Long-term opioid therapy for chronic noncancer pain: second update of the German guidelines

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Abstract

Introduction: The opioid epidemic in North America challenges national guidelines worldwide to define the importance of opioids for the management of chronic noncancer pain (CNCP).

Methods: The second update of the German guidelines on long-term opioid therapy for CNCP was developed by 26 scientific associations and 2 patient self-help organizations. A systematic literature search in CENTRAL, Medline, and Scopus (to May 2019) was performed. Meta-analyses of randomized controlled trials and open-label extension studies with opioids for CNCP were conducted. Levels of evidence were assigned according to the Oxford Centre for Evidence-Based Medicine classification system. The formulation and strength of recommendations were established by multistep formalized procedures to reach a consensus according to German Association of the Medical Scientific Societies regulations. The guidelines underwent external review by 4 experts and public commentary.

Results: Opioids are one drug-based treatment option for short- (4–12 weeks), intermediate- (13–26 weeks), and long-term (>26 weeks) therapy of chronic pain in osteoarthritis, diabetic polyneuropathy, postherpetic neuralgia, and low back pain. Contraindications are primary headaches, functional somatic syndromes, and mental disorders with the (cardinal) symptom of pain. For specified other clinical pain conditions, short- and long-term therapy with opioids should be evaluated on an individual basis. Long-term therapy with opioids is associated with relevant risks.

Conclusion: Responsible application of opioids requires consideration of possible indications and contraindications, as well as regular assessment of clinical response and adverse effects. Neither uncritical opioid prescription nor general rejection of opioids is justified in patients with CNCP.

1. Introduction

Chronic noncancer pain (CNCP) includes any painful condition that persists for at least 3 months and is not associated with malignant disease. In 2014, the prevalence of CNCP in the general German population was 28.3%, with 7.3% of participants of a population survey meeting criteria for chronic disabling noncancer pain. Chronic low back pain (CLBP) and osteoarthritis (OA) pain are the most frequent CNCP syndromes and leading causes of global disability.

Opioids are frequently used for the treatment of CNCP in first world countries. In 2018, Germany had the second highest rate per capita of opioid prescribing in the world when measured using defined daily doses per million inhabitants per day. Approximately 70% of opioid prescriptions in Germany are for...
Approximately 1% of the German population are on continuous opioid treatment for CNCP defined as at least one opioid prescription in at least 3 consecutive quarters of a year.\textsuperscript{22,28} Despite the high prescription rates for opioids, there are currently no signals of an opioid epidemic in Germany.\textsuperscript{36}

In view of the opioid crisis in North America,\textsuperscript{8} increasing concerns about opioid treatment for CNCP have been raised, especially for longer treatment periods.\textsuperscript{5} With the objective to help mitigate the opioid crisis in North America, Canadian guidelines for opioid therapy and CNCP were updated in 2017.\textsuperscript{4} In contrast to the 2010 version,\textsuperscript{14} in which most statements supported the prescribing of opioids, 7 of 10 recommendations of the 2017 version focussed on harm reduction. Likewise, the recommendations of the U.S. 2016 guideline of the Centers of Disease Control addressed problematic prescribing (eg, high-dose prescribing, overlapping opioid, and benzodiazepine prescriptions) to reduce the U.S. overdose epidemic.\textsuperscript{10}

The rules of the Standing Guideline Commission of the Association of Scientific Medical Societies in Germany (AWMF) for guideline development require an update every 5 years.\textsuperscript{16} The previous versions of the German opioid guidelines were published in 2009\textsuperscript{35} and 2014.\textsuperscript{20} Both previous versions met the highest classification for German guideline levels, namely an evidence- and consensus-based guideline with a representative committee, systematic reviews, synthesis of evidence, and a structured consensus development. This current updated guideline incorporates all new evidence published after the literature search for the 2014 guideline. The full guideline includes 8 statements, 89 recommendations, and 18 tools for clinical practice.\textsuperscript{22} We present the main recommendations and discuss similarities and differences between the German and the Canadian and U.S. guidelines.

2. Scope
The purpose of this clinical practice guideline is to promote evidence-based safe prescribing of opioids for patients of any age with CNCP. The target audience includes those who prescribe opioids (physicians), those who take opioids (patients), or those who create policy regarding this issue.

