Guideline recommendations on the pharmacological management of non-specific low back pain in primary care – is there a need to change?

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Expert Rev Clin Pharmacol. 2019 Feb;12(2):145-157

ABSTRACT

Introduction

Analgesic drugs are often prescribed to patients with low back pain (LBP). Recommendations for non-invasive pharmacological management of LBP from recent clinical practice guidelines were compared with each other and with the best available evidence on drug efficacy.

Methods

Guideline recommendations concerning opioids, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, antidepressants, anticonvulsants and muscle relaxants from national primary care guidelines published within the last 3 years were included in this review. For each pharmacotherapy, the most recent systematic review was included as the best available evidence on drug efficacy and common adverse effects were summarized.

Results

Eight recent national clinical practice guidelines were included in this review (from Australia, Belgium, Canada, Denmark, The Netherlands, UK and US). Guidelines are universally moving away from pharmacotherapy due to the limited efficacy and the risk of adverse effects. NSAIDs have replaced paracetamol as the first choice analgesics for LBP in many guidelines. Opioids are considered to be a last resort in all guidelines, but prescriptions of these medications have been increasing over recent years. Only limited evidence exists for the efficacy of antidepressants and anticonvulsants in chronic LBP. Muscle relaxants are one of the analgesics of first choice in the US, but aren't widely available and thus not widely recommended in most other countries.

Conclusions

Upcoming guideline updates should shift their focus from pain to function and from pharmacotherapy to non-pharmacologic treatment options.

INTRODUCTION

Low back pain (LBP) is one of the most prevalent musculoskeletal symptoms and the number one cause of disability worldwide (1, 2). Research into the natural course of LBP in the general population demonstrated that recent onset LBP often improves rapidly during the first 2 months of follow up (3). However, the one-year risk of recurrence is estimated to be around 33% (2, 4, 5). Furthermore, 19.6% of all adults between 20 and 59 develop chronic LBP (i.e. LBP with a duration of more than 12 weeks), which is responsible for a high burden due to disability as well as high cost due to direct medical costs, and indirect costs due to work absenteeism and loss of productivity (6). In up to 99% of patients presenting with LBP in primary care, no specific nociceptive source for their complaints is found. These patients are often labeled as having non-specific LBP (NSLBP), which is essentially a basket term for LBP without a known cause (7, 8).

Many LBP patients use analgesics for symptom relief (9). Over recent years, there has been an increase in the prescription of opioids, antidepressants and anticonvulsants for back pain in primary care (10). Estimates of analgesic usage in LBP range from 55% (11) to 72% in elderly patients (age >55 years) (12). A recent Australian study reported analgesics were recommended at a rate of 892.2 per 1000 spinal pain problems managed between 2013 and 2014 (10). Findings from this study showed that the noninvasive pharmacological options that were most often prescribed in primary care were (in order of descending recommendation rate per 1000 spinal problems managed between 2013 and 2014): opioids (277.2 recommendations), non-steroidal anti-inflammatory drugs (NSAIDs; 165.9 recommendations), simple analgesics such as paracetamol (acetaminophen; 137.2 recommendations), antidepressants and anticonvulsants (76.2 recommendations) and muscle relaxants (<106.1 recommendations, in the category 'other medicine group') (10). Invasive pharmacological options for the treatment of LBP include epidural, spinal, facet joint or sacroiliac analgesic or corticosteroid injections; however, these therapies are not commonly used in primary care and will therefore not be discussed in this review.

In order to rationalize care, many countries have developed and issued clinical practice guidelines containing recommendations for the diagnosis and treatment of LBP (including tools for the recognition of specific causes of LBP and recommendations for the management of NSLBP) (13); the first of these guidelines was published in 1987 by the Quebec Task Force on Spinal Disorders (14). During recent years, many national guidelines for the management of LBP in primary care have been updated. The main aims of this review are twofold: first, to compare the recommendations for pharmacological treatment of NSLBP in primary care between recently published national guidelines and second, to compare these guideline recommendations with best available evidence regarding the efficacy of pharmacological treatments. A secondary aim of this review is to summarize the most common adverse effects (AEs) of noninvasive pharmacological treatments in NSLBP in primary care.

METHODS

This review focuses on recent clinical practice guidelines for the management of NSLBP in primary care and recent (Cochrane) systematic reviews and meta-analyses of randomized controlled trials (RCTs) about noninvasive pharmacological treatment of NSLBP. The search for clinical guidelines was conducted using the following databases: PubMed (key words: low back pain, clinical guidelines), National Guideline Clearinghouse (www.guideline.gov, keyword: low back pain), National Institute for Health and Care Excellence (NICE) (www.nice.org.uk, key word: low back pain) and Physiotherapy Evidence Database (PEDro) (key words: low back pain, guideline). Furthermore, the contents and reference lists of reviews of guidelines were hand searched. Clinical practice guidelines had to meet the following inclusion criteria: (1) the main topic of the guideline was the management of LBP (recommendations regarding the management of sciatica will not be considered), (2) the guideline concerns the primary care setting, (3) the guideline provides recommendations for pharmacotherapy in NSLBP, and (4) the guideline was written in English, German or Dutch as these languages could be read by the reviewers. Guidelines published before January 1st 2016 were not considered to be recent and were excluded from this review. One guideline was included per country. Clinical practice guidelines from the following countries and agencies were included in this review:

- Australia, New South Wales Agency for Clinical Innovation (2016) (15)
- Belgium, Belgian Health Care Knowledge Centre (KCE) (2017) (16)
- Canada, Institute of Health Economics (IHE) (2017) (17)
- Denmark, Danish Health Authority (DHA) (2018) (18)
- Germany, German Association for Quality Assurance in Medicine (ÄZQ) (2017) (19)
- The Netherlands, Dutch College of General Practitioners (NHG) (2017) (20)
- United Kingdom (UK), NICE (2017) (21)
- United States (US), American College of Physicians (ACP) (2017) (22)

Efficacy of pharmacological treatments

Based on the recent study by Mathieson et al (10), we identified the following six pharmacological treatments of NSLBP (in order of descending recommendation rate per 1000 spinal problems managed between 2013 and 2014): (1) opioids, (2) NSAIDs, (3) paracetamol, (4) antidepressants, (5) anticonvulsants and (6) muscle relaxants. To obtain evidence regarding the efficacy of these treatments, we started by hand-searching the reviews of the Cochrane Back and Neck Group (back.cochrane.org) for all Cochrane reviews and meta-analyses concerning these pharmacological treatments published until May 2018. Six Cochrane reviews and meta-analyses were found in this search (23-28).

