Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2026-B-030 VER-01 (Extrakt aus Cannabisblüten)

Stand: April 2026

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

VER-01 (Extrakt aus Cannabisblüten)
[chronischer Kreuzschmerz mit radikulärer (neuropathischer) Komponente]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	– Physiotherapie inkl. physikalische Therapien und Ergotherapie (gemäß Heilmittelrichtlinie/HeilM-RL, sowie des Heilmittelkatalogs) – Akupunktur
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Verordnungseinschränkungen und -ausschlüsse (AM-RL, Anlage III): 6. Analgetika in fixer Kombination mit nicht analgetischen Wirkstoffen, ausgenommen Kombinationen mit Naloxon Zugelassene Ausnahmen zum gesetzlichen Verordnungsausschluss (AM-RL, Anlage I): 3. Acetylsalicylsäure und Paracetamol nur zur Behandlung schwerer und schwerster Schmerzen in Co-Medikation mit Opioiden. Beschluss des G-BA hinsichtlich des Einsatzes von Akupunktur zur Behandlung chronischer Gonarthroseschmerzen/chronischer Schmerzen der Lendenwirbelsäule (Beschluss vom 19.09.2006) DMP-Anforderungen-Richtlinie nach § 137f Absatz 2 SGB V: Anlage 15 Anforderungen an das strukturierte Behandlungsprogramm für Patientinnen und Patienten mit chronischem Rückenschmerz (1. Oktober 2021)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet[1]

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Extrakt aus Cannabisblüten Exilby	Anwendungsgebiet laut Beratungsantrag: Exilby ist indiziert als Monotherapie zur Behandlung chronischer Kreuzschmerzen mit radikulärer (neuropathischer) Komponente bei Erwachsenen, bei denen eine vorherige Therapie mit nicht-Opioid Analgetika nicht zu einer ausreichenden Schmerzlinderung geführt hat oder wegen Kontraindikationen oder Unverträglichkeiten ungeeignet ist.
Opioid-Analgetika	
Morphin N02AA01 Morphin Merck	Starke und stärkste Schmerzen. Stand FI: September 2023
Hydromorphon N02AA03 Hydromorphon-HCl Hormosan	Behandlung von starken Schmerzen. Stand FI: Oktober 2022
Oxycodon N02AA05 Oxycodon-HCl AbZ	Starke Schmerzen, die nur mit Opioid-Analgetika angemessen behandelt werden können. Stand FI: Januar 2025
Dihydrocodein N02AA08 DHC Ennogen Retardkapseln	60 mg: mittelstarke Schmerzen. 90 mg: mittelstarke Schmerzen. 120 mg: mittelstarke bis starke Schmerzen. Stand FI: März 2024

[1] Aufgrund der Vielzahl der verfügbaren Wirkstoffe wird eine Auswahl von Wirkstoffen dargestellt.

II. Zugelassene Arzneimittel im Anwendungsgebiet[1]	
Fentanyl N02AB03 Fentanyl AbZ Matrixpflaster	Fentanyl AbZ wird angewendet zur Behandlung starker chronischer Schmerzen, die eine kontinuierliche Langzeitanwendung von Opioiden erfordern. Stand FI: Februar 2024
Tramadol N02AX02 Tramadol 50 Kapseln - 1A Pharma	Behandlung von mäßig starken bis starken Schmerze Stand FI: Mai 2024
Tilidin/Naloxon N02AX01 Tilicomp beta	Zur Behandlung starker und sehr starker Schmerzen. Stand FI: März 2022
Nicht-Opioid Analgetika	
Metamizol N02BB02 Metamizol AbZ	Metamizol AbZ ist angezeigt für Erwachsene und Jugendliche ab 15 Jahre zur Behandlung von […] – sonstigen akuten oder chronischen starken Schmerzen, soweit andere therapeutische Maßnahmen nicht indiziert sind Stand FI: November 2024
Paracetamol N02BE01 Paracetamol - 1A Pharma	Symptomatische Behandlung leichter bis mäßig starker Schmerzen wie Kopfschmerzen, Zahnschmerzen, Regelschmerzen und/oder von Fieber. Stand FI: Januar 2025
Nicht-steroidale Antirheumatika	
Acetylsalicylsäure N02BA01 Aspirin	Symptomatische Behandlung bei leichten bis mäßig starken Schmerzen und/oder Fieber. Stand FI: Oktober 2023
Ibuprofen M01AE01	Leichte bis mäßig starke Schmerzen, Fieber Stand FI: Oktober 2024

II. Zugelassene Arzneimittel im Anwendungsgebiet[1]	
Ibuprofen AL 400	
Naproxen M01AE02 Dolormin GS mit Naproxen 250mg	Symptomatische Behandlung leichter bis mäßig starker Schmerzen z.B. bei bekannter Arthrose Stand FI: Mai 2025
Diclofenac M01AB05 Voltaren dolo 25mg	Zur symptomatischen Behandlung von leichten bis mäßig starken Schmerzen. Stand FI: August 2025
Andere Wirkstoffe	
Amitriptylin N06AA09 Amitriptylin-neuraxpharm	Amitriptylin-neuraxpharm wird angewendet: […] – zur Behandlung von neuropathischen Schmerzen bei Erwachsenen Stand FI: November 2025
Imipramin N06AA02 Imipramin-neuraxpharm	- Langfristige Schmerzbehandlung im Rahmen eines therapeutischen Gesamtkonzeptes Stand FI: Dezember 2020
Clomipramin N06AA04 Clomipramin-neuraxpharm	- Langfristige Schmerzbehandlung im Rahmen eines therapeutischen Gesamtkonzeptes Stand FI: November 2025

III. Zugelassene Arzneimittel im Anwendungsgebiet[1]	
Gabapentin N02BF01 Gabapentin-ratiopharm	Gabapentin ist zur Behandlung von peripheren neuropathischen Schmerzen wie schmerzhafter diabetischer Neuropathie und postherpetischer Neuralgie bei Erwachsenen indiziert Stand FI: August 2024
Pregabalin N02BF02 Pregabalin AbZ	Pregabalin AbZ wird angewendet zur Behandlung von peripheren und zentralen neuropathischen Schmerzen im Erwachsenenalter. Stand FI: Juli 2024
Capsaicin N01BX04 Qutenza 179 mg kutanes Pflaster	Qutenza wird zur Behandlung von peripheren neuropathischen Schmerzen bei Erwachsenen angewendet. Qutenza kann als Monotherapie oder in Kombination mit anderen Arzneimitteln zur Behandlung von Schmerzen angewendet werden. Stand FI: Oktober 2023

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2026-B-030 (Beratung nach § 35a SGB V) VER-01/Exilby®

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	9. April 2026

Inhaltsverzeichnis

Abkürzungsverzeichnis

AHRQ	Agency for Healthcare Research and Quality
AE	Adverse event
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CI	Confidence interval
CNS	Central nervous system
CPG	Clinical practice guideline
CPLBP	Chronic primary low back pain
CV	Cardiovascular
CVD	Cardiovascular disease
DoD	Department of Defense
EC	Expert consensus
ECG	Electrocardiogram
ECRI	Emergency Care Research Institute
EtD	Evidence to decision
FDA	Federal Drug Agency
GDG	Guideline development group
GI	Gastrointestinal
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICTRP	International Clinical Trials Registry Platform
JSE	Joint safety event
KQ	Key question
LBP	Low back pain
LBPI	Low back pain intensity
LoE	Level of Evidence
LRS	Lumbosacral radicular syndrome
mAB	Monoclonal antibody
MDD	Major depressive disorder
mhGAP	Mental health gap action programme
NICE	National Institute for Health and Care Excellence
NRS	Numerical rating scale
NSAID	Nichtsteroidales Antirheumatikum
OA	Osteoarthritis

ODI	Oswestry Disability Index
PCP	Primary care provider
RCT	Randomized Controlled Trial
RMDQ	Roland Morris Disability Questionnaire
RPOA	Rapidly progressive osteoarthritis
SC	Subcutaneous
SIGN	Scottish Intercollegiate Guidelines Network
SMT	Spinal manipulative therapy
SNRI	Serotonin and norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressants
TeCa	Tetracyclic antidepressant
TENS	Transcutaneous electrical nerve stimulation
TRIP	Turn Research into Practice Database
VA	Department of Veterans Affairs
VAS	Visual analogue scale
WHO	World Health Organization

1 Indikation

Behandlung chronischer Kreuzschmerzen mit radikulärer (neuropathischer) Komponente bei Erwachsenen, bei denen eine vorherige Therapie mit nicht-Opioid Analgetika nicht zu einer ausreichenden Schmerzlinderung geführt hat oder wegen Kontraindikationen oder Unverträglichkeiten ungeeignet ist.

Hinweis zur Synopse: „Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt“.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Kreuzschmerzen* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 03.03.2026 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 2816 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Alle eingeschlossenen Referenzen wurden im Volltext beschafft. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen im Volltext gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet.

Basierend darauf, wurden insgesamt 7 Referenzen eingeschlossen.

Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Ferraro M et al., 2025 [4].

Antidepressants for low back pain and spine-related leg pain

Fragestellung

To assess the benefits and harms of antidepressants for nonspecific low back pain and spine-related leg pain.

Methodik

Population:

- We included studies in adults, aged 18 years and above, with nonspecific low back pain or spine-related leg pain, of any duration.
- Non-specific low back pain was defined as pain between the costal margin and the inferior gluteal fold, with or without associated leg pain (Dionne 2008).
- Spine-related leg pain was defined as somatic referred pain, radicular pain with radiculopathy, or radicular pain without radiculopathy, or other descriptions suggestive of those definitions.
- Included participants may or may not have reported depressive symptoms.

Intervention/Komparator:

- We included studies comparing a systemically administered dose of an antidepressant medicine with a placebo, an active placebo (i.e. a medicine with no effect on pain that mimics the active drug's side effects), continuation of usual care, no treatment, or a waiting list. Trials comparing an antidepressant plus another medicine with a placebo plus the other medicine were also included.
- Participants in the antidepressant and comparator arms may have received co-interventions such as oral medicines, physical therapies, and psychological therapies. We included studies where participants received such co-interventions if they were applied equally across treatment arms.
- We grouped comparisons of antidepressants versus reference treatments into the following categories:
  - antidepressant versus placebo;
  - antidepressant versus usual care;
  - antidepressant versus no treatment/waiting list.
- We classed antidepressants using codes from the Anatomical Therapeutic Chemical (ATC) classification system controlled by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHO 2022).

Endpunkte:

- Primary outcomes:
  - Participant-reported pain intensity, measured using a visual analogue scale (VAS), a numerical rating scale (NRS), a Likert scale, a rating scale within a composite measure of pain (e.g. McGill Pain Questionnaire), or an ordinal scale.

  - Disability, defined as low back-specific disability, measured on a subjective rating scale (e.g. Oswestry Disability Index (ODI) and Roland Morris Disability Questionnaire (RMDQ)), a rating scale within a composite measure of disability, or an ordinal scale.
  - Total adverse events, measured by the number of participants who experienced an adverse event. We defined an adverse event as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related" (FDA 2020).
- Secondary outcomes:
  - Serious adverse events, measured by the number of participants who experienced a serious adverse event. We defined a serious adverse event as "death, threat to life, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions" (FDA 2020).
  - Withdrawals due to adverse events, measured by the number of participants who discontinued treatment due to adverse events.
  - Depressive symptoms, measured using a formal rating scale of depressive symptoms (e.g. Beck Depression Inventory and Montgomery-Åsberg Depression Rating Scale).
  - Health-related quality of life, measured using a validated quality of life scale (e.g. EuroQol-5D, 12-item Short-Form Health-Related Qualify of Life Survey).

Recherche/Suchzeitraum:

- For this updated review, we included the previous review as a source of studies, and searched the following databases from inception to 14 November 2024, with no language restrictions:
  - Cochrane Central Register of Controlled Trials (CENTRAL; 2024, Issue 11);
  - MEDLINE (Ovid; 1946 to 14 November 2024);
  - Embase (Ovid; 1947 to 14 November 2024).
- In this update, we amended our original search strategies using terms developed by the Cochrane Musculoskeletal group. We did not search the PsycINFO database for the current version.
- We also searched ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), and the EU Clinical Trials Register (www.clinicaltrialsregister.eu).
- We checked reference lists of all primary studies and review articles for additional references. We contacted experts in the field for unpublished and ongoing studies. Where necessary, we contacted study authors for additional information. We screened the titles of all included studies and citations on the Retraction Watch database to ensure none were retracted (Center for Scientific Integrity 2018).

Qualitätsbewertung der Studien:

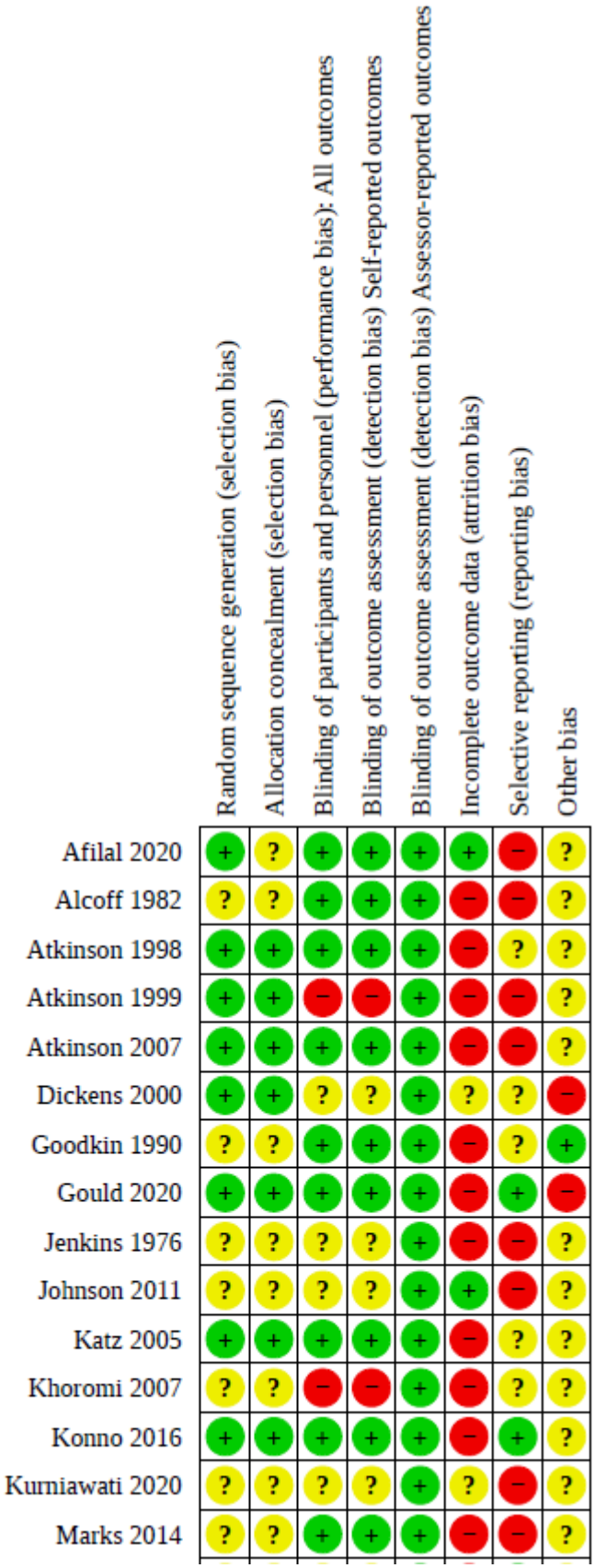
- Cochrane's risk of bias (RoB) 1 tool, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017).

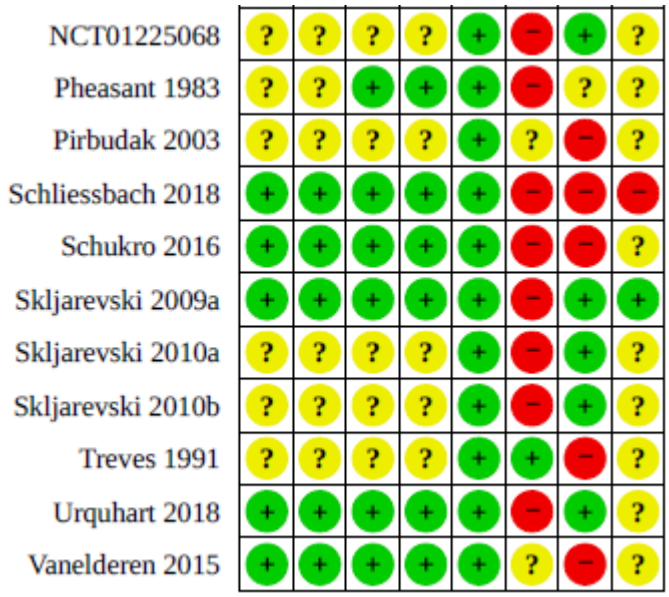
Ergebnisse

Anzahl eingeschlossener Studien:

- 26 studies (n=2932)
- 20 studies included in the quantitative synthesis (meta-analysis)

Qualität der Studien:





Studienergebnisse:

Summary of findings 3. Summary of findings table - Tricyclic antidepressants compared to placebo for adults with non-specific low back pain and spine-related leg pain

Tricyclic antidepressants compared to placebo for adults with non-specific low back pain and spine-related leg pain

Patient or population: adults with non-specific low back pain and spine-related leg pain
Setting: outpatient (primary care clinics), inpatient (hospital rheumatology and neurology departments) and community
Intervention: tricyclic antidepressants
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with tricyclic antidepressants				
Pain intensity (non-specific low back pain) Scale from: 0 to 100 follow-up: range 4 weeks to 16 weeks	The mean pain intensity was **38.2**	MD **2 lower** (7.25 lower to 3.24 higher)	-	417 (4 RCTs)	⊕⊕⊕⊖ Moderate[a]	Tricyclic antidepressants probably result in little to no difference in pain intensity in people with non-specific low back pain.

Pain intensity (spine-related leg pain) Scale from: 0 to 100 follow-up: range 4 weeks to 16 weeks	The mean pain intensity was **33**	MD **23 lower** (32.12 lower to 13.88 lower)	-	60 (1 RCT)	⊕⊕⊙⊙ Low[b]	Tricyclic antidepressants may have a large effect on pain intensity in people with spine-related leg pain.
Disability (non-specific low back pain) assessed with: Roland Morris Disability Questionnaire Scale from: 0 to 24 follow-up: range 4 weeks to 16 weeks	The mean disability was **7.4**	MD **1.76 lower** (2.7 lower to 0.82 lower)	-	330 (3 RCTs)	⊕⊕⊕⊙ Moderate[a]	Tricyclic antidepressants probably have a small effect on disability in people with non-specific low back pain.
Disability (spine-related leg pain) assessed with: Oswestry Disability Index Scale from: 0 to 100 follow-up: range 4 weeks to 16 weeks	The mean disability was **35**	MD **13 lower** (19.4 lower to 6.6 lower)	-	60 (1 RCT)	⊕⊕⊙⊙ Low[b]	Tricyclic antidepressants may have a moderate effect on disability in people with spine-related leg pain.
Total adverse events (non-specific low back pain and spine-related leg pain)	351 per 1000	**618 per 1000** (277 to 1000)	**RR 1.76** (0.79 to 3.90)	474 (7 RCTs)	⊕⊕⊙⊙ Low[c,d]	The evidence is uncertain about the risk of adverse events with tricyclic antidepressant use in people with non-specific low back pain and spine-related leg pain.
Serious adverse events (non-specific low back pain and spine-related leg pain)	0 per 1000	**0 per 1000** (0 to 0)	**OR 6.64** (0.41 to 106.72)	142 (1 RCT)	⊕⊙⊙⊙ Very low[e,f]	The evidence is very uncertain about the risk of serious adverse events with tricyclic antidepressant use in people with non-specific low back pain and spine-related leg pain, due to the small number of studies and few events. We could not estimate absolute risk as there were no events in the control group.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_447774841358666296.