The guideline covers all oral and transdermal opioids (including opioids with an additional mode of action) that can be prescribed for chronic pain management in Germany (tilidine, morphine, buprenorphine, hydromorphone, fentanyl, oxycodone, tapentadol, tramadol).

This guideline does not address the management of acute or subacute pain (<4 weeks) treatment and end-of-life care, but focusses on the long-term opioid therapy of CNCP. Definitions of long-term opioid therapy vary widely. Most studies define long term as ≥90 days of opioid use.\textsuperscript{1} Based on study duration of randomized controlled trials (RCTs), we defined duration of opioid therapy for evidence-based recommendations for indication of opioids as follows: short-term (4–12 weeks), intermediate-term (13–26 weeks), and long-term (>26 weeks).

3. Disclaimer
German guidelines do not represent a regulation for action or omission, a process agreed by a legally legitimate institution, fixed in writing and published. They are not legally binding for this institution and will not result in defined penalties if not followed. A guideline will only become clinically effective if the strength of recommendations is considered clinically relevant and can be integrated into individual patient care that includes a shared decision-making partnership. The decision to follow a specific recommendation should rest with the treating physician in the context of the care of an individual patient and with consideration of the available resources.

4. Methods
4.1. Framework
In developing this guideline, the German Pain Society followed standards for trustworthy guidelines as defined by the rules of the AWMF Standing Guideline Commission.\textsuperscript{41} These standards include innovative approaches for key components such as patient involvement, balanced committee composition, and conflicts of interest (COIs) management. Systematic reviews were conducted, and the Grading of Recommendations Assessment, Development and Evaluation system was applied to meet standards of evidence assessment and recommendation development.\textsuperscript{25}

4.2. Guideline development group
The board of the German Pain Society named 10 persons (clinicians, experts on guideline preparation, and patient representatives) to the steering committee for the creation of this updated guideline. These persons included practitioners of primary care medicine, anesthesiology, general internal medicine, geriatrics, neurology, orthopedic surgery, psychosomatic medicine, palliative care medicine, and clinical psychology. They were selected on the basis of their clinical and/or scientific or personal (patient) expertise. In addition, a representative of the AWMF was included as a consultant for methodology.

The evidence synthesis team consisted of the 2 chairs of the steering committee, 3 practitioners, and a licensed librarian, who were not part of the guideline development group.

All societies representing a medical specialty in which physicians caring for adult patients must undergo continuing medical education in Germany were invited to participate in the consensus group. Finally, one representative each of 23 medical associations accepting the invitation, 3 nonphysician associations (pharmacy, nursing, pain psychology), and 2 patient self-help organisations formed the consensus group (see E-Table 1 for composition of the steering committee and guideline group, available as supplemental digital content at http://links.lww.com/PR9/A72).

4.3. Managing conflicts of interest
The COIs were declared according to the rules of the AWMF Standing Guideline Commission by the members of the guideline group before the start of the update.\textsuperscript{16} They were evaluated by 2 directors of the German Pain Society (a physiologist and a physician) who did not participate in the development of the guideline. The degree of financial COIs with pharmaceutical companies producing opioids was classified as follows:

\begin{itemize}
  \item (1) None: No interaction
  \item (2) Slight: Only honoraria for lectures
  \item (3) Moderate: Advisory board; study support
  \item (4) High: Patent; employee of a pharmaceutical company
\end{itemize}

Thirty two members of the guideline group (including the 2 chairs of the steering committee) had no COIs, 2 members had slight COIs, and 3 members had moderate financial COIs. One member of the steering committee with moderate COIs was excluded from preparing recommendations. The strength of consensus of the recommendations was assessed twice: with and without the votes of the members with moderate COIs.
4.4. Topics of the guideline (research questions)

The topics of the guideline were defined as follows:
(1) All members of the guidelines group and all members of the German Pain Society were invited by email to suggest topics that should be addressed.
(2) The evidence synthesis team reviewed the 2014 German guidelines as well as 3 other recently published guidelines (identified by PubMed and Guidelines International Network) for safe and effective use of opioids for CNCP and summarized all prior recommendations.4,10,30

Topics identified by the methods described above were further subselected by a Delphi process within the steering committee. A final 50 research questions were identified, 34 of which had been addressed in the previous version, and 16 were new. Furthermore, the guideline also considered special situations with consensus statements and practical guidance tools (E-Table 2, available as supplemental digital content at http://links.lww.com/PR9/A72).

4.5. Systematic reviews

The evidence synthesis team updated previous systematic reviews and meta-analyses of RCTs of at least 4-week double-blind duration comparing opioids with placebo for CLBP,32 osteoarthritis pain,37 and neuropathic pain,39 as well as a systematic review of open-label extension studies of at least 6-month61 duration opioid therapy in CNCP. A search for RCTs in Clinicaltrials.gov, CENTRAL, MEDLINE, and PsycINFO was conducted from October 2013 to May 2019. The systematic reviews underwent external peer review for publication in European Journal of Pain. In addition, a systematic search was conducted in CENTRAL, Medline, and Scopus from October 2013 to December 2018 for systematic reviews of RCTs and RCTs with opioids for any CNCP syndrome. A systematic search for risks of opioid therapy reported in observational studies was conducted through January 2019 in Medline for secondary search, see E-Figure 1, available as supplemental digital content at http://links.lww.com/PR9/A72).

For evidence-based recommendations for potential indications, the evidence synthesis team created evidence summaries using the Grading of Recommendations Assessment, Development and Evaluation system.25

4.6. Meta-analyses

The results of the respective meta-analyses for CLBP,33 osteoarthritis pain,43 and neuropathic pain,40 and open-label extension studies of these RCTs6 were used for evidence-based recommendations for potential indications for opioids. The following primary outcomes were analysed: pain relief of 50% or greater, patient global impression to be much or very much improved, disability, dropout rates to adverse events (tolerability), frequency of serious adverse events, and death. Secondary outcomes were pain relief of 30% or greater, mean pain intensity, sleep problems, withdrawal symptoms, and abuse/dependence of prescribed opioids.

4.7. Strengths of recommendations

The guideline included 2 categories of recommendations: evidence-based (supported by evidence from systematic reviews of RCTs, single RCTs, or observational studies) and consensus-based (supported by little or no published evidence) recommendations. The wording and meaning of both types of recommendations are outlined in E-Table 3 (available as supplemental digital content at http://links.lww.com/PR9/A72).

The strengths of recommendation were formulated as specified in the AWMF regulations.16 The evidence levels (according to the Oxford 2009 scheme31) were of prime importance for the derivation of recommendation grades: the higher the evidence level, the stronger the recommendation. In general, a grade A (strong) recommendation was assigned on the basis of grade 1 evidence, a grade B recommendation on the basis of grade 2 evidence, and a discretionary (open) recommendation on the basis of evidence of grade 3, 4, or 5. Aside from the level of evidence, the assignment of recommendation grades also took into consideration the following aspects: physicians’ ethical responsibilities, the clinical relevance of the efficacy measures used in the trials, the applicability of the trial findings to the target group of patients, patients’ wishes, and the practicality of clinical implementation. This process could result in a weaker or stronger recommendation with respect to the evidence grade alone16 (see E-Figure 2, available as supplemental digital content at http://links.lww.com/PR9/A72). The steering committee used a Delphi process to define a priori which criteria would be used for strengthening or weakening a recommendation.

At the final guideline conference, the strength of each consensus recommendation was determined as follows: strong consensus: >95% agreement; consensus: >75% to 95% agreement; majority: >50% to 75% agreement; and no consensus: ≤50% agreement.

4.8. Patient preferences

Patients were involved in defining the research questions, the recommendations, and the evaluation of a patient version of the guideline.

A search in PubMed (patient preferences AND opioids AND CNCP) produced 6 hits. We found one systematic review, which ranked pain relief, nausea, and vomiting as highly significant outcomes across studies. When considered in the studies, the adverse effect of personality changes was rated as equally important. Constipation was assessed in most studies and was an important outcome, but secondary to pain relief, nausea, and vomiting. The only 2 studies that evaluated addiction found that addiction was less important to patients than pain relief.17

In addition, rare but relevant side effects of opioids such as increased risk of addiction and mortality—in agreement with the patients of the guideline group—were addressed.