An additional search for systematic reviews and meta-analyses published since the above Cochrane reviews was performed in Medline Ovid, PubMed and Embase. Key-

words used for the searches were low back pain and name of the pharmacotherapy, e.g. "low back pain" AND paracetamol. For each pharmacological treatment, the most recent review was selected. Six additional studies were found during this search (29-34).

Next, we determined which articles would be used as best available evidence. For each of the five pharmacological treatments, we chose the most recent review available. For the final selection of systematic reviews, see Box 1.

MS and CL independently scored the quality of the all reviews included for efficacy of the five pharmacological treatments based on the additional search using the AMSTAR 2 tool, a validated critical appraisal tool for systematic reviews (35). This checklist consists of 16 questions that can be answered with Yes, Partial Yes, No or Other. Systematic reviews scoring at least 8 out of 16 items with 'Yes' were considered to have adequate quality for inclusion; systematic reviews scoring 7 or less out of 16 were excluded from the review and replaced by an older available systematic review on the same pharmacological treatment. A consensus meeting was held to discuss articles about which there was disagreement between the reviewers. In case a consensus could not be reached, a third independent reviewer (BK) made the final decision whether or not to include the article into the review.

In order to summarize the most common AEs of noninvasive pharmacological treatments for NSLBP in primary care, we searched for evidence about safety and AEs (observational studies and systematic reviews) in Medline Ovid, PubMed and Embase. Keywords used for the searches were combinations of the name of the pharmacotherapy and the extra keywords "safe" or "adverse", e.g. paracetamol AND safe* OR adverse.

Quality of evidence

All included systematic reviews in Box 1 scored at least 8 out of 16 questions of the AMSTAR 2 tool with 'Yes' and were thus considered to have adequate quality for inclusion in this review.

Box 1: Final selection of systematic reviews

Opioids	Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: a systematic review and meta-analysis (2016) (29).
NSAIDs	Non-steroidal anti-inflammatory drugs for spinal pain: a systematic review and meta-analysis (2017) (34).
Paracetamol	Paracetamol for low back pain (2016) (26).
Antidepressants	Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline (2017) (30).
Anticonvulsants	Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials (2017) (31).
Muscle relaxants	Efficacy and tolerability of muscle relaxants for low back pain: Systematic review and meta-analysis (2017) (32).

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; NSLBP: Non-Specific Low Back Pain.

RESULTS

Pharmacotherapy recommendations in guidelines

Eight recent national clinical practice guidelines were included in this review (from Australia, Belgium, Canada, Denmark, Germany, The Netherlands, UK and US). Recommendations for each of the pharmacological treatments are summarized in tables (Table 1-6); each pharmacological treatment is discussed separately below in order of descending recommendation rate per 1000 spinal problems managed between 2013 and 2014 (10), preceded by a general section describing the recommendations of the different national guidelines regarding commencement of pharmacotherapy in NSLBP.

Recommendations regarding the initiation of pharmacotherapy for NSLBP in primary care

Variations exist between clinical practice guidelines on when to consider commencing pharmacological management for LBP in primary care. Five guidelines (Australia, Belgium, Canada, The Netherlands and the UK) present pharmacotherapy as a treatment option that may be considered if required by the patient. Both the Dutch and German guideline specifically mention that analgesics are only used to support patients to return to their usual activities.

The guidelines from Denmark and the US are more hesitant in recommending the prescription of analgesics to patients with LBP: the Danish guideline states that physicians should only prescribe pain medication after careful consideration, while the American guideline specifically recommends selecting non-pharmacological treatment with superficial heat, massage, acupuncture or spinal manipulation over pharmacological treatment options.

Guideline recommendations and best available evidence regarding opioids

An overview of guideline recommendations related to opioids for NSLBP is presented in Table 1. Guidelines universally recommend avoiding opioids, specifically stating that the prescription of opioids should only be considered in case other treatment options have been contra-indicated, have not been tolerated or have failed to reduce pain. The Canadian and German guidelines mention reassessment of patients to whom opioids have been prescribed; the latter mentions this should happen with intervals no longer than four weeks. Duration of opioid treatment in acute LBP was mentioned in two guidelines (Canada and The Netherlands); The Canadian guideline reports a period of less than one or two weeks while the Dutch guideline reports a maximum of five days. The Belgian guideline states no specific period but instead mentions opioids should be used for acute LBP for the shortest period possible.

Table 1: Guideline recommendations concerning opioids for non-specific low back pain

