients ($p=0.004$)
Skljarevski *et al.*, 2009[93]	Adults with chronic LBP (≥6 months) with Quebec Task Force system Class 1[a] or 1[b] pain Average weekly pain ratings ≥4 (0–10 Likert scale)	Mixed	13-week, multicentre, randomized, double-blind, parallel group study	Duloxetine 20 mg ($n=56$) OR Duloxetine 60 mg ($n=116$) OR Duloxetine 120 mg ($n=116$) OR Placebo ($n=116$)	Duloxetine 60 mg yielded significantly greater reductions than placebo in mean 24-hour average pain (assessed using 0–10 Likert scale) during weeks 3–11, but this superiority was not maintained to week 13
Skljarevski *et al.*, 2010[96]	Patients with chronic LBP who were considered responders (≥30% reduction in mean BPI score) in a 13-week placebo-controlled trial	Mixed	41-week extension study	Patients receiving duloxetine in the acute phase remained on duloxetine, and those receiving placebo in the acute phase switched to duloxetine: Duloxetine 60 mg OR Duloxetine 120 mg ($n=181$; numbers for separate treatment groups not given)	Pain reduction was maintained during the extension period and a further significant pain reduction (within-group) was observed
Staiger *et al.*, 2003[90]	Randomized, placebo-controlled studies of patients with back pain treated with oral antidepressants	Mixed	Systematic review	7 studies included ($n=440$)	Tricyclic and tetracyclic antidepressants produce moderate symptom reductions This benefit is independent of a patient's depression status

(*continued*)

Table 3. Continued.

Reference	Main inclusion/exclusion criteria	Pain type	Trial design	Intervention(s) and dose	Principle outcome
Salerno *et al.*, 2002[89]	English language randomized placebo-controlled trials of antidepressant medication use in adults with chronic LBP	Mixed	Meta-analysis	9 studies included with 10 treatment arms ($n=504$)	Antidepressants are more effective than placebo for reducing pain intensity but not for improving functional status
Urquhart *et al.*, 2008[91]	Randomized controlled trials comparing antidepressants to placebo in patients with nonspecific LBP with or without radiation and with or without leg pain	Mixed	Meta-analysis by Cochrane collaboration	10 studies included	There is no clear evidence suggesting that antidepressants are more effective than placebo in the management of patients with chronic LBP
Anticonvulsants					
Remmers *et al.*, 2000[100]	Chronic LBP	Mixed	2 × studies (details not given)	Pregabalin (dose not given) (*n* number not given) OR Placebo (*n* number not given)	No significant difference was observed between pregabalin and placebo in mean pain scores
Yaksi *et al.*, 2007[102]	Lumbar spinal stenosis with neurologic intermittent claudication Patients with other pain syndromes excluded	Neuropathic	4-month randomized study	Gabapentin 900–2400 mg + standard treatment (therapeutic exercises, lumbosacral corset with steel bracing and NSAIDs) ($n=28$) OR Standard treatment ($n=27$)	Increase in walking distance was significantly greater with gabapentin than with placebo ($p=0.001$) Improvements in pain scores and sensory deficit were significantly greater with gabapentin than with placebo ($p<0.05$)
Levendoglu *et al.*, 2004[103]	20–65 years Paraplegic patients with complete traumatic spinal cord injury at thoracic and lumbar level Neuropathic pain for >6 months Moderate to severe pain (>4 on Neuropathic Pain Scale)	Neuropathic	18-week, prospective, randomized, double-blind study: 4-week titration period, 4-week maintenance period, 2-week washout period	Gabapentin 900–3600 mg AND Placebo ($n=20$)	Gabapentin significantly reduced pain scores (0–100 mm VAS) and pain frequency at week 8 ($p<0.0001$) Gabapentin significantly reduced all neuropathic pain types ($p<0.05$) except itchy, dull, sensitive and cold
Khoromi *et al.*, 2005[104]	18–75 years Lumbar radiculopathy Pain intensity ≥4 (0–10 scale)	Neuropathic	18-week double-blind 2-way crossover study: 2-week screening period, 4-week titration period, 2-week maintenance period, 2-week washout period	Topiramate 50–400 mg AND Active placebo (dipenhydramine 6.25–50 mg) ($n=29$)	Topiramate reduced average leg pain by 19% compared with placebo ($p=0.065$) Percentage pain reduction scores significantly better with topiramate than with placebo for average back pain, average overall pain and worst overall pain
Topical					
Gimble *et al.*, 2003[108]	Non-radicular acute/subacute, short-term chronic or long-term chronic LBP	Mixed	2-week, prospective, open-label, non-randomized pilot study	Up to 4 lidocaine plasters/24 hours + current analgesic regimen Acute/sub-acute ($n=20$) Short-term chronic ($n=33$) Long-term chronic ($n=76$)	In Groups 1 and 3, significant improvements were observed in pain intensity ($p<0.001$) and pain relief ($p<0.0001$), as assessed by BPI In Group 2, significant improvements were observed in worst pain ($p<0.001$), average pain ($p<0.01$) and pain right now ($p<0.01$)