[a] Downgraded once for risk of bias: high risk of attrition, reporting, and other bias.
[b] Downgraded twice for risk of bias: high risk of reporting bias and unclear risk of selection, performance, detection, attrition, and other bias.
[c] Downgraded once for risk of bias: high risk of attrition bias and unclear risk of selection bias.
[d] Downgraded once for imprecision: 95% CI compatible with an increased risk and a decreased risk.
[e] Downgraded twice for risk of bias: high risk of attrition and other bias.
[f] Downgraded twice for imprecision: 95% CI compatible with an increased risk and a decreased risk.

Anmerkung/Fazit der Autoren

Moderate-certainty evidence suggests that for people with non-specific low back pain, serotonin and norepinephrine reuptake inhibitors (SNRIs) probably have small effects on pain intensity, trivial effects on disability, and are probably associated with adverse effects. Moderate-certainty evidence suggests that tricyclic antidepressants (TCAs) probably have little to no effect on pain intensity, but probably have a small effect on disability in people with non-specific low back pain. For both SNRIs and TCAs, effects were observed in people with chronic symptoms (≥ three months) up to 14 weeks following a treatment course of at least seven weeks. It remains unclear whether the duration of symptoms or medicine dose modify the treatment effect. These findings may not apply to older people, or those with significant comorbidities, as these populations were generally excluded from studies. There is insufficient evidence to support or refute the use of selective serotonin reuptake inhibitors (SSRIs), TeCAs (tetracyclic antidepressants), or other antidepressants in non-specific low back pain, or any antidepressant class in spine-related leg pain. Critically, these findings do not imply that severely depressed people with non-specific low back pain or spine-related leg pain should not be treated with antidepressants. The findings of this review might be considered in future updates to clinical practice guidelines for low back pain and spine-related leg pain.

Kommentare zum Review

Der Review identifizierte Studien zu folgenden Wirkstoffklassen:

- Serotonin-Noradrenalin-Wiederaufnahmehemmer (SNRI)
- Selektive Serotonin-Wiederaufnahmehemmer (SSRI)
- Trizyklische Antidepressiva
- Tetrazyklische Antidepressiva
- Andere Antidepressiva

Im vorliegenden Anwendungsgebiet sind die trizyklischen Antidepressiva Amitriptylin und Clomipramin zugelassen, weshalb die Ergebnisse zu den trizyklischen Antidepressiva aus diesem Cochrane Review extrahiert wurden.

3.2 Systematische Reviews

Ward J et al., 2024 [6].

A Meta-analysis Exploring the Efficacy of Neuropathic Pain Medication for Low Back Pain or Spine-Related Leg Pain: Is Efficacy Dependent on the Presence of Neuropathic Pain?

Fragestellung

This meta-analysis aimed to determine how neuropathic pain is identified in clinical trials for people taking neuropathic pain medication for low back pain or spine-related leg pain and whether subgrouping based on the presence of neuropathic pain influences efficacy.

Methodik

Population:

- participants with any duration of LBP with or without spine-related leg pain were included

Intervention/Komparator:

- Eligible neuropathic pain medications were commonly prescribed first-line oral medications as recommended by NeuPSIG guidelines (SNRI, including duloxetine or venlafaxine; TCAs, including amitriptyline, nortriptyline, or desipramine; and anticonvulsants, including gabapentin or pregabalin)
- Comparators were placebo or usual care.
- As most medication studies allow add-on or rescue medication, usual care could include other pain medications, if both groups had the same access to this medication. We therefore also included comparative effectiveness studies, if both groups took a matching dose of a non-neuropathic pain medication (A) and one group had an additional neuropathic pain medication added (A plus B).

Endpunkte:

- Primary outcomes were average leg pain intensity (or back pain, where leg pain was not reported) [3, 43] and disability outcomes. Where possible, outcomes were grouped by timepoints into (a) short term (< 12 weeks), (b) medium term (≥ 12 weeks, < 52 weeks), and (c) long term (≥ 52 weeks). If multiple outcomes were reported within one period, the outcome closest to 7 weeks, 6 months, and 12 months was used.

Recherche/Suchzeitraum:

- A single investigator searched EMBASE, MEDLINE, CENTRAL, CINAHL (EBSCO), and APA PsycINFO databases from inception to 9 May, 2022, and updated on 14 May, 2024.
- Ongoing trials were searched for in Clinical.Trials.gov and the World Health Organization International Clinical Trials Registry and data requests sent to authors of studies <3 years old. The search strategy (ESM) was developed with a medical librarian.

Qualitätsbewertung der Studien:

- Cochrane Collaboration Risk of Bias tool (RoB2)

Ergebnisse

Anzahl eingeschlossener Studien:

- 27 studies [57–83] summarizing findings from *n* = 3619 participants

Charakteristika der Population/Studien:

Table 2 (continued)

Study design Recruited; completed	Group 1 (G1) Recruited; drop out; age; gender; duration; severity	Group 2 (G2) Recruited; drop out; age; gender; duration; severity	Medication duration; dose (plus rescue meds allowed)	Primary (PO)/secondary outcome (SO) (where specified	Primary pain outcome (as reported in study) and between-group *p* value	Primary disability outcome (as reported in the study)
McCleane 2001 [68] Randomized, double-bind, placebo-controlled study Recruited *n* = 80 Completed *n* = 65	*n* = 40 participants Drop out *n* = 9 Age 41.3 (13.1) years Duration 63.1 (45.3) months Female 48.4% Severity neuropathic painS (0–10) leg pain 6.37 (2.27)	*n* = 40 Drop out *n* = 6 Age 47.8 (11.7) years Duration 74.5 (82) months Female 61.8% Severity neuropathic painS (0–10) leg pain 6.57 (2.32)	G1; 6 weeks gabapentin Weeks; 1; 300 mg OD 2; 300 mg BD 3; 300 mg TDS 4; 300 mg QDS 4-6; maximum dose maintained G2; 6 weeks placebo	Primary outcome not specified but recorded average NRS daily back pain, daily spine-related leg pain and daily ability to flex spine reported by subjects at baseline and 8 weeks	Mean (SD) final value VAS (0–10) 8 weeks leg pain; G1; 5.92 (2.61) G2; 6.33 (2.39) [$p > 0.05$]	Not measured
Yaksi 2007 [58] Randomized controlled study Recruited *n* = 55. Completed *n* = 55	*n* = 28 Drop out *n* = 0 Age 50.7 (9.6) years Duration not reported Female 79% Severity VAS (0–10) 7.0 (1.5)	*n* = 27 Drop out *n* = 0 Age 50.9 (10.5) years Duration not reported Female 56% Severity VAS 6.7 (1.2)	G1; 4 months of gabapentin 300 mg TDS. Increasing by 300 mg each week up to a maximum of 2400 mg for 4 months plus usual care (as per G2) G2; 4 months of usual care (physiotherapy lumbosacral corset and NSAIDs)	Primary outcome not specified but recorded walking distance, motor and sensory deficits, and back and spine-related leg pain on movement at baseline and 4 months	Mean (SD) final value NRS (0–10) 2 months; G1; at 4.3 (2.1) G2; 5.0 (1.8) [$p = 0.119$] 4 months G1; 2.9 (2.6) G2; 4.7 (2.2) [$p = 0.006$]	Not measured
Yildirim 2003 [57] Randomized placebo-controlled study Recruited *n* = 50 Completed *n*=43	*n* = 25 Drop out *n* = 2 Age 38 (7.4) years Female 60% Duration 69.3 (56) months Severity pain at rest (0–3 scale) 1.6 (0.94)	*n* = 25 Drop out *n* = 5 (inefficacy) Female 68% Age 40.5 (10.5) years Duration 67.7 (63.4) months Severity score for pain at rest (0–3 scale) 1.68 (0.67)	G1; 8 weeks gabapentin from 300 mg up to a total of 1200 mg TDS. Dose increased every 3 days depending upon AE G2; 8 weeks of placebo Add-on meds; nil allowed	Primary outcome not specified but recorded; location of pain, severity of pain on 0–3 scale, limitation of spinal flexion, SLR, reflexes, sensory change and muscle strength at 8 weeks	8 weeks pain score (scale 0–3); G1; 0.56 (0.58) G2; 1.36 + 0.59 ($p < 0.001$)	Not tested

Table 3 (continued)

Study ID	Exclusions of neuropathic pain	Descriptors or screening tools of neuropathic pain	Bedside neurological examination or QST	Confirmatory diagnostic tests including imaging or neurophysiology	Judgment of neuropathic pain (unclear, unlikely, possible, probable, or definite)
Yaksi 2007 [58]	Exclusions of relevance include subjects with signs of advanced disc herniation on MRI, although no further details provided on how this was judged	Inclusion criteria: back and leg pain and signs of neurogenic spinal stenosis such as numbness/feebleness and cramps in legs on walking/standing. Although the actual numbers of patients reporting numbness was not detailed, bedside tests and MRI were performed in all participants	61% of Rx/70% of the control group had sensory deficits in either L4/5 or S1 dermatomes. 17% of Rx/15% of the control group had motor deficits (mostly in dorsiflexion with a range from grade 2 to grade 4/5 on the Oxford Scale)	All patients had evidence of degenerative lumbar spinal stenosis on CT or MRI	Definite: inclusion criteria included symptoms suggestive of neuropathic pain, >50% of participants had sensory loss on examination and all patients had signs of stenosis on MRI or CT
Yildirim 2003 [57]	None	Inclusion criteria was lumbosacral radiculopathy. At baseline assessment, 84% of subjects reported to have unilateral radiculopathy, and 16% bilateral. The overall mean pain distribution was to heel or ankle in both Rx and control groups. No mention of neuropathic pain descriptors such as burning or shooting pain was used	At baseline, mean testing in both treatment and control groups: sensory changes averaged 1.78 (0.42) in the Rx group and 1.78 (0.58) in the control group, where 1 is mild change and 2 is moderate sensory loss. Given the small standard deviations, [89] the majority of participants appear to have had some sensory loss. SLR, reflexes, and muscle strength were also examined	Spinal MRI showed that all participants had L4–5 and/or L5-S1 bulging and/or protrusion without significant spinal stenosis	Definite: inclusion criteria included symptoms suggestive of neuropathic pain, >50% of participants had sensory loss on examination and all patients had signs of disc bulge on MRI

Qualität der Studien:

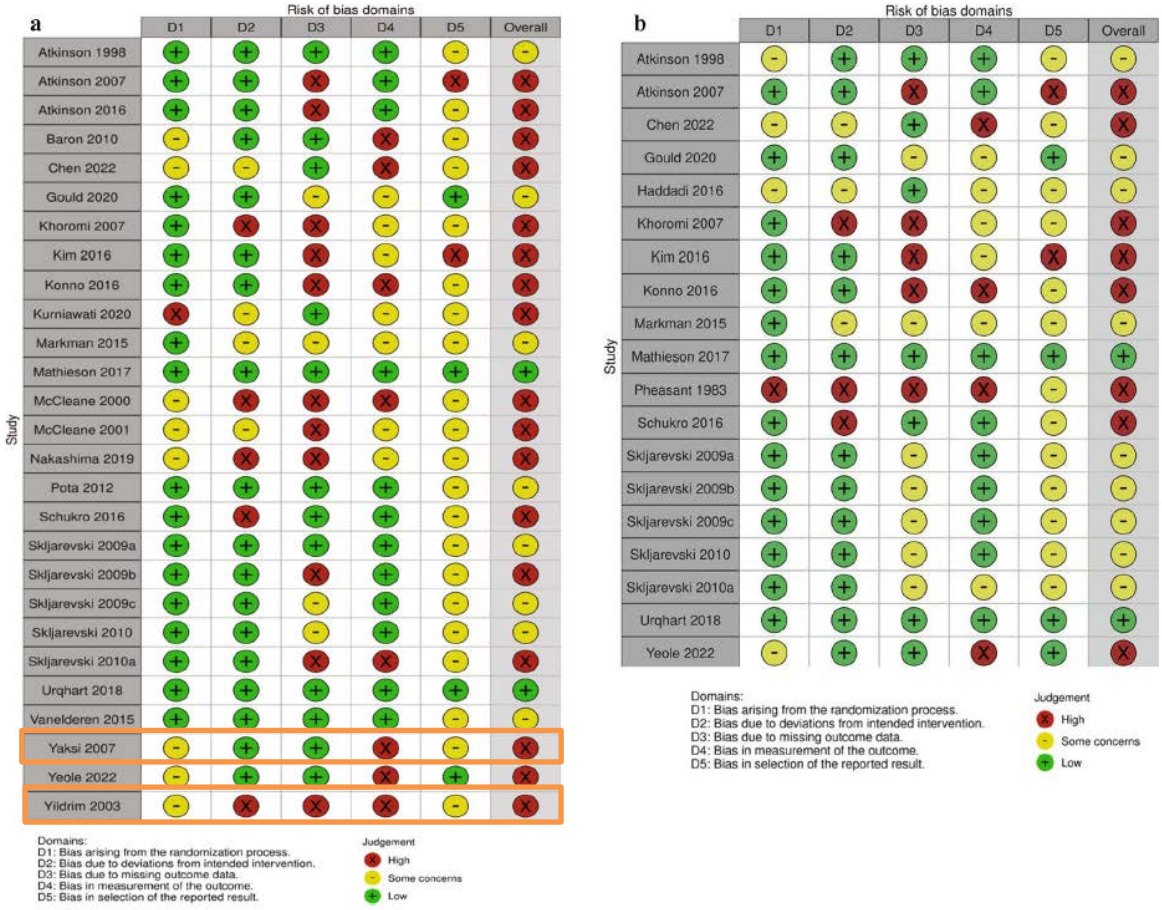
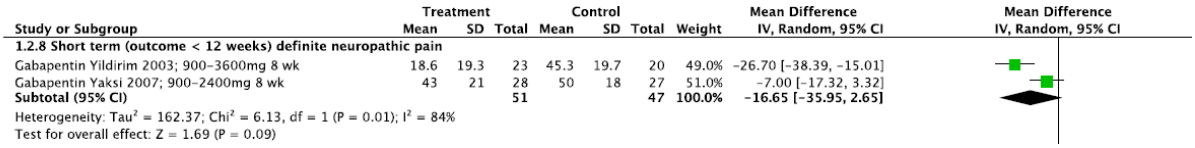


Fig. 2 Risk of bias (2) assessment of **A** pain and **B** disability outcomes

Studienergebnisse:

a



b

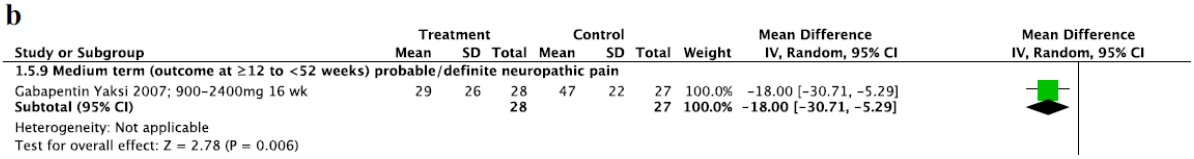


Fig. 4 **A** Pain outcomes reported at short-term timepoints, subgrouped by certainty of neuropathic pain (definite/probable/possible/unclear/unlikely neuropathic pain). **B** Pain outcomes reported at medium-term timepoints, subgroups clustered by certainty of neuropathic pain (definite/probable vs possible/unclear/unlikely neuropathic pain). *CI* confidence interval, *NSAID* non-steroidal anti-inflammatory drug, *SD* standard deviation, *SNRI* serotonin-norepinephrine reuptake inhibitors, *TCA* tricyclic antidepressant, *wk* weeks

Anmerkung/Fazit der Autoren

Low to very low certainty evidence revealed a trend towards larger (albeit moderate to small) effect sizes on pain and disability at short term and medium term in participants with

definite/probable neuropathic pain, compared with negligible-to-small effect sizes in those with possible/unclear/unlikely neuropathic pain.

Kommentare zum Review

Bitte beachten, dass aus diesem systematischen Review lediglich die Studien/Meta-Analysen zu Gabapentin extrahiert wurden, da Gabapentin die einzige Intervention in diesem Review ist, die im vorliegenden Anwendungsgebiet zugelassen ist.

3.3 Leitlinien

Leitlinien der AWMF:

Die AWMF S3-Leitlinien „Kreuzschmerz“ und „Langzeitanwendung von Opioiden bei chronischen nicht-tumorbedingten Schmerzen“ befinden sich derzeit in Überarbeitung und werden voraussichtlich zum 01.07.2026 bzw. 31.08.2026 fertiggestellt.

World Health Organization, 2023 [7].

WHO guideline for non-surgical management of chronic primary low back pain in adults in primary and community care settings

Zielsetzung/Fragestellung

The purpose of the guideline is to provide evidence-based recommendations on nonsurgical interventions for CPLBP in adults, including older people, that can be delivered in primary and community care settings to improve CPLBP-related health and well-being outcomes. For this reason, the guideline does not consider interventions typically delivered in secondary or tertiary care settings (e.g. surgical or other invasive procedures) or workplace interventions.

What are the health and well-being benefits and harms of non-surgical interventions in the management of chronic primary low back pain, with or without spine-related leg pain, in community-dwelling adults in primary or community care settings, including older people (60 years and older), compared with placebo, no intervention or usual care?

Methodik

<u>Grundlage der Leitlinie</u>

- Repräsentatives Gremium: **Trifft zu**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **Trifft zu**
- Systematische Suche, Auswahl und Bewertung der Evidenz: **Trifft zu**
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: **Trifft zu**
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: **Trifft teilweise zu** – die Empfehlungen sind eindeutig mit LoE und GoR, jedoch ist eine Verknüpfung der Evidenz mit den Empfehlungen nur indirekt über den Hintergrundtext möglich und Referenzen sind nicht immer angegeben.
- Regelmäßige Überprüfung der Aktualität gesichert: **Trifft zu**

Recherche/Suchzeitraum:

- Seven review teams were commissioned to undertake systematic reviews of benefits and harms of the prioritized interventions, either performing a new review or by updating an existing Cochrane review or non-Cochrane review (appraised by the Technical Unit as high or moderate quality using the AMSTAR-2 tool (65)) published between 2011-2021.
- WHO commissioned quantitative systematic evidence syntheses of randomized controlled trials (RCTs) to evaluate the benefits and harms (as reported in included trials) of each of the prioritized interventions compared with no care (including trials where the effect of an intervention could be isolated), placebo or usual care for each of the critical outcomes (refer to Table 2 for the PICO criteria for selecting evidence).
- Research designs other than RCTs were not considered.
- Non-English publications were considered.
- Systematic evidence reviews were undertaken in accordance with the methods described in the Cochrane Handbook for Systematic Reviews of Interventions and the Agency for Healthcare Research and Quality (AHRQ) Methods Manual (68, 69). Cochrane and AHRQ standards were followed for systematic searches, risk of bias assessment and estimates of treatment effect.
- Data from RCTs were aggregated for meta-analyses where pooling was considered appropriate, or in a narrative summary where pooling of data was considered inappropriate by the systematic review team.
- Each systematic review team developed a full protocol to describe their planned methods for literature searching including databases searched and time periods used, search strategies, trial selection, data extraction, appraisal/risk of bias assessment, and data synthesis and reporting. Protocols were reviewed and edited by the WHO Technical Unit, independent methodologist and shared with the GDG for feedback, prior to being finalized and published in an open access repository (Web Annex B).

LoE/Gor

- Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Sonstige methodische Hinweise

- Each recommendation is relevant to community-dwelling adults experiencing CPLBP, with or without spine-related leg pain. While the population definition allowed for the inclusion of comorbid spine-related leg pain, the guideline development group (GDG) was not able to confidently interpret the effects of interventions in this subpopulation since classification systems varied across trials and some trials did not report prevalence of leg pain. Inconsistency in classification of spine-related leg pain and its reporting in trials is a recognized limitation in the literature, prompting the development of recent recommendations for terminology and the identification of neuropathic pain in people with spine-related leg pain (67).

Empfehlungen

B Physical interventions

B.1 Structured exercise therapies or programmes

A structured exercise therapy or programme may be offered as part of care to adults, including older people, with CPLBP *(conditional recommendation in favour of use, low certainty evidence)*.