Guideline	Recommendations
Australia (2016)	-
Belgium (2017)	• Think about weak opioids (with or without paracetamol) for the shortest period possible for managing acute low back pain with or without radicular pain only if an NSAID is contraindicated, not tolerated or has been ineffective. • Do not routinely offer opioids for managing chronic low back pain with or without radicular pain.
Canada (2017)	• Cautious and responsible use of opioids should only be considered for carefully selected patients with severe acute pain not controlled with acetaminophen and NSAIDs, at a minimum effective dose only for a limited period of time, usually less than one to two weeks. • Ongoing need for opioids is an indication for reassessment. • Evidence is lacking for long-term use of opioids for chronic low back pain. However, there is some evidence of the benefit of opioids for short-term pain and function improvements. • Long-term use of opioids should only follow an unsuccessful trial of non-opioid analgesics. In severe chronic pain, strong opioids require careful consideration. • Long-acting opioids are preferred as they can establish a steady state blood and tissue level that may minimize the patient's experience of unsteady dosing (cyclical improvement and/or withdrawal) from short-acting opioids. Any use of opioids over the long term will lead to physical dependence. • Avoid escalating doses above 50 mg/day if initiating, and above 90 mg/day oral morphine equivalent for ongoing use. • Careful attention to incremental improvements in pain or function is required to justify ongoing use of opioids. Because little is known about the long-term effects of therapy it should be monitored carefully. • A history of addiction is a relative contraindication. Consultation with an addictions specialist may be helpful in these cases.
Denmark (2018)	• Do only offer patients with recent onset LBP opioids in addition to usual care after careful consideration, as the evidence points towards no short-term effect.
Germany (2017)	• Opioid drugs can be a treatment option for acute non-specific low back pain if non-opioid analgesics are contraindicated or have been found to be ineffective in the individual patient. • The indication for opioid drugs should be regularly reassessed at intervals of no longer than 4 weeks. • [opioids] can be used to treat chronic non-specific low back pain for 4 to 12 weeks initially. • If this brief period of treatment brings about a relevant improvement in the patient's pain and/or subjective physical impairment, while causing only minor or no side effects, then opioid drugs can also be a long-term therapeutic option.
The Netherlands (2017)	• Prescribe opioids only to patients with severe acute low back pain, for whom weaker analgesics were ineffective. Inform patients about the side-effects of opioids and minimize duration of treatment, to a maximum of five days. • Prescribe opioids only to patients with chronic non-specific low back pain who experience severe disability, in order to support stepwise increase of activity. Minimize duration of treatment, to a maximum of one to two weeks.

Table 1: Guideline recommendations concerning opioids for non-specific low back pain (continued)

Guideline	Recommendations
UK (2017)	• Do not routinely offer opioids for managing acute low back pain. • Consider weak opioids (with or without paracetamol) for managing acute low back pain only if an NSAID is contraindicated, not tolerated or has been ineffective. • Do not offer opioids for managing chronic low back pain.
US (2017)	• Opioids should be the last treatment option considered and should be considered only in patients for whom other therapies have failed because they are associated with substantial harms.
Best available evidence	**Main findings**
Efficacy, Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain: A Systematic Review and Meta-analysis. (2016)	• For people with chronic low back pain who tolerate the medicine, opioid analgesics provide modest short-term pain relief but the effect is not likely to be clinically important within guideline recommended doses. • Evidence on long-term efficacy is lacking. • The efficacy of opioid analgesics in acute low back pain is unknown.

LBP: low back pain; mg: milligrams; NSAID: non-steroidal anti-inflammatory drug; UK: United Kingdom; US; United States of America.

For chronic LBP, recommendations concerning opioid prescription are presented with hesitation in nearly all guidelines. The British guideline recommends not prescribing opioids at all for patients with chronic LBP, while the Belgian, Canadian, Dutch and American guidelines advise caution but are generally less strict. The German guideline recommends the use of opioids for the treatment of chronic LBP. The guideline from Canada has by far the most comprehensive recommendations: even the use of long-acting versus short-acting opioids and specific doses for oral morphine are mentioned. Furthermore, this is the only guideline specifically discussing addiction in its recommendations. The Australian guideline only states that opiates are usually less effective for neuropathic pain than other analgesics; for this reason, no recommendation on the prescription of opioids was included in this review.

Duration of opioid treatment in chronic LBP was mentioned in two guidelines (Germany and The Netherlands); the Dutch guideline limits the use of opioids to a maximum of one to two weeks, while the German guideline suggests an initial treatment period of four to 12 weeks, stating that opioid treatment may be continued in the long term if patients experience a relevant improvement in pain or impairments and have only minor or no AEs. The guideline from Denmark only concerns acute LBP and thus presents no recommendations for the use of opioids in chronic LBP.

The 2016 review about opioids for both acute and chronic LBP was considered to be the best available evidence (29). For acute LBP, the efficacy of analgesics remains unknown, as no placebo-controlled trials enrolled patients with acute LBP (29). The review presented moderate-quality evidence that opioids have a small short-term effect on pain (mean difference of 10.1 points on a 100-point pain scale, 95% Confidence Interval (CI) 7.4-12.8 points) (29); however, the authors reported large numbers of patients withdrawing from trials because of AEs or lack of efficacy (29). No trials investigated long term effects (29).

Apart from the aforementioned drug dependence, common AEs of opioids are nausea, dizziness, constipation, vomiting, somnolence, dry mouth and an increased risk of falling and fractures; the risk ratio of experiencing any AE in short term opioid use was found to be 1.4 when compared to placebo (36-38). Furthermore, patients who use opioids for a longer period of time may experience depression and sexual dysfunction (38); meanwhile, patients attempting to stop taking opioids after prolonged use may develop a withdrawal syndrome (with symptoms including agitation, insomnia, diarrhea, rhinorrhea, piloerection and hyperalgesia) (38). Risks of misuse (estimated rates 21-29%, 95% CI 13-38%) and of developing drug-dependence (estimated rates 8-12%, 95% CI 3-17%) have been demonstrated in patients with chronic non-cancer pain (such as LBP) (39).

Guideline recommendations and best available evidence regarding non-steroidal anti-inflammatory drugs (NSAIDs)

An overview of guideline recommendations related to NSAIDs for NSLBP is presented in Table 2. All guidelines recommend NSAIDs for acute LBP; for the guidelines that recommended against the use of paracetamol, NSAIDs are the analgesic of first choice except in the US, where physicians are advised to choose between NSAIDs and skeletal muscle relaxants (SMRs) based on patient preferences and risk profiles. The Danish guideline is the only guideline stating that no effect on LBP is expected of NSAIDs; in the Dutch guideline, it is stated that NSAIDs are not expected to be more effective than paracetamol for LBP.