4.9. Consensus-finding procedure

The recommendations of the guideline were prepared by the 2 chairs of the steering committee and discussed, modified, and agreed on by the steering committee in 19 Delphi rounds. The consensus group then voted online on the recommendations from September 2, 2019, to October 6, 2019. The group held a final consensus conference, moderated by a representative of the AWMF, on November 16, 2019. At this conference, all statements and recommendations that did not reach a strong consensus in the online vote were discussed and modified if necessary, with the aim to reach a strong consensus.

4.10. External peer review

The guideline was reviewed by 4 physicians experienced in chronic pain management. In response to their reviews, 30 accompanying comments were modified, but no recommendation was changed.
These decisions were taken by Delphi rounds of the chairs of the steering committee, and consented by the steering committee.

4.11. Public comments
The German Pain Society released a press statement in December 2, 2019, which invited the public to comment on the online draft of the guideline. The press statement was sent by email to their 3400 members and participating bodies. The public was given the opportunity to comment on the guideline until January 18, 2020. In response to 6 comments, one statement and 6 accompanying explanations were modified and consented by the steering committee.

Neither the direction nor strength of any recommendation changed because of feedback.

4.12. Final approval
The guideline was approved by the boards of all medical and nonmedical associations involved in the guideline development and by the clearing house of German guidelines.

4.13. Guideline formats
The guideline is available in the following formats: a full and short version, a pocket version, and a full and short patient version.

5. Results: main recommendations
5.1. Importance of opioids for the management of chronic noncancer pain
5.1.1. Importance of opioids for the management of chronic noncancer pain
Before starting opioids, nonpharmacological treatment options should be optimised and pharmaceutical alternatives should be considered. Strong consensus-based recommendation, strong consensus.

5.1.2. Monotherapy with opioid analgesics
Opioid analgesics should not be the sole treatment for CNCP. Self-help resources and physical, physiotherapeutic, and/or psychotherapeutic techniques (including patient education), and/or lifestyle modification, should accompany any drug treatment for pain. Strong consensus-based recommendation, strong consensus.

5.1.3. Selection of drugs
The selection of drugs should consider the type of CNCP, the comorbidities of the patient, contraindications, patient’s preferences, benefits and harms of previous therapies, and the benefit-risk ratio of available pharmacological and nonpharmacological alternative treatment options. Strong consensus-based recommendation, strong consensus.

5.2. Starting rules
5.2.1. Potential evidence-based indications for opioids
Evidence-based recommendations based on RCTs with opioids were available for CLBP, OA pain, and some neuropathic pain syndromes (see Table 1; for details, see E-tables 3–10, available as supplemental digital content at http://links.lww.com/PR9/A72).

The potential indications for opioids for CLBP and OA pain were restricted by these consensus-based recommendations:

- Opioids should only be used if there is a relevant somatic factor in the onset and maintenance of CLBP according to medical/psychological/physiotherapeutical assessment and there is an insufficient response to nonpharmacological treatments. Strong consensus-based recommendation, strong consensus.

Opioids should only be used for chronic OA pain in these situations: Failure of nonpharmacological treatments; failure of or contraindication for other analgesics; joint replacement not possible or refused by the patient. Strong consensus-based recommendation, strong consensus.

5.2.2. Potential consensus-based indications for opioids
All medical associations of the guideline group were asked to identify diseases or syndromes within their specialties for which opioids were considered useful in clinical practice. This was discussed and confirmed by the consensus process (Table 2).

5.2.3. Evidence- and consensus-based contraindications for opioids
The recommendations against use of opioids for primary headache and inflammatory bowel disease were based on cohort studies indicating increased risks of opioid therapy (Table 3). The recommendation against opioids for chronic pancreatitis pain was based on a negative RCT assessing opioid use. In addition, the negative recommendations for primary headache, irritable bowel syndrome, fibromyalgia syndrome, and somatoform disorders were in accordance with current German guidelines specifically addressing these diseases.

5.2.4. Treatment goals
Individual and realistic treatment goals should be determined together with the patient. Strong consensus-based recommendation, strong consensus.

5.2.5. Initial dose
The initial dose should be low. Strong consensus-based recommendation, strong consensus.

5.2.6. Optimal dose and treatment response
The optimal dose is reached when the previously determined goals of treatment have been attained (eg, improvement of function and/or pain relief of 30% and more) and adverse effects, if any, are mild and tolerable (=positive treatment response). Strong consensus-based recommendation, strong consensus.

5.2.7. Maximum dose
Generally, a morphine equivalent dose of 120 mg/d should only be exceeded in exceptional cases. Strong evidence-based recommendation, strong consensus.

5.2.8. Long-term treatment
Treatment for longer than 3 months should be restricted to patients identified as treatment responders. Strong consensus-based recommendation, strong consensus.

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Potential evidence-based indications for opioids.

| Pain syndrome                              | 4–12 weeks                                                                 | 13–26 weeks                                                                 | >26 weeks                                                                 |
|--------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Chronic low back pain                      | Level of evidence: 1a<br>Quality of evidence: low to very low<br>Strength of recommendation: Weak for | Level of evidence: 1a<br>Quality of evidence: low to very low<br>Strength of recommendation: weak for* | Level of evidence: 1b/2a<br>Quality of evidence: low<br>Strength of recommendation: open* |
| Osteoarthritis pain                        | Level of evidence: 1a<br>Quality of evidence: low to very low<br>Strength of recommendation: weak for | Level of evidence: 1a<br>Quality of evidence: low to very low<br>Strength of recommendation: weak for* | Level of evidence: 2a<br>Quality of evidence: Low<br>Strength of recommendation: open* |
| Painful diabetic polyneuropathy            | Level of evidence: 1a<br>Quality of evidence: low to very low<br>Strength of recommendation: strong for | Level of evidence: 5<br>Quality of evidence: NA<br>Strength of recommendation: open* | Level of evidence: 2b<br>Quality of evidence: Low<br>Strength of recommendation: open* |
| Postherpetic neuralgia                     | Level of evidence: 1a<br>Quality of evidence: low to very low<br>Strength of recommendation: weak for | Level of evidence: 5<br>Quality of evidence: NA<br>Strength of recommendation: open* | Level of evidence: 5<br>Quality of evidence: Low<br>Strength of recommendation: open* |
| Phantom limb pain                          | Level of evidence: 1b<br>Quality of evidence: very low<br>Strength of recommendation: weak for | Level of evidence: 5<br>Quality of evidence: NA<br>Strength of recommendation: open* | Level of evidence: 5<br>Quality of evidence: Low<br>Strength of recommendation: open* |
| Chronic pain after spinal cord injury      | Level of evidence: 1b<br>Quality of evidence: low to very low<br>Strength of recommendation: weak against | Level of evidence: 5<br>Quality of evidence: NA<br>Strength of recommendation: open* | Level of evidence: 5<br>Quality of evidence: Low<br>Strength of recommendation: open* |
| Radicular pain                             | Level of evidence: 1b<br>Quality of evidence: low to very low<br>Strength of recommendation: open | Level of evidence: 5<br>Quality of evidence: NA<br>Strength of recommendation: open* | Level of evidence: 5<br>Quality of evidence: Low<br>Strength of recommendation: open* |
| Painful nondiabetic polyneuropathies       | Level of evidence: 1b<br>Quality of evidence: low to very low<br>Strength of recommendation: weak for | Level of evidence: 5<br>Quality of evidence: NA<br>Strength of recommendation: open* | Level of evidence: 5<br>Quality of evidence: Low<br>Strength of recommendation: open* |
| Chronic pain in rheumatoid arthritis       | Level of evidence: 1b<br>Quality of evidence: very low<br>Strength of recommendation: open | Level of evidence: 5<br>Quality of evidence: NA<br>Strength of recommendation: open* | Level of evidence: 5<br>Quality of evidence: Low<br>Strength of recommendation: open* |
| Restless legs syndrome                     | Level of evidence: 1b<br>Quality of evidence: low to very low<br>Strength of recommendation: weak for | Level of evidence: 5<br>Quality of evidence: NA<br>Strength of recommendation: open* | Level of evidence: 5<br>Quality of evidence: Low<br>Strength of recommendation: open* |
| Parkinson disease                          | Level of evidence: 1b<br>Quality of evidence: very low<br>Strength of recommendation: weak against | Level of evidence: 5<br>Quality of evidence: NA<br>Strength of recommendation: open* | Level of evidence: 5<br>Quality of evidence: Low<br>Strength of recommendation: open* |

* If positive therapy response is present (predefined goals of treatment reached and tolerable side effects). NA, not assessed.

