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# Between guidelines and clinical trials: evidence-based advice on the pharmacological management of non-specific chronic low back pain

Filippo Migliorini[1,2*], Raju Vaishya[3], Gaetano Pappalardo[4], Marco Schneider[5,6], Andreas Bell[7] and Nicola Maffulli[8,9,10]

**Abstract**

The pharmacological management of nonspecific chronic low back pain (NCLBP) aims to restore patients' daily activities and improve their quality of life. The management of NCLBP is not well codified and extremely heterogeneous, and residual symptoms are common. Pharmacological management should be considered as co-adjuvant to non-pharmacological therapy, and should be guided by the symptoms reported by the patients. Depending on the individual severity of NCLPB, pharmacological management may range from nonopioid to opioid analgesics. It is important to identify patients with generalized sensory hypersensitivity, who may benefit from dedicated therapy. This article provides an evidence-based overview of the principles of pharmacological management of NCLPB.

**Keywords** Spine, Low back pain, Chronic, Pharmacological therapy

*Correspondence:
Filippo Migliorini
migliorini.md@gmail.com
[1]Department of Orthopaedic, Trauma, and Reconstructive Surgery, RWTH University Hospital of Aachen, 52064 Aachen, Germany
[2]Department of Orthopaedic and Trauma Surgery, Academic Hospital of Bolzano (SABES-ASDAA), Bolzano 39100, Italy
[3]Department of Orthopedics, Indraprastha Apollo Hospitals Institutes of Orthopaedics, New Delhi, India
[4]Department of Spine Surgery, 14482 Oberlinhaus, Potsdam, Germany
[5]Department of Medicine and Dentistry, University of Witten/Herdecke, 58455 Witten, Germany
[6]Department of Arthroscopy and Joint Replacement, MVZ Praxisklinik Orthopädie Aachen, RWTH University Hospital Aachen, 52074 Aachen, Germany
[7]Department of Orthopedics, Eifelklinik St. Brigida, Simmerath, Germany
[8]Department of Medicine, Surgery and Dentistry, University of Salerno, Baronissi 84081, Italy
[9]Barts and the London School of Medicine and Dentistry, Queen Mary University of London, Mile End Hospital, London E1 4DG, England
[10]School of Pharmacy and Bioengineering, Stoke on Trent, Keele University Faculty of Medicine, Keele, England

## Introduction

Nonspecific chronic low back pain (NCLBP) is the single most common cause of pain and disability in industrialised countries and a common cause for consultation in primary care. The world population of adults aged 60 years or older is expected to double by 2050, and NCLBP might become a major public health burden worldwide [1]. The prevalence of NCLBP in adults aged 60 years or older is approximately 36.1%, with an annual incidence of 15 to 20% in the United States [2, 3]. The prevalence of NCLPB in women is double compared to men [4, 5]. Up to 95% of low back pain is not attributable to a formal anatomically based aetiology and is therefore defined as nonspecific [6–8]. Low back pain is considered "chronic" when symptoms last more than three months [9–12]. Though chronic LBP may develop after a definite injury, in many patients no precipitating event can be identified [13–15]. Pharmacological management should be

considered as co-adjuvant to non-pharmacological therapy if symptoms still do not promote relevant improvement in the quality of life of the patients, considering the risk of adverse events [9–12, 16–34]. Assessment of patient general health, including blood tests to evaluate kidney and liver function, is recommended before pharmacological therapy is started, and repeated systematically to monitor the possible occurrence of adverse events.

The management of NCLBP is not well codified and is heterogeneous, and residual symptoms, such as stiffness, muscle spasms, and axial back pain, are common [35, 36]. Internationally accepted recommendations and guidelines are still missing. This review aims to provide an evidence-based overview of the principles of pharmacological management of NCLPB.

Management of NCLBP.

Pharmacological management aims to restore patients' daily activities and improve their quality of life. No magic bullet exists for NCLBP; pharmacological interventions to manage pain and disability are available with acceptable short-term results [37]. However, their long-term efficacy is unpredictable. Tolerance, desensitisation, and addiction are a concern in patients managed pharmacologically. This is often hard to accept for clinicians and patients and provides fertile soil to quacks, faith healers, and gurus to promote miraculous non-evidence-based solutions. Clinicians have to choose from drugs with very modest effects and variable risk profiles [38]. Hence the widespread recommendations to use pharmacological options as a last resort [39]; the benefits are just not there to justify the routine of prolonged use of any drug in NCLBP [38, 40, 41]: this is the major challenge for clinicians. The pharmacological management of patients with NCLBP should be individualised according to the patient's symptoms, but at present little evidence is available. Recommendations from guidelines are heterogeneous (Table 1) with also within-country differences.

A medical history of the characteristics of pain is required, as previous positive experiences or undesired adverse events may influence treatment prescription. The visual analogue scale (VAS) or numeric rating system (NRS) should be used to monitor pain intensity and therapy efficacy. Non-pharmacological approaches, including manipulation, education and psychological strategies, and structured physical activity programs, are recommended as first-line therapy for chronic low back pain [9–12, 16–31, 34, 49–52]. Physical therapy aims to improve function and prevent disability, and should be considered first-line therapy in patients with NCLBP [53, 54]. Despite the several heterogeneous physiotherapy regimes advocated, a consensus on the best modality

**Table 1** Overview of international guidelines (CCS: corticosteroids; NSAIDs: non-steroidal anti-inflammatory drugs; SSRI: Serotonin-Noradrenalin-Reuptake-Inhibitors; TCAs: tricyclic antidepressants)

| Guidelines | NSAID (selective) | NSAID (non selective) | Paracetamol | Opioids (weak) | Opioids (strong) | CCS | Antibiotics | Duloxetine | Gabapentinoids | SSRIs | TCAs | Myorelaxans |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Canada [30] | *favour* | *favour* | *favour* | *inconclusive* | *inconclusive* | *against* | *against* | *against* | *against* | *against* | *favour* | *favour* |
| USA [42] | *favour* | *favour* | *against* | *favour* | *favour* | *inconclusive* | *against* | *inconclusive* | - | - | - | *against* |
| USA, Canada, Chile, Switzerland [43] | *inconclusive* | *inconclusive* | *against* | *inconclusive* | *inconclusive* | *against* | - | *against* | *against* | - | *inconclusive* | *against* |
| North America [44] | *inconclusive* | *favour* | *against* | *inconclusive* | *inconclusive* | *against* | *against* | *against* | *inconclusive* | - | *against* | *against* |
| USA [45] | *inconclusive* | *inconclusive* | *inconclusive* | *against* | *against* | *against* | - | *favour* | *inconclusive* | - | *favour* | *inconclusive* |
| ICSI/USA | *inconclusive* | *inconclusive* | *inconclusive* | *inconclusive* | *inconclusive* | *inconclusive* | *inconclusive* | - | - | *inconclusive* | *inconclusive* | - |
| Denmark [12] | *inconclusive* | *inconclusive* | *inconclusive* | *inconclusive* | *inconclusive* | *inconclusive* | *inconclusive* | - | - | *inconclusive* | *inconclusive* | - |
| UK [46] | *favour* | *favour* | *against* | *favour* | *inconclusive* | *inconclusive* | - | - | *against* | *against* | *against* | *against* |
| France [47] | *favour* | *favour* | *favour* | *favour* | *favour* | *inconclusive* | *against* | - | *against* | *against* | *against* | *against* |
| Germany [9] | *favour* | *favour* | *against* | *favour* | *favour* | - | - | - | - | - | - | - |
| Belgium [48] | *favour* | *favour* | *against* | *favour* | *inconclusive* | *inconclusive* | *against* | - | *against* | *against* | *against* | *against* |

has not yet been reached. Kinesiotherapy, specifically global postural re-education using the Souchard [55] or Mezieres [56] methods, massages and manipulation, trunk muscle activation, and strengthening and mobilization of soft tissues are recommended [57]. Moreover, other non-physical therapies have been introduced for the management of NCLBP, including dry needling, manual therapy, acupuncture, and McKenzie exercises [42, 48, 58]. Given the neuropathic mechanisms which largely contribute to NCLBP and the oxidative stress which might cause nerve damage typical of neuropathic pain [59], antioxidants administration has been proposed as an adjuvant in the multimodal management of NCLBP. Ozone therapy has been also advocated in NCLPB [52]. A highly oxidizing oxygen-ozone mixture causes a controlled "micro oxidation" that produces a modulation of the cellular antioxidant system and the inflammation system could increase tissue diffusion, immunomodulation, and analgesia, and could reduce oedema [60–62]. Computer tomography-guided oxygen ozone infiltration combined with oral administration of alpha-lipoic acid (ALA) with palmitoylethanolamide (PEA) and myrrh can be also considered as an adjuvant for the management of NCLBP [63, 64]. Similarly, also alpha-lipoic acid (ALA), superoxide dismutase (SOD), and PEA have been advocated to improve neuroprotection and reduce symptoms [65–68]. Previous evidence showed that the oral combination of ALA and SOD might improve function and reduce the use of analgesics in NCLPB [69, 70]. The action of PEA, especially if combined with complementary and alternative medicine therapies, may also represent a valid additional non-pharmacological alternative for NSLCBP, especially if resistant to conventional therapies [71, 72].