Cyclo-oxygenase 2 inhibitors (COX-2-inhibitors) are mentioned in the Australian, Canadian, German and American guidelines. The Australian and German guidelines recommend considering contra-indications of COX-2-inhibitors when prescribing them. The guideline from the US does not make a recommendation about prescribing COX-2-inhibitors, as they were not assessed for their effect on pain or function. The Canadian guideline only mentions COX-2-inhibitors in the context of the prescription of proton pump inhibitors (PPIs) to those using NSAIDs over 45 years of age.

Only the Canadian and American guidelines specifically mention chronic LBP. The guideline from Canada recommends paracetamol and NSAIDs for both acute and chronic LBP. The guideline from the US states that in patients with chronic LBP, NSAIDs had a

small to moderate effect on pain and no effect on function, but should be the first option considered nonetheless.

A 2017 review on the effects of NSAIDs for LBP and neck pain (together referred to as 'spinal pain') concluded that although NSAIDs are effective for pain reduction when compared to placebo, differences between NSAIDs and placebo were not clinically relevant (34). In acute LBP, NSAIDs were associated with small improvements in pain intensity within 2 weeks (immediate term) when compared to placebo (mean difference 6.4 points on a 100-point pain scale, 95% CI 2.5 – 10.3 points); furthermore, the short term effects of NSAIDs on pain (follow-up duration 2 weeks to 3 months) were non-significant when compared to placebo (mean difference 1 point on a 100-point pain scale, 95% CI -3.9 – 5.9 points). In chronic LBP, NSAIDs were associated with significant results on pain relief when compared to placebo at both the immediate term (mean difference 11.1 points on a 100-point pain scale, 95% CI 8.4 – 13.8 points) and short term (mean difference 9.8 points on a 100-point pain scale, 95% CI 7.0 – 12.7 points)(34).

For disability, this review found NSAIDs had a significant effect on disability when compared to placebo in patients with acute LBP at the immediate term (mean difference 7.1 points on a 100-point disability scale, 95% CI 1.9 – 12.4 points) but no difference at the short term (mean difference 0.4 on a 100-point disability scale, 95% CI -4.5 – 5.4 points). In chronic LBP, NSAIDs were associated with small but significant differences in disability when compared to placebo at both the immediate term (mean difference 8.4 on a 100-point disability scale, 95% CI 6.3 – 10.6 points) and the short term (mean difference 7.9 on a 100-point disability scale, 95% CI 4.0 – 11.8 points)(34). Furthermore, the risk of gastro-intestinal AEs was reported to have increased 2.5 times (risk ratio; 95% CI 1.2 – 5.2) for those using NSAIDs when compared to placebo; however, observational studies rather than randomized trials are suited to study the prevalence of AEs of medication.

Use of all NSAIDs (both conventional and COX-2-inhibitors) leads to an increased risk of cardiovascular disorders (such as myocardial infarction, cerebrovascular events and heart failure; increase in overall cardiovascular risk of 35-40% for all NSAIDs except naproxen when compared to placebo) (37, 40, 41). Gastro-intestinal AEs are also common (41), but may be avoided by simultaneously prescribing PPIs (42). All but the Danish guidelines directly alert their readers to the risk of AEs when using NSAIDs. The four guidelines that recommend NSAIDs as first choice analgesic (Belgium, Germany, UK and US) all state that NSAIDs should be prescribed in the lowest effective dose and for the shortest possible period of time. The Canadian guideline is the only document that recommends the use of PPIs to all patients over 45 years of age using NSAIDs. Only the guideline from The Netherlands mentions dermal NSAIDs as an alternative to oral NSAIDs in order to avoid systemic AEs.

Table 2: Guideline recommendations concerning NSAIDs for non-specific low back pain

Guideline	Recommendations
Australia (2016)	• NSAIDs are recommended for reducing pain for short periods. However, assessment for contraindications is required before prescribing NSAIDs. These include severe hypertension, renal disease, previous gastrointestinal haemorrhage and current corticosteroid use. The lower incidence of gastrointestinal side effects must be balanced with increased cardiovascular risks associated with some CoX-2 NSAIDs (Cyclo-oxygenase 2 inhibitors are anti-inflammatory medications that have lower gastrointestinal side effects when compared to other NSAIDs).
Belgium (2017)	• If a medication is required for managing low back pain with or without radicular pain (e.g. due to severity of the pain and patients' preferences), consider oral NSAIDs taking into account potential differences between NSAIDs in gastrointestinal, liver and cardio-renal toxicity and the person's risk factors, including age. • When prescribing oral NSAIDs for low back pain, think about appropriate clinical assessment, ongoing monitoring of the evolution of risk factors, and the use of gastro protective treatment. • When prescribing oral NSAIDs for low back pain, select the lowest effective dose for the shortest possible period of time.
Canada (2017)	• Acute low back pain: Prescribe medication, if necessary, for pain relief preferably to be taken at regular intervals. First choice acetaminophen; second choice NSAIDs. • Chronic low back pain: Recommend acetaminophen and NSAIDs. • A proton pump inhibitor (PPI) should be considered for patients over 45 years of age when using an oral NSAID/COX-2 inhibitor.
Denmark (2018)	• Do only offer patients with recent onset LBP NSAIDs in addition to usual care after careful consideration, as the evidence points towards no short-term effect
Germany (2017)	• To minimize side effects NSAIDs should be given in the lowest effective dose and for the shortest possible time. • Considering the contraindications, COX-2-inhibitors can be used if NSAIDs are contraindicated or poorly tolerated (off-label-use).
The Netherlands (2017)	• NSAIDs are not expected to be more effective than paracetamol for low back pain. • Dermal NSAIDs may be considered as an alternative to oral NSAIDs. Dermal NSAIDs have fewer systemic side-effects and may therefore be also used in elderly people with reduced renal function or heart failure (given their skin is intact).
UK (2017)	• Consider oral non-steroidal anti-inflammatory drugs (NSAIDs) for managing low back pain, taking into account potential differences in gastrointestinal, liver and cardio-renal toxicity, and the person's risk factors, including age. • When prescribing oral NSAIDs for low back pain, think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment. • Prescribe oral NSAIDs for low back pain at the lowest effective dose for the shortest possible period of time.