5.3. Stopping rules

5.3.1. Regular treatment monitoring

The physician prescribing opioids should determine at regular intervals whether the treatment goals are still met and should check for presence of adverse effects (eg, loss of interest or attention deficit, falls) or misuse of the prescribed drug. Strong consensus-based recommendation, strong consensus.

An interval of 4 weeks is recommended for the initial phase of therapy.

5.3.2. Discontinuation of a treatment trial

If the individual therapeutic goals are not reached during the titration phase (maximum 12 weeks), or (in the view of the patient and/or the physician) insufficiently treatable or intolerable adverse events occur, treatment with opioid analgesics should be tapered. Strong consensus-based recommendation, strong consensus.

5.3.3. Discontinuation of treatment >12 weeks

Long-term treatment should be tapered:

(1) If the individual therapeutic goals are no longer achieved, or (in the view of the patient and/or the physician) insufficiently treatable or intolerable adverse events occur,

(2) If the individual therapeutic goals are achieved by other medical (eg, surgery, radiation therapy, sufficient treatment of the underlying condition), physical, or psychotherapeutic measures,

(3) If the patient uses the prescribed opioid in an abusive manner despite concomitant treatment from an addiction specialist.

5.3.4. Drug holidays

After 6 months of opioid treatment that has provided a satisfactory response, a dose reduction or drug holiday should be discussed. In a shared decision-making process with the patient, the need for continued treatment should be reviewed and a potential response to concomitant nonpharmacological treatments (eg, multimodal therapy) should be discussed. Strong consensus-based recommendation, strong consensus.

6. Discussion

All 3 recent guidelines for use of opioids in CNCP, the Canadian, German, and U.S. guidelines, have used similar methods (systematic literature search; qualitative and quantitative analysis of the evidence; structured approach to build recommendations) to develop recommendations. All guidelines agree on the limited yet relevant role of opioids in the management of CNCP. Optimization of nonpharmacologic therapy before starting...
opioids as well as during long-term opioid treatment is recommended. German patients are privileged and advantaged regarding access to nonpharmacological treatments. Compared to patients of most other countries, German patients are able to access nonpharmacological treatments (physiotherapy, psychotherapy, and interdisciplinary multimodal pain management) that are available and whose cost covered by statutory and private health insurance companies.

When drug therapy is considered for CNCP of any type, opioids are not a first-line drug for short and/or intermediate treatment. Opioids are not the most effective drugs for CNCP. Direct and indirect comparisons have demonstrated that

Table 2
Potential consensus-based indications for short-term use of opioids; long-term continuation only if positive therapy response is present (predefined goals of treatment reached and tolerable side effects).

| Clinical entity                                                                 | Level of evidence (Oxford) | Strength of recommendation | Strength of consensus |
|--------------------------------------------------------------------------------|----------------------------|----------------------------|-----------------------|
| Chronic pain due to brain lesions (eg, status after thalamic stroke, multiple sclerosis) | 5                          | Open                       | Strong consensus      |
| Chronic pain due to complex regional pain syndrome (CRPS), types I and II        | 5                          | Open                       | Strong consensus      |
| Chronic secondary headache (eg, after subarachnoidal hemorrhage)                | 5                          | Open                       | Strong consensus      |
| Chronic osteoporosis pain (eg, new vertebral body fractures)                    | 5                          | Open                       | Strong consensus      |
| Chronic pain due to other inflammatory rheumatic diseases except rheumatoid arthritis (eg, systemic lupus erythematoses and seronegative spondylarthritis) | 5                          | Open                       | Strong consensus      |
| Chronic postsurgical pain (eg, postthoracotomy, poststernotomy, and postmastectomy syndrome, and after abdominal, facial, or hernia surgery) | 5                          | Open                       | Strong consensus      |
| Chronic pain due to ischemic or inflammatory arterial occlusive disease         | 5                          | Open                       | Strong consensus      |
| Chronic pain due to grade 3 and 4 decubitus ulcers                              | 5                          | Open                       | Strong consensus      |
| Chronic pain due to fixed contractures in nursing-dependent patients            | 5                          | Open                       | Consensus             |
| Posttraumatic trigeminal neuropathy                                             | 5                          | Open                       | Strong