## Symptomatic therapy for NCLPB

Some guidelines advocated the stepwise administration of paracetamol (acetaminophen), non-steroidal anti-inflammatory drugs (NSAIDs), and opiates [20, 22, 24]. Considerable uncertainty exists about the clinical efficacy of paracetamol for NCLBP, with limited evidence and low-level recommendations. Current guidelines worldwide are contradictory: most guidelines recommend the use of paracetamol [10, 25, 27–30, 73], some guidelines advise against it [9, 11, 12, 16, 17, 19, 23, 34, 50]. Compared to a placebo, the administration of paracetamol did not promote any improvement in pain or disability. Following these considerations, the Agency for Clinical Innovation (ACI) approve the use of paracetamol in NCLBP but advises that it might not be effective [74, 75]. The evidence supporting the use of paracetamol is limited [13, 75, 76]. However, paracetamol can be considered an adjuvant in combination with other drugs, especially opiates [77–80].

The use of NSAIDs in NCLBP has been supported by high-quality evidence [13, 80–89] and is advocated by several guidelines [11, 19, 20, 22, 24, 26–30, 34, 73, 90, 91]. To minimize adverse effects, the lowest effective dose for the shortest possible period is recommended [89]. NSAIDs target in a more or less reversible fashion the binding site of the two isoforms of cyclooxygenase (COX): COX-1, which is constitutively produced and ubiquitous under physiological conditions, and COX-2, which is inducible and present mostly in the active inflammatory phase. Two types of NSAIDs are available: selective and non-selective for COX-2. Non-selective NSAIDs, while reducing inflammation and platelet aggregation (especially aspirin), increase the risk of gastrointestinal ulcers and bleeding [92, 93]. Selective COX-2 inhibitors have fewer gastrointestinal effects [94, 95], but they promote thrombosis and substantially increase the risk of a heart attack. Consequently, selective NSAIDs are generally contraindicated in patients with a higher risk of cardiovascular and renal diseases, and non-selective NSAIDs in patients with a higher risk of gastrointestinal ailments.

Current evidence demonstrated that opioids promote clinically relevant benefits in pain and disability in the short term (with most placebo-controlled RCTs ≤ 6 weeks in duration) [77, 83, 96–110]; however, evidence on long-term opioids administration is lacking, and they are unlikely to exert clinically important effects in patients with NCLBP, even at dangerously high doses [38]. Their administration should be cautiously considered, given their high risk of abuse, addiction, tolerance, and desensitisation [111–113]. Other major risks associated with the use of opioids include cardiovascular events, endocrinologic ailments, increased risk of road accidents, hormonal changes and life-threatening respiratory depression [114–117]. Nausea, confusion, constipation, and hyperalgesia are minor adverse effects, but are common among patients who use opioids [118, 119]. Current guidelines recommend the use of weak opioids in NCLBP for the shortest period in chronic LBP if other analgesics are contraindicated, not tolerated, or ineffective [9, 11, 19, 20, 27–29, 50]. [120–123]. Opioid therapy should be attempted when the benefits for pain and function are expected to outweigh the risks [124–127]. If opioids are used, they should be combined with non-pharmacological therapy and nonopioid pharmacological therapy [128–130]. At the time of opioid therapy setting, clinicians should establish realistic treatment goals with their patients [131–133]. Immediate-release opioids at the lowest effective dosage should be preferred instead of extended-release/long-acting opioids [109, 134]. If pain and function do not improve as desired, opioid therapy should be discontinued [134–136]. In general, dose increases that do not provide sustained improvement

should be reversed [137, 138]. Weak opioids (e.g. tramadol, tilidine/naloxone) should be attempted at first [137, 139]. Strong opioids (e.g. oxymorphone, buprenorphine) should only be considered as a last resort within a multimodal therapy framework and in cooperation with specialists in pain therapy [109, 111, 140, 141].

The use of corticosteroid administration in NCLBP is not supported by the current evidence [26, 142], with no established administration protocol. Long-term corticosteroid administration should be avoided, as they induce hyperglycaemia, osteoporosis, immunosuppression, sexual dysfunction, hypertension, depression, and other hormonal dysfunctions [143]. We advise against antibiotics administration for NCLBP, which demonstrated no benefit in NCLBP and elevated risk of adverse events, especially subsequent microbiological resistance [27, 144, 145]. The use of antibiotics was based on the hypothesis that NCLBP may be induced by a low-grade infection [145], but this has not been verified.

## Central sensitisation

NCLBP affects both physical and mental health. The latter is impacted by long-term anatomical, biochemical, and functional alterations to the central nervous system that affects the way pain is modulated and perceived, as central sensitization is often present [146, 147]. Central sensitization is defined as "an amplification of neural signalling within the central nervous system that elicits pain hypersensitivity" [148], "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" [149], or "an augmentation of responsiveness of central neurons to input from unimodal and polymodal receptors" [150]. Despite this difference, all these definitions agreed on the neurophysiological mechanism of increased response to stimuli in central nervous system neurons responsible for the lower pain thresholds, larger receptive fields, and abnormal pain in response to external stimuli [151–155]. In addition, patients with central sensitization from NCLBP may also present chronic pain in multiple body areas [156, 157]. Sensitization in the central nervous system may perpetuate pain even in the absence of anatomical damage [158–161]. Despite improved knowledge of the processes leading to central sensitization, it is still difficult to diagnose [162, 163]. Methods to classify pain aetiology and predominance (e.g. central sensitization, neuropathic, or nociceptive) have been developed [164, 165]; however, no guideline or validated diagnostic algorithm has been yet developed. A targeted therapy addressed to this generalized sensory hypersensitivity may be considered in isolation or combined with the first-line symptomatic therapy [160, 164, 166]. There is little evidence that duloxetine, an analgesic inhibiting serotonin and norepinephrine reuptake, may promote improvement in pain and disability in NCLBP [37, 40, 167–171]. Given its central pain pathway inhibition [172], duloxetine should be administered in patients with a greater central sensitization component as second-line co-therapy [40], especially in those patients with multiple and chronic painful sites. Flupirtine is an aminopyridine central acting non-opioid analgesic with no anti-inflammatory properties [107, 173]. Flupirtine demonstrated efficacy in the management of NCLBP [107] and also in other acute and subacute musculoskeletal pain ailments [174, 175]. However, given its high risk of hepatotoxicity, potential addiction, and unclear benefit, flupirtine administration for NCLBP should be cautiously monitored. Guidelines from Germany advise against the use of flupirtine in NCLBP [19]. As fatigue is very common following flupirtine administration, the ability to operate a motor vehicle is impaired [176]. The present evidence should benefit from further high-quality investigation to attest to the efficacy and safety profile of flupirtine for NCLBP. The current evidence on Gabapentinoids (gabapentin and pregabalin) administration for NCLBP is limited and demonstrates the considerable risk of adverse effects, including drowsiness, somnolence, dizziness, ataxia, fatigue, respiratory depression, and if combined with opioids, they might promote cardiac insufficiency [83, 177, 178] without proved benefit [79, 83, 84, 177–179], with high costs, and addiction risks [180] and is not supported by current guidelines [11, 19, 20, 26, 27]. Gabapentinoids administration for NCLBP merits caution and further high-quality investigations are required. Overall, the evidence is not yet sufficient to recommend the use of anticonvulsive drugs in the treatment of LBP [40, 181]. Indeed, topiramate in the management of NCLBP did not induce improvement [182, 183]. The use of topiramate has limited evidence [184], and is not recommended by several guidelines [11, 19, 20, 26, 27]. Most guidelines advised against the use of antidepressants in NCLBP [11, 19, 20, 26, 27]. Selective Serotonin-Noradrenalin-Reuptake-Inhibitors (SSNRIs) should not be used on a regular basis, and only if relevant psychiatric comorbidities (severe depression, anxiety disorder) justify their use [19, 90]. Tricyclic antidepressants (TCAs) interfere with serotonin reuptake and binding receptors, interacting with α2-adrenoreceptors (noradrenergic system). TCAs differentially regulate opioid receptors with a preferential agonist activity, which may contribute to their therapeutic and/or side effects [185]. Other important effects of TCAs are the binding to N-methyl-D-aspartate (NMDA) and amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptors, the inhibition of peripheral adenosine uptake, and the block of sodium channels. TCAs are not effective as a single therapy in the management of NCLPB [186–191], and should be administered only as co-therapy in patients

with neurological pain [22], as they did not score better than placebo in the management of NCLBP [186, 192].

## Myorelaxants

Although muscle tension and spasm may be a primary or secondary cause for LBP, the administration of central myorelaxants in NCLBP is controversial. While prescribed to relieve pain arising from muscle spasms, muscle relaxants might offer short-term pain relief, but have no effects on muscle spasm itself, and their effectiveness is uncertain [32, 33, 193]. Previous evidence demonstrated that non-benzodiazepine myorelaxants might promote minimal improvement in NCLBP at approximately two weeks in isolation or as co-medication [40, 181, 194]. Recommendations for central myorelaxants are variable: some guidelines recommend them for the management of NCLBP as second line therapy in exacerbations [10, 26, 28, 30], and others discourage their administration [9, 19, 20, 24, 27, 29, 31, 34]. However, given their multiple collateral effects and interactions, the risk for addiction and tolerance, along with the limited evidence, central myorelaxants should be only indicated for short-term acute exacerbation in NSCLPB under closed monitoring. Future studies should investigate validated methods to identify and quantify the muscular component of NCLBP, to establish proper candidates for the administration of central myorelaxants.

## Conclusion

The management of NCLBP is not well codified and is extremely heterogeneous, and residual symptoms are common. A non-pharmacological approach is a first-line therapy for NCLBP.

Pharmacological management should be considered as co-adjuvant to non-pharmacological therapy and should be guided by the symptoms of the patients. Depending on the individual diagnostic picture, pharmacological management may range from nonopioid to opioid analgesics. Current guidelines are heterogeneous, with a variable range of indications and contraindications, with contrasting recommendations. For a proper management of NCLBP, further high-quality RCTs and shared guidelines are required.