Keitel *et al.*, 2001[109]	Chronic non-specific LBP Pain rating ≥5 (11-grade VAS)	Mixed	3-week, double-blind, randomized, parallel-group study	Capsicum plaster ($n=74$) OR Placebo ($n=76$)	Response rate (≥30% pain reduction) significantly higher with capsicum plaster (60.8%) than with placebo (42.1%; $p=0.0219$) Response rate (≥50% pain reduction) significantly higher with capsicum plaster (35.1%) than with placebo (17.1%; $p=0.0118$)
Levin and Moseikin, 2009[107]	Vertebrogenic lumbalgia or lumboischialgia with exacerbation for ≥1 month	Mixed	5-day study	Lidocaine plaster 1 to 3 plasters/12 hours + diclofenac 100 mg ($n=40$) OR Diclofenac 100 mg ($n=20$)	Significant clinical effect observed in 63% of patients receiving lidocaine plaster Lidocaine plaster led to a significant reduction in neuropathic pain characteristics; this remained after the end of treatment
Other monotherapy					
Matsudaira *et al.*, 2009[111]	50–85 years Neurogenic intermittent claudication and cauda equina symptoms MRI-confirmed central stenosis with acquired degenerative lumbar spinal stenosis Patients with radicular pain only and suspected disc herniation excluded	Neuropathic	8-week, randomized, open-label study	Limaprost 15 μg tid ($n=39$) OR Etodolac 400 mg bid ($n=40$)	Significantly greater improvements with limaprost than with etodolac in SF-36 items physical functioning ($p=0.01$), role physical ($p=0.03$), bodily pain ($p<0.01$), physical health component summary and vitality ($p=0.02$) and mental health ($p<0.01$)
Tafazal *et al.*, 2007[112]	Symptoms of neurogenic claudication and MRI-proven lumbar spinal stenosis Unilateral or bilateral leg pain Patients with previous lumbar spinal stenosis surgery excluded	Neuropathic	16-week, randomized, double-blind study: 4-week treatment period, 6-week washout period, 6-week treatment period	*Weeks 1–4* Nasal salmon calcitonin 200 IU ($n=20$) OR Placebo ($n=20$) *Weeks 4–10* Nasal salmon calcitonin 200 IU ($n=37$)	No significant difference between calcitonin and placebo in ODI, LBOS, VAS for leg or back pain and shuttle walking distance After 10 weeks, improvements in mean ODI were similar between calcitonin (3.7 points) and placebo (3.8 points)
Waikakul and Waikakul, 2000[113]	Degenerative lumbar spinal stenosis	Neuropathic	2-year single-blind study: 6-month treatment period	Methylcobalamin 0.5 mg tid ($n=70$) OR Control ($n=82$)	Most patients showed improvement but no significant difference was observed between methylcobalamin and controls in pain improvement and neurological signs, except neurogenic claudication distance (better with methylcobalamin)
Van Tulder *et al.*, 2003[110]	Randomized and/or double-blind controlled trials in patients with non-specific LBP treated with muscle relaxants (monotherapy or combination therapy)	Mixed	Meta-analysis by Cochrane collaboration	30 trials included (6 studies in chronic LBP; $n=637$)	Muscle relaxants are effective for relieving symptoms in chronic LBP, but drowsiness, dizziness and other ADRs are common

ADR = adverse drug reaction; bid = twice daily; BPI = Brief Pain Inventory; od = once daily; LBP = low back pain; LBOS = Low Back Outcome Score; Mixed = mixed nociceptive and neuropathic pain; MPQ = McGill Pain Questionnaire; MRI = magnetic resonance imaging; NSAIDs = non-steroidal anti-inflammatory drugs; ODI = Oswestry Disability Index; SR = sustained release; tid = three times daily; VAS = visual analogue scale.
[a]Quebec Task Force system Class 1: pain without radiation to an extremity and without neurological signs.
[b]Quebec Task Force system Class 2: pain with radiation to an extremity, but not below the knee and without neurological signs.