B.2 Needling therapies (traditional Chinese medicine acupuncture and other dry needling modalities)

Needling therapies such as acupuncture may be offered as part of care to adults, including older people, with CPLBP *(conditional recommendation in favour of use, low certainty evidence)*.

B.3 Spinal manipulative therapy

Spinal manipulative therapy (SMT) may be offered as part of care to adults, including older people, with CPLBP *(conditional recommendation in favour of use, very low certainty evidence).*

B.4 Massage

Massage may be offered as part of care to adults, including older people, with CPLBP *(conditional recommendation in favour of use, very low certainty evidence).*

B.5 Traction

Traction should not be used as part of routine care for adults, including older people, with CPLBP *(conditional recommendation against use, very low certainty).*

B.6 Therapeutic ultrasound

Therapeutic ultrasound should not be used as part of routine care for adults, including older people, with CPLB *(conditional recommendation against use, low certainty evidence).*

B.7 Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) should not be used as part of routine care for adults, including older people, with CPLBP *(conditional recommendation against use, very low certainty evidence).*

D Medicines

D.1 Systemic pharmacotherapies

D.1.1 Opioid analgesics

Opioid analgesics should not be used as part of routine care for adults, including older people, with CPLBP *(conditional recommendation against use, moderate certainty).*

Remarks: There are potentially serious adverse events associated with the use of opioid analgesics, such as dependence and overdose.

Outcomes:

- In the comparison of opioids (treatment duration ≥ 1 month with placebo (27 trials, 8688 participants), the certainty of evidence ranged from high to very low and benefits were observed for pain, function and health-related quality of life (physical domain).
  - Opioids probably offered a small reduction in pain intensity compared to placebo at one month to less than six months (moderate certainty evidence). Estimates were similar for opioid agonists, partial agonists and mixed agents. A meta-regression that evaluated the opioid dose as a continuous variable found no association between higher doses and greater effects of opioids on pain (p=0.26), with a plateauing of effects at around 50 mg morphine equivalents per day.
  - Opioids were probably associated with a small increased likelihood of experiencing an improvement in pain at one month to less than six months (moderate certainty evidence).

  - Opioids probably offered a small improvement in function compared to placebo at one month to less than six months (moderate certainty evidence). Estimates were similar when the analysis was stratified by opioid type. When measuring function as the likelihood of experiencing a > 30% reduction in disability, opioids may be associated with a trivial increased likelihood of achieving this outcome at one month to less than six months (low certainty evidence; two trials not meta-analysed).
  - Opioids improved health-related quality of life (physical domain) by a trivial amount at one month to less than six months (high certainty evidence). Opioids probably made little to no difference to health-related quality of life (mental domain) at one month to less than six months (moderate certainty evidence).
  - It was uncertain whether opioids made little to no difference in psychological well-being at one month to less than six months (very low certainty evidence; one trial with non-significant group difference).
  - Three trials found similar effects of opioids in older people and younger adults. Two trials reported similar effects of opioids in groups defined by sex or race.
- Harms were monitored across the trials and various adverse events were identified with the potential for serious adverse events.
- Opioids may be associated with a moderate increased likelihood of treatment discontinuation and large increased likelihood of nausea and pruritus (moderate certainty evidence).
- Opioids are associated with a large increased likelihood of constipation, vomiting and somnolence at one month to less than six months (high certainty evidence).
  - Opioids may be associated with an increased risk of serious adverse events, though the estimate was imprecise and not statistically significant (low certainty).
  - There was probably no difference between opioids versus placebo concerning the risk of headache (moderate certainty).
  - Findings for harms were generally consistent in the analyses stratified by opioid type, though mixed agents were associated with higher risks of constipation, nausea, vomiting and pruritis. There was no clear dose response relationship with harms.
- In the comparison of opioids (treatment duration < 1 month) with placebo (1 trial, 25 participants), benefit was observed for pain reduction. However, it was uncertain whether opioids offer a large reduction in pain intensity compared to placebo at <1 month, since the certainty of evidence was very low. The trial reported no adverse events in either group.

Rationale for judgement:

For all adults and older people, the GDG judged overall net benefits as small to moderate. The GDG noted that there were no trials specifically in older people, but that the age ranges in the trials included older people. The majority of the GDG judged harms to be moderate, while some members considered harms to be small, based on the evidence from included RCTs. The GDG explicitly noted that RCTs were not the appropriate study design to monitor harms and referred to indirect evidence from other sources where data relating to adverse events and serious adverse events including dependence and overdose were compelling; as a consequence, some members judged harms to be large for opioids. The GDG noted indirect evidence from the recently published OPAL placebo-controlled trial from Australia (122). That trial assessed the benefits and harms of short-term use (up to 6 weeks) of oxycodone-naloxone (up to 20 mg oxycodone per day orally) in adults with at least moderately severe acute LBP and/or neck pain, identifying no difference in pain outcomes at 6 weeks between the groups and a higher risk of misuse in the opioid group at one year (122). The GDG also noted the recent Stanford-Lancet commission on responding to the opioid crisis in North America and other nations, summarizing the scale of opioid-related morbidity and mortality in the last 25 years, in particular fatal overdose and dependence outcomes (123). The GDG referred to the WHO factsheet on opioids overdose statistics (August 2021) and WHO Guideline on community management of opioid overdose (114). The GDG judged the overall certainty of evidence to be moderate. The majority of GDG judged that the balance of benefits to harms for opioid analgesics did not favour opioids based on the evidence of harms as well as other widely reported indirect evidence highlighting adverse events, such as dependence and overdose. A minority of GDG members suggested that the balance probably favoured opioids based on the systematic review evidence, particularly the moderate certainty evidence of some benefit to pain and function between one month and less than six months. When considering the totality of direct and indirect evidence available, the GDG rationalized that while some benefits might be observed, the risk of serious harm outweighed potential benefits for opioid analgesics. A description of GDG members' judgements relevant to all systemic pharmacotherapies for the EtD domains of values and preferences, resource implications, equity and human rights, acceptability and feasibility is presented in the introduction to this intervention class and summarized in Annex 3 (Table C15). Table C15 also provides a summary of judgements made by the GDG for benefits, harms, balance of benefits to harms, and overall certainty for opioid analgesics. The GDG also referred to the qualitative evidence synthesis and took the view that older

people were less accepting of opioid analgesics as well as having concerns about dependence (moderate confidence). From an equity perspective, the GDG took the view that many people who take opioids might encounter stigma from health workers and others in the community. The GDG highlighted the need for awareness about stigma and strategies to address stigma relating to opioid use to ensure that all people are treated with compassion, dignity and respect. The GDG reached a consensus decision to recommend against the use of opioid analgesics. This decision was based on the GDG's judgement that the balance of benefits to harms did not favour opioids, particularly when considering indirect evidence of adverse events associated with long-term use, including the risk of overdose. The GDG also considered data from the qualitative evidence synthesis, where moderate confidence evidence pointed to the lack of acceptability of some medicines, especially opioids, for older people, due to their potential for dependence, fatal overdose and side-effects. This decision also reflected the GDG's judgement that in some countries opioid analgesics were not widely available and associated with high cost. One GDG member did not agree with a conditional recommendation against opioid analgesics. The GDG also noted that WHO recommends opioids for the management of cancer pain in the WHO Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents (124).

D.1.2 Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs may be offered as part of care to adults with CPLBP *(conditional recommendation in favour of use, moderate certainty).*

Remarks:

- NSAIDs should be used/prescribed as a short-term or intermittent treatment option, irrespective of the selected class of NSAID and of the safety profile of the person with CPLBP.
- When NSAIDs are offered to people with CPLBP, they should be considered as part of a broader suite of effective treatments (i.e. not offered as a single intervention in isolation), based on a biopsychosocial assessment.
- When selecting an NSAID, prescribers should consider the chemical profile of the drug (COX-2 selective vs non-selective NSAIDs), its side-effect profile, and the risk profile of the person with CPLBP, including pre-existing renal impairment, cardiovascular disease, use of other drugs and prior gastrointestinal events. In general, non-selective NSAIDs are contraindicated in people at increased risk of gastrointestinal adverse events. Very careful clinical judgements of benefit and risk should be made for people with renal impairment.
- A co-prescribed gastroprotective agent may be considered to reduce the risk of gastrointestinal adverse events, such as ulceration or bleeding.
- For older people with multiple comorbidities such as cardiovascular diseases and renal impairment and who commonly take other medicines (e.g. anticoagulant agent), NSAIDs may be contraindicated. Prescription therefore requires careful attention to the older person's medical history, a medicines review, close follow-up and the shortest duration of treatment.

Outcomes:

- In the comparison of NSAIDs (treatment duration ≥ 12 weeks) with placebo (4 trials, 1301 participants), the certainty of evidence ranged from high to low, and benefits were observed for pain and function.
  - NSAIDs probably offered a small reduction in pain intensity at three to six months (moderate certainty evidence). Effects were larger in trials of the COX2-selective NSAID etoricoxib than the nonselective NSAID naproxen.
  - NSAIDs probably offered a small increased likelihood of experiencing ≥ 30% reduction in pain at three to six months, but the estimate was imprecise and not statistically significant (moderate certainty evidence).
  - NSAIDs probably offered a small improvement in function at three to six months (moderate certainty evidence). Effects were larger in trials of the COX2- selective NSAID etoricoxib than the nonselective NSAID naproxen.

  - NSAIDs (etoricoxib only) made little to no difference to mental quality of life at three to six months (high certainty evidence) and offered trivial improvement to physical quality of life at three to six months (high certainty evidence). Harms were monitored across the trials and were identified for nausea. Serious adverse events were not detected.
  - NSAIDs may be associated with an increased likelihood of nausea (low certainty evidence), but the estimate was imprecise and not statistically significant.
  - NSAIDs may not increase the likelihood of serious adverse events at three to six months (low certainty evidence).
  - NSAIDs may make little to no difference to the likelihood of discontinuation due to adverse events at three to six months (low certainty evidence).
- In the comparison of NSAIDs (treatment duration < 12 weeks) with placebo (four trials of five non-selective NSAIDs, 449 participants), the certainty of evidence ranged from high to very low and benefits were observed for pain and function.
  - NSAIDs may offer a small reduction in pain intensity at < 1 month (low certainty evidence).
  - NSAIDs offered a small reduction in pain intensity at 1 to 3 months (high certainty evidence).
  - NSAIDs may offer a small improvement in function at 1 to 3 months (low certainty evidence).
- Harms were monitored in the trials.
  - NSAIDs probably made little to no difference to the likelihood of adverse events generally (moderate certainty evidence).
  - NSAIDs may increase the likelihood of nausea, constipation, and dizziness (low certainty evidence, small effects, risk estimates imprecise and not statistically significant).
  - It was uncertain whether NSAIDs increased the likelihood of discontinuation due to adverse events (very low certainty evidence, risk estimate imprecise and not statistically significant).
  - NSAIDs may reduce the risk of pruritic and headache (large effects, risk estimates imprecise and not statistically significant; low certainty evidence).
- It was uncertain whether NSAIDs reduced the risk vomiting and pruritis (large effects), since the certainty of the evidence was very low (risk estimates imprecise and not statistically significant).
- NSAIDs may make little to no difference to somnolence (low certainty evidence).

Rationale for judgements:

The GDG judged overall net benefits as small to moderate. The majority of the GDG judged harms to be small to moderate, with one GDG member judging harms as uncertain. The GDG referred to the indirect evidence of harms associated with non-selective (diclofenac, etodolac, flurbiprofen, ketorolac, ibuprofen, indomethacin, meloxicam, naproxen, piroxicam, sulindac) and COX-2 selective (celecoxib, rofecoxib, valdecoxib) NSAIDs in older people (mean age 80 years) with osteoarthritis or rheumatoid arthritis derived from a health claims administrative database (125). This indirect evidence highlighted that COX-2 selective users experienced an increased risk of cardiovascular events, although in a sensitivity analysis where rofecoxib and valdecoxib users were removed the risk was no longer elevated. Rates of gastrointestinal bleeding were reduced in COX-2 selective users, irrespective of the sensitivity analysis. One GDG member commented that the standard best Clinical practice for the prescription of NSAIDs was to limit the treatment duration to less than 30 days, and that judgements about benefits and harms for a treatment duration of more than 12 weeks were, therefore, not relevant to current Clinical practice. The GDG judged the overall certainty of evidence to be moderate. The GDG judged that the balance of benefits to harms for NSAIDs favoured or probably favoured NSAIDs. One GDG member suggested that judging this balance without considering the difference in benefits and harms based on NSAID selectivity was unhelpful since selectivity is usually considered when prescribing NSAIDs (refer to Remarks). The evidence review team noted, however, that there were limited trials to perform stratified analyses by NSAID selectivity and indirect evidence would need to be considered to evaluate harms more comprehensively, and by NSAID selectivity. A description of GDG members' judgements relevant to all systemic pharmacotherapies for the EtD domains of values and preferences, resource implications, equity and human rights, acceptability and feasibility is presented in the introduction to this intervention class and summarized in Annex 3 (Table C16). Table C16 also provides a summary of judgements made by the GDG for benefits, harms, balance of benefits to harms, and overall certainty for NSAIDs. The GDG reached a consensus decision to make a conditional recommendation in favour of NSAIDs for adults. This decision was based on the GDG's judgement that the balance of benefits to harms was in favour of NSAIDs for most people. Since the mean age across the included trials was less than 60 years and there was indirect evidence of increased harm for older people, a conditional recommendation in favour that included older people specifically could not be made. The GDG noted the importance of considering NSAID selectivity and careful attention and monitoring of adverse events. Members noted the limitations in the current evidence to stratify benefits and harms by COX-2 selectivity, and stated that for this reason a

recommendation based on selectivity could not be made. However, the GDG elected to include information about NSAID selectivity in the Remarks to highlight this issue as an important clinical practice consideration.

D.1.3 Serotonin and noradrenaline reuptake inhibitor (SNRI) antidepressants

SNRI antidepressants should not be used as part of routine care for adults, including older people, with CPLBP *(conditional recommendation against use, low certainty).*

Remarks:

- The moderate increased risk of adverse events associated with SNRI antidepressants outweigh the small benefits offered.
- There are potentially serious adverse events associated with SNRI antidepressants among older people, including hyponatraemia, memory impairment, gastrointestinal events and falls, without evidence of benefit.

Outcomes:

- In the comparison of SNRI antidepressants (treatment duration ≥ 12 weeks) with placebo (4 trials, 1499 participants), the certainty of evidence ranged from moderate to very low and benefits were observed for pain, while benefits for function, quality of life and psychological well-being were trivial. All trials evaluated duloxetine.
  - SNRI antidepressants probably offered a small reduction in pain intensity at three to six months (moderate certainty evidence). Results were similar when the analysis was restricted to a duloxetine dose of 60 mg/day and when stratified by trial quality.
  - SNRI antidepressants probably offered a small increase in the likelihood of reduced in pain intensity (≥ 30% improvement) at three to six months (moderate certainty evidence). Results were similar when the analysis was restricted to a duloxetine dose of 60 mg/ day and when stratified by trial quality. › SNRI antidepressants probably offered a trivial improvement in function at three to six months (moderate certainty evidence). Results were similar when the analysis was restricted to a duloxetine dose of 60 mg/day and when stratified by trial quality.
  - SNRI antidepressants may offer a trivial improvement in quality of life and psychological well-being at three to six months (low certainty evidence).
  - It was uncertain whether SNRI antidepressants made little to no difference to work-related outcomes (low to very low certainty evidence).
- Harms were monitored across the trials and were identified for nausea, constipation, dizziness and somnolence.
  - SNRI antidepressants were probably associated with a large increase in the likelihood of discontinuation due to adverse events, nausea, constipation, dizziness and somnolence (moderate certainty evidence).
  - It was uncertain whether SNRI antidepressants were associated with a small increased likelihood of serious adverse events (very low certainty evidence).
- In the comparison of SNRI antidepressants (treatment duration < 12 weeks) with placebo (5 trials, 263 participants), the certainty of evidence was very low. It was uncertain whether SNRI antidepressants made little to no difference to pain or psychological well-being at < 1 month or at 1–3 months; or to function or quality of life at 1–3 months.
- Harms were monitored in the included trials, however, the certainty of evidence was very low. It was therefore uncertain whether SNRI antidepressants:
  - increased the likelihood of treatment discontinuation due to adverse events (large effect) and nausea (large effect);
  - made little to no difference to the likelihood of adverse events, serious adverse events, constipation, dizziness, somnolence, dry mouth, pruritus or headache; or
  - increased the likelihood of vomiting (large effect), although the risk ratio estimates exceeded 1.0.

Rationale for judgement

For all adults, the GDG judged overall net benefits as trivial to small, limited mostly to a small effect on pain in the short-term. The GDG judged the harms to be small to moderate based on evidence from the RCTs. In particular, the GDG noted the moderate certainty evidence of a large increased risk of discontinuation due to adverse events, nausea, constipation, dizziness and somnolence in treatment durations of three months or more, and similarly large risks for short-duration treatment, albeit with very low certainty evidence. The

GDG also noted indirect evidence of publication bias towards the positive effects of anti-depressant agents when compared with the US Food and Drug Administration analysis of the evidence (126). Considering the higher certainty of evidence for outcomes of trials with longer duration treatment and lower certainty of evidence for outcomes of trials with shorter duration therapy, the GDG largely judged the overall certainty of evidence to be low (three members judged its certainty to be moderate). The GDG was mixed in its judgement concerning the balance of benefits to harms for SNRI antidepressants. Some members judged that the balance probably favoured SNRI antidepressants based on moderate certainty of evidence of small effects on pain with longer term therapy, while most judged that the balance probably did not favour SNRI antidepressants in view of the evidence of little to no benefits offered with short-term therapy and only trivial benefits offered in terms of function, quality of life and psychosocial well-being for long-term treatment. A description of GDG members' judgements relevant to all systemic pharmacotherapies for the EtD domains of values and preferences, resource implications, equity and human rights, acceptability and feasibility is presented in the introduction to this intervention class and summarized in Annex 3 (Table C17). Table C17 also provides a summary of judgements made by the GDG for benefits, harms, balance of benefits to harms, and overall certainty for SNRI antidepressants. The GDG reached a consensus decision to recommend against SNRI antidepressants (conditional recommendation). This decision was based on the GDG's judgement that the balance of benefits to harms was not in favour of SNRI antidepressants when considering trivial to small benefits and moderate certainty evidence of a large increased risk of adverse events. The GDG also noted an absence of trial evidence in older people while acknowledging potentially serious adverse events in this group including hyponatraemia, memory impairment, gastrointestinal events and falls, without evidence of benefit. The GDG also noted that, to date, no SNRI antidepressant has been recommended in the WHO Model List of Essential Medicines or WHO mhGAP intervention guide (106). Three GDG members did not agree with a recommendation against of SNRI antidepressants and suggested a conditional recommendation in favour would be appropriate. The GDG also acknowledged that people who experience CPLBP often concurrently experience negative impacts on mental health, for which specific management of mental health conditions might be indicated, based on a clinical assessment. WHO provides guidance through the WHO mhGAP intervention guide (106).

D.1.4 Tricyclic antidepressants

Tricyclic antidepressants should not be used as part of routine care for adults, including older people, with CPLBP *(conditional recommendation against use, very low certainty).*

Remarks:

The potential harms associated with tricyclic antidepressants outweigh the trivial to small benefits offered.

There are potentially serious adverse events associated with tricyclic antidepressants among older people, including postural hypotension, falls and delirium.