### Abbreviations

| | |
|---|---|
| NCLBP | nonspecific chronic low back pain |
| VAS | visual analogue scale |
| NRS | numeric rating system |
| NSAIDs | non-steroidal anti-inflammatory drugs |
| COX | cyclooxygenase |
| SSNRIs | selective serotonin-noradrenalin-reuptake-inhibitors |
| TCAs | tricyclic antidepressants |
| NMDA | N-methyl-D-aspartate |
| AMPA | amino-3-hydroxy-5-methyl-4-isoxazole propionic acid |

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### Consent to participate

Not applicable.

### Ethical approval

This study complies with ethical standards.

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### References

1. Kanasi E, Ayilavarapu S, Jones J. The aging population: demographics and the biology of aging. Periodontol 2000. 2016;72(1):13–8. https://doi.org/10.1111/prd.12126.
2. de Souza IMB, Sakaguchi TF, Yuan SLK, Matsutani LA, do Espirito-Santo AS, Pereira CAB, Marques AP. Prevalence of low back pain in the elderly population: a systematic review. Clin (Sao Paulo). 2019;74:e789. https://doi.org/10.6061/clinics/2019/e789.
3. Bhangle SD, Sapru S, Panush RS. Back pain made simple: an approach based on principles and evidence. Cleve Clin J Med. 2009;76(7):393–9. https://doi.org/10.3949/ccjm.76a.08099.
4. Meucci RD, Fassa AG, Faria NM. Prevalence of chronic low back pain: systematic review. Rev Saude Publica. 2015;49:1. https://doi.org/10.1590/S0034-8910.2015049005874.
5. Wong CK, Mak RY, Kwok TS, Tsang JS, Leung MY, Funabashi M, Macedo LG, Dennett L, Wong AY. Prevalence, incidence, and factors Associated with non-specific chronic low back Pain in Community-Dwelling older adults aged 60 years and older: a systematic review and Meta-analysis. J Pain. 2022;23(4):509–34. https://doi.org/10.1016/j.jpain.2021.07.012.
6. Bardin LD, King P, Maher CG. Diagnostic triage for low back pain: a practical approach for primary care. Med J Aust. 2017;206:268–73.
7. Russo M, Deckers K, Eldabe S, Kiesel K, Gilligan C, Vieceli J, Crosby P. Muscle control and non-specific chronic low back Pain. Neuromodulation. 2018;21(1):1–9. https://doi.org/10.1111/ner.12738.
8. Krath A, Kluter T, Stukenberg M, Zielhardt P, Gollwitzer H, Harrasser N, Hausdorf J, Ringeisen M, Gerdesmeyer L. Electromagnetic transduction therapy in non-specific low back pain: a prospective randomised controlled trial. J Orthop. 2017;14(3):410–5. https://doi.org/10.1016/j.jor.2017.06.016.
9. Chenot JF, Greitemann B, Kladny B, Petzke F, Pfingsten M, Schorr SG. Non-specific low back Pain. Dtsch Arztebl Int. 2017;114(51–52):883–90. https://doi.org/10.3238/arztebl.2017.0883.
10. Guevara-Lopez U, Covarrubias-Gomez A, Elias-Dib J, Reyes-Sanchez A, Rodriguez-Reyna TS, Consensus Group of Practice Parameters to Manage Low Back P. Practice guidelines for the management of low back pain.

Consensus Group of Practice Parameters to manage low back Pain. Cir Cir. 2011;79(3):264–79.
11. NNIfHCE. Low back pain and sciatica in over 16s: Assessment and management (NG59). London: National Institute for Health Care Excellence; 2016.
12. Stochkendahl MJ, Kjaer P, Hartvigsen J, Kongsted A, Aaboe J, Andersen M, Andersen MO, Fournier G, Hojgaard B, Jensen MB, Jensen LD, Karbo T, Kirkeskov L, Melbye M, Morsel-Carlsen L, Nordsteen J, Palsson TS, Rasti Z, Silbye PF, Steiness MZ, Tarp S, Vaagholt M. National Clinical Guidelines for non-surgical treatment of patients with recent onset low back pain or lumbar radiculopathy. Eur Spine J. 2018;27(1):60–75. https://doi.org/10.1007/s00586-017-5099-2.
13. Bedaiwi MK, Sari I, Wallis D, O'Shea FD, Salonen D, Haroon N, Omar A, Inman RD. Clinical efficacy of Celecoxib compared to Acetaminophen in Chronic nonspecific low back Pain: results of a Randomized Controlled Trial. Arthritis Care Res (Hoboken). 2016;68(6):845–52. https://doi.org/10.1002/acr.22753.
14. Fan Y, Liu F, Li M, Ruan X, Wu M, Su K, Gao J, Feng X. Observation of curative effect on meridian theory-based extracorporeal shock wave therapy for non-specific low back pain: study protocol for a randomized controlled trial. J Orthop Surg Res. 2022;17(1):265. https://doi.org/10.1186/s13018-022-03146-w.
15. Migliorini F, Rath B, Tingart M, Baroncini A, Quack V, Eschweiler J. Autogenic mesenchymal stem cells for intervertebral disc regeneration. Int Orthop. 2019;43(4):1027–36. https://doi.org/10.1007/s00264-018-4218-y.
16. Authority] SSDH. National klinisk retningslinje for behandling af nyopståede lænderygsmerter [National clinical guideline for the treatment of recent onset low back pain]. Copenhagen, Denmark: Sundhedsstyrelsen. Copenhagen, Denmark; 2016.
17. Authority] SSDH. National klinisk retningslinje for ikke-kirurgisk behandling af nylig opstået lumbal nerverodspåvirkning [National clinical guideline for the non-surgical treatment of recent onset lumbar nerve root compression (lumbar radiculopathy)]. Denmark: Copenhagen; 2016.
18. Authority] SSFdMdTFNH. (2013) Recommandations de Bonne Pratique sur la surveillance médico-professionnelle du risque lombaire pour les travailleurs exposés à des manipulations de charges [Clinical practice guidelines for medical and occupational surveillance of the low back risk in workers exposed to manual handling of loads]. Paris, France
19. BÄK (Bundesärztekammer), KBV (Kassenärztliche Bundesvereinigung), Fachgesellschaften) AAdWM. (2017) Nationale VersorgungsLeitlinie Nichtspezifischer Kreuzschmerz – Langfassung, 2. Auflage. Version 1. [National Guideline: Non-specific low back pain. Long version: 2nd edition, version 1].
20. Bons SCS, Borg MAJP, van den Donk M, Koes BW, Kuijpers T, Ostelo RWJG, Schaafstra A, Spinnewijn WEM, Verburg-Oorthuizen AFE, Verweij HA. NHG Standaard Aspecifieke lagerugpijn (tweede herziening) [NHG Standard non-specific lower back pain (2nd revision)]. Huisarts En Wetenschap. 2017;60:2–31.
21. Corp N, Mansell G, Stynes S, Wynne-Jones G, Morso L, Hill JC, van der Windt DA. Evidence-based treatment recommendations for neck and low back pain across Europe: a systematic review of guidelines. Eur J Pain. 2021;25(2):275–95. https://doi.org/10.1002/ejp.1679.
22. Glocker F, S2k-Leitlinie. (2018) Lumbale Radikulopathie, 2018: Leitlinien für Diagnostik und Therapie in der Neurologie [Lumbar radiculopathy, S2k Guideline 2018: Guidelines for Diagnostics and Therapy in Neurology].