Table 4. Summary of identified studies examining combination pharmacotherapy of chronic low back pain.

Reference	Main inclusion/exclusion criteria	Pain type	Trial design	Intervention(s) and dose	Principle outcome
Romano *et al.*, 2009[60]	18–75 years Chronic LBP for >6 months due to disc prolapse, lumbar spondylosis and/or spinal stenosis Minimum VAS >40 mm (on a scale of 0–100 mm). Patients with neurological disease excluded	Mixed	12-week, prospective, randomized, 3-way crossover-study	4 weeks' treatment with each therapy: Celecoxib 3–6 mg/kg/die + placebo ($n = 36$) AND Pregabalin 1 mg/kg/die for the first week, then 2–4 mg/kg/die + placebo ($n = 36$) AND Celecoxib 3–6 mg/kg/die + pregabalin 1 mg/kg/die for the first week, then 2–4 mg/kg/die ($n = 36$)	Combination therapy was more effective than either monotherapy for mean pain reduction (assessing using 0–100 mm VAS)
Gatti *et al.*, 2009[116]	Chronic LBP (>6 months) Moderate to severe (>3 on a 0–10 VAS) Pain not responsive to previous systemic or local analgesic treatment Patients were classified according to osteoarticular pain (Group A) or neuropathic pain (Group B)	Nociceptive (Group A) and Neuropathic (Group B)	6-week prospective, observational, open-label study	*Group A* Previous treatment discontinued Fixed combination of oxycodone 5 mg + paracetamol 325 mg/8 hours ($n = 78$) *Group B* Previous treatment (except gabapentin) discontinued Fixed combination of oxycodone 5 mg + paracetamol 325 mg/8 hours ($n = 72$)	*Group A* 73.9% and 78.3% reported improvement in 'pain preventing sleep' and 'walks with aid' (assessed using 0–10 VAS), respectively *Group B* All patients reported improved or stable neuropathic pain symptoms except pain preventing sleep
Khoromi *et al.*, 2007[80]	18–65 years Evidence of lumbar radiculopathy Average leg pain score ≥4 (0–10 cm VAS) Patients with polyneuropathy and peripheral vascular disease associated with symptoms of numbness, or patients with burning pain in the lower extremities, were excluded	Neuropathic	Single-centre, crossover, randomized trial: 5-week titration period followed by 2-week maintenance period followed by 2-week tapering period	Morphine 15–90 mg AND Nortriptyline 25–100 mg AND Morphine 15–90 mg + nortriptyline 25–100 mg	No significant reductions in mean leg pain (assessed using 0–10 VAS) or other leg or back pain were observed in any treatment group Pain reduction relative to placebo was 14% for nortriptyline, 7% for morphine and 7% for combination therapy

Gatti *et al.*, 2009[101]	Uncontrolled chronic neuropathic pain ≥6 months	Neuropathic	90-day, multi-centre, prospective, open-label study	*Patients with partial pain control* Pregabalin (starting dose as recommended for condition and titrated to stable tolerable dose) ($n=134$) *Patients with uncontrolled pain* Oxycodone CR (starting dose as recommended for condition and titrated to stable tolerable dose) ($n=106$) OR Oxycodone CR + pregabalin (starting dose as recommended for condition and titrated to stable tolerable dose) ($n=169$)	Mean reduction in pain (score on 0–10 numerical rating scale) was significantly greater with combination therapy (80%) than with pregabalin (46%; $p<0.003$) or oxycodone CR monotherapy (76%; $p<0.001$) Improvements in quality of life significantly greater with combination therapy than with monotherapy ($p=0.0009$)
Pota *et al.*, 2007[117]	Chronic LBP	Mixed	2-month study	*Month 1* Buprenorphine TDS 35 μg/ml *Month 2* Buprenorphine TDS 35 μg/ml + pregabalin 150 mg OR Buprenorphine TDS 35 μg/ml + placebo	Significant reductions in pain (assessed using 0–100 VAS) were observed after month 1 ($p<0.01$) Significant reductions in pain after month 2 were only observed in the combination group ($p<0.01$)
Ruoff *et al.*, 2003[118]	25–75 years Moderate or severe chronic LBP Pain intensity ≥40 (0–100 mm VAS)	Mixed	91-day, multi-centre, randomized, double-blind, parallel group study: 21-day washout period, 10-day titration period, 81-day treatment period	Tramadol 37.5–300 mg + paracetamol 325–2600 mg ($n=161$) OR Placebo ($n=157$)	Significantly lower final mean pain score (assessed by 0–100 mm VAS) with combination therapy than with placebo ($p=0.015$)
Peloso *et al.*, 2004[119]	>18 years Ambulatory patients with chronic LBP Pain intensity ≥40 (0–100 mm VAS) Patients with neurologic deficits in lower extremities, symptomatic disk herniation, severe spinal stenosis or spondylolisthesis excluded	Nociceptive	91-day, multi-centre, randomized, double-blind study: 21-day washout period, 91-day double-blind treatment period	Tramadol 37.5–300 mg + paracetamol 325–2600 mg ($n=167$) OR Placebo ($n=169$)	Mean final pain intensity scores (assessed using 0–100 mm VAS) were significantly lower with combination therapy (47.4) than with placebo (62.9; $p<0.001$), as were mean final pain relief scores (assessed on 6-point Likert scale: 1.8 and 0.7, respectively, $p<0.001$)