Table 2: Guideline recommendations concerning NSAIDs for non-specific low back pain (continued)

Guideline	Recommendations
US (2017)	• We recommend that the choice between NSAIDs and SMRs be individualized on the basis of patient preferences and likely individual medication risk profile. • Clinicians should therefore assess renovascular and gastrointestinal risk factors before prescribing NSAIDs and recommend the lowest effective doses for the shortest periods necessary. • Although they are associated with lower risk for adverse effects than nonselective NSAIDs, COX-2–selective NSAIDs were not assessed for improvement in pain or function. • Pharmacologic therapy should be considered for patients with chronic low back pain who do not improve with nonpharmacologic interventions. Nonsteroidal anti-inflammatory drugs had a small to moderate effect on pain (moderate-quality evidence) and no to small effect on function (low-quality evidence) and should be the first option considered. • Moderate-quality evidence showed no difference in pain improvement when different NSAIDs were compared with one another.
Best available evidence	Main findings
Non-steroidal anti-inflammatory drugs for spinal pain: a systematic review and meta-analysis. (2017)	• NSAIDs reduced pain and disability, but provided clinically unimportant effects over placebo. • Six participants (95% CI 4 to 10) needed to be treated with NSAIDs, rather than placebo, for one additional participant to achieve clinically important pain reduction. • When looking at different types of spinal pain, outcomes or time points, in only 3 of the 14 analyses were the pooled treatment effects marginally above our threshold for clinical importance. • NSAIDs increased the risk of gastrointestinal reactions by 2.5 times (95% CI 1.2 to 5.2), although the median duration of included trials was 7 days.

CI: confidence interval; COX-2: Cyclo-oxygenase 2; LBP: low back pain; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor; UK: United Kingdom; US; United States of America.

Guideline recommendations and best available evidence regarding paracetamol

An overview of guideline recommendations related to paracetamol (acetaminophen) for NSLBP is presented in Table 3. Four out of eight included guidelines recommend paracetamol for acute LBP (Australia, Canada, Denmark and The Netherlands). In both the Australian and Danish guideline, this recommendation is accompanied by a statement that paracetamol has no short-term effect. The Belgian, German, British and American guidelines recommend against the use of paracetamol in acute LBP. Only the Canadian and German guidelines specifically mentioned chronic LBP; in the former, the use of paracetamol is recommended in chronic LBP while the latter advises against using this pharmacological treatment for patients with either acute or chronic LBP.

The 2016 Cochrane review concluded that there is no significant difference between paracetamol and placebo for pain, quality of life, function, impression of recovery, sleep

Table 3: Guideline recommendations concerning paracetamol for non-specific low back pain

Guideline	Recommendations
Australia (2016)	• Regular paracetamol is recommended for acute LBP. However, both clinician and patients should be mindful that a recent trial demonstrated it was no more effective than a placebo plus 'best evidence education'. • If during the course of treatment, patients find that paracetamol is not helping, then cessation and review for additional analgesia, such as non-steroidal anti-inflammatory drugs (NSAIDs), is suggested.
Belgium (2017)	• Do not routinely offer paracetamol (as single medication) for managing low back pain with or without radicular pain.
Canada (2017)	• Acute low back pain: Prescribe medication, if necessary, for pain relief preferably to be taken at regular intervals. First choice acetaminophen; second choice NSAIDs. • Chronic low back pain: Recommend acetaminophen and NSAIDs.
Denmark (2018)	• Do only offer patients with recent onset LBP paracetamol in addition to usual care after careful consideration, as the evidence points towards no short-term effect.
Germany (2017)	• In the light of new evidence, paracetamol (= acetaminophen) should no longer be used. In comparison to placebo, the use of this drug did not lead to any improvement in pain or functional ability in patients with either acute or chronic non-specific low back pain.
The Netherlands (2017)	• Paracetamol may be prescribed regularly or as-needed; there is no difference in effectiveness. • NSAIDs are not expected to be more effective than paracetamol for low back pain.
UK (2017)	• Do not offer paracetamol alone for managing low back pain.
US (2017)	• The updated evidence showed that acetaminophen was not effective at improving pain outcomes versus placebo. […] we recommend against these drugs for treatment of acute low back pain.
Best available evidence	**Main findings**
Paracetamol for low back pain (Cochrane review, 2016)	• For acute LBP, there is high-quality evidence for no difference between paracetamol (4 g per day) and placebo at 1 week (immediate term), 2 weeks, 4 weeks, and 12 weeks (short term) for the primary outcomes. • There is high-quality evidence that paracetamol has no effect on quality of life, function, global impression of recovery, and sleep quality for all included time periods. • There were also no significant differences between paracetamol and placebo for adverse events, patient adherence, or use of rescue medication. • For chronic LBP, there is very low-quality evidence (based on a trial that has been retracted) for no effect of paracetamol (1 g single intravenous dose) on immediate pain reduction. • Finally, no trials were identified evaluating patients with subacute LBP.

LBP: low back pain; g: grams; NSAID: non-steroidal anti-inflammatory drug; UK: United Kingdom; US; United States of America.

quality, AEs, patient adherence and rescue medication in patients with acute LBP (26). There is low quality evidence for no effect of paracetamol in chronic LBP (26).

Paracetamol is generally perceived as safe, but this perception may be misguided (43, 44). Although severe AEs of paracetamol are relatively rare, paracetamol remains the leading cause of acute liver failure worldwide and overdosing may lead to severe liver damage and even death (37, 45). Apart from hepatotoxicity, a review of observational studies suggests that paracetamol may be associated with an increased risk of cardiovascular, gastrointestinal and renal AEs (respective risk ratios 1.19 – 1.68, 1.11 – 1.49 and 1.40 – 2.19) (44).