23. Kassolik K, Rajkowska-Labon E, Tomasik T, Pisula-Lewadowska A, Gieremek K, Andrzejewski W, Dobrzycka A, Kurpas D. Recommendations of the Polish Society of Physiotherapy, the Polish Society of Family Medicine and the College of Family Physicians in Poland in the field of physiotherapy of back pain syndromes in primary health care. Family Med Prim Care Rev. 2017;19:323–34. https://doi.org/10.5114/fmpcr.2017.69299.
24. Schaafstra A, Spinnewijn W, Bons S, Borg M, Koes B, Osteol R, Spijker-Huiges A, Burgers J, Bouma M, Verburg A. NHG-Standaard Lumbosacraal radiculair syndroom (tweede herziening) [NHG standard lumbar radicular syndrome (2nd revision)]. Huisarts En Wetenschap. 2015;58:308–20.
25. Staal JB, Hendriks EJM, Heijmans M, Kiers H, Lutgers-Boomsma AM, Rutten G, van Tulder MWden, Boer J, Ostelo R, Custers JWH. (2017) KNGF-richtlijn Lage rugpijn: Praktijkrichtlijn [KNGF clinical practice guideline for physical therapy in patients with low back pain]. Amersfoort, Netherlands
26. Toscana CSRR. (2015) Mal Di Schiena: Linee Guida Diagnostico Terapeutiche E Raccomandazioni Per La Costruzione Di Percorsi Assistenziali [Back pain: therapeutic and diagnostic guidelines and recommendations for treatment plans].
27. Wambeke P, Desomer A, Ailliet L, Berquin A, Demoulin C, Depreitere B, Dewachter J, Dolphens M, Forget P, Fraselle V, Hans G, Hoste D, Mahieu G, Michielsen J, Nielens H, Orban T, Parlevliet T, Simons E, Tobbackx Y, van Schaeybroeck P, van Zundert J, vanderstraeten J, Vlaeyen J, Jonckheer P. (2017) Low back pain and radicular pain: Assessment and management.
28. (PARM) PAoR. (2017) Clinical Practice Guidelines on theDiagnosis and Management of LowBack Pain.
29. Rached RDVA, Rosa CDP, Alfieri FM et al. (2013) Lombalgia inespecífica crônica: reabilitação [chronic aspecific lumbago: rehabilitation]. Revista da Associação Médica Brasileira 59 (6):536–553
30. practice) CTto. (2019) Evidence-informed primary care management of low back pain. Edmonton (AB). Accessed at: https://www.cfpc.ca/CFPC/media/Resources/Pain-Management/Low_Back_Pain_Guidelines_Oct19.pdf. Accessed 22 June 2022.
31. Elleuch MEMA, Griene B, Nejmi M, Ndongo S, Serrie A. Formalized consensus: clinical practice recommendations for the management of acute low back pain of the african patient. Pan Afr Med J. 2015;22:240.
32. Das S, Agrawal A. Baclofen and Back Pain: a paradoxical phenomena. Indian J Psychol Med. 2017;39(3):386–7. https://doi.org/10.4103/IJPSYM.IJPSYM_60_17.
33. Friedman BW, Irizarry E, Solorzano C, Zias E, Pearlman S, Wollowitz A, Jones MP, Shah PD, Gallagher EJ. A randomized, placebo-controlled trial of Ibuprofen Plus Metaxalone, Tizanidine, or Baclofen for Acute Low Back Pain. Ann Emerg Med. 2019;74(4):512–20. https://doi.org/10.1016/j.annemergmed.2019.02.017.
34. Vernooij RW, Sanabria AJ, Sola I, Alonso-Coello P, Martinez Garcia L. Guidance for updating clinical practice guidelines: a systematic review of methodological handbooks. Implement Sci. 2014;9:3. https://doi.org/10.1186/1748-5908-9-3.
35. Guo X, Li L, Yan Z, Li Y, Peng Z, Yang Y, Zhang Y, Schmitz C, Feng Z. Efficacy and safety of treating chronic nonspecific low back pain with radial extracorporeal shock wave therapy (rESWT), rESWT combined with celecoxib and eperisone (C + E) or C + E alone: a prospective, randomized trial. J Orthop Surg Res. 2021;16(1):705. https://doi.org/10.1186/s13018-021-02848-x.
36. Maher C, Underwood M, Buchbinder R. Non-specific low back pain. Lancet. 2017;389(10070):736–47. https://doi.org/10.1016/S0140-6736(16)30970-9.
37. Migliorini F, Maffulli N, Eschweiler J, Betsch M, Catalano G, Driessen A, Tingart M, Baroncini A. The pharmacological management of chronic lower back pain. Expert Opin Pharmacother. 2021;22(1):109–19. https://doi.org/10.1080/14656566.2020.1817384.
38. Abdel Shaheed C, Maher CG, Williams KA, Day R, McLachlan AJ. Efficacy, tolerability, and dose-dependent Effects of Opioid Analgesics for Low Back Pain: a systematic review and Meta-analysis. JAMA Intern Med. 2016;176(7):958–68. https://doi.org/10.1001/jamainternmed.2016.1251.
39. Baroncini A, Maffulli N, Eschweiler J, Molsberger F, Klimuch A, Migliorini F. Acupuncture in chronic aspecific low back pain: a bayesian network meta-analysis. J Orthop Surg Res. 2022;17(1):319. https://doi.org/10.1186/s13018-022-03212-3.
40. Qaseem A, Wilt TJ, McLean RM, Forciea MA, Clinical Guidelines Committee of the American College of P. Noninvasive treatments for Acute, Subacute, and chronic low back Pain: a clinical practice Guideline from the American College of Physicians. Ann Intern Med. 2017;166(7):514–30. https://doi.org/10.7326/M16-2367.
41. Baroncini A, Maffulli N, Eschweiler J, Knobe M, Tingart M, Migliorini F. Management of facet joints osteoarthritis associated with chronic low back pain: a systematic review. Surgeon. 2021;19(6):e512–8. https://doi.org/10.1016/j.surge.2020.12.004.
42. Qaseem A, McLean RM, O'Gurek D, Batur P, Lin K, Kansagara DL, Clinical Guidelines Committee of the American College of P, Commission on Health of the P, Science of the American Academy of Family, Cooney P, Forciea TG, Crandall MA, Fitterman CJ, Hicks N, Horwitch LA, Maroto C, McLean M, Mustafa RM, Tufte RA, Vijan J, Williams S Jr. (2020) Nonpharmacologic and Pharmacologic Management of Acute Pain From Non-Low Back, Musculoskeletal Injuries in Adults: A Clinical Guideline From the American College of Physicians and American Academy of Family Physicians. Ann Intern Med 173 (9):739–748. https://doi.org/10.7326/M19-3602.
43. Chou R, Cote P, Randhawa K, Torres P, Yu H, Nordin M, Hurwitz EL, Haldeman S, Cedraschi C. The Global Spine Care Initiative: applying evidence-based guidelines on the non-invasive management of back and neck pain to low- and middle-income communities. Eur Spine J. 2018;27(Suppl 6):851–60. https://doi.org/10.1007/s00586-017-5433-8.
44. Kreiner DS, Matz P, Bono CM, Cho CH, Easa JE, Ghiselli G, Ghogawala Z, Reitman CA, Resnick DK, Watters WC 3rd, Annaswamy TM, Baisden J, Bartynski WS, Bess S, Brewer RP, Cassidy RC, Cheng DS, Christie SD, Chutkan NB, Cohen