Outcomes:

- In the comparison of tricyclic antidepressants (treatment duration ≥ 12 weeks) with placebo (3 trials, 294 participants), the certainty of evidence ranged from moderate to very low and benefits were observed for pain and function.
    - Tricyclic antidepressants may be associated with a trivial to small reduction in pain intensity at three to less than six months, and a small reduction in pain intensity at six months (low certainty evidence). These estimates were not meta-analysed and were not statistically significant.
    - Tricyclic antidepressants may be associated with a small increase in the likelihood of experiencing reduced pain by ≥ 30% or > 75% at three to less than six months (low certainty evidence), although the relative risk estimates were imprecise (derived from a single trial) and not statistically significant.
    - Tricyclic antidepressants may be associated with a trivial to small improvement in function at three to less than six months (low certainty evidence) and a trivial improvement in function at six months (low certainty evidence, estimate not statistically significant).
    - Tricyclic antidepressants may offer a trivial benefit in terms of quality of life or psychological well-being outcomes at three to less than six months or at six months (low certainty evidence, estimates not statistically significant and derived from a single trial).
    - Tricyclic antidepressants may be associated with a trivial decrease in work absence at three to less than six months, although the estimate was imprecise and not statistically significant (low certainty evidence). At six months, it was uncertain whether tricyclic antidepressants increased work absence: the estimate was imprecise and not statistically significant (very low certainty evidence).
- Harms were monitored across the trials and were identified for dry mouth.

- Tricyclic antidepressants were probably associated with an increased likelihood of dry mouth at three to less than six months (large effect; moderate certainty).
- Relative risk estimates for serious adverse events, discontinuation due to adverse events, nausea, constipation and somnolence were imprecise (very low certainty evidence).

- In the comparison of tricyclic antidepressants (treatment duration <12 weeks) with placebo (6 trials, 290 participants), the certainty of evidence was very low. It was uncertain whether tricyclic antidepressants:
  - offered a trivial to small reduction in pain intensity at 1 to 3 months;
  - offered a small benefit to psychological well-being at 1 to 3 months (small effect, 1 trial, effect estimate not statistically significant); or
  - made little to no difference to function or quality of life at 1 to 3 months.
- Harms were monitored in the included trials; however, since the certainty of evidence was very low, it was uncertain whether tricyclic antidepressants:
  - increased the likelihood of constipation (large effect) and dry mouth (small effect); or
  - made little to no difference to the likelihood of adverse events, withdrawals due to adverse events or somnolence.

Rationale for judgement:

For all adults, the GDG judged overall net benefits to be trivial across critical outcomes, particularly for pain where effects were not meta-analysed and not statistically significant in long-term therapy trials, while other GDG members judged benefits to be uncertain on the basis of low to very low certainty of evidence. The GDG judged the harms to be uncertain due to the very low certainty of evidence for most harms other than dry mouth. While no trials considered older people specifically, GDG members reflected (based on their own experience) on potentially serious adverse events associated with tricyclic antidepressants in older people, including postural hypotension, falls and delirium. The GDG judged the overall certainty of evidence to be very low. The GDG judged that the balance of benefits to harms for tricyclic antidepressants did not favour or probably did not favour tricyclic antidepressants based on its assessment of benefits as being trivial or uncertain, and the potential for harms based on large risks of adverse events including dry mouth (moderate certainty) and constipation (very low certainty evidence). One GDG member judged the balance to be uncertain, given the low to very low certainty evidence for benefits and harms. A description of GDG members' judgements relevant to all systemic pharmacotherapies for the EtD domains of values and preferences, resource implications, equity and human rights, acceptability and feasibility is presented in the introduction to this intervention class and summarized in Annex 3 (Table C18). Table C18 also provides a summary of judgements made by the GDG for benefits, harms, balance of benefits to harms, and overall certainty for tricyclic antidepressants. The GDG reached a consensus decision to recommend against the use of tricyclic antidepressants (conditional recommendation). This decision was based on the lack of consistent evidence for a clinically worthwhile effect on critical outcomes and considering that potential harms, particularly for older people, outweighed possible benefits. One GDG member suggested no recommendation would be appropriate given the absence of sufficient evidence to judge the balance of benefits and harms.

D.1.5 Anticonvulsants

Anticonvulsants should not be used as part of routine care for adults, including older people, with CPLBP *(conditional recommendation against use, very low certainty).*

Remarks:

- The large increased risk of adverse events associated with anticonvulsants substantially outweigh the small and short-term benefits offered.
- Harms associated with anticonvulsants might be more pronounced in older people. Furthermore, serious breathing difficulties. have been associated with the use of gabapentin in people who have respiratory risk factors, such as chronic obstructive pulmonary disease, concomitant use of opioids and/or other central nervous system depressants, and in older people.

Outcomes:

- In the comparison of anticonvulsants (treatment duration ≥ 12 weeks) with placebo (1 trial, 108 participants with and without spine-related leg pain, 43% had "radicular" pain), the certainty of evidence was very low and no benefits were observed. It was uncertain whether anticonvulsants (gabapentin)

made little to no difference to pain intensity, the likelihood of experiencing a reduction in pain, or psychological well-being at three to six months.

- Harms were monitored in the trial; since the certainty of evidence was very low however, it was uncertain whether anticonvulsants (gabapentin):
  - were associated with a large increased likelihood of failing memory, dry mouth, loss of balance and concentration difficulties;
  - were associated with a moderate increased likelihood of asthenia (weakness and fatigue);
  - were associated with a moderate increased likelihood of sedation and dizziness (not statistically significant);
  - were associated with a small increased likelihood of discontinuation due to adverse events, although the estimate was imprecise and not statistically significant; or
  - made little to no difference to the likelihood of serious adverse events, constipation or nausea/vomiting.
- In the comparison of anticonvulsants (treatment duration < 12 weeks) with placebo (3 trials, 206 participants), the certainty of evidence ranged from very low to moderate. **All trials excluded participants with neuropathic pain**, but two trials included participants with spine-related leg pain (somatic referred leg pain). Benefits were observed for pain.
  - Anticonvulsants probably made little to no difference to pain intensity at less than 1 month (moderate certainty evidence).
  - Anticonvulsants probably offered a trivial to small reduction in pain intensity at 1 to 3 months (moderate certainty evidence).
  - It was uncertain whether anticonvulsants offered a trivial to small improvement in function, quality of life and psychological well-being at 1 to 3 months (very low certainty evidence).
- Harms were monitored in the included trials and identified for adverse events as a group.
  - It was uncertain whether anticonvulsants increased the likelihood of adverse events (very low certainty evidence, large effect).
  - Anticonvulsants may increase the likelihood of nausea, constipation, dizziness, headache and somnolence (low certainty evidence); the risk estimates were imprecise however, and not statistically significant.
  - It was uncertain whether anticonvulsants made little to no difference to the likelihood of withdrawals due to adverse events or pruritus (very low certainty evidence).

Rationale for judgement:

For all adults, the GDG largely judged overall net benefits as trivial, while some members judged benefits to be small or uncertain due to very low certainty of evidence. Although the GDG noted moderate certainty evidence of a benefit to pain at one to three months for short-term treatment, the size of the effect was trivial to small and there was no consistent signal of benefit across other time-points for pain. The GDG judged harms to be uncertain given the very low certainty evidence for harms outcomes, while noting signs of moderate to large effects for some adverse outcomes, including failing memory, concentration difficulties, dry mouth, loss of balance and asthenia. The GDG inferred that the risk of these harms, and potentially others, would be greater in older people, based on their experience. To support their judgements on harms, the GDG also referred to indirect evidence from the US Food and Drug Authority in December 2019 regarding the risk of serious breathing difficulties associated with the use of gabapentin in people who had respiratory risk factors such as chronic obstructive pulmonary disease, concomitant use of opioids and/or other central nervous system depressants, and in older people. The GDG also referred to other important external context and indirect evidence relating to the use of anticonvulsants in people with CPLBP, highlighting that these agents were increasingly used in practice without evidence of benefit (127), and that, despite the indication, there was no current evidence of benefit to pain and disability for gabapentin or topiramate in the context of co-existing possible or probable neuropathic spine-related leg pain (moderate to high certainty) (128). The GDG judged the overall certainty of evidence to be very low. Since there was inconsistency in estimates and certainty ratings, the lowest certainty rating (very low) was applied. The GDG judged that the balance of benefits to harms for anticonvulsants did not favour anticonvulsants based on findings of little to no clinically worthwhile benefits and the potential for harm. A description of GDG members' judgements relevant to all systemic pharmacotherapies for the EtD domains of values and preferences, resource implications, equity and human rights, acceptability and feasibility is presented in the introduction to this intervention class and summarized in Annex 3 (Table C19). Table C19 also provides a summary of judgements made by the GDG for benefits, harms, balance of benefits to harms, and overall certainty for anticonvulsants. The GDG reached a consensus decision to recommend against the use of anticonvulsants (conditional recommendation) on the basis of limited clinical benefit and because harms substantially outweighed possible benefit. While ten GDG

members suggested that a strong recommendation against the use of anticonvulsants would be appropriate, this proportion did not meet the threshold for a consensus decision for a strong recommendation. One GDG member suggested no recommendation would be appropriate given the absence of sufficient evidence to judge the balance of benefits and harms.

D.1.6 Skeletal muscle relaxants

Skeletal muscle relaxants should not be used as part of routine cate for adults, including older people, with CPLBP (conditional recommendation against use, very low certainty)

Remarks:

- The potential harms associated with skeletal muscle relaxants outweigh the trivial to small benefits offered.
- There are potentially serious adverse events such as confusion, drowsiness, falls associated with with skeletal muscle relaxants (baclofen) among older people, especially those with chronic kidney disease.

Outcomes:

- In the comparison of skeletal muscle relaxants (treatment duration < 12 weeks) with placebo (4 trials, 143 participants), the certainty of evidence ranged from very low to moderate and benefits were observed for pain and function. All trials evaluated botulinum toxin A delivered via intramuscular injection into the paravertebral muscles.
  - It was uncertain whether skeletal muscle relaxants increased the likelihood of a reduction in pain intensity (≥ 50% difference in pre- and post-treatment scores on a 0–10 scale) at less than 1 month (very low certainty evidence, large effect)
  - Skeletal muscle relaxants probably increased the likelihood of a reduction in pain intensity (≥ 50% difference in pre- and post-treatment scores on a 0–10 scale) at 1 to 4 months (moderate certainty evidence, large effect).
  - It was uncertain whether skeletal muscle relaxants made little to no difference to pain intensity (continuous outcome) at 1 to 4 months (very low certainty evidence).
  - Skeletal muscle relaxants probably increased the likelihood of improved function, defined as “significant improvement” at 1 to 4 months (moderate certainty evidence, large effect).
  - It was uncertain whether skeletal muscle relaxants made little to no difference to function, quality of life or work-related outcomes at 1 to 4 months (very low certainty evidence).
- Harms were monitored in the trials and none was identified. Skeletal muscle relaxants made little to no difference to the likelihood of adverse events (low certainty evidence).
  - In the comparison of skeletal muscle relaxants (treatment duration <12 weeks) with no treatment (one trial of baclofen, 42 participants), the certainty of evidence was very low, and no differences were observed. It was uncertain whether skeletal muscle relaxants (baclofen) made little to no difference to pain intensity at less than 1 month, pain intensity at 1 to 3 months, or function at 1 to 3 months. The trial did not report on harms. Refer to web Annex D.D1.6 for detailed GRADE evidence profile tables for skeletal muscle relaxants.

D.1.8 Paracetamol (acetaminophen)

There were no trials identified that evaluated the benefits or harms of paracetamol (acetaminophen) in the management of CPLBP in adults.

- Given the absence of direct evidence aligned to the PICO question, the GDG ruled not to undertake an EtD process for paracetamol and no recommendation was made. However, the GDG recognized that paracetamol (acetaminophen) is used in practice and that there may be important adverse events to consider when using this medicine. As such, key considerations were formulated to guide practice. A summary of these key considerations is also provided in *Box 1* in the executive summary.
- Key considerations:
  - Paracetamol is commonly used as first-line analgesic medication and is included on the WHO Model List of Essential Medicines for the indication of pain.
  - Available evidence for the use of paracetamol for LBP suggests it is no better than placebo for reducing pain in acute LBP (131). There is high-quality evidence that paracetamol has no effect on quality of

life, function, global impression of recovery and sleep quality. There is no biological reason why its effectiveness would be different in CPLBP.

- The adverse events profile of paracetamol is now better understood. There are substantial increases in the risk of potential cardiovascular, renal and gastrointestinal harms and increased mortality risk, based on a systematic review of harms in observational studies (132).
- Older people and people with hepatic or renal impairment are likely to be at greatest risk of harm from paracetamol (133).
- Overdose of paracetamol is dangerous and potentially fatal.

D.2 Cannabis-related pharmaceutical preparations for therapeutic use

- There were no trials identified that evaluated the benefits or harms of cannabinoids in the management of CPLBP, based on an ongoing (living) Agency for Healthcare Research and Quality (AHRQ) systematic review of cannabis for chronic pain (134, 135).
- Given the absence of direct evidence aligned to the PICO question, the GDG ruled not to undertake an EtD process for cannabinoids and no recommendation was made. However, the GDG recognized that cannabinoids are used in practice and that there might be important adverse events to consider when using this medicine. As such, key considerations were formulated to guide practice.
- Key considerations:
  - Cannabinoids are not likely to be an appropriate medicine for the management of CPLBP due to a current lack of direct evidence for benefit in this condition and evidence of possible adverse events, including in older people (136). While indirect evidence from trials in populations with other pain conditions suggests benefits to pain relief, physical functioning and sleep quality, the effects were small to very small (137).
  - The potential for a small to very small clinical effect associated with cannabinoids must be considered alongside evidence for harms, which may be more severe for older people. There is indirect evidence of harms in populations with other pain conditions, including harms related to non-medicinal use (138). These harms, for example, may include short-term adverse events such as disturbances in the level of consciousness, cognition, perception, driving skills, affect or behaviour, other psychophysiological functions and responses, and adverse physical health effects, such as stroke or acute coronary syndrome. In the longer term, adverse events may include dependence, cognitive impairment, mental disorders (psychoses, depression, anxiety and suicidal behaviour), and adverse physical health effects such as cardiovascular disease, chronic obstructive pulmonary disease and respiratory and other cancers (138).
  - Regarding the importance of addressing the harms of associated with cannabinoids, the WHO mhGap 2023 guideline update currently states: “Considering high prevalence and well documented health risks associated with cannabis use, wider implementation and scale up of simple advice, brief interventions and, when appropriate, offer of referral to treatment can result in significant health gains at population level” (139).

D.4 Herbal Medicines

Topical Cayenne pepper [Capsicum frutescens] may be offered as part of care to adults with CPLBP, including older people (conditional recommendation in favour of use, low certainty evidence).

Remarks:

- When topical Cayenne pepper [*Capsicum frutescens*] is offered , information about possible adverse skin reactions should be outlined so that people may make informed decisions about accepting this intervention.
- When topical Cayenne pepper [*Capsicum frutescens*] is offered to people with CPLBP, it should be considered as part of a broader suite of effective treatments (i.e. not offered as a single intervention in isolation), based on a biopsychosocial assessment.

Outcomes:

- In the comparison of topical Cayenne pepper [Capsicum frutescens] with placebo (3 trials), benefit was observed for pain. Cayenne pepper probably reduced pain (moderate effect) in the short term (moderate

certainty evidence). Cayenne pepper may increase adverse events related to skin irritation in the short term (low certainty evidence).

- In the comparison of topical Cayenne pepper [Capsicum frutescens] with no intervention, or where the effect of the intervention could be isolated, no trials were identified.
- In the comparison of topical Cayenne pepper [Capsicum frutescens] with usual care, no trials were identified.

Rationale for judgement

For all adults and older people, the GDG judged overall net benefits as small to moderate, although a few suggested that benefits were uncertain due to limited evidence, that pain relief was estimated as a dichotomous outcome only rather than a continuous mean difference, and that outcomes were limited to short-term followup only. The GDG judged non-serious adverse events to be small to moderate. The GDG judged the overall certainty of evidence to be low. Most of the GDG judged that the balance of benefits to harms for topical Cayenne pepper probably favoured the intervention based on moderate certainty evidence of short-term benefit with regard to pain reduction, and considering that adverse events were likely to be non-serious, transient and expected, based on the therapeutic mechanism of action of topical Cayenne pepper. However, some GDG members considered this balance to be uncertain. A description of GDG members' judgements relevant to all herbal medicines for the EtD domains of values and preferences, resource implications, equity and human rights, acceptability and feasibility is presented in the introduction to this intervention class and summarized in *Annex 3 (Table C23). Table C23* also provides a summary of judgements made by the GDG for benefits, harms, balance of benefits to harms, and overall certainty for topical Cayenne pepper. The GDG reached a consensus decision to make a conditional recommendation in favour of topical Cayenne pepper based on moderate certainty evidence of a pain-reduction benefit in the short term. The GDG noted that the harms associated with Cayenne pepper were non-serious, acknowledging that unpleasant skin reactions were likely to be transient and expected as part of the therapeutic mechanism of action. The GDG was uncertain about the benefits and harms of Cayenne pepper beyond the short term.

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Department of Veterans Affairs / Department of Defense, 2022 [3].

VA/DoD clinical practice guideline for the diagnosis and treatment of low back pain

Zielsetzung/Fragestellung

The patient population of interest for this CPG is adults (ages 18 years or older) with acute, subacute, or chronic LBP with or without neurological symptoms, who are eligible for care in the VA or DoD healthcare delivery systems and those who receive care from community-based clinicians. It includes Veterans and Service Members as well as their dependents. Recommended interventions in this CPG are applicable regardless of care setting, unless otherwise indicated, for any patient in the VA and DoD healthcare system.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: **Trifft zu**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **Trifft zu**
- Systematische Suche, Auswahl und Bewertung der Evidenz: **Trifft zu**

- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: **Trifft zu**
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: **Trifft zu**
- Regelmäßige Überprüfung der Aktualität gesichert: **Trifft zu**

Recherche/Suchzeitraum:

- Embase and Medline, PsycINFO, PubMed (In-process and Publisher records): October 1, 2016, to February 1, 2021
- Grey Literature: Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Veterans Affairs (VA) Evidence Synthesis Program

LoE

- Risk of bias of individual diagnostic, observational, and interventional studies using the USPSTF method. Each study is assigned a rating of Good, Fair, or Poor based on a set of criteria that vary depending on study design. Detailed lists of criteria and definitions appear in Appendix VI of the USPSTF procedure manual.(221)
- GRADE

GoR

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend…
Weak for	We suggest …
Neither for nor against	There is insufficient evidence to recommend for or against …
Weak against	We suggest against …
Strong against	We recommendagainst…

Sonstige methodische Hinweise

Table 5. Recommendation Categories and Definitions[a]

Evidence Reviewed	Recommendation Category	Definition
Reviewed[b]	New-added	New recommendation
	New-replaced	Recommendation from previous CPG was carried forward and revised
	Not changed	Recommendation from previous CPG was carried forward but not changed
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted
Not reviewed[c]	Not changed	Recommendation from previous CPG was carried forward but not changed
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted

[a] Adapted from the NICE guideline manual (2012) (25) and Garcia et al. (2014) (26)

[b] The topic of this recommendation was covered in the evidence review carried out as part of the development of the current CPG.

[c] The topic of this recommendation was not covered in the evidence review carried out as part of the development of the current CPG.