CR = controlled release; LBP = low back pain; Mixed = mixed nociceptive and neuropathic pain; TDS: Transdermal delivery system; VAS = visual analogue scale.

more common with the combination (68.9%) than with placebo (46.5%), as were ADRs (23.6% *versus* 3.8%) and rates of discontinuation due to AEs (18.6% *versus* 5.7%). Nausea, somnolence and constipation were significantly more frequent with combination treatment than with placebo ($p<0.05$)[118]. In the second study, patients with at least moderate chronic LBP received tramadol 37.5 mg/paracetamol 325 mg in a fixed combination tablet[119]. VAS scores after 3 months were significantly lower with tramadol/paracetamol than with placebo ($p<0.001$). Combination therapy was also associated with significantly improved scores on several measures, including RDQ score and physical-related items on the SF-MPQ and SF-36 ($p<0.05$). Similar results to those reported above by Ruoff *et al.* (2003)[118] were observed for discontinuation due to insufficient pain relief, the proportion of patients rating treatment as 'good' or 'very good' and the incidence of AEs[119].

These findings reiterate the importance of evaluating combined treatments. While pregabalin was found to be ineffective when used as a monotherapy[100], in combination with celecoxib[60] or CR oxycodone[101] or buprenorphine[117], it appears to confer additional benefits over and above those derived from the co-administered drug. Tramadol alone[87] and in combination with paracetamol[118,119] also appeared to be effective. The single study of morphine in combination with nortriptyline[80] does not provide sufficient data to evaluate the opioid–antidepressant combination for the treatment of chronic LBP, but further study in a larger population is warranted.

Table 4 summarizes the included studies examining combination pharmacotherapy of chronic LBP.

Conclusions

Chronic LBP often comprises both nociceptive and neuropathic components. Therefore, a multimodal and individualized treatment approach is necessary for effective management. Treatment decisions should be guided by the pathological mechanisms contributing to pain symptoms, and should take into consideration pain quality as well as pain intensity. The complexity of chronic LBP management highlights the need for early intervention in patients with acute LBP in order to prevent progression to chronic LBP.

Combining drugs with different mechanisms of action represents a rational approach to the management of chronic LBP with both nociceptive and neuropathic components. Combinations comprising an agent with μ-receptor activity plus an agent of a different class (paracetamol or pregabalin) have been shown to be effective in this setting. While free combinations of analgesics may appear rational, their utility is limited by the difficulty of maintaining the dose ratio within the desired therapeutic range, and the possibility of poor adherence. Fixed-dose combinations and the design of novel strong-acting analgesics with more than one mechanism of action within the same molecule can potentially overcome these limitations. In addition, the relative lack of systemic side effects with topical agents suggests they should be further evaluated as potential first-line treatments or combination treatments with systemic agents.

Transparency

Declaration of funding
This study was funded by Grünenthal GmbH.

Declaration of financial/other relationships
B.M. has disclosed that he has acted as a speaker, consultant and/or clinical science investigator for several pharmaceutical companies involved in the sale and/or research of analgesics, but receives no royalty (cash or otherwise) from the sale of any product.

Acknowledgement
Medical writing support was provided by Julian Martins and Claire Byrne of *in*Science Communications, a Wolters Kluwer business, and that service was funded by Grünenthal GmbH.

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