Guideline recommendations and best available evidence regarding antidepressants

An overview of guideline recommendations related to antidepressants for NSLBP is presented in Table 4. The American, British and Dutch guidelines recommend against prescribing antidepressants for LBP. It is stated in the Canadian guideline that insufficient evidence exists to recommend antidepressants or for acute LBP. For those with chronic LBP with or without leg pain, this guideline suggests TCA's may have a small to moderate effect on pain. The guideline from Belgium advises against prescribing antidepressants to patients with acute LBP and against prescribing selective serotonin reuptake inhibitors (SSRIs) for those with chronic LBP, but keeps the prescription of tricyclic antidepressants (TCAs) or selective serotonin and noradrenalin reuptake inhibitors (SNRIs) for patients with chronic LBP open for consideration. The Danish and German guidelines make no recommendations for or against prescribing antidepressants in LBP; the Australian guideline only makes recommendations about antidepressants for those with neuropathic pain; for this reason, these recommendations were not included in this review.

The recent systematic review on pharmacologic therapies for low back pain was considered to be the best available evidence for the prescription of antidepressants for LBP in primary care (30). The effects of antidepressants were not evaluated in patients with acute LBP (30). For antidepressants in chronic LBP, no difference in the effect on pain was found between TCAs and SSRIs and placebo (30); antidepressants were not associated with reduced depression or improved function in patients with chronic LBP (30). Small but significant effects were found for duloxetine, an SNRI (30).

The AEs of antidepressants have been summarized in a recent review and meta-analysis (46). This study found that dry mouth, dizziness, nausea, headache and constipation were most often reported by patients; the overall risk ratios for AEs ranged from 1.06 for milacipran to 3.78 for fluoxetine (46).

Table 4: Guideline recommendations concerning antidepressants for non-specific low back pain

Guideline	Recommendations
Australia (2016)	-
Belgium (2017)	• Do not offer selective serotonin reuptake inhibitors (SSRI) for managing low back pain with or without radicular pain. • Do not routinely offer tricyclic antidepressants or non-selective serotonin–norepinephrine reuptake inhibitors (SNRI) for managing low back pain with or without radicular pain. This recommendation is applicable only for chronic pain; the use of antidepressants is not recommended in acute pain.
Canada (2017)	• Acute low back pain: There is insufficient evidence to recommend for or against analgesic antidepressants such as amitriptyline, other tricyclic antidepressants, or serotonin-norepinephrine reuptake inhibitors (SNRIs) for acute low back pain with or without leg dominant pain. • Chronic low back pain: Tricyclic antidepressants amitriptyline and nortriptyline may have a small to moderate effect for chronic low back pain with or without leg dominant pain at much lower doses than might be used for depression.
Denmark (2018)	-
Germany (2017)	-
The Netherlands (2017)	• The use of neuropathic pain medication, such as anti-depressants and anti-convulsants, is not recommended for the reduction of pain.
UK (2017)	• Do not offer selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors or tricyclic antidepressants for managing low back pain.
US (2017)	• Moderate-quality evidence showed that TCAs did not effectively improve pain or function (low-quality evidence) in patients with chronic low back pain, which is contrary to the 2007 guideline. In addition, moderatequality evidence showed that SSRIs did not improve pain.
Best available evidence	**Main findings**
Antidepressants: Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline (2017)	• No trial evaluated antidepressants or antiseizure medications for acute low back pain. • For chronic low back pain, no significant difference was found in pain between tricyclic antidepressants or selective serotonin reuptake inhibitors and placebo. • Antidepressants were not associated with reduced depression or improved function. • Small but significant effects were found for the serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine when compared to placebo.

SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; UK: United Kingdom; US; United States of America.

Table 5: Guideline recommendations concerning anticonvulsants for non-specific low back pain

Guideline	Recommendations
Australia (2016)	-
Belgium (2017)	• Do not offer anticonvulsants for managing low back pain with or without radicular pain in absence of a neuropathic pain component.
Canada (2017)	• Acute low back pain: There is insufficient evidence to recommend for or against anticonvulsants (gabapentin, topiramate) for acute low back pain with or without leg dominant pain.
Denmark (2018)	-
Germany (2017)	-
The Netherlands (2017)	• The use of neuropathic pain medication, such as anti-depressants and anti-convulsants, is not recommended for the reduction of pain.
UK (2017)	• Do not offer anticonvulsants for managing low back pain.
US (2017)	-
Best available evidence	**Main findings**
Anticonvulsants: Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials (2017)	• Existing evidence on the use of gabapentinoids in CLBP is limited and demonstrates significant risk of adverse effects without any demonstrated benefit. • Given the lack of efficacy, risks, and costs associated, the use of gabapentinoids for CLBP merits caution.

CLBP: chronic low back pain; UK: United Kingdom; US; United States of America.

Guideline recommendations and best available evidence regarding anticonvulsants

An overview of guideline recommendations related to anticonvulsants for NSLBP is presented in Table 5. The Belgian, British and Dutch guidelines recommend against using anticonvulsants. It is stated in the Canadian guideline that insufficient evidence exists to recommend anticonvulsants for acute LBP; no recommendation is made in this guideline about the prescription of anticonvulsants in chronic LBP. The Danish and German guidelines make no recommendations for or against prescribing anticonvulsants in

LBP. The guideline from the US does not make a clear recommendation on the use of anticonvulsants either; however, it is mentioned elsewhere in the guideline document that insufficient evidence exists to make a recommendation about using anticonvulsants in LBP. The Australian guideline only makes recommendations about anticonvulsants for those with neuropathic pain; for this reason, these recommendations were not included in this review.

A systematic review of the commonly used anticonvulsants gabapentin and pregabalin concluded that the existing evidence for the efficacy of these drugs for chronic LBP is limited, while they are associated with substantial risk of AEs as well as high costs (31).

When compared with placebo, patients using gabapentin were more likely to report dizziness (risk ratio 1.99), fatigue (risk ratio 1.85), difficulties with mentation (risk ratio 3.34) and visual disturbances (risk ratio 5.72) (37, 47).