Abbreviation: CPG: clinical practice guideline

Empfehlungen

Topic	#	Recommendation	Strength[a]	Category[b]
Evaluation and Diagnostic Approach	1.	For patients with low back pain, we recommend the history and physical examination include evaluation for progressive or otherwise serious neurologic deficits and other red flags (e.g., signs, symptoms, history) associated with serious underlying pathology (e.g., malignancy, fracture, infection).	Strong for	Reviewed, Amended
	2.	For patients with low back pain, we recommend diagnostic imaging and appropriate laboratory testing when neurologic deficits are progressive or otherwise serious or when other red flags (e.g., signs, symptoms, history) are present.	Strong for	Reviewed, Amended
	3.	For patients with acute low back pain, without focal neurologic deficits or other red flags (e.g., signs, symptoms, history), we recommend against routinely obtaining imaging studies or performing invasive diagnostic tests.	Strong against	Reviewed, New-replaced
	4.	For patients with low back pain, we suggest assessing psychosocial factors and using predictive screening instruments (e.g., STarT Back and The Orebro Musculoskeletal Pain Screening Questionnaire) to inform treatment planning.	Weak for	Reviewed, New-replaced
	5.	For patients with low back pain, with or without radicular symptoms, there is insufficient evidence to recommend for or against specific physical exam maneuvers to assist in the diagnosis of facet or sacroiliac joint pain, or a lumbar/lumbo-sacral radiculopathy.	Neither for nor against	Reviewed, New-added
Patient Education and Self-care	6.	For patients with low back pain, there is insufficient evidence to recommend for or against pain neuroscience education, clinician-directed education with patient-led goal setting, or back school.	Neither for nor against	Reviewed, New-replaced
	7.	For the self-management of low back pain, there is insufficient evidence to recommend for or against technology-based modalities.	Neither for nor against	Reviewed, New-added
Non-pharmacologic and Non-invasive Therapy	8.	For patients with chronic low back pain, we suggest cognitive behavioral therapy.	Weak for	Reviewed, New-replaced
	9.	For patients with low back pain, we suggest a structured clinician-directed exercise program (e.g., aerobic, aquatic, mechanical diagnosis and therapy, mobility, motor control, Pilates, strengthening exercises, structured walking program, tai chi).	Weak for	Reviewed, New-replaced
	10.	For patients with chronic low back pain, we suggest spinal mobilization/manipulation.	Weak for	Reviewed, New-replaced
	11.	For patients with acute low back pain, there is insufficient evidence to recommend for or against spinal mobilization/manipulation.	Neither for nor against	Reviewed, New-replaced
	12.	For patients with chronic low back pain, there is insufficient evidence to recommend for or against mindfulness-based stress reduction.	Neither for nor against	Reviewed, New-replaced
	13.	For patients with low back pain, there is insufficient evidence to recommend for or against lumbar supports.	Neither for nor against	Reviewed, Amended

Topic	#	Recommendation	Strength[a]	Category[b]
Non-pharmacologic and Non-invasive Therapy (cont.)	14.	For patients with low back pain, with or without radicular symptoms, there is insufficient evidence to recommend for or against mechanical lumbar traction.	Neither for nor against	Reviewed, New-replaced
	15.	For patients with chronic low back pain, there is insufficient evidence to recommend for or against auricular acupressure.	Neither for nor against	Reviewed, New-added
	16.	For patients with low back pain, there is insufficient evidence to recommend for or against yoga or qi gong.	Neither for nor against	Reviewed, New-replaced
	17.	For patients with low back pain, there is insufficient evidence to recommend for or against cupping, laser therapy, transcutaneous electrical nerve stimulation, and ultrasound.	Neither for nor against	Reviewed, New-replaced
Pharmacotherapy	18.	For patients with chronic low back pain, we suggest duloxetine.	Weak for	Reviewed, New-replaced
	19.	For patients with low back pain, we suggest nonsteroidal anti-inflammatory drugs.	Weak for	Reviewed, New-replaced
	20.	For patients with low back pain, with or without radicular symptoms, there is insufficient evidence to recommend for or against gabapentin or pregabalin.	Neither for nor against	Reviewed, Amended
	21.	For patients with low back pain, there is insufficient evidence to recommend for or against tricyclic antidepressants.	Neither for nor against	Reviewed, New-added
	22.	For patients with low back pain, there is insufficient evidence to recommend for or against topical preparations.	Neither for nor against	Reviewed, Amended
	23.	For patients with acute low back pain, there is insufficient evidence to recommend for or against a non-benzodiazepine muscle relaxant for short-term use.	Neither for nor against	Reviewed, New-replaced
	24.	For patients with chronic low back pain, we suggest against offering a non-benzodiazepine muscle relaxant.	Weak against	Reviewed, Not changed
	25.	For patients with low back pain, we suggest against acetaminophen.	Weak against	Reviewed, New-replaced
	26.	For patients with low back pain, we suggest against monoclonal antibodies.	Weak against	Reviewed, New-added
	27.	For patients with chronic low back pain, we suggest against opioids. For patients who are already using long-term opioids, see the VA/DoD CPG for the Use of Opioids in the Management of Chronic Pain.[c]	Weak against	Reviewed, New-replaced
	28.	For patients with low back pain, with or without radicular symptoms, we suggest against systemic corticosteroids (oral or intramuscular injection).	Weak against	Not reviewed, Amended
	29.	For patients with low back pain, we recommend against benzodiazepines.	Strong against	Reviewed, Not changed
Dietary Supplements	30.	For patients with low back pain, there is insufficient evidence to recommend for or against any specific diet or nutritional, herbal, or homeopathic supplements (e.g., anti-inflammatory diet, turmeric, vitamin D), cannabis, or cannabinoids.	Neither for nor against	Reviewed, New-replaced

Topic	#	Recommendation	Strength[a]	Category[b]
Non-surgical Invasive Therapy	31.	For patients with chronic low back pain, we suggest lumbar medial branch and/or sacral lateral branch radiofrequency ablation.	Weak for	Reviewed, New-replaced
	32.	For patients with low back pain, there is insufficient evidence to recommend for or against sacroiliac joint injections.	Neither for nor against	Reviewed, New-added
	33.	For patients with low back pain, we suggest against the injection of corticosteroids for intra-articular facet joint injections and therapeutic medial branch blocks with steroid.	Weak against	Reviewed, New-replaced
	34.	For patients with chronic low back pain, we suggest acupuncture.	Weak for	Reviewed, Amended
	35.	For patients with acute low back pain, there is insufficient evidence to recommend for or against acupuncture.	Neither for nor against	Reviewed, Amended
	36.	For patients with low back pain, there is insufficient evidence to recommend for or against ortho-biologics (e.g., platelet-rich plasma, stem cells).	Neither for nor against	Reviewed, New-added
	37.	For patients with low back pain, with radicular symptoms, there is insufficient evidence to recommend for or against epidural steroid injections.	Neither for nor against	Reviewed, New-replaced
	38.	For patients with low back pain, we suggest against spinal cord stimulation.	Weak against	Reviewed, New-added
Team Approach	39.	For patients with chronic low back pain, we suggest a multidisciplinary or interdisciplinary program. These programs should include at least one physical component and at least one other component of the biopsychosocial model (psychological, social, and/or occupational) used in an explicitly coordinated manner.	Weak for	Reviewed, Amended

[a] For additional information, see Determining Recommendation Strength and Direction.

[b] For additional information, see Recommendation Categorization and Appendix D.

[c] For additional information, see the VA/DoD Clinical Practice Guideline for the Use of Opioids in the Management of Chronic Pain. Available at: https://www.healthquality.va.gov/.

Abbreviations: CPG: clinical practice guideline; DoD: Department of Defense; VA: Department of Veterans Affairs

18.For patients with chronic low back pain, we suggest duloxetine

(Weak for | Reviewed, New-replaced)

The evidence review identified one SR by Kolber et al. (2021),(154) which included four RCTs comparing duloxetine versus placebo,(155-158) and found that duloxetine (n=832) provided a clinically relevant improvement in pain, defined as a >30% reduction in pain compared to baseline. The analysis revealed 58% of patients receiving duloxetine (n=832) and 47% of patients receiving placebo (n=667) had clinically significant pain relief (risk ratio [RR]: 1. 25; 95% CI: 1.13 to 1.38, p<0.00001). The benefit of duloxetine for chronic LBP for pain and function is demonstrated by moderate quality evidence.(154) However, the amount of pain reduction over placebo was not consistently clinically meaningful as duloxetine resulted in 0.46 to 0.82 points less than placebo on a 10 point scale in two of the studies reviewed in the Kolber et al. (2021).(155, 158)

When function was measured by the RMDQ, the comparative data were inconclusive.(113) It is also important to keep in mind that the effects of selective serotonin reuptake inhibitors (SSRI) on LBP are inconclusive.(113) Of the serotonin and norepinephrine reuptake inhibitors (SNRI) class, only studies on duloxetine met criteria for inclusion for the evidence review. Theoretically, the SNRI class may demonstrate some benefit given a similar mechanism of action to duloxetine.

Within the studies reviewed in the Kolber SR, there was a high rate of discontinuation due to AEs for those in the duloxetine arms compared with the placebo arms. Within three of the four studies that documented study dropout rates, the discontinuation rate due to AEs versus placebo was: 15.2% versus 5.4% (p=0.002) for duloxetine 60 mg,(157) 13.9% versus 5.8% (p=0.047) for duloxetine 120 mg,(158) and 24.1% vs. 8.5% for duloxetine 120 mg.(156) While there were no serious AEs found in the evidence review, there are more adverse effects associated with duloxetine when compared to placebo. These include nausea, insomnia, dry mouth, constipation, somnolence, fatigue, and hyperhidrosis.(113) Duloxetine also has sexual side effects that may diminish treatment acceptability and adherence. Additionally, duloxetine has a risk of hepatotoxicity and should not be used in patients with substantial alcohol use or evidence of chronic liver disease. Combining

duloxetine with other serotonergic medications increases the risk of serotonin syndrome and should be used with caution. There is a black box warning with antidepressants, including duloxetine, in the treatment of major depressive disorder (MDD) and other psychiatric disorders for increased risk of suicidal thinking and behavior in children, adolescents, and young adults.(159)

19. For patients with low back pain, we suggest nonsteroidal anti-inflammatory drugs*

(Weak for | Reviewed, New-replaced)

* Recommendations for "patients with low back pain" encompass patient populations with acute, subacute, or chronic LBP with or without neurological symptoms.

Two SRs and one RCT assessed the potential benefits of NSAIDs compared to placebo.(113, 154, 160) Moderate quality evidence from one SR by Kolber et al. (2021) suggests use of NSAIDs (n=993) in patients with chronic LBP is associated with an improvement in pain and function, defined as a 30% reduction in pain or combination of pain reduction and functional improvement, compared with placebo (n=644), with a number needed to treat (NNT) of 6.(154) Follow-up ranged from 4 – 16 weeks. Low quality evidence found no difference between NSAIDs (n=383) and placebo (n=271) at 12 weeks or greater.(154)

Low quality evidence from the Kolber et al. (2021) SR demonstrated no significant difference in AEs between placebo and NSAIDs with a follow-up duration of 4 – 12 weeks.(154) The Chou et al. (2016) SR included five studies that compared cyclooxygenase-2 (COX-2) NSAIDs with traditional NSAIDs.(113) No statistically significant difference for pain relief for acute LBP was seen in four studies. The fifth study found no differences in pain relief between COX-2 and traditional NSAIDs for chronic LBP.(161)

Most comparative trials between NSAIDs showed no significant differences in pain relief. A large noninferiority trial randomized 24,081 patients to receive celecoxib, naproxen, or ibuprofen and found the cardiovascular (CV) risk associated with celecoxib was noninferior to the non-selective NSAIDs.(162) This trial was limited by high rates of drug discontinuation (68.8%), study dropout (27.4%), and the restrictions on the doses of celecoxib. Most patients in the trial (90%) had OA. The dose of celecoxib was limited to 200 mg/day in this group, but dose escalation was allowed for ibuprofen and naproxen.

All NSAIDs have a black box warning for increased risk of CV events and gastrointestinal (GI) events, and these safety issues continue to be high priority when choosing an NSAID.(163) If an NSAID is required in a patient with CV risk, naproxen may be a viable option.(164, 165) Providers should consider other patient risk factors, primarily GI toxicity, when determining whether relatively COX-2 selective NSAIDs should be used over non-selective NSAIDs. The use of relatively selective COX-2 inhibitors reduces the risk for GI events; however, this benefit is negated if the patient is using aspirin.(164) NSAIDs can also exacerbate heart failure and worsen hypertension and renal function. NSAIDs must be used cautiously or avoided in patients with renal impairment or in elderly patients, as these agents may increase serum creatinine, cause sodium and water retention, and cause acute renal failure.(164) FDA guidance indicates NSAID prescribing should be used at the lowest effective dose for the shortest duration possible to reduce CV, GI, and renal AEs.

20. For patients with low back pain, with or without radicular symptoms, there is insufficient evidence to recommend for or against gabapentin or pregabalin

(Neither for nor against | Reviewed, Amended)

The evidence review identified an SR by Shanthanna et al. (2017), which evaluated patients with radicular and non-radicular chronic LBP and included three RCTs.(167) The SR found no difference between gabapentin (n=91) and placebo (n=94) in reducing pain severity or functional outcomes. The same SR (n=163) found an overall improvement in pain with pregabalin (n=163) versus active analgesic control (n=169), with a pooled SMD of 0.42, (p=0.0002); however, the quality of the evidence was very low. Additionally, the individual studies included in the SR had mixed results, with one of the three studies reporting no benefit for pain with pregabalin versus active analgesic control.(168) The duration of follow-up with the studies ranged from 4 – 14 weeks. An RCT studying the treatment of pregabalin in patients with radiculopathy, which was not included in the systematic evidence review carried out as part of this CPG and did not influence the strength of the recommendation, reported no significant reduction in leg pain intensity and a higher incidence of AEs.(169)

There are significant adverse effects associated with the use of gabapentin or pregabalin. Evidence from the Shanthanna et al. (2017) SR and another SR by Atkinson et al. (2016) found higher adverse effects with gabapentin versus placebo, including fatigue, dizziness, loss of balance, and difficulties with mental concentration, memory, and visual accommodation.(167, 170) An increased risk of dizziness was reported with pregabalin when compared to placebo.(167) Additionally, some subpopulations may be at greater risk of sedation and falls with the use of pregabalin or gabapentin. Antiepileptic medications, including pregabalin and gabapentin, increase the risk of suicidal thoughts or behavior in patients taking these medications for

any indications. Patients should be monitored for the emergence of worsening depression, suicidal thoughts or behavior, and/or any changes in mood or behavior.(171)

Pregabalin is a controlled substance with the potential for abuse and dependence. Gabapentin is not a federally scheduled medication; however, some states have scheduled gabapentin as a controlled substance due to concerns of addiction and dependence. Additionally, one study, which was not included in the systematic evidence review carried out as part of this CPG and did not influence the strength of the recommendation, indicates that gabapentin in combination with opioids significantly increases the risk of opioid-related mortality and respiratory depression.(172) Gabapentin or pregabalin may be beneficial in patients with comorbid anxiety or insomnia, as these agents have been used off-label for these indications.

21. For patients with low back pain, there is insufficient evidence to recommend for or against tricyclic antidepressants*

(Neither for nor against | Reviewed, New-added)

*Recommendations for "patients with low back pain" encompass patient populations with acute, subacute, or chronic LBP with or without neurological symptoms

The evidence for the use of tricyclic antidepressants (TCAs) demonstrates limited benefit with low to very low quality evidence. In an RCT comparing desipramine (n=37) to benztropine mesylate 0.125 mg (n=33), there was no difference in function (as measured by the RMDQ) or for pain severity at 12 weeks.(175) Another RCT demonstrated no benefit with low dose amitriptyline (n=72) versus benztropine mesylate (n=74) for function or pain severity at 3 – 6 month follow-up.(176) Active placebo in these RCTs was chosen to mimic the side effects of the treatment group. In addition, an SR by Chou et al. (2016) demonstrated no benefit with TCAs for either function or pain.(113) However, older studies have shown that TCAs as a class provide improvement in pain intensity (moderate effect size of 0.43), but were inconclusive in regards to function, QoL, or healthcare utilization.(177, 178)

Providers should use caution when prescribing TCAs to patients with cardiovascular disease (CVD) or a family history of sudden death. A baseline electrocardiogram (ECG) is indicated in patients who are aged >50 years or with significant cardiac risk factors.(179) The anticholinergic burden should also be considered when used in patients aged >65 years, and considerations for the use of secondary amines such as nortriptyline or desipramine may be warranted due to decreased anticholinergic burden. When utilizing TCAs, some subpopulations may be at greater risk of sedation and falls. There is also a risk of serotonin syndrome, particularly when combining with other medications (e.g., antidepressants). All antidepressants carry the black box warning of increased risk of suicidality in children, adolescents, and young adults when taking antidepressants for MDD or other psychiatric disorders.(180)

22.For patients with low back pain, there is insufficient evidence to recommend for or against topical preparations.*

(Neither for nor against | Reviewed, Amended)

* Recommendations for "patients with low back pain" encompass patient populations with acute, subacute, or chronic LBP with or without neurological symptoms

Similar to the 2017 VA/DoD LBP CPG, no studies on the effect of topical preparations met inclusion criteria for the 2022 VA/DoD LBP CPG systematic evidence review. However, the Work Group decided the subject still warranted a recommendation because topical preparations (e.g., capsaicin creams, diclofenac gel, lidocaine patches) are widely used. Moreover, the use of these agents generates frequent questions for PCPs.

These medications were addressed in a KQ for the systematic evidence review of this CPG. Therefore, although no new evidence was identified, this is a Reviewed, Amended recommendation. As there was no evidence on this topic, the Work Group could not determine the balance of benefits and harms. Patient values and preferences were somewhat varied because many patients see topicals as less risky and less harmful than oral medications and prefer non-invasive treatment options. Providers also value these medications as having less risk for AEs and as being more acceptable by patients. For this reason, the Work Group decided upon a Neither for nor against recommendation.

24. For patients with chronic low back pain, we suggest against offering a non-benzodiazepine musclerelaxant

(Weak against | Reviewed, Not changed)

When considering long-term use, there is no evidence to suggest benefit for the use of skeletal muscle relaxants for chronic LBP. One SR included a low quality study demonstrating there was no benefit of skeletal muscle relaxants when compared to placebo in patients with chronic LBP;(182) another SR also showed no benefit.(113)

25. For patients with low back pain, we suggest against acetaminophen (Weak against | Reviewed, New-replaced)

* Recommendations for "patients with low back pain" encompass patient populations with acute, subacute, or chronic LBP with or without neurological symptoms.

Although the effect of acetaminophen was covered in the 2022 VA/DoD LBP CPG systematic evidence review, no studies on this topic met inclusion criteria. Therefore, the Work Group considered the evidence included in the 2017 VA/DoD LBP CPG and consolidated two recommendations (on acute and chronic LBP) to form this recommendation.

A large SR (n=1,825) found there was no difference between acetaminophen and placebo in treating acute LBP for the outcomes of pain, disability, QoL, or function through 12 weeks.(183) The same SR found no effect of acetaminophen on immediate pain reduction for an acute exacerbation of chronic LBP. In a second SR, the evidence suggested that acetaminophen was no more effective than placebo in treating acute LBP for the outcomes of pain or function through three weeks.(113) In addition, for chronic LBP, this SR found there was insufficient evidence to determine the effects of acetaminophen versus NSAIDs in one trial and versus other interventions in four trials.

Over half of the 2,000 annual cases of acute liver failure in the U.S. are due to intentional and unintentional acetaminophen toxicity.(184) In addition, acetaminophen is the most frequent cause of acute liver injury, with associated healthcare costs and morbidity.(184) Other considerations include ease of accessibility, as acetaminophen is inexpensive and available at a relatively low cost to the patient and the system. It is also readily accessible, both OTC and on formulary. Unfortunately, it is easily overused without proper education, thus risks and adverse effects may not be well understood by the public. This has led to some variation in values and preferences. Some patients may think that acetaminophen is innocuous and be unaware of the adverse effects of taking too much. In addition, elderly individuals and patients with hepatic insufficiency are subgroups that may be at the most risk for harm. As no benefits were shown in the evidence, the Work Group suggested against the use of acetaminophen; the risk of harm in taking acetaminophen predominates other considerations. Other options, such as NSAIDs (see Recommendation 19), can be offered to the patient based on the benefits outweighing the harms.

26. For patients with low back pain, we suggest against monoclonal antibodies

(Weak against | Reviewed, New-added)

The utilization and clinical potential of monoclonal antibodies (mAb) for diverse disease processes and illnesses has markedly increased recently. The systematic evidence review found only two RCTs investigating the effectiveness of anti-nerve growth factors fasinumab and tanezumab. At the time of this review, these products were still investigational; neither of them have received final FDA approval in the U.S.

In the RCT by Dakin et al. (2020), fasinumab, with both IV and subcutaneous (SC) delivery methods and two different doses (6 mg and 9 mg) at varying intervals (dosed every 4 or 8 weeks), was compared against placebo.(185) Even though there were some trends toward improvement in functional status and pain severity, many study arms showed no significant difference in effect. More significantly, the interpretation and applicability of this study is confounded by an FDA safety intervention. Due to an adverse joint safety event (JSE) in a patient with co-existing OA, the study was placed on an FDA hold and then terminated early. This led to many patients receiving less than the planned doses (only 35 – 56% of patients received the complete planned dosage). Serious AEs were reviewed at greater than 16 weeks, and in all groups receiving fasinumab some participants developed rapidly progressive osteoarthritis (RPOA). Additionally, a higher number of RPOA cases were reported in the higher dosage group.