BA, Dagenais S, Enix DE, Dougherty P, Golish SR, Gulur P, Hwang SW, Kilincer C, King JA, Lipson AC, Lisi AJ, Meagher RJ, O'Toole JE, Park P, Pekmezci M, Perry DR, Prasad R, Provenzano DA, Radcliff KE, Rahmathulla G, Reinsel TE, Rich RL Jr, Robbins DS, Rosolowski KA, Sembrano JN, Sharma AK, Stout AA, Taleghani CK, Tauzell RA, Trammell T, Vorobeychik Y, Yahiro AM. Guideline summary review: an evidence-based clinical guideline for the diagnosis and treatment of low back pain. Spine J. 2020;20(7):998–1024. https://doi.org/10.1016/j.spinee.2020.04.006.

45. Pangarkar SS, Kang DG, Sandbrink F, Bevevino A, Tillisch K, Konitzer L, Sall J. VA/DoD Clinical Practice Guideline: diagnosis and treatment of low back Pain. J Gen Intern Med. 2019;34(11):2620–9. https://doi.org/10.1007/s11606-019-05086-4.
46. Bernstein IA, Malik Q, Carville S, Ward S. Low back pain and sciatica: summary of NICE guidance. BMJ. 2017;356:i6748. https://doi.org/10.1136/bmj.i6748.
47. Bailly F, Trouvin AP, Bercier S, Dadoun S, Deneuville JP, Faguer R, Fassier JB, Koleck ML, Lassalle L, Le Vraux T, Brigitte L, Petitprez K, Ramond-Roquin A, Renard JO, Roren A, Rozenberg S, Sebire C, Vuides G, Rannou FO, Audrey P. Clinical guidelines and care pathway for management of low back pain with or without radicular pain. Joint Bone Spine. 2021;88(6):105227. https://doi.org/10.1016/j.jbspin.2021.105227.
48. van Wambeke P, Desomer A, Jonckheer P, Depreitere B. The belgian national guideline on low back pain and radicular pain: key roles for rehabilitation, assessment of rehabilitation potential and the PRM specialist. Eur J Phys Rehabil Med. 2020;56(2):220–7. https://doi.org/10.23736/S1973-9087.19.05983-5.
49. H AM, C Y, D. S M, C MM. N. H (2016) Malaysian low back pain management guideline Malaysian association for the study of pain, first edition. Available from: http://www.masp.org.my/index.cfm?&menuid=23. Accessed June 2022.
50. Qaseem A, Wilt TJ, McLean RM, Forciea M, Physicians FtcgcotACo. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the american college of physicians. Ann Intern Med. 2017;166:514–30.
51. Al-Najjim M, Shah R, Rahuma M, Gabbar OA. Lumbar facet joint injection in treating low back pain: Radiofrequency denervation versus SHAM procedure. Systematic review. J Orthop. 2018;15(1):1–8. https://doi.org/10.1016/j.jor.2017.10.001.
52. Migliorini F, Maffulli N, Eschweiler J, Bestch M, Tingart M, Baroncini A. Ozone injection therapy for intervertebral disc herniation. Br Med Bull. 2020;136(1):88–106. https://doi.org/10.1093/bmb/ldaa032.
53. Shipton EA. Physical therapy approaches in the treatment of low back Pain. Pain Ther. 2018;7(2):127–37. https://doi.org/10.1007/s40122-018-0105-x.
54. Foster NE, Anema JR, Cherkin D, Chou R, Cohen SP, Gross DP, Ferreira PH, Fritz JM, Koes BW, Peul W, Turner JA, Maher CG, Lancet Low Back Pain Series Working G. Prevention and treatment of low back pain: evidence, challenges, and promising directions. Lancet. 2018;391(10137):2368–83. https://doi.org/10.1016/S0140-6736(18)30489-6.
55. Bonetti F, Curti S, Mattioli S, Mugnai R, Vanti C, Violante FS, Pillastrini P. Effectiveness of a 'global postural reeducation' program for persistent low back pain: a non-randomized controlled trial. BMC Musculoskelet Disord. 2010;11:285. https://doi.org/10.1186/1471-2474-11-285.
56. Lena O, Todri J, Todri A, Papajorgji P, Martinez-Fuentes J. A randomized controlled trial concerning the implementation of the postural Mezieres treatment in elite athletes with low back pain. Postgrad Med. 2022;134(6):559–72. https://doi.org/10.1080/00325481.2022.2089464.
57. George SZ, Fritz JM, Silfies SP, Schneider MJ, Beneciuk JM, Lentz TA, Gilliam JR, Hendren S, Norman KS. Interventions for the management of Acute and Chronic Low Back Pain: Revision 2021. J Orthop Sports Phys Ther. 2021;51(11):CPG1–CPG60. https://doi.org/10.2519/jospt.2021.0304.
58. Kreiner DS, Matz P, Bono CM, Cho CH, Easa JE, Ghiselli G, Ghogawala Z, Reitman CA, Resnick DK, Watters WC 3rd, Annaswamy TM, Baisden J, Bartynski WS, Bess S, Brewer RP, Cassidy RC, Cheng DS, Christie SD, Chutkan NB, Cohen BA, Dagenais S, Enix DE, Dougherty P, Golish SR, Gulur P, Hwang SW, Kilincer C, King JA, Lipson AC, Lisi AJ, Meagher RJ, O'Toole JE, Park P, Pekmezci M, Perry DR, Prasad R, Provenzano DA, Radcliff KE, Rahmathulla G, Reinsel TE, Rich RL Jr, Robbins DS, Rosolowski KA, Sembrano JN, Sharma AK, Stout AA, Taleghani CK, Tauzell RA, Trammell T, Vorobeychik Y, Yahiro AM. (2021) Corrigendum to "Guideline summary review: an evidence-based clinical guideline for the diagnosis and treatment of low back pain" [The Spine Journal 20/7 (2020) p 998–1024]. Spine J 21 (4):726–727. https://doi.org/10.1016/j.spinee.2021.02.006.
59. Carrasco C, Naziroglu M, Rodriguez AB, Pariente JA. Neuropathic Pain: delving into the oxidative origin and the possible implication of transient receptor potential channels. Front Physiol. 2018;9:95. https://doi.org/10.3389/fphys.2018.00095.
60. Re L, Sanchez GM, Mawsouf N. Clinical evidence of ozone interaction with pain mediators. Saudi Med J. 2010;31(12):1363–7.
61. Hidalgo-Tallon FJ, Torres-Morera LM, Baeza-Noci J, Carrillo-Izquierdo MD, Pinto-Bonilla R. Updated review on ozone therapy in Pain Medicine. Front Physiol. 2022;13:840623. https://doi.org/10.3389/fphys.2022.840623.
62. Oliviero A, Giordano L, Maffulli N. The temporal effect of intra-articular ozone injections on pain in knee osteoarthritis. Br Med Bull. 2019;132(1):33–44. https://doi.org/10.1093/bmb/ldz028.
63. Bonetti M, Lauritano D, Ottaviani GM, Fontana A, Frigerio M, Zambello A, Della Gatta L, Muto M, Carinci F. New Approach to Chronic Back Pain treatment: a Case Control Study. Biomedicines. 2022;11(1). https://doi.org/10.3390/biomedicines11010073.
64. Bonetti M, Lauritano D, Ottaviani GM, Fontana A, Zambello A, Della Gatta L, Muto M, Carinci F. Oxygen-ozone Therapy Associated with Alpha Lipoic Acid Plus Palmitoylethanolamide and Myrrh versus ozone therapy in the Combined treatment of sciatic Pain due to herniated discs: Observational Study on 318 patients. Int J Environ Res Public Health. 2022;19(9). https://doi.org/10.3390/ijerph19095716.
65. Skaper SD, Facci L, Fusco M, Della Valle MF, Zusso M, Costa B, Giusti P. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. Inflammopharmacology. 2014;22(2):79–94. https://doi.org/10.1007/s10787-013-0191-7.
66. Papanas N, Ziegler D. Efficacy of alpha-lipoic acid in diabetic neuropathy. Expert Opin Pharmacother. 2014;15(18):2721–31. https://doi.org/10.1517/14656566.2014.972935.
67. Li S, Li Q, Li Y, Li L, Tian H, Sun X. Acetyl-L-carnitine in the treatment of peripheral neuropathic pain: a systematic review and meta-analysis of randomized controlled trials. PLoS ONE. 2015;10(3):e0119479. https://doi.org/10.1371/journal.pone.0119479.
68. Younus H. Therapeutic potentials of superoxide dismutase. Int J Health Sci (Qassim). 2018;12(3):88–93.
69. Battisti E, Albanese A, Guerra L, Argnani L, Giordano N. Alpha lipoic acid and superoxide dismutase in the treatment of chronic low back pain. Eur J Phys Rehabil Med. 2013;49(5):659–64.
70. Letizia Mauro G, Cataldo P, Barbera G, Sanfilippo A. Alpha-lipoic acid and superoxide dismutase in the management of chronic neck pain: a prospective randomized study. Drugs R D. 2014;14(1):1–7. https://doi.org/10.1007/s40268-013-0035-3.
71. Scaturro D, Asaro C, Lauricella L, Tomasello S, Varrassi G, Letizia Mauro G. Combination of rehabilitative therapy with Ultramicronized Palmitoylethanolamide for Chronic Low Back Pain: an observational study. Pain Ther. 2020;9(1):319–26. https://doi.org/10.1007/s40122-019-00140-9.
72. Chirchiglia D, Paventi S, Seminara P, Cione E, Gallelli L. N-Palmitoyl ethanol Amide Pharmacological treatment in patients with nonsurgical lumbar Radiculopathy. J Clin Pharmacol. 2018;58(6):733–9. https://doi.org/10.1002/jcph.1070.
73. Pohjolainen T, Leinonen V, Franten J et al. (2015) Update on current care guideline: low back pain. Duodecim 131:92–94
74. Inovation) NNSWAAfC. (2016) Management of people with acute low back pain model of care. Available from: https://www.aci.health.nsw.gov.au/__data/assets/pdf_file/0007/336688/acute-low-back-pain-moc.pdf. Accessed June 2022.
75. Williams CM, Maher CG, Latimer J, McLachlan AJ, Hancock MJ, Day RO, Lin CW. Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. Lancet. 2014;384(9954):1586–96. https://doi.org/10.1016/S0140-6736(14)60805-9.
76. Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW. Non-steroidal anti-inflammatory drugs for low back pain. Cochrane Database Syst Rev. 2008;1CD000396. https://doi.org/10.1002/14651858.CD000396.pub3.
77. Perrot S, Krause D, Crozes P, Naim C, Group G-Z-S. Efficacy and tolerability of paracetamol/tramadol (325 mg/37.5 mg) combination treatment compared with tramadol (50 mg) monotherapy in patients with subacute low back pain: a multicenter, randomized, double-blind, parallel-group, 10-day treatment study. Clin Ther. 2006;28(10):1592–606. https://doi.org/10.1016/j.clinthera.2006.10.001.
78. Ruoff GE, Rosenthal N, Jordan D, Karim R, Kamin M, Protocol C-SG. Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: a multicenter, randomized, double-blind, placebo-controlled