Guideline recommendations and best available evidence regarding muscle relaxants

An overview of guideline recommendations related to muscle relaxants for NSLBP is presented in Table 6. There are significant variations between guidelines in their recommendations on the prescription of muscle relaxants for LBP. The guidelines from Belgium and The Netherlands recommend against prescribing muscle relaxants in LBP. The Canadian guideline only recommends the prescription of muscle relaxants to patients with acute LBP in which pain reduction could not be achieved with paracetamol or NSAIDs. For chronic LBP, the guideline from Canada states that skeletal muscle relaxants (SMRs) may be appropriate for symptomatic relief in selected patients.

Meanwhile, the American guideline recommends SMRs as one of its first choice analgesics, together with NSAIDs; the document states that the choice between NSAIDs and SMRs should be made based on patient preferences and risk profiles. This guideline does warn clinicians for the AEs associated with SMRs.

The Australian, British, Danish and German guidelines make no recommendations for or against prescribing benzodiazepines or SMRs in LBP. However, the British guideline does recommend more research should be done to assess the effectiveness of benzodiazepines, as current evidence in the field of muscle relaxants is either insufficient to make a recommendation or concerns medications that are not licensed for use in the UK (SMRs such as cyclobenzaprine and carisoprodol).

A 2017 systematic review and meta-analysis was used as best available evidence for the efficacy of muscle relaxants; drug groups considered are both benzodiazepines and SMRs (32). This review provides evidence for a clinically significant short-term effect of SMRs on pain relief in acute LBP (21.3 points difference on a 100-point pain scale (95% CI 13.5-29.0 points))(32). For chronic LBP, the efficacy of muscle relaxants remains unknown (32). No evidence exists for the efficacy of benzodiazepines in LBP (32).

Common AEs of muscle relaxants include headache, nausea and dizziness (32, 37); the AE rate for muscle relaxants was found to be similar to that of placebo (14.1% versus 16.0%) (32). Benzodiazepines are known to carry a substantial risk of misuse (3% of users) or drug dependence (2% of users) (48).

Table 6: Guideline recommendations concerning muscle relaxants for non-specific low back pain

Guideline	Recommendations
Australia (2016)	-
Belgium (2017)	• Do not offer skeletal muscle relaxants for managing low back pain with or without radicular pain.
Canada (2017)	• Acute low back pain: Only consider adding a short course of muscle relaxant (benzodiazepines, cyclobenzaprine, or antispasticity drugs) on its own, or added to NSAIDs, if acetaminophen or NSAIDs have failed to reduce pain. • Chronic low back pain: Muscle relaxants (e.g., cyclobenzaprine) may be appropriate in selected patients for symptomatic relief of pain and muscle spasm.
Denmark (2018)	-
Germany (2017)	-
The Netherlands (2017)	• Benzodiazepines are not recommended. A positive effect of muscle relaxation on pain or function has not been demonstrated. Meanwhile, these medicaments do have side-effects and a risk of dependence exists.
UK (2017)	-
US (2017)	• We recommend that the choice between NSAIDs and SMRs be individualized on the basis of patient preferences and likely individual medication risk profile. • Skeletal muscle relaxants are associated with central nervous system adverse effects, especially sedation.
Best available evidence	**Main findings**
Efficacy and tolerability of muscle relaxants for low back pain: Systematic Review and meta-analysis (2017)	• A total of five trials (496 participants) provide high quality evidence that muscle relaxants provide clinically significant pain relief in the short term for acute LBP; MD-21.3, [-29.0,-13.5]. There was no information on long-term outcomes. • The median adverse event rate in clinical trials for muscle relaxants was similar to placebo 14.1% IQR (7.0–28.7%) and 16.0% (4.1–31.2%); p = 0.5, respectively. • There is no evidence for the efficacy of benzodiazepines in LBP. • For people with acute LBP, muscle relaxants provide clinically significant short-term pain relief. • For chronic LBP, the efficacy of muscle relaxants is largely unknown. There was no eligible RCT evidence to support the efficacy of benzodiazepines in LBP. Prolonged use of these medicines in LBP cannot be guided by trial evidence.

IQR: interquartile range; LBP: low back pain; MD: mean difference; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial; SMR: skeletal muscle relaxant; UK: United Kingdom; US; United States of America.

CONCLUSION

Eight national clinical practice guidelines for the management of LBP have been updated in the last three years. This review aimed to compare the recommendations for pharmacological treatment of NSLBP in primary care of these guidelines with the best available evidence regarding treatment efficacy; these recommendations may not apply to patients for whom a specific cause for LBP has been identified. The findings from systematic reviews that were considered to be best available evidence are echoed in most of the included clinical practice guidelines. Differences exist between guidelines in terms of the first-line analgesic in acute LBP. Although best available evidence suggests paracetamol is ineffective in acute LBP, four out of eight guidelines still recommend prescribing paracetamol for this condition. However, two of these guidelines immediately state that no short-term effect of this medication is to be expected. In the other four guidelines, NSAIDs have become the first choice analgesics in LBP; in the American guideline, clinicians are encouraged to choose between NSAIDs and SMRs based on preferences and risk profile of the patient.

When compared to the previous generation of clinical practice guidelines, where prescription of time-contingent paracetamol or NSAIDs was considered the norm(13), this generation is universally moving away from recommending pharmacotherapy, presenting the prescription of analgesics as an option that may be considered if this is required by the patient. The guidelines from Denmark and the US seem to be the most progressive in this respect, actively discouraging the pharmacological treatment of NSLBP and recommend non-pharmacological options instead.

As has been recently demonstrated in Australian data, opioids are now the most prescribed analgesics for LBP in primary care. All guidelines consider opioids as a last resort option in case all other pharmacological options have failed, but opinions differ concerning reassessment intervals and treatment duration in general. Only limited evidence exists for the efficacy of antidepressants and anticonvulsants in chronic LBP; best available evidence does suggest a small but significant effect of duloxetine (an SNRI) for chronic LBP. Regarding recommendations about muscle relaxants, the field is most divided: four guidelines don't make any recommendations for or against muscle relaxants, while two countries advise against the prescription of this medication, one guideline only recommends muscle relaxants to selected patients and, as mentioned above, the last guideline (from the US) considers SMRs as one of the analgesics of first choice.