In the RCT by Markman et al. (2020),(186) tanezumab dosed at 5 mg or 10 mg subcutaneously every eight weeks was compared to placebo or active control (tramadol 100 mg – 300 mg). In the critical outcome of pain severity as determined by LBPI, the 5 mg dosage did not statistically differ from the placebo or control. In the 10 mg arm, there was no difference versus control. However, the 10 mg dosage showed a statistically significant difference versus placebo: LBPI: -0.40 (CI: -0.76 to -0.04); on a scale of 1 – 10; which was considered not clinically meaningful. Although neither dosage of tanezumab met the primary endpoint for statistically and clinically significant improvement, the authors did assess secondary outcomes. Using a LBPI improvement of >30% both dosages demonstrated significant improvement in all comparisons. However, a conclusion of

superiority could not be made using only this secondary endpoint. There was an improvement in functional status (as measured by the RMDQ) that reached statistical significance for both 5 mg and 10 mg tanezumab versus placebo and active control at 16 weeks follow-up.

In the evaluation of serious and severe AEs at 16 weeks follow-up, both mAb dosages resulted in fewer AEs than the active control, but an equal or greater number when compared to placebo.(186)

Patients achieving >30% improvement in LBPI, or >15% improvement from baseline in weeks 1 – 15, continued in a longitudinal follow-up focused on AEs.(186) In this phase, the patients originally assigned placebo were placed into one of the tanezumab groups (5 mg or 10 mg every eight weeks), and the control was tramadol. At 24 and 56 weeks, the authors reported no treatment-related mortality. Serious and severe AEs were lower in the 5 mg group versus control and slightly higher in the 10 mg treatment group.

More significantly, overall JSEs were reported through 80 weeks follow-up. The authors determined 30 patients had joint AEs that were assessed in depth. The most concerning event was RPOA, which occurred more frequently in tanezumab 5 mg (n=5) than active control (n=1) or placebo (n=0). In addition, the number of RPOA cases (n=16) was higher in the tanezumab 10 mg group, suggesting a dose related effect.

27. For patients with chronic low back pain, we suggest against opioids. For patients who are already using long-term opioids, see the VA/DoD CPG for the Use of Opioids in the Management of Chronic Paint

(Weak against | Reviewed, New-replaced)

While the literature base suggests potential benefit in some patients, the *Weak against* recommendation for opioids is based on the significant risks associated with use of opioids as determined in the VA/DoD CPG for the Use of Opioids in the Management of Chronic Pain.t None of the studies from the current LBP CPG systematic evidence review provided data to allow making conclusions on the long-term (more than six months) efficacy and safety of opioids for chronic LBP.

The evidence related to use of opioids in chronic LBP includes one SR and meta-analysis by Petzke et al. (2020) that consisted of 21 RCTs for chronic LBP, with only three RCTs published since the 2017 VA/DoD LBP CPG and the majority rated fair quality.(187) Thus, the majority of evidence for consideration by the Work Group was already included in the 2017 VA/DoD LBP CPG. The current systematic evidence review also included two fair quality individual RCTs.(186, 188)

The RCTs included in Petzke et al. (2020) examined at least four weeks of treatment with opioids for chronic LBP.(187) Opioids in this SR included buprenorphine (transdermal and buccal), hydrocodone, hydromorphone, morphine, oxycodone, oxycodone/naloxone, oxycodone/naltrexone, oxymorphone, tapentadol, and tramadol. Overall, for a 4 – 15 week follow-up period, most of the evidence comparing opioids with placebo for chronic LBP favored opioids. For the critical outcome of functional status, moderate quality evidence from this SR suggests patients in the opioids group experienced a greater reduction in disability compared with those in the placebo group at 4 – 15 weeks follow-up for all meta-analyses performed.(187) The authors considered the benefit of opioids in the reduction of disability clinically meaningful in comparison to placebo. For the critical outcome of pain severity, moderate to low quality evidence from this SR suggests that pain improved at follow-up for patients receiving opioids compared with those receiving placebo for all pain measures: ≥50% pain relief, ≥30% pain relief, mean pain intensity, and patient global impression questionnaire.

The two individual RCTs provide moderate to low quality evidence demonstrating no difference between opioids and placebo for pain or function. Low quality evidence from one RCT comparing tramadol with placebo in a chronic LBP treatment refractory population reported that improvement assessed using the RMDQ did not differ between groups at any time point during weekly assessments up to 16 weeks follow-up, and pain intensity was slightly reduced only at weeks one and eight.(186) Evidence from one RCT suggests that patients receiving extended-release oxycodone and sequestered naltrexone did not differ from the placebo group at 12 weeks follow-up regarding functional impairment, as assessed by the Work Productivity and Activity Impairment (WPAI) Questionnaire for percentage of work time missed, impairment while working, overall work impairment, and activity impairment.(188) The quality concerns were attrition >20% in one RCT (186) and study design in the other RCT,(188) with an uncontrolled open-label titration period resulting in a study population enriched with treatment responders.

The evidence base also included two SRs already considered in the 2017 VA/DoD LBP CPG that showed small additional analgesic effects with opioids beyond those seen with placebo for acute or chronic LBP (moderate quality evidence).(113, 189) In the meta-analysis by Abdel et al. (2016), the MD between single-ingredient opioids and placebo in pain intensity was -8.1 on a 0 – 100 VAS.(189) In another SR, the standardized MD between strong opioids (e.g., hydromorphone, morphine, oxycodone, oxycodone/naltrexone combination, oxymorphone, and tapentadol) and placebo was -0.43 (seven trials), equivalent to an MD of about one point

on a 0 – 10 NRS.(113) Neither study reported the percentage of patients who achieved clinically important (≥30%) improvements from baseline in pain intensity.

According to a meta-analysis of three RCTs, opioids produced no clinically important improvements in function relative to placebo at 30 to 91 days; however, results were inconclusive with a wide CI.(189) In an SR, short-term therapy (less than six months) with opioids resulted in small, clinically unimportant additional improvements in function over placebo.(113) The standardized MD relative to placebo was -0.26 (four trials), representing a difference of about one point on a 24-point RMDQ scale. Trials that compared opioids and other drug therapies (e.g., acetaminophen, NSAIDs, antidepressants) were limited, and the strength of evidence was insufficient to make conclusions for either pain or functional outcomes.

Regarding AEs, low quality evidence from one SR indicates that opioid and placebo groups did not differ in serious AEs or mortality.(187) One RCT reported an inconclusive result for serious and severe AEs that were similar in the tramadol and placebo group.(186) The meta-analysis by Abdel et al. (2016) showed that the median incidence of AEs was 68.9% for opioid groups and 49.1% for placebo groups, with a RR of 1.3 (eight trials). In four of the eight trials, 50% of study patients discontinued treatment because of AEs or lack of efficacy. Thus, the small differential benefits of short-term opioid use were counterbalanced by increases in risks of adverse effects seen with short-term opioid use.

In many of the RCTs in the SR by Petzke et al. (2020), there were concerns around randomization and allocation procedures, high attrition, and lack of blinding.(187) The authors themselves identified limitations due to industry sponsoring and publication bias. They note that these were research studies, with most studies excluding patients with clinically relevant somatic or psychiatric diseases, in particular, patients with current or previous substance abuse. None of these studies were in the primary care setting, and there was a lack of diversity, as the majority of the participants were middle-aged white women. They also noted that sleep problems, physical dependence, abuse, and addiction of prescribed opioids were only analyzed in some studies.

Of major concern is that these studies do not allow making conclusions on the long-term (more than six months) efficacy and safety of opioids for chronic LBP. Petzke et al. (2020) noted the limited data for longer than 12 weeks, and the weak finding in the subgroup analysis indicated increased dropout rates for studies with a duration of more than 12 weeks.(187)

The trials included in the SRs did not assess the risks of long-term opioid use. Opioid risks and risk assessment for chronic non-cancer pain are discussed in more detail in the VA/DoD CPG for the Use of Opioids in the Management of Chronic Pain that documents serious risks with opioid therapy, in particular opioid use disorder (OUD) and overdose, that increase with longer duration and with higher dosage of, opioid therapy but may occur even at low opioid dosage and short-term use.

No clinical trials identified by the systematic evidence review evaluated time-limited (less than seven days) opioid therapy, as such studies were not part of the evidence base. Therefore, the Work Group decided to not make a recommendation regarding the short-term use of opioids for acute LBP or acute exacerbation of chronic LBP.

Despite moderate to low quality evidence of benefit of opioids compared with placebo for pain and function at 4 – 15 weeks follow-up in the SR by Petzke et al. (2020), and inconclusive evidence for serious AEs and mortality, the Work Group concluded that the potential harms of opioids outweigh the potential benefits in patients with LBP.(187) The available evidence from this SR was only 15 weeks with low quality evidence demonstrating no serious AE. Assessment of abuse and addiction was incomplete. Based on what is known for chronic non-cancer pain in general (not specific to LBP), the small benefit of short-term opioid use seen in LBP trials may be substantially outweighed by serious risks, including potentially fatal respiratory depression, overdose, misuse, abuse, addiction, and diversion — risks that pose considerable harms not only to the patient, but also relatives, friends, and the public. The risk of addiction during opioid use, which may start with the first dose administered, increases substantially with duration and dosage of opioid therapy, and needs to be taken into consideration and weighed against the actual therapeutic benefits in individual cases. Thus, the Work Group issued a weak recommendation against the use of opioids for chronic LBP.

While not included in the evidence base of this CPG due to the study design (e.g., open-label RCT, no crossover design, allowance for use of tramadol in the non-opioid group) and a mixed treatment population consisting of patients with moderate pain from hip and knee OA in addition to LBP, the study by Krebs et al. (2018) is the only opioids study published that extends to 12 months.(190) Treatment with opioids was not superior to treatment with non-opioid medications for improving pain-related function over 12 months (overall p=0.58). Pain intensity was slightly, but significantly better in the non-opioid group (overall p=.03); and adverse medication-related symptoms were more common in the opioid group over 12 months (overall p=.03).

Patients' values, preferences, and treatment goals regarding opioids can vary widely, both between individuals and in the same individual over time. Some patients may be reluctant to take opioids because of the risk of addiction or fear of stigma, while others may seek a therapeutic opioid trial despite the marginal

benefits over placebo. Additionally, some subpopulations may be at greater risk of sedation and falls with the use of opioids. The patient focus group participants indicated a desire for education about pain medications, particularly opioids.

The severity of pain, level of pain-related disability, refractoriness to other therapies, co-occurring medical conditions, current or prior psychiatric or substance use disorders (SUD), social history, age, frailty, opioid dose, formulation, route of administration, drug interactions, and other factors may influence decisions regarding whether or not to try a time-limited course. For LBP refractory to NSAIDs, or for patients with contraindication to NSAIDs (such as due to anticoagulation), opioids are the only remaining drug treatment with evidence of effectiveness, although the analgesic effects were small relative to placebo and pertained to short-term therapy, with no clear evidence of long-term benefit.

The findings from one SR comparing opioids with placebo, identified in the current systematic evidence review, are in line with the evidence from the 2017 VA/DoD LBP CPG. Moderate to low quality evidence shows a benefit of opioids compared with placebo for pain and function at 4 – 15 weeks follow-up, in patients with chronic LBP, and there is inconclusive evidence for serious AEs and mortality.

29. For patients with low back pain, we recommend against benzodiazepines*

(Strong against | Reviewed, Not changed)

*Recommendations for “patients with low back pain” encompass patient populations with acute, subacute, or chronic LBP with or without neurological symptoms.

The systematic evidence review included a single RCT for acute LBP, in addition to an SR from the 2017 VA/DoD LBP CPG. The RCT by Friedman et al. (2017) demonstrated, with moderate quality evidence in patients with acute non-radicular back pain, the lack of benefit from adding diazepam to naproxen, with no difference regarding the critical outcomes of pain severity and functional status, after one week and three months.(192) Specifically, in the active treatment group, diazepam 5 mg tablets with 1 – 2 tablets every 12 hours as needed were added to naproxen 500 mg twice a day. The RMDQ score of 112 patients after one week was identical between groups. However, more patients reported moderate or severe LBP in the diazepam group (18 of 57 patients, 32%; 95% CI: 21% to 45%) than in the placebo group (12 of 55 patients, 22%; 95% CI: 13% to 35%). At three months follow-up, 6 of 50 patients on diazepam (12%) versus 5 of 53 patients receiving placebo (9%) reported moderate or severe LBP. AEs were reported by 12 of 57 patients in the diazepam group (21%) and 8 of 55 in the placebo group (15%).

The evidence in chronic LBP is less conclusive. A good quality SR by Chou et al. (2016) found inconclusive evidence between diazepam and placebo with respect to LBP improvement.(113) The SR identified one RCT (n=60) by Brotz et al. (2010) which reported efficacy data for patients randomized to receive placebo or diazepam two times 5 mg daily, followed by a taper.(193) Follow-up examinations were scheduled at six weeks and one year after discharge. The median duration of the stay in the hospital was shorter in the placebo arm (eight versus ten days, p=0.008), and the probability of pain reduction on the VAS by more than 50% was twice as high in placebo patients (12 of 29 patients for diazepam, 23 of 29 for placebo) (p=0.0015). Other outcome measures, though inconclusive, tended to favor placebo over diazepam including workdays lost, disability, and healthcare utilization.

The SR reported low quality evidence for CNS AEs such as somnolence, fatigue, and lightheadedness with benzodiazepines versus placebo.(113) In addition, the potential for abuse, addiction/dependence, overdose potentially resulting in death, respiratory depression, and sleep apnea do not justify their use. Some subpopulations are at greater risk of sedation and falls with use of benzodiazepines.

30. For patients with low back pain, there is insufficient evidence to recommend for or against any specific diet or nutritional, herbal, or homeopathic supplements (e.g., anti-inflammatory diet, turmeric, vitamin D), **cannabis, or cannabinoids.***

(Neither for nor against | Reviewed, New-replaced)

*Recommendations for “patients with low back pain” encompass patient populations with acute, subacute, or chronic LBP with or without neurological symptoms.

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Bailly F et al., 2021 [2].

French National Authority for Health (FNAH)

Clinical guidelines and care pathway for management of low back pain with or without radicular pain

Zielsetzung/Fragestellung

The objective was to develop guidelines including a care pathway for managing LBP and based on previous international guidelines in addition to updated literature.

The target population for the guidelines was adults with non-specific low back pain, with or without radiculalgia. All patients with radiological abnormalities (such as herniated disc, narrow lumbar canal, posterior joint osteoarthritis) except scoliosis (which was not considered as non-specific low back pain) could be included. Surgical management and job

retention were excluded due to recent guidelines in this field [19,20]. All other drug or non-drug treatments could be included.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter Evidenz in der Indikation des chronischen Kreuzschmerzes mit radikulärer (neuropathischer) Komponente, wird die LL jedoch ergänzend dargestellt.

- Repräsentatives Gremium: **Trifft zu**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **Trifft zu**
- Systematische Suche, Auswahl und Bewertung der Evidenz: **Trifft zu**
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: **Trifft zu**
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: **Trifft teilweise zu** – die Empfehlungen sind eindeutig mit LoE und GoR, jedoch ist eine Verknüpfung der Evidenz mit den Empfehlungen nur indirekt über den Hintergrundtext möglich und Referenzen sind nicht immer angegeben.
- Regelmäßige Überprüfung der Aktualität gesichert: **Trifft zu** – die Leitlinie soll innerhalb von 5 Jahren aktualisiert werden

<u>Recherche/Suchzeitraum:</u>

- […] a systematic search of guidelines published over the previous 5 years was conducted as was a search for systematic reviews and meta-analysis published over the previous 3 years in MEDLINE, Cochrane Library, and other sources.
- A systematic review of articles published between January 2013 and December 2018 in English or French was performed

LoE

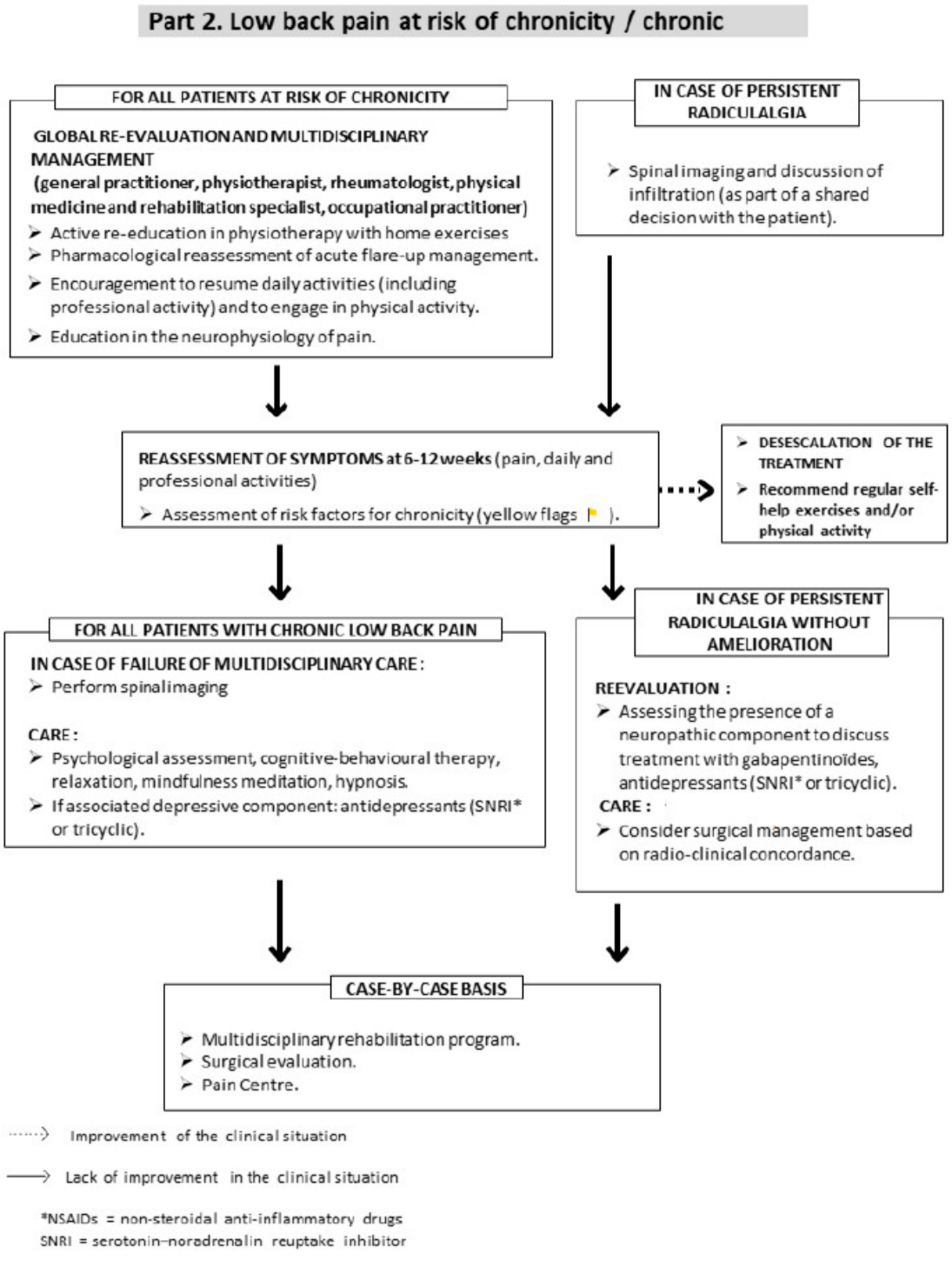
Level of scientific evidence provided by the literature (for clinical studies)	Recommendation grading
Level 1	Grade A
- High-power randomised comparative studies	Established scientific evidence
- Meta-analysis of randomised comparative studies	
- Decision analysis based on well-conducted studies	
Level 2	Grade B
- Low-power randomised comparative studies	Scientific presumption evidence
- Well-conducted non-randomised comparative studies	
Level 3	Grade C
- Case–control studies	Low level of evidence
Level 4	
- Comparative studies with major bias	
- Retrospective studies	
- Case series	
In the absence of studies, guidelines are based on a consensus between working experts after consulting the peer review group	Expert consensus (EC)

GoR

- Each expert evaluated each of the guidelines on a scale of 1 to 9 (1, complete disagreement and 9, complete agreement).
- Each area of the guideline was considered:
  - "appropriate" with median score ≥ 7 and agreement among members of the working group
  - "inappropriate" with median score ≤ 3.5 and agreement among members of the working group
  - "uncertain" with median score 4 to 6.5 (indecision) or no consensus among members of the working group.
- Strong approval was considered if the rating was 7 to 9, and strong disapproval 1 to 3.
- Weak approval was considered if the rating was 5 to 9, and weak disapproval 1 to 5.
- Because the working group consisted of more than 16 members, an extreme value could be excluded from the global rating, according to the RAND/UCLA method.