outpatient study. Clin Ther. 2003;25(4):1123–41. https://doi.org/10.1016/s0149-2918(03)80071-1.
79. Sakai Y, Ito K, Hida T, Ito S, Harada A. Pharmacological management of chronic low back pain in older patients: a randomized controlled trial of the effect of pregabalin and opioid administration. Eur Spine J. 2015;24(6):1309–17. https://doi.org/10.1007/s00586-015-3812-6.
80. Tetsunaga T, Tetsunaga T, Tanaka M, Ozaki T. Efficacy of tramadol-acetaminophen tablets in low back pain patients with depression. J Orthop Sci. 2015;20(2):281–6. https://doi.org/10.1007/s00776-014-0674-4.
81. Birbara CA, Puopolo AD, Munoz DR, Sheldon EA, Mangione A, Bohidar NR, Geba GP, Etoricoxib Protocol 042 Study G. Treatment of chronic low back pain with etoricoxib, a new cyclo-oxygenase-2 selective inhibitor: improvement in pain and disability–a randomized, placebo-controlled, 3-month trial. J Pain. 2003;4(6):307–15. https://doi.org/10.1016/s1526-5900(03)00633-3.
82. Coats TL, Borenstein DG, Nangia NK. MT. B (2004) Effects of valdecoxib in the treatment of chronic low back pain: results of a randomized, placebo-controlled trial. 26 (8):1249–60. https://doi.org/10.1016/S0149-2918(04)80081-X.
83. Hwang CJ, Lee JH, Kim JH, Min SH, Park KW, Seo HY, Song KS. (2019) Gabapentin versus Transdermal Fentanyl Matrix for the Alleviation of Chronic Neuropathic Pain of Radicular Origin: A Randomized Blind Multicentered Parallel-Group Noninferiority Trial. Pain Res Manag 2019:4905013. https://doi.org/10.1155/2019/4905013.
84. Romano CL, Romano D, Bonora C, Mineo G. Pregabalin, celecoxib, and their combination for treatment of chronic low-back pain. J Orthop Traumatol. 2009;10(4):185–91. https://doi.org/10.1007/s10195-009-0077-z.
85. Shell WE, Charuvastra EH, DeWood MA, May LA, Bullias DH, Silver DS. A double-blind controlled trial of a single dose naproxen and an amino acid medical food theramine for the treatment of low back pain. Am J Ther. 2012;19(2):108–14. https://doi.org/10.1097/MJT.0b013e3181f4b297.
86. Takahashi N, Omata JI, Iwabuchi M, Fukuda H, Shirado O. Therapeutic efficacy of nonsteroidal anti-inflammatory drug therapy versus exercise therapy in patients with chronic nonspecific low back pain: a prospective study. Fukushima J Med Sci. 2017;63(1):8–15. https://doi.org/10.5387/fms.2016-12.
87. Yang JH, Suk KS, Lee BH, Jung WC, Kang YM, Kim JH, Kim HS, Lee HM, Moon SH. Efficacy and safety of different Aceclofenac treatments for chronic Lower Back Pain: prospective, randomized, single Center, open-label clinical trials. Yonsei Med J. 2017;58(3):637–43. https://doi.org/10.3349/ymj.2017.58.3.637.
88. Zerbini C, Ozturk ZE, Grifka J, Maini M, Nilganuwong S, Morales R, Hupli M, Shivaprakash M, Giezek H, Etoricoxib CSG. Efficacy of etoricoxib 60 mg/day and diclofenac 150 mg/day in reduction of pain and disability in patients with chronic low back pain: results of a 4-week, multinational, randomized, double-blind study. Curr Med Res Opin. 2005;21(12):2037–49. https://doi.org/10.1185/030079905X75069.
89. Migliorini F, Maffulli N, Eschweiler J, Tingart M, Baroncini A. Non-steroidal anti-inflammatory drugs and gabapentinoids for chronic lumbar pain: a bayesian network meta-analysis of randomized controlled trials. Br Med Bull. 2021;138(1):85–95. https://doi.org/10.1093/bmb/ldab003.
90. Ferreira GE, McLachlan AJ, Lin CC, Zadro JR, Abdel-Shaheed C, O'Keeffe M, Maher CG. Efficacy and safety of antidepressants for the treatment of back pain and osteoarthritis: systematic review and meta-analysis. BMJ. 2021;372:m4825. https://doi.org/10.1136/bmj.m4825.
91. Qaseem A, Wilt TJ, McLean RM, Forciea MA. Clinical guidelines committee of the American College of Physicians: noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017;166:514–30.
92. Seibert K, Zhang Y, Leahy K, Hauser S, Masferrer J, Perkins W, Lee L, Isakson P. Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain. Proc Natl Acad Sci U S A. 1994;91(25):12013–7. https://doi.org/10.1073/pnas.91.25.12013.
93. Laine L, Smith R, Min K, Chen C, Dubois RW. Systematic review: the lower gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther. 2006;24(5):751–67. https://doi.org/10.1111/j.1365-2036.2006.03043.x.
94. Emery P, Zeidler H, Kvien TK, Guslandi M, Naudin R, Stead H, Verburg KM, Isakson PC, Hubbard RC, Geis GS. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. Lancet. 1999;354(9196):2106–11. https://doi.org/10.1016/S0140-6736(99)02332-6.
95. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA. 2000;284(10):1247–55. https://doi.org/10.1001/jama.284.10.1247.
96. Katz J, Pennella-Vaughan J, Hetzel RD, Kanazi GE, Dworkin RH. A randomized, placebo-controlled trial of bupropion sustained release in chronic low back pain. J Pain. 2005;6(10):656–61. https://doi.org/10.1016/j.jpain.2005.05.002.
97. Katz N, Rauck R, Ahdieh H, Ma T, van der Gerritsen R, Kerwin R, Podolsky G. A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naive patients with chronic low back pain. Curr Med Res Opin. 2007;23(1):117–28. https://doi.org/10.1185/030079906x162692.
98. Allan L, Richarz U, Simpson K, Slappendel R. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naive patients with chronic low back pain. Spine (Phila Pa 1976). 2005;30(22):2484–90. https://doi.org/10.1097/01.brs.0000186860.23078.a8.
99. Baron R, Martin-Mola E, Muller M, Dubois C, Falke D, Steigerwald I. Effectiveness and safety of Tapentadol prolonged release (PR) versus a combination of Tapentadol PR and Pregabalin for the management of severe, chronic low back Pain with a neuropathic component: a Randomized, Double-blind, phase 3b study. Pain Pract. 2015;15(5):455–70. https://doi.org/10.1111/papr.12200.
100. Buynak R, Shapiro DY, Okamoto A, Van Hove I, Rauschkolb C, Steup A, Lange B, Lange C, Etropolski M. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled phase III study. Expert Opin Pharmacother. 2010;11(11):1787–804. https://doi.org/10.1517/14656566.2010.497720.
101. Chu LF, D'Arcy N, Brady C, Zamora AK, Young CA, Kim JE, Clemenson AM, Angst MS, Clark JD. Analgesic tolerance without demonstrable opioid-induced hyperalgesia: a double-blinded, randomized, placebo-controlled trial of sustained-release morphine for treatment of chronic nonradicular low-back pain. Pain. 2012;153(8):1583–92. https://doi.org/10.1016/j.pain.2012.02.028.
102. Gordon A, Callaghan D, Spink D, Cloutier C, Dzongowski P, O'Mahony W, Sinclair D, Rashiq S, Buckley N, Cohen G, Kim J, Boulanger A, Piraino PS, Eisenhoffer J, Harsanyi Z, Darke AC, Michalko KJ. Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. Clin Ther. 2010;32(5):844–60. https://doi.org/10.1016/j.clinthera.2010.04.018.
103. Hale ME, Ahdieh H, Ma T, Rauck R, Oxymorphone ERSG. Efficacy and safety of OPANA ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: a 12-week, randomized, double-blind, placebo-controlled study. J Pain. 2007;8(2):175–84. https://doi.org/10.1016/j.jpain.2006.09.011.
104. Klinger R, Kothe R, Schmitz J, Kamping S, Flor H. Placebo effects of a sham opioid solution: a randomized controlled study in patients with chronic low back pain. Pain. 2017;158(10):1893–902. https://doi.org/10.1097/j.pain.0000000000000977.
105. Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, Kroenke K, Bair MJ, Noorbaloochi S. Effect of Opioid vs Nonopioid Medications on Pain-Related function in patients with Chronic Back Pain or hip or knee Osteoarthritis Pain: the SPACE Randomized Clinical Trial. JAMA. 2018;319(9):872–82. https://doi.org/10.1001/jama.2018.0899.
106. Steiner DJ, Sitar S, Wen W, Sawyerr G, Munera C, Ripa SR, Landau C. Efficacy and safety of the seven-day buprenorphine transdermal system in opioid-naive patients with moderate to severe chronic low back pain: an enriched, randomized, double-blind, placebo-controlled study. J Pain Symptom Manage. 2011;42(6):903–17. https://doi.org/10.1016/j.jpainsymman.2011.04.006.
107. Uberall MA, Mueller-Schwefe GH, Terhaag B. Efficacy and safety of flupirtine modified release for the management of moderate to severe chronic low back pain: results of SUPREME, a prospective randomized, double-blind, placebo- and active-controlled parallel-group phase IV study. Curr Med Res Opin. 2012;28(10):1617–34. https://doi.org/10.1185/03007995.2012.726216.
108. Webster LR, Butera PG, Moran LV, Wu N, Burns LH, Friedmann N. Oxytrex minimizes physical dependence while providing effective analgesia: a randomized controlled trial in low back pain. J Pain. 2006;7(12):937–46. https://doi.org/10.1016/j.jpain.2006.05.005.
109. Migliorini F, Maffulli N, Baroncini A, Eschweiler J, Tingart M, Quack V. Opioids for chronic low back pain management: a bayesian network meta-analysis. Expert Rev Clin Pharmacol. 2021;14(5):635–41. https://doi.org/10.1080/17512433.2021.1903316.

110. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared with placebo or other treatments for chronic low back pain: an update of the Cochrane Review. Spine (Phila Pa 1976). 2014;39(7):556–63. https://doi.org/10.1097/BRS.0000000000000249.
111. Edlund MJ, Martin BC, Russo JE, DeVries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. Clin J Pain. 2014;30(7):557–64. https://doi.org/10.1097/AJP.0000000000000021.
112. Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain–development of a typology of chronic pain patients. Drug Alcohol Depend. 2009;104(1–2):34–42. https://doi.org/10.1016/j.drugalcdep.2009.03.021.
113. Boscarino JA, Rukstalis M, Hoffman SN, Han JJ, Erlich PM, Gerhard GS, Stewart WF. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. Addiction. 2010;105(10):1776–82. https://doi.org/10.1111/j.1360-0443.2010.03052.x.
114. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. J Intern Med. 2013;273(5):511–26. https://doi.org/10.1111/joim.12035.
115. Deyo RA, Smith DH, Johnson ES, Tillotson CJ, Donovan M, Yang X, Petrik A, Morasco BJ, Dobscha SK. Prescription opioids for back pain and use of medications for erectile dysfunction. Spine (Phila Pa 1976). 2013;38(11):909–15. https://doi.org/10.1097/BRS.0b013e3182830482.
116. Rubinstein A, Carpenter DM. Elucidating risk factors for androgen deficiency associated with daily opioid use. Am J Med. 2014;127(12):1195–201. https://doi.org/10.1016/j.amjmed.2014.07.015.
117. Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM. Opioid dose and risk of road trauma in Canada: a population-based study. JAMA Intern Med. 2013;173(3):196–201. https://doi.org/10.1001/2013.jamainternmed.733.
118. Nuckols TK, Anderson L, Popescu I, Diamant AL, Doyle B, Di Capua P, Chou R. Opioid prescribing: a systematic review and critical appraisal of guidelines for chronic pain. Ann Intern Med. 2014;160(1):38–47. https://doi.org/10.7326/0003-4819-160-1-201401070-00732.
119. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, Glaser SE, Vallejo R. Opioid complications and side effects. Pain Physician. 2008;11(2 Suppl):105–20.
120. Hayden JA, van Tulder MW, Malmivaara A, Koes BW. Exercise therapy for treatment of non-specific low back pain. Cochrane Database Syst Rev. 2005;3CD000335. https://doi.org/10.1002/14651858.CD000335.pub2.
121. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev. 2015;1:CD004376. https://doi.org/10.1002/14651858.CD004376.pub3.
122. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Exercise for osteoarthritis of the hip. Cochrane Database Syst Rev. 2014;4:CD007912. https://doi.org/10.1002/14651858.CD007912.pub2.
123. Williams AC, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev. 2012;11:CD007407. https://doi.org/10.1002/14651858.CD007407.pub3.
124. Wallen M, Gillies D. Intra-articular steroids and splints/rest for children with juvenile idiopathic arthritis and adults with rheumatoid arthritis. Cochrane Database Syst Rev. 2006;1CD002824. https://doi.org/10.1002/14651858.CD002824.pub2.
125. Buchbinder R, Green S, Youd JM. Corticosteroid injections for shoulder pain. Cochrane Database Syst Rev. 2003;1CD004016. https://doi.org/10.1002/14651858.CD004016.
126. Kamper SJ, Apeldoorn AT, Chiarotto A, Smeets RJ, Ostelo RW, Guzman J, van Tulder MW. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: Cochrane systematic review and meta-analysis. BMJ. 2015;350:h444. https://doi.org/10.1136/bmj.h444.
127. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain–United States, 2016. JAMA. 2016;315(15):1624–45. https://doi.org/10.1001/jama.2016.1464.
128. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older P. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc. 2009;57(8):1331–46. https://doi.org/10.1111/j.1532-5415.2009.02376.x.
129. Chou R, Qaseem A, Snow V, Casey D, Cross JT Jr, Shekelle P, Owens DK, Clinical Efficacy Assessment Subcommittee of the American College of P, American College of P, American Pain Society Low Back Pain Guidelines P. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007;147(7):478–91. https://doi.org/10.7326/0003-4819-147-7-200710020-00006.
130. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, Egger M, Juni P. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ. 2011;342:c7086. https://doi.org/10.1136/bmj.c7086.
131. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, Schoelles KM. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010;1CD006605. https://doi.org/10.1002/14651858.CD006605.pub2.
132. Krebs EE, Lorenz KA, Bair MJ, Damush TM, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. J Gen Intern Med. 2009;24(6):733–8. https://doi.org/10.1007/s11606-009-0981-1.
133. Ostelo RW, Deyo RA, Stratford P, Waddell G, Croft P, Von Korff M, Bouter LM, de Vet HC. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. Spine (Phila Pa 1976). 2008;33(1):90–4. https://doi.org/10.1097/BRS.0b013e31815e3a10.
134. Miller M, Barber CW, Leatherman S, Fonda J, Hermos JA, Cho K, Gagnon DR. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. JAMA Intern Med. 2015;175(4):608–15. https://doi.org/10.1001/jamainternmed.2014.8071.
135. Liang Y, Turner BJ. Assessing risk for drug overdose in a national cohort: role for both daily and total opioid dose? J Pain. 2015;16(4):318–25. https://doi.org/10.1016/j.jpain.2014.11.007.
136. Zedler B, Xie L, Wang L, Joyce A, Vick C, Kariburyo F, Rajan P, Baser O, Murrelle L. Risk factors for serious prescription opioid-related toxicity or overdose among Veterans Health Administration patients. Pain Med. 2014;15(11):1911–29. https://doi.org/10.1111/pme.12480.
137. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. MMWR Recomm Rep. 2016;65(1):1–49. https://doi.org/10.15585/mmwr.rr6501e1.
138. Jones T, Lookatch S, Grant P, McIntyre J, Moore T. Further validation of an opioid risk assessment tool: the brief risk interview. J Opioid Manag. 2014;10(5):353–64. https://doi.org/10.5055/jom.2014.0226.
139. Lee C, Crawford C, Swann S, Active Self-Care Therapies for Pain, Working G. Multimodal, integrative therapies for the self-management of chronic pain symptoms. Pain Med. 2014;15(Suppl 1):76–85. https://doi.org/10.1111/pme.12408.
140. Gwira Baumblatt JA, Wiedeman C, Dunn JR, Schaffner W, Paulozzi LJ, Jones TF. High-risk use by patients prescribed opioids for pain and its role in overdose deaths. JAMA Intern Med. 2014;174(5):796–801. https://doi.org/10.1001/jamainternmed.2013.12711.
141. Jamison RN, Sheehan KA, Scanlan E, Matthews M, Ross EL. Beliefs and attitudes about opioid prescribing and chronic pain management: survey of primary care providers. J Opioid Manag. 2014;10(6):375–82. https://doi.org/10.5055/jom.2014.0234.
142. Oliveira CB, Amorim HE, Coombs DM, Richards B, Reedyk M, Maher CG, Machado GC. Emergency department interventions for adult patients with low back pain: a systematic review of randomised controlled trials. Emerg Med J. 2021;38(1):59–68. https://doi.org/10.1136/emermed-2020-209588.
143. Kapugi M, Cunningham K. Corticosteroids Orthop Nurs. 2019;38(5):336–9. https://doi.org/10.1097/NOR.0000000000000595.
144. Urquhart DM, Zheng Y, Cheng AC, Rosenfeld JV, Chan P, Liew S, Hussain SM, Cicuttini FM. Could low grade bacterial infection contribute to low back pain? A systematic review. BMC Med. 2015;13:13. https://doi.org/10.1186/s12916-015-0267-x.
145. Braten LCH, Rolfsen MP, Espeland A, Wigemyr M, Assmus J, Froholdt A, Haugen AJ, Marchand GH, Kristoffersen PM, Lutro O, Randen S, Wilhelmsen M, Winsvold BS, Kadar TI, Holmgard TE, Vigeland MD, Vetti N, Nygaard OP, Lie BA, Hellum C, Anke A, Grotle M, Schistad EI, Skouen JS, Grovle L, Brox JI, Zwart JA, Storheim K, group AIMs. Efficacy of antibiotic treatment in patients with chronic low back pain and modic changes (the AIM study): double blind, randomised, placebo controlled, multicentre trial. BMJ. 2019;367:l5654. https://doi.org/10.1136/bmj.l5654.
146. Nijs J, Van Houdenhove B, Oostendorp RA. Recognition of central sensitization in patients with musculoskeletal pain: application of pain neurophysiology in manual therapy practice. Man Ther. 2010;15(2):135–41. https://doi.org/10.1016/j.math.2009.12.001.