EXPERT OPINION

In general, most clinical practice guideline recommendations match review findings. However, pharmacological treatments such as paracetamol and anticonvulsants which have not been shown to be effective in RCTs are still recommended in a number of guidelines. Furthermore, pharmacological treatments for which efficacy has been demonstrated, such as NSAIDs and opioids, only have small to moderate effects at best at the immediate term and short term. Meanwhile, all pharmacological treatments discussed in this article are associated with risks of AEs. This means careful consideration is prudent before recommending the use of any analgesic to patients with NSLBP; this notion has been incorporated in some form or another in all clinical practice guidelines, but could be presented more prominently in some.

Based on the available evidence, NSAIDs and SMRs may be the best possible drug choices in case pharmacotherapy is deemed absolutely necessary for the management of NSLBP. However, in Australia and several European countries, SMRs have not been registered due to risk of abuse or addiction, automatically making NSAIDs the analgesics of first choice. The only guideline discussing NSAIDs and SMRs as equal options is the American guideline; this document however does not provide clear patient characteristics on which a choice between these pharmacological treatments can be based; instead, it recommends individualizing this choice "on the basis of patient preferences and […] individual medication risk profile". This feels like a step away from the 'one size fits all' approach of RCTs and corresponding meta-analyses and towards the unpredictability of clinical practice, although there currently is insufficient information available to determine what medication to prescribe to individual patients in order to maximize treatment effect. Guiding clinicians in personalized medical decisions is a challenge for researchers, and this task is complicated by the fact that NSLBP is a heterogeneous disorder and most RCTs are insufficiently powered to identify subgroups or individuals using typical subgroup analyses (49-51); furthermore, it is often unclear whether observed improvements in LBP symptoms of individual patients are attributable to medication effects or explained by other phenomena such as natural recovery. Alternative statistical approaches such as individual participant data meta-analysis (IPDMA) may be helpful in creating personalized medicine strategies (50); research protocols have been published for IPDMA of exercise therapy and spinal manipulative therapy for chronic LBP (52, 53). So far, no protocols for IPDMA of pharmacological treatments in LBP have been published.

According to the best available evidence, paracetamol has no effect on the outcomes of LBP when compared to placebo. However, one should realize that this evidence is mainly based on a single, though large RCT; quality of evidence regarding the efficacy of paracetamol in LBP is therefore considered to be low in some guidelines (16, 22). Therefore, it is important to replicate the aforementioned efficacy trial, comparing

paracetamol not only to placebo, but also to other available (non-)pharmacological treatment alternatives in order to strengthen recommendations in future guidelines.

The prescription of anticonvulsants and antidepressants for NSLBP should be recommended against in future primary care clinical practice guidelines, as these pharmacological treatments should be reserved for patients with neuropathic pain, which is unlikely to be non-specific. As already stated in the current American guideline, opioids should only be prescribed as a last resort; we suggest new guidelines provide clinicians with clear instructions for duration of treatment and regular reassessment of patients taking opioids, similar to the current recommendations in the Dutch guidelines.

Although most of the guidelines discussed in this article already are hesitant in their recommendations to prescribe analgesics as stated above, none of the publications is as strict as the American guideline, which specifically states that non-pharmacological treatments should be first selected for the treatment of acute NSLBP, as most patients will improve regardless of treatment. The German guideline echoes this recommendation, stating that the treatment of LBP with drugs is purely symptomatic and should only be prescribed in support of non-pharmacological measures. In spite of these recommendations, pharmacotherapy for NSLBP is still ubiquitous in clinical practice and both patients and clinicians often do not consider analgesics to be merely optional. Most alarmingly, there has been a marked increase in the prescription of opioids for non-cancer pain in recent years. This trend was initially seen in the US and Canada (38), but the number of opioid prescriptions has increased in other parts of the world as well (54, 55). This development may reflect a continuing focus on pain rather than function in the field of NSLBP.

We consider the fact that many NSLBP patients still routinely receive analgesic prescriptions as a major challenge for the future, especially in the case of opioids. The authors believe that upcoming guideline updates should therefore follow the American example and explicitly shift their focus from pain to function and from pharmacotherapy to non-pharmacological treatment options (8). Of course this means non-pharmacological treatment options should be credible and feasible; this is where a challenge lies for researchers in the field of NSLBP, as evidence is limited for comparative effectiveness between pharmacological and non-pharmacological treatment options as well as between different non-pharmacological treatment options.

Apart from the recommendations made by guidelines, special attention should be given to the translation of these recommendations to clinical practice. It has been shown that there still are evidence-practice gaps in the management of LBP (56-58). Misconceptions about back pain and focus on a pathophysiological model of care have been identified as barriers to successful implementation of LBP guidelines (59) and excellent initiatives for improving the implementation of guideline recommendations have already

been developed (8); using these strategies on a larger scale may lead to an increased uptake of guidelines and consequently to an improvement in quality of LBP care.

Changing treatment routines from pharmacotherapy to non-pharmacological treatment is not only a challenge for clinicians, but also for NSLBP patients, who will need to understand and accept these changes. Public health interventions such as mass media campaigns to educate patients about the limited benefits and side effects of medication could be a first step in order to achieve this (60); media campaigns have been proven to be successful in changing patients beliefs and behaviors in the past (8). Another possible approach to changing NSLBP patients' beliefs and behaviors may be through patient information websites (61) or using consumer versions of guidelines (62, 63). If both clinicians and patients see the benefits of avoiding analgesics, the rise in prescriptions to NSLBP patients could be halted and maybe even reversed.

As most LBP guidelines are updated approximately every ten years, we don't expect any major changes in policy or clinical practice in the upcoming years. However, we hope new evidence for non-pharmacological treatment options, increased focus on guideline implementation and patient education through mass media campaigns, patient information websites and consumer versions of guidelines can help to slowly steer physicians and patients towards non-pharmacological treatments as the interventions of first choice for NSLBP, with improved quality of care as a result.

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