Empfehlungen

Care pathway



Non-drug management

8. Before considering non-drug management, the medical diagnosis of common LBP must have been made (EC). Physical activity is the main treatment for the favourable evolution of common LBP (Grade B). Appropriate; strong consensus

First line management:

8. Self-management and return to daily activities (including early return to work if possible): Indicated (Grade B). Appropriate; strong consensus

9. Adapted physical activities and sports activities (Progressive and fractionated activity according to the patient's preference): Indicated (Grade B). Appropriate, strong consensus

10. Physiotherapy for patients with chronic LBP or at risk of chronicity: Indicated (Grade B). The use of therapeutic exercises adapted to the clinical context, taught by a physiotherapist and then continued at home, is recommended (Grade B). The physiotherapist participates in the patient's education (reinsurance, fight against fears and beliefs, awareness of physical activity benefits) as part of a bio-psycho-social management (EC). The performance of physiotherapy must involve the active participation of the patient (Grade B). Passive therapies should not be used in isolation because they have no effect on improving LBP (EC). Appropriate, strong consensus

Second line management:

11. Education in pain neurophysiology for patients with chronic LBP or at risk of chronicity: Indicated (EC) Appropriate; weak consensus

12. Manual techniques (manipulations, mobilizations) only as a part of a multimodal combination of treatments including a supervised exercise program: Possible (Grade B). Appropriate; weak consensus

13. Psychological interventions such as cognitive behavioural therapy, only as a part of a multimodal combination of treatments including a supervised exercise program, conducted by a cognitive behavioural therapist professional or a team trained in pain: Possible (Grade B) Appropriate; strong consensus

Third line management:

14. Multidisciplinary physical, psychological, social and occupational rehabilitation program in patients with persistent low back or root pain, in the presence of psychosocial risk factors that interfere with their recovery, or with failure of recommended active management. Those programs must be adjusted according to the patient's medical, psychosocial and professional context. Programs should include supervised active exercises, a multidisciplinary approach, cognitive behavioural therapy, and social care. Appropriate; strong consensus

<u>Drug management</u>

15. No analgesic drug has proven its efficacy in the medium term on the improvement of LBP acute flare-up. Nevertheless, graduated analgesic management, starting with level I analgesics, can be implemented for managing painful episodes (EC). It is recommended to recall the correct use of analgesics and their intended use in symptomatic and non-curative effects (EC). The choice of treatment should consider medical history, previous experience with analgesics, patient preferences and risk of misuse. Appropriate; strong consensus

First line management:

16. Paracetamol may be useful in a symptomatic intention to treat pain (EC). Appropriate; strong consensus

17. Non-steroid anti-inflammatory drugs (NSAIDs) can be offered after evaluation of the benefit/risk balance based on history, for the shortest possible time, at the lowest effective dose (Grade A). Appropriate; strong consensus

Second line management:

18. Opioids: The risk of misuse must be considered. Weak opioids may be offered in addition or not to paracetamol, at low doses, with failure or contraindication to NSAIDs, for the shortest possible time (Grade B). Strong opioids are reserved for refractory LBP despite a well-managed treatment (including multidisciplinary rehabilitation program) for the shortest possible time (Grade B). The patient should be informed about the risk of opioid misuse. The continuation of low or strong opioid therapy should be regularly reassessed according to the benefits previously established with the patient (EC). Tools are available to detect misuse risk before the first prescription (Opioid Risk-Tool) and before renewal (POMI scale). With risk of misuse, close patient monitoring is recommended (EC). With proven misuse, joint management with a pain or an addiction centre is recommended (EC). Appropriate; strong consensus

19. Antidepressants (tricyclic or serotonin/noradrenaline reuptake inhibitors) are not indicated with LBP acute flare-up with or without radiculalgia (Grade A). **They can be considered with chronic radiculalgia with a neuropathic component or with associated anxiety and depression disorders, considering the benefit/risk balance (Grade B)**. Neuropathic component can be assessed using DN4 score or Pain detect. The patient should be informed about how antidepressants work (delayed effect) and side effects (EC; appropriate; strong consensus).

20. Gabapentinoids are not indicated for LBP acute flare-up with or without radiculalgia (Grade A). **They may be considered with chronic radiculalgia with a neuropathic component, considering the benefit/risk balance (Grade B)**. Neuropathic component can be assessed using DN4 score or Pain detect. The patient should be informed about how gabapentinoids work (delayed effect) and side effects (EC; appropriate; strong consensus).

<u>Possible care under conditions/not recommended</u>

21. Ultrasound use and lumbar traction are not recommended (Grade B). Appropriate; strong consensus

22. Orthopaedic insoles are not recommended (Grade B). Appropriate; strong consensus

23. Acupuncture, acupressure and dry needling have not been found effective in alleviating LBP. Appropriate; strong consensus

24. In the absence of a good-quality study, we cannot rule on the effectiveness of sophrology, relaxation, “mindfulness meditation” or hypnosis. However, these can be considered part of a multimodal combination of treatments including active patient management (EC). Appropriate; strong consensus

25. Lumbar belt or corset wearing can be considered for a short period of time to help with recovery even if it has not been found effective in alleviating LBP (EC). Appropriate; weak consensus

26. For the neuropathic component of pain, after failure of other therapeutic alternatives (including multidisciplinary management), spinal cord stimulation can be discussed in a pain center (EC). Appropriate; strong consensus

27. In the absence of study, we cannot determine the benefit of Nefopam or corticosteroids (EC). Appropriate; strong consensus

28. Muscle relaxants have an unfavourable benefit/risk balance in common LBP (EC). Appropriate; weak consensus

29. There is no indication for antibiotics (Grade B), vitamin D (Grade B), lidocaine patch (EC) or anti-TNF alpha (EC). Appropriate; strong consensus

Secondary prevention

31. Patients experiencing an LBP episode should practice regular physical activity and/or self-rehabilitation exercises to reduce the risk of recurrence (Grade B). The choice of physical activity should be decided according to the patient's preference (EC). Appropriate; strong consensus

Recommendations based on data from the literature and expert consensus but not included in the synthesis for health professionals:

Text of the recommendation	Level of scientific evidence	Reason of non-inclusion in the synthesis guideline
Radiofrequency denervation can only be considered in the presence of lumbago resistant to usual treatments (including multidisciplinary management) in patients with two positive facet diagnostic blocks.	Grade B	not included in the synthesis because radiofrequency denervation is very little performed in France
In the absence of good quality studies, it is not possible to conclude on the effectiveness of ozone therapy.	Expert consensus	not included in the synthesis because ozone therapy is very little performed in France
Transcutaneous electrical nerve stimulation (TENS) has no effect on the development of low back pain. TENS should not be proposed as the sole treatment for chronic low back pain. It may be useful as an adjunct in some patients for pain control to reduce the need for medication, as a complement to non-drug therapy	Expert consensus	not included in the synthesis because TENS prescription is limited to pain centres that can provide education on its use

Für die Evidenzbasis und Entscheidungsgrundlagen für Empfehlungen wird auf das LL-Dokument verwiesen.

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Developed by European Pain Federation (EFIC). Endorsed by European Academy of Neurology (EAN), European Federation of Addiction Societies (EUFAS), European Federation of Psychologists' Associations (EFPA), European Headache Federation (EHF), European Psychiatric Association (EPA), European Region -World Confederation of Physical Therapy (ER-WCPT), European Society of Anaesthesiology and Intensive Care (ESAIC), European Society of Physical and Rehabilitation Medicine (ESPRM),European Society of Regional Anaesthesia & Pain Therapy (ESRA) and Pain Alliance Europe (PAE).

European clinical practice recommendations on opioids for chronic noncancer pain –Part 1: Role of opioids in the management of chronic noncancer pain

Zielsetzung/Fragestellung

The purpose of the European Clinical Practice Recommendations is to support appropriate decision making and, if warranted, appropriate prescribing of opioids for patients of any age with chronic (persistent or recurrent >3 months) noncancer pain.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: **Trifft teilweise zu** – Es wird keine Methodikexpertin oder Methodikexperte genannt
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **Trifft zu**
- Systematische Suche, Auswahl und Bewertung der Evidenz: **Trifft zu**
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: **Trifft zu**
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: **Trifft zu**
- Regelmäßige Überprüfung der Aktualität gesichert: **Unklar** – Es werden keine Angaben zu einem Aktualisierungsverfahren gemacht.

Recherche/Suchzeitraum:

- For the review of potential opioid indications and contraindications, we focused on systematic reviews (with or without meta-analysis) of randomized controlled trials (RCTs) of opioids for CNCP with at least 4 weeks double-blind duration and open label extensions studies of these trials with at least 6 months duration and evidence-based guidelines concerned with the management of CNCP.
- PubMed was searched on 11 February 2020 (from 2015) with the search terms ['opioid' AND 'chronic pain' AND 'systematic review'].
- PROSPERO was searched 8 March 2020 with the search terms ['opioids' and 'chronic non-cancer pain'].
- For the section on special situations, we conducted a selective search of literature in PubMed in April 2020 with the search term ['opioids'] and the respective term of the GCP statement.
- The literature for the ECPRs was selected by the members of the evidence synthesis team. The reference lists of the systematic reviews and guidelines selected were also considered for the recommendations and clinical practice statements of the position paper. Discrepancies were resolved by consensus.

LoE

- We used the systematic review with the most recent search of literature or the most studies included in the analyses.
- If reported, the GRADE system was used for the evidence summaries to provide a description of benefits and harms, along with a rating of the certainty of the evidence on an outcome-by-outcome basis (Langendam et al., 2013).
- If no GRADE rating was available, we used the UpToDate® rating of the quality of evidence (UptoDate, 2020a, 2020b).

GoR

Quality rating	Rationale
Strong	Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.
Moderate	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.
Low	Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain.

Note: The general categories that lower the quality of evidence from RCTs are:

Methodologic problems likely to cause bias:

- Inconsistent results
- Indirectness of evidence
- Few observed events

The factors that may raise the quality of evidence from observational studies are:

- Large magnitude of effect
- All plausible biases would reduce a demonstrated effect
- Dose-response gradient

This position paper provides prescribers and patients with a basis for decisions about using opioids to manage chronic noncancer pain. Prescribers, patients and other stakeholders – particularly regulatory agencies or the courts – should not view the recommendations and good clinical practice statements in this guideline as absolute. No guideline can account for the unique features of patients and their clinical circumstances; this guideline is not meant to replace clinical judgment.

A strong recommendation means that benefits clearly outweigh risks and burdens or vice versa. It indicates that all or almost all fully informed patients would choose the recommended course of action, and indicate to clinicians that the recommendation is appropriate for almost all patients.

A weak recommendation means that benefits, risks, and burdens are closely balanced or uncertain. It indicates that the majority of informed patients would choose the suggested course of action, but an appreciable minority would not. With weak recommendations, clinicians should recognize that different choices will be appropriate for individual patients, and they should help patients arrive at a decision consistent with their values and preferences.

The term 'Should be considered' in a good clinical practice statement means, that the good clinical practice statement is appropriate for almost all patients.

The term 'Can be considered' in a good clinical practice statement means, that the good clinical practice statement is appropriate for the majority of patients.

Sonstige methodische Hinweise

- The ECPRs are not intended to contradict disease-specific evidence-based guidelines. They are expert consensus statements rather than a guideline and incorporate the expertise of the TF membership. The TF members acknowledge the conclusions of robust evidence-based guidelines but the clinical practice recommendations recognize that individual responses to therapy may differ from average responses described in evidence-based guidelines. The ECPRs represent a consensus statement of healthcare professionals who work with people with pain provides an experienced perspective, acknowledging the evidence, to support clinical decision making.

Empfehlungen

1. Optimization of non-opioid treatment

Before considering opioid treatment, we first suggest optimizing non-pharmacological treatments (e.g. exercise, physiotherapy, psychological therapies) and considering non-opioid analgesics. Weak recommendation, strong consensus (16/16; 11/11).

2. When to consider opioids

We suggest considering a trial of opioids if established non-pharmacological treatments and established non-opioid analgesics are:

- Not effective and/or
- Not tolerated and/or
- Contraindicated
- Not available

**Established = Guideline recommended or –if not available –current medical standard.

Weak recommendation, strong consensus (15/15; 10/10).

Evidence summary:

A systematic review of RCTs comparing opioids with non-opioid analgesics found that nonopioid analgesics were superior to opioids in terms of improvement of physical function

and tolerability in short-term (4–12 weeks) therapy of neuropathic, low back and osteoarthritis pain (moderate quality UptoDate evidence) (Welsch et al., 2015). These results are in accordance with the findings of the recent review on behalf of the US Agency for Healthcare Research and Quality (Chou et al., 2020).

3. Selection of medications

The selection of medications should consider the type of chronic non-cancer pain, the comorbidities of the patient, contraindications, patient preferences, benefits and harms of previous therapies and the benefit-risk ratio of available pharmacological alternative treatment options. Good clinical practice statement. Strong Consensus (16/16; 11/11)

4. Indication

We suggest considering opioids for the chronic secondary pain syndromes listed below. Weak recommendation

Clinical entity (ICD-10 code)	Quality of evidence (GRADE)	Strength of Consensus
Chronic low back pain with predominant nociceptive and/or neuropathic pain mechanisms[a] (M42.16-M41.19, M42.90, M42.96-99, M43.0, M43.1, M47.26, M47.27, M47.29, M47.86, M47.87, 47.88, M47.99, M48.06, M48.2, M54.16, M54.5, M55.3, M.99.33; M99.43, M99.53)	Low	Consensus (16/17; 11/15)
Chronic osteoarthritis pain (M15-19)	Very low to low	Consensus (13/14; 8/9)
Chronic painful diabetic polyneuropathy (G 63.2)	Very low	Consensus/Majority (11/14; 6/9)
Postherpetic neuralgia (B02.2)	Very low	Consensus/Majority (11/14; 6/9)

[a] Unspecific chronic low back pain with predominant nociplastic pain mechanisms is much more frequent than specific chronic low back pain with predominant nociceptive and/or neuropathic pain mechanisms (Maher et al., 2017). As outlined in the section 'Potential contraindications', opioids are not indicated for unspecific low back pain

Evidence summary

There is low to very low quality GRADE evidence from 21 RCTs of 4–15 weeks with 7,650 participants that opioids are superior in reducing pain and disability, inferior in tolerability and not different in safety compared to placebo for CLBP-pain (Petzke et al., 2020)

There is low to very low quality GRADE evidence from 22 RCTs of 4–26 weeks with 8,942 participants that opioids are superior in reducing pain and disability, inferior in tolerability and not different in safety compared to placebo for OA-pain (Welsch et al., 2020).

There is low to very low quality GRADE evidence from 16 RCTs of 4–12 weeks with 2,199 participants that opioids are superior in reducing pain and disability, inferior in tolerability and not different in safety compared to placebo for some neuropathic pain syndromes (Sommer et al., 2020).

There is very low quality GRADE evidence from 15 open label extension studies of up to 4 years duration with 3,590 participants that in self-selected patients with chronic low back, neuropathic and OA pain, reductions of pain and disability can be maintained. Drop out rate due to adverse events and deaths increase with study duration (Bialas et al., 2020).

The low rate of serious adverse events in RCTs with opioids is in sharp contrast to the results of observational studies in North America which have demonstrated important risks of nonfatal and fatal unintentional overdose, very frequent physical dependence and frequent addiction (Busse et al., 2017). Routine clinical care data from some European countries did not show signals of an opioid epidemic (Bedene et al., 2019; Chenaf et al., 2019; Kalkman et al., 2019; Rosner et al., 2019). Potential explanations of these divergences are as follows:

a. Most RCTs excluded patients with current or a history of substance abuse and with major medical diseases. These (relative) contraindications for opioids might have been neglected in routine medical care in North America. Opioids have been prescribed to the most vulnerable part of the population (unemployment, poverty, mental health problems) (deWeerdt, 2019).

b. The surveillance of patients in the context of clinical studies is closer than the one in routine clinical care.

c. There are differences in the health care systems between North America and Europe (e.g. availability of non-pharmacological treatments; expectations of patients to get medication prescription; financial benefits by increasing the number of patients by opioid prescriptions).

d. Most RCTs did not systematically assess non-medical use and dependence or opioid use disorder and therefore may have underestimated their prevalence.

4.2. Opioids can be considered for the chronic secondary pain syndromes listed below. Good clinical practice statements

Clinical entity (ICD-10 code)	Quality of evidence (UptoDate)	Clinical practice statement	Strength of Consensus
Chronic pain after spinal cord injury (S24)[a]	Moderate[b]	Can be considered	Consensus (11/13; 6/8)
Chronic non-diabetic polyneuropathy pain (G60-64)[a]	Moderate[c]	Can be considered	Consensus (11/12; 6/7)
Chronic phantom limb pain (G54.6)[a]	Moderate[b]	Can be considered	Consensus/Majority (10/12; 5/7)
Chronic radicular pain (M54.1)[a]	Moderate[c]	Can be considered	Consensus (11/12; 6/7)
Chronic pain in rheumatoid arthritis (M06.-)[a]	Moderate[b]	Can be considered	Consensus (13/13; 8/8)
Chronic pain in Parkinson's disease (G20, 21)[a]	Moderate[b]	Can be considered	Consensus (12/13; 7/8)
Chronic pain in restless legs syndrome (G25)[a]	Moderate[b]	Can be considered	Consensus (11/12; 6/7)
Chronic pain due to brain lesions (e.g. status post thalamic stroke, multiple sclerosis)	Low[d]	Can be considered	Consensus (10/11; 5/6)
Chronic pain due to complex regional pain syndrome (CRPS), types I and II (G90.5, G90.6)	Low[d]	Can be considered	Consensus (12/13; 7/8
Chronic secondary headache (e.g. after subarachnoidal haemorrhage) (G44.8)	Low[d]	Can be considered	Consensus (10/11; 5/6)
Chronic osteoporosis pain (e.g. new vertebral body fractures) (M80.-)	Low[d]	Can be considered	Strong Consensus (13/13; 8/8)
Chronic pain due to other inflammatory rheumatic diseases except rheumatoid arthritis (e.g. systemic lupus erythematosis, seronegative spondylarthritis) (M45-M49)	Low[d]	Can be considered	Strong Consensus (12/12; 7/7)
Chronic postsurgical pain (e.g. post-thoracotomy, post-sternotomy, and postmastectomy syndrome, and after abdominal, facial or hernia surgery) (T80-88)	Low[d]	Can be considered	Consensus (11/13; 6/8)
Chronic pain due to ischemic or inflammatory arterial occlusive disease (I70-I79)	Low[d]	Can be considered	Strong Consensus (11/11;6/6)
Chronic pain due to grade 3 and 4 decubitus ulcers (L 89)	Low[d]	Can be considered	Strong Consensus (13/13; 8/8)
Chronic pain due to fixed contractures in nursing-dependent patients (M67)	Low[d]	Can be considered	Consensus (10/11; 5/6)
Chronic posttraumatic trigeminal neuropathy (G 50.9)	Low[d]	Can be considered	Consensus (11/13; 6/8)
Chronic pelvic pain by extensive adhesions (N73.6) and/or extensive and /or infiltrating endometriosis (N80.x)	Low[d]	Can be considered	Consensus/Majority (10/12; 5/7)

[a] See Supplementary Material 5. [b] One RCT available. [c] Two RCTs available. [d] No RCT available; expert Consensus.