147. Seifert F, Maihofner C. Central mechanisms of experimental and chronic neuropathic pain: findings from functional imaging studies. Cell Mol Life Sci. 2009;66(3):375–90. https://doi.org/10.1007/s00018-008-8428-0.
148. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):2–S15. https://doi.org/10.1016/j.pain.2010.09.030.
149. Merskey H. (1994) Part III: Pain terms, a current list with definitions and notes on usage. In: Merskey H, editor Classification of Chronic Pain. Second Edition. IASP Press, Seattle, USA, pp 209–214
150. Meyer RA, Campbell IT, Raja SN. Peripheral neural mechanisms of nociception. In: Wall PD, Melzack R, editors. Textbook of Pain. 3rd ed. Edinburgh: Churchill Livingstone; 1995. pp. 13–44.
151. Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. Curr Opin Anaesthesiol. 2010;23(5):611–5. https://doi.org/10.1097/ACO.0b013e32833c348b.
152. Meeus M, Nijs J, Van de Wauwer N, Toeback L, Truijen S. Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: an experimental study. Pain. 2008;139(2):439–48. https://doi.org/10.1016/j.pain.2008.05.018.
153. Delpierre Y. Fear-avoidance beliefs, anxiety and depression are associated with motor control and dynamics parameters in patients with chronic low back pain. J Orthop. 2022;29:44–9. https://doi.org/10.1016/j.jor.2022.01.005.
154. Bobos P, Ziebart C, Furtado R, Lu Z, MacDermid JC. Psychometric properties of the global rating of change scales in patients with low back pain, upper and lower extremity disorders. A systematic review with meta-analysis. J Orthop. 2020;21:40–8. https://doi.org/10.1016/j.jor.2020.01.047.
155. Li L, Du X, Ling H, Li Y, Wu X, Jin A, Yang M. Gene correlation network analysis to identify regulatory factors in sciatic nerve injury. J Orthop Surg Res. 2021;16(1):622. https://doi.org/10.1186/s13018-021-02756-0.
156. Filatova E, Latysheva N, Kurenkov A. Evidence of persistent central sensitization in chronic headaches: a multi-method study. J Headache Pain. 2008;9(5):295–300. https://doi.org/10.1007/s10194-008-0061-7.
157. Raphael KG, Janal MN, Anathan S, Cook DB, Staud R. Temporal summation of heat pain in temporomandibular disorder patients. J Orofac Pain. 2009;23(1):54–64.
158. Deyo RA, Weinstein JN. Low back pain. N Engl J Med. 2001;344(5):363–70. https://doi.org/10.1056/NEJM200102013440508.
159. Borenstein DG. Epidemiology, etiology, diagnostic evaluation, and treatment of low back pain. Curr Opin Rheumatol. 2001;13(2):128–34. https://doi.org/10.1097/00002281-200103000-00006.
160. Roussel NA, Nijs J, Meeus M, Mylius V, Fayt C, Oostendorp R. Central sensitization and altered central pain processing in chronic low back pain: fact or myth? Clin J Pain. 2013;29(7):625–38. https://doi.org/10.1097/AJP.0b013e31826f9a71.
161. Smart KM, Blake C, Staines A, Doody C. Self-reported pain severity, quality of life, disability, anxiety and depression in patients classified with 'nociceptive', 'peripheral neuropathic' and 'central sensitisation' pain. The discriminant validity of mechanisms-based classifications of low back (+/-leg) pain. Man Ther. 2012;17(2):119–25. https://doi.org/10.1016/j.math.2011.10.002.
162. Julius D, Basbaum AI. Molecular mechanisms of nociception. Nature. 2001;413(6852):203–10. https://doi.org/10.1038/35093019.
163. Allegri M, Montella S, Salici F, Valente A, Marchesini M, Compagnone C, Baciarello M, Manferdini ME, Fanelli G. (2016) Mechanisms of low back pain: a guide for diagnosis and therapy. F1000Res 5. https://doi.org/10.12688/f1000research.8105.2.
164. Nijs J, Torres-Cueco R, van Wilgen CP, Girbes EL, Struyf F, Roussel N, van Oosterwijck J, Daenen L, Kuppens K, Vanwerweeen L, Hermans L, Beckwee D, Voogt L, Clark J, Moloney N, Meeus M. Applying modern pain neuroscience in clinical practice: criteria for the classification of central sensitization pain. Pain Physician. 2014;17(5):447–57.
165. Nijs J, Apeldoorn A, Hallegraeff H, Clark J, Smeets R, Malfliet A, Girbes EL, De Kooning M, Ickmans K. Low back pain: guidelines for the clinical classification of predominant neuropathic, nociceptive, or central sensitization pain. Pain Physician. 2015;18(3):E333–346.
166. Nijs J, Malfliet A, Ickmans K, Baert I, Meeus M. Treatment of central sensitization in patients with 'unexplained' chronic pain: an update. Expert Opin Pharmacother. 2014;15(12):1671–83. https://doi.org/10.1517/14656566.2014.925446.
167. Konno S, Oda N, Ochiai T, Alev L. Randomized, Double-blind, placebo-controlled phase III trial of Duloxetine Monotherapy in japanese patients with chronic low back Pain. Spine (Phila Pa 1976). 2016;41(22):1709–17. https://doi.org/10.1097/BRS.0000000000001707.
168. Schukro RP, Oehmke MJ, Geroldinger A, Heinze G, Kress HG, Pramhas S. Efficacy of Duloxetine in Chronic Low Back Pain with a neuropathic component: a Randomized, Double-blind, placebo-controlled crossover trial. Anesthesiology. 2016;124(1):150–8. https://doi.org/10.1097/ALN.0000000000000902.
169. Skljarevski V, Desaiah D, Liu-Seifert H, Zhang Q, Chappell AS, Detke MJ, Iyengar S, Atkinson JH, Backonja M. Efficacy and safety of duloxetine in patients with chronic low back pain. Spine (Phila Pa 1976). 2010;35(13):E578–585. https://doi.org/10.1097/BRS.0b013e3181d3cef6.
170. Skljarevski V, Zhang S, Chappell AS, Walker DJ, Murray I, Backonja M. Maintenance of effect of duloxetine in patients with chronic low back pain: a 41-week uncontrolled, dose-blinded study. Pain Med. 2010;11(5):648–57. https://doi.org/10.1111/j.1526-4637.2010.00836.x.
171. Skljarevski V, Zhang S, Desaiah D, Alaka KJ, Palacios S, Miazgowski T, Patrick K. Duloxetine versus placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. J Pain. 2010;11(12):1282–90. https://doi.org/10.1016/j.jpain.2010.03.002.
172. Jones CK, Peters SC, Shannon HE. Efficacy of duloxetine, a potent and balanced serotonergic and noradrenergic reuptake inhibitor, in inflammatory and acute pain models in rodents. J Pharmacol Exp Ther. 2005;312(2):726–32. https://doi.org/10.1124/jpet.104.075960.
173. Devulder J. Flupirtine in pain management: pharmacological properties and clinical use. CNS Drugs. 2010;24(10):867–81. https://doi.org/10.2165/11536230-000000000-00000.
174. Ueberall MA, Mueller-Schwefe GH, Terhaag B. Efficacy and tolerability of flupirtine in subacute/ chronic musculoskeletal pain - results of a patient level, pooled re-analysis of randomized, double-blind, controlled trials. Int J Clin Pharmacol Ther. 2011;49(11):637–47. https://doi.org/10.5414/cp210000.
175. Worz R, Bolten W, Heller B, Krainick JU, Pergande G. [Flupirtine in comparison with chlormezanone in chronic musculoskeletal back pain. Results of a multicenter randomized double-blind study]. Fortschr Med. 1996;114(35–36):500–4.
176. Biehl B. [The effect of the analgesic flupirtine on automobile driving]. Arzneimittelforschung. 1985;35(1):77–81.
177. Atkinson JH, Slater MA, Capparelli EV, Patel SM, Wolfson T, Gamst A, Abramson IS, Wallace MS, Funk SD, Rutledge TR, Wetherell JL, Matthews SC, Zisook S, Garfin SR. A randomized controlled trial of gabapentin for chronic low back pain with and without a radiating component. Pain. 2016;157(7):1499–507. https://doi.org/10.1097/j.pain.0000000000000554.
178. Robertson K, Marshman LAG, Plummer D, Downs E. Effect of Gabapentin vs Pregabalin on Pain Intensity in adults with chronic Sciatica: a Randomized Clinical Trial. JAMA Neurol. 2019;76(1):28–34. https://doi.org/10.1001/jamaneurol.2018.3077.
179. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev. 2014;1:CD007115. https://doi.org/10.1002/14651858.CD007115.pub3.
180. Hagg S, Jonsson AK, Ahlner J. Current evidence on abuse and misuse of gabapentinoids. Drug Saf. 2020;43(12):1235–54. https://doi.org/10.1007/s40264-020-00985-6.
181. Koes BW, van Tulder M, Lin CW, Macedo LG, McAuley J, Maher C. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. Eur Spine J. 2010;19(12):2075–94. https://doi.org/10.1007/s00586-010-1502-y.
182. Khoromi S, Patsalides A, Parada S, Salehi V, Meegan JM, Max MB. Topiramate in chronic lumbar radicular pain. J Pain. 2005;6(12):829–36. https://doi.org/10.1016/j.jpain.2005.08.002.
183. Muehlbacher M, Nickel MK, Kettler C, Tritt K, Lahmann C, Leiberich PK, Nickel C, Krawczyk J, Mitterlehner FO, Rother WK, Loew TH, Kaplan P. Topiramate in treatment of patients with chronic low back pain: a randomized, double-blind, placebo-controlled study. Clin J Pain. 2006;22(6):526–31. https://doi.org/10.1097/ajp.0000192516.58578.a4.
184. Enke O, New HA, New CH, Mathieson S, McLachlan AJ, Latimer J, Maher CG, Lin CC. Anticonvulsants in the treatment of low back pain and lumbar radicular pain: a systematic review and meta-analysis. CMAJ. 2018;190(26):E786–93. https://doi.org/10.1503/cmaj.171333.
185. Khong TK, Lall K. No benefit from amitriptyline for chronic low back pain? Drug Ther Bull. 2020;58(4):53–4. https://doi.org/10.1136/dtb.2019.000088.
186. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, Mannion AF, Reis S, Staal JB, Ursin H, Zanoli G, Pain CBWGoGfCLB. Chap. 4. European guidelines for the management of chronic nonspecific low back pain. Eur Spine J. 2006;15(Suppl 2):192–300. https://doi.org/10.1007/s00586-006-1072-1.

187. Atkinson JH, Slater MA, Wahlgren DR, Williams RA, Zisook S, Pruitt SD, Epping-Jordan JE, Patterson TL, Grant I, Abramson I, Garfin SR. Effects of noradrenergic and serotonergic antidepressants on chronic low back pain intensity. Pain. 1999;83(2):137–45. https://doi.org/10.1016/s0304-3959(99)00082-2.
188. Pheasant H, Bursk A, Goldfarb J, Azen SP, Weiss JN, Borelli L. Amitriptyline and chronic low-back pain. A randomized double-blind crossover study. Spine (Phila Pa 1976). 1983;8(5):552–7. https://doi.org/10.1097/00007632-198307000-00012.
189. Schliessbach J, Siegenthaler A, Butikofer L, Limacher A, Juni P, Vuilleumier PH, Stamer U, Arendt-Nielsen L, Curatolo M. Effect of single-dose imipramine on chronic low-back and experimental pain. A randomized controlled trial. PLoS ONE. 2018;13(5):e0195776. https://doi.org/10.1371/journal.pone.0195776.
190. Schliessbach J, Siegenthaler A, Butikofer L, Vuilleumier P, Juni P, Stamer U, Arendt-Nielsen L, Curatolo M. Predicting drug efficacy in chronic low back pain by quantitative sensory tests. Eur J Pain. 2018;22(5):973–88. https://doi.org/10.1002/ejp.1183.
191. Urquhart DM, Wluka AE, van Tulder M, Heritier S, Forbes A, Fong C, Wang Y, Sim MR, Gibson SJ, Arnold C, Cicuttini FM. Efficacy of low-dose amitriptyline for chronic low back Pain: a Randomized Clinical Trial. JAMA Intern Med. 2018;178(11):1474–81. https://doi.org/10.1001/jamainternmed.2018.4222.
192. Urquhart DM, Hoving JL, Assendelft WW, Roland M, van Tulder MW. Antidepressants for non-specific low back pain. Cochrane Database Syst Rev. 2008;1CD001703. https://doi.org/10.1002/14651858.CD001703.pub3.
193. Morgan DJ, Dhruva SS, Wright SM, Korenstein D. 2016 Update on Medical Overuse: a systematic review. JAMA Intern Med. 2016;176(11):1687–92. https://doi.org/10.1001/jamainternmed.2016.5381.
194. Cashin AG, Folly T, Bagg MK, Wewege MA, Jones MD, Ferraro MC, Leake HB, Rizzo RRN, Schabrun SM, Gustin SM, Day R, Williams CM, McAuley JH. Efficacy, acceptability, and safety of muscle relaxants for adults with non-specific low back pain: systematic review and meta-analysis. BMJ. 2021;374:n1446. https://doi.org/10.1136/bmj.n1446.

## Publisher's Note