5. Potential contraindications

Opioids should not be considered for primary pain syndromes. Good clinical practice statement

Medical condition (ICD-10 code)	Quality of evidence (UptoDate)	Clinical practice statement	Strength of Consensus
Primary headache (Migraine, tension headache) (G43.x, G44.0, G44.2, G44.8)	Low	Should not be considered	Consensus/Strong Consensus (15/16; 11/11)
Other chronic primary headache or orofacial pain (Temporomandibular joint disorder, chronic primary orofacial pain [atypical face pain]) (M26.60, G50.1)	Low	Should not be considered	Strong Consensus (14/14; 9/9)
Functional somatic disorders (e.g. fibromyalgia syndrome, irritable bowel syndrome) (M79.70; F45.32/K58.0/K58.1)	Low	Should not be considered	Consensus/strong Consensus (14/15; 9/9)
Other chronic primary visceral pain syndromes (Chronic primary chest pain [atypical chest pain], chronic primary epigastric pain syndrome [functional dyspepsia], chronic primary bladder pain syndrome [overactive bladder], chronic primary pelvic pain syndrome [pelvic and perineal pain] (R07.89. K30, N32.81, R102.]	Low	Should not be considered	Strong Consensus (14/14; 9/9)
Chronic primary musculoskeletal pain syndromes (cervical, thoracic, low back, limb pain) (no corresponding ICD-10 codes available)	Low	Should not be considered	Consensus/strong Consensus (14/15; 9/9)
Chronic pain as a major manifestation of a mental disorder (atypical depression, persistent somatoform pain disorder, generalized anxiety disorder, post-traumatic stress disorder) (F41, F43, F32, F33, F45)	Low	Should not be considered	Strong Consensus (15/15; 10/10)

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Royal Dutch Society for Physical Therapy (KNGF)

Management of low back pain and lumbosacral radicular syndrome: the Guideline of the Royal Dutch Society for Physical Therapy (KNGF)

Zielsetzung/Fragestellung

To update and develop an evidence-based guideline for the comprehensive management of LBP and lumbosacral radicular syndrome (LRS) without serious specific conditions (red flags) for Dutch physical therapists and Cesar and Mensendieck Therapists.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: **Trifft zu**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **Trifft teilweise zu** – Interessenkonflikte und Finanzierung werden dargelegt, jedoch bleibt unklar, wie mit potenziellen Interessenkonflikten umgegangen wird.
- Systematische Suche, Auswahl und Bewertung der Evidenz: **Trifft zu**
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: **Trifft zu**
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: **Trifft zu**
- Regelmäßige Überprüfung der Aktualität gesichert: **Trifft zu**

Recherche/Suchzeitraum:

- On April 14th, 2020 the project group of the KNGF guideline instructed an information specialist to carry out a systematic search for systematic reviews and evidence-based guidelines for patients with LBP for the period January 1st, 2015 until April 14th, 2020.
- The search in PubMed, MEDLINE, Embase, Emcare, Web of Science and the Cochrane Library produced 2439 unique hits.
- The results were supplemented by the findings from Dutch-language evidence-based guidelines on treating patients with LBP that were not included in the selected databases. 28, 29, 50-56

- For each clinical question, an assessment was done to see whether there were published guidelines, systematic reviews or narrative reviews among these unique hits with which clinical questions could be answered, whether the studies met the inclusion criteria and whether the studies were sufficiently current and of sufficient methodological quality.

LoE

- Grading of Recommendations Assessment, Development and Evaluation (GRADE)

TABLE II.—*GRADE approach to certainty of evidence.*

High	The actual effect is close to the estimation of the effect
Moderate	The actual effect is likely close to the estimation of the effect, but it is possible for the actual effect to substantially deviate from the estimation of the effect
Low	The actual effect may differ substantially from the estimation of the effect
Very low	The actual effect likely differs substantially from the estimation of the effect

GRADE: Grading of Recommendations Assessment, Development and Evaluation methodology.

GoR

- For each clinical question strong (offer or do not offer) or conditional (consider or consider not to) recommendations in favor of or against the intervention were formulated.

Sonstige methodische Hinweise

- In dieser Leitlinie werden ausschließlich physiotherapeutische Maßnahmen thematisiert
- Whenever 'LBP' is mentioned, this means both LBP and LRS, without signs and symptoms that could indicate an underlying serious pathology (alarm signs and symptoms). If different or supplementary recommendations apply to patients with LRS, these are described in a separate section.
- Interpretation of the size of the effect:

TABLE III.—*Interpretation of the size of effect.*

Parameter	Small effect	Moderate effect*	Large effect*
Standardized mean difference (SMD)	<0.3	0.3 to 0.5	>0.5
VAS/NPRS (0-10), MD	<1	1 to 2	>2
RMDQ (0-24), MD	<2	2 to 5	>5
ODI / QBPDS (0-100), MD	<10	10 to 20	>20
Quality of life (SF-12, SF 36, PCS 0-100), MD	<10	10 to 20	>20
Quality of life (SF-12, SF 36, MCS 0-100), MD	<10	10 to 20	>20

VAS: Visual Analogue Scale; NPRS: Numeric Pain Rating Scale; MD: mean difference; RMDQ: Roland Morris Disability Questionnaire; ODI: Oswestry Disability Index; QBPDS: Quebec Back Pain Disability Scale; SF-12: 12-items Short Form Health Survey; SF-36: 36-items Short Form Health Survey; PCS: physical component summary; MCS: mental component summary.
*A moderate and large effect are also considered to be clinically relevant.

Empfehlungen

Treatment profiles

TABLE VI.—*Recommendations treatment profiles.*	
Evaluate the risk of persistent complaints upon initial contact with the patient by assessing whether there are prognostic factors for persistent LBP complaints (see prognostic factors). Then select among the following profiles:	
Profile 1	• Low risk of persistent symptoms There are no dominant* prognostic factors for delayed recovery present
Profile 2	• Moderate risk of persistent LBP There are some non-dominant* prognostic factors for delayed recovery present
Profile 3	• High risk of persistent LBP There are dominant* prognostic factors for delayed recovery present
Based on the treatment profiles, consider offering simpler and less intensive support to people who are likely to recovery quickly and more complex and intensive support to people with a higher risk of persistent complaints	
StarT Back Screening Tool (SBST)	Consider using the SBST to support the evaluation of the risk of persistent complaints. Never base the evaluation solely on the SBST
*Dominant/non-dominant: a dominant presence is when the factor greatly contributes to perpetuating the pain and/or limitations in physical functioning.	

Exercise therapy

TABLE VIII.—*Recommendations on exercise therapy.*	
Exercise therapy for patients with LBP	
Profile 1	• Consider giving instructions for exercise therapy to be done independently
Profile 2 and 3	• Offer exercise therapy
Type exercise therapy	• Focus the exercise therapy on the patient's needs, preferences and capabilities as determined during the medical history taking and the physical examination • Encourage the patient to resume or expand activities, preferably gradually and in a time contingent manner • Consider group exercise therapy as a follow-up to one or more individual sessions, if you as a therapist estimate that group exercise therapy will lead to faster recovery
Guidance	• If permissible, scale back the guidance during the treatment period and do this in consultation with the patient. In this case, it is important to not decrease the exercise frequency and intensity; the focus will shift to independent exercising and physical activity
Exercise therapy for patients with LRS	
Profile 1,2,3	• Consider exercise therapy if there is a need for assistance related to limitations in activities of daily living and/or social participation based on movement-related functioning
Type exercise therapy	• Focus on pain alleviation in the presence of high irritability. In the presence of moderate irritability, increased pain of short duration (a part of a day) is acceptable • Increase the exercise therapy depending on the pain. If good progress is made, expand the activities to the prior level in 6 to 12 weeks based on the frequency, intensity and time span of the various types of exercise therapy

Based on the systematic search, 15 systematic reviews 90-104 were identified that describe the effectiveness of exercise therapy. The AMSTAR-2 rating of the overall confidence in the results of the review was high for one systematic review,95 moderate for two 90, 104 and low for the other 12 reviews.

For patients with chronic LBP, the most recent systematic review of high methodological quality found a clinically relevant effect of exercise therapy compared to no exercise therapy on pain and physical functioning in the short term, with moderate certainty of evidence.95 For exercise therapy compared to other conservative treatment, conflicting results were found for pain and physical functioning in the short term; the small (not clinically relevant) effects were sometimes in favor of exercise therapy and sometimes in favor of other conservative treatments. In the long term, no clinically relevant effects of exercise therapy were found for these outcome measures compared to no exercise therapy or other forms of exercise therapy.

The effectiveness of motor control exercise (MCE) is described in 12 systematic reviews.103, 105-115 None of the systematic reviews were qualified of high or moderate methodological quality according to the AMSTAR-2 score.

For patients with chronic LBP, evidence was found of a clinically relevant effect on pain when MCE was compared to minimal intervention (placebo physical therapy, education or advice and no treatment) in the short and long term, but no clinically relevant effect was found on physical functioning (low to moderate certainty of evidence). However, no clinically relevant difference was found between MCE and other forms of exercise therapy on pain and physical functioning in the short and long term (low to high certainty of evidence).

The effectiveness of MDT (mechanical diagnosis and therapy according to McKenzie) is described in six systematic reviews,116-121 and all were found of critically low methodological quality according to the AMSTAR-2 score. In patients with chronic LBP, MDT does not lead to clinically relevant effects on pain and physical functioning in the short term compared to another intervention. The long-term effect of the method is not known in patients with chronic LBP.

Behavior-oriented treatments

TABLE X.—*Recommendations behavior-oriented treatments.*

Profiles 1 and 2	• A thorough explanation and focus on the biopsychosocial model are sufficient
Profile 3	• Consider behavior-oriented treatment* in patients with dominant (psychosocial) prognostic factors • Consider personalizing the behavior-oriented treatment by aiming this specifically at the psychosocial prognostic factors, as described in Table IX • Focus behavior-oriented treatment on encouraging movement behavior with or despite pain
Type	• Discuss the choice of behavior-oriented treatment with the patient and align with the patient's needs, preferences and capabilities and your own knowledge and skills as a therapist • Only apply the forms of behavior-oriented treatment for which you are competent and authorized

*Forms of treatment aimed at a different manner of dealing with pain are designated as behavior-oriented interventions. These treatment forms use operant (*e.g.* graded activity), cognitive (*e.g.* exposure *in vivo*) and respondent learning processes (*e.g.* relaxation exercises, mindfulness and electromyography biofeedback training [EMG biofeedback]).[40] Behavior-oriented treatment interventions also include interventions such as Acceptance and Commitment Therapy (ACT) and interview techniques (*e.g.* motivational interviewing).[153] Pain education, including learning to deal with pain and anxiety differently, are basic components of graded activity and exposure *in vivo*.

The NICE guideline on LBP and sciatica31 and The Belgian national guideline on LBP and radicular pain86 conclude that behavior-oriented treatment has added value as a supplement to physical therapy for patients with LBP. There is no proof of the effectiveness of isolated forms of behavior-oriented treatment. However, both guidelines state that behavior-oriented treatment in combination with exercise therapy may be cost-effective compared to interventions that do not take into account psychosocial factors.78, 124, 125 Cognitive behavioral therapy should be considered for people with LBP, with or without radicular pain, but only as part of a multimodal treatment with a supervised exercise program. The guideline of the American College of Physicians (ACP)123 recommends the following for people with chronic LBP(complaint duration >12 weeks): mindfulness aimed at stress reduction (moderate certainty of evidence), progressive relaxation therapy, EMG feedback, operant therapy and cognitive behavioral therapy (low certainty of evidence).

The systematic search on April 14th, 2020 for systematic reviews (see section development) investigating the effectiveness of behavior-oriented treatments in patients with LBP whereby treatments were administered either entirely or to a significant extent by physical therapists or other paramedical professionals yielded eight literature reviews.126-133 Two systematic reviews pooled the results130, 133 and the other six presented a narrative synthesis of the included studies. All reviews were found of critically low methodological quality according to the AMSTAR-2 score.

The systematic reviews generally found positive effects of behavior-oriented treatment (either as a supplement to physical therapy or on its own) compared to various types of control treatments on pain and/or physical functioning in the short term and/or long term. The positive effects on pain and physical functioning were less clear or inconsistent when the behavior-oriented treatment was compared to a physically active treatment. The effectiveness of behavior-oriented treatment was more favorable if it was aligned with the needs of the patient. Three systematic reviews127, 132, 133 evaluated the adverse effects of behavior-oriented treatment. They concluded that these treatments were not studied frequently, but that the chance of adverse effects is likely very small and that these are rare or never serious.

In two systematic reviews130, 132 in which the certainty was evaluated according to the GRADE method, the researchers concluded that the certainty for the effectiveness of behavior-oriented treatments is moderate to high.

Mobilization and manipulations

TABLE XI.—*Recommendations mobilizations and manipulations.*	
Profiles 1	• Do not perform mobilizations or manipulations
Profile 2 and 3	• Consider performing mobilizations and/or manipulations on patients with LBP, but only as a supplement to exercise therapy if the problem is mechanical in nature due to disorders within the neuromusculoskeletal system (*e.g.* decreased regional mobility during lumbar flexion or extension) • Evaluate and analyze the effects of mobilizations and/or manipulations immediately within the treatment session and at the start of the next session. Be alert to serious (rare) adverse effects, such as significant increase of pain or motor deficit • Discuss the choice of mobilization or manipulation with the patient and align with the patient's needs, preferences and capabilities and your own knowledge and skills as a therapist. When doing so, pay attention to potential negative effects and discuss this with the patient prior to the treatment
Do not perform mobilizations or manipulations: • as singular intervention • if you are not competent and authorized to do this or you have insufficient knowledge to determine the indication and contra-indications It is preferable not to perform mobilizations or manipulations on patients with LRS	
Mobilizations are understood to mean passive arthrogenic mobilizations. Manipulations are understood to mean high-velocity-thrust techniques on synovial joints.	

The effect of mobilization and/or manipulation plus exercise therapy was compared with exercise therapy alone or with exercise therapy plus another intervention aligned with the guideline in the short term (≤4 months) in 11 RCTs,156, 173, 177, 180, 182, 189, 197, 203, 204, 210, 212 and in the long term (>4 months) in seven RCTs.156, 173, 177, 180, 189, 203, 212 On the short term the effects were small (not clinically relevant) positive on the critical outcome measures pain with low certainty of evidence and on physical functioning with very low certainty of evidence. On the long term the effects were small positive on pain with moderate certainty of evidence and on physical functioning with very low certainty of evidence. On most important outcome measures the effects were small positive with very low to moderate certainty of evidence.

The effect of mobilization and/or manipulation was compared with another intervention aligned with the guideline in the short term (≤4 months) in 21 RCTs,158, 160, 162, 163, 169, 171, 172, 176, 178, 180, 181, 185, 187, 188, 195, 198, 200, 201, 206, 208, 209 and in the long term (>4 months) in 12 RCTs.158, 160, 162, 163, 169, 172, 176, 180, 187, 195, 201, 209 On the short and long term the effects were small positive on pain and physical functioning with low certainty of evidence. On the important outcome measures the effects were small positive or negative with very low certainty of evidence.

The effect of mobilization and/or manipulation was compared with sham mobilization and/or manipulation in the short term (≤4 months) in eight RCTs,157, 164, 167, 171, 179, 183, 205, 206 and in the long term (>4 months) in two RCTs.179, 205 On the short term the effects were moderate (clinically relevant) positive on pain, large (clinically relevant) positive on physical functioning and moderate positive on quality of life, with the evidence being of very low certainty. On the long term the effects were small positive on pain with very low certainty of evidence, physical functioning with low certainty of evidence and on quality of life with very low certainty of evidence.

The effect of mobilization and/or manipulation was compared to placebo in the short term (≤4 months) in two RCTs.165, 184 No RCTs were found that studied the effect in the long term (>4 months). On the short term the effects were small positive on pain with low certainty of evidence, moderate positive on physical functioning with low certainty of evidence and small positive on the number of patients without work restrictions with very low certainty of evidence.

The effect of manipulation was compared with mobilization in the short term (≤4 months) in six RCTs,159, 161, 168, 186, 190, 192 and in the long term (>4 months) in two RCTs.168, 190 On the short term the effects for manipulation were small positive on pain with very low certainty of evidence, moderate positive on physical functioning with very low certainty of evidence, and mixt on quality of life with low certainty of evidence. On the long term the effects for manipulation were small positive on pain with low certainty of evidence and moderate positive on physical functioning with very low certainty of evidence. The exact results can be found in the KNGF LBP and LRS guideline.49

Almost all studies used the duration of the LBP as a criterion for including or excluding patients. However, when evaluating the results, there were no differences in treatment results between patients with short-term (<4 months) and persistent (>4 months) LBP.

Most studies included a mix of patients with or without LRS. Because there were only a few studies in which exclusively patients with or patients without LRS were included, it was not possible to adequately compare the treatment with the various control interventions.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 03 of 12, March 2026) am 02.03.2026

#	Suchschritt
1	[mh "chronic pain"]
2	[mh "back pain"]
3	((back OR chronic) AND (pain OR ache)):ti
4	[mh "Low back pain"]
5	((Low OR lower) AND (backache OR (back AND (ache OR pain)))):ti,ab,kw
6	(Vertebrogenic AND (pain OR syndrom*)):ti,ab,kw
7	Lumbago:ti,ab,kw
8	[mh Sciatica]
9	((Sciatic* AND (neuralg* OR pain)) OR sciatica):ti,ab,kw
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	#10 with Cochrane Library publication date from Mar 2021 to present, in Cochrane Reviews
12	#10 with Cochrane Library publication date from Mar 2024 to present, in Cochrane Reviews
13	#11 NOT #12

Leitlinien und systematische Reviews in PubMed am 02.03.2026

verwendete Suchfilter für Leitlinien:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.02.2026

verwendeter Suchfilter für systematische Reviews:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 01.01.2026.

#	Suchschritt
	Leitlinien
1	Chronic Pain[majr] OR Back Pain[majr:noexp]
2	(back[ti] OR chronic[ti]) AND (pain[ti] OR ache[ti])
3	Low back pain[mh]
4	(Low[tiab] OR lower[tiab]) AND (backache OR (back[tiab] AND (ache[tiab] OR pain[tiab])))
5	Vertebrogenic[tiab] AND (pain[tiab] OR syndrom*[tiab])
6	Lumbago[tiab]
7	Sciatica[mh]
8	(Sciatic*[tiab] AND (neuralg*[tiab] OR pain[tiab])) OR sciatica[tiab]

#	Suchschritt
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10	(#9) AND (Guideline[pt] OR Practice Guideline[pt] OR Consensus Statement [pt] OR Consensus Development Conference, NIH[pt] OR guideline*[ti] OR recommendation*[ti])
11	(#10) AND ("2021/03/01"[PDAT] : "3000"[PDAT])
12	(#11) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "preprint"[pt])
	systematische Reviews
13	#3 OR #4 OR #5 OR #6 OR #7 OR #8
14	(#13) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
15	(#14) AND ("2021/03/01"[PDAT] : "3000"[PDAT])
16	(#15) NOT "The Cochrane database of systematic reviews"[Journal]
17	(#16) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
18	(#17) NOT (#12)
19	(#18) AND ("2024/03/01"[PDAT] : "3000"[PDAT])
20	#18 NOT #19

Iterative Handsuche nach grauer Literatur, abgeschlossen am 03.03.2026

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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4. **Ferraro MC, Urquhart DM, Ferreira GE, Wewege MA, Abdel Shaheed C, Traeger AC, et al.** Antidepressants for low back pain and spine-related leg pain. Cochrane Database of Systematic Reviews [online]. 2025(3):Cd001703. URL: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001703.pub4/pdf/full.
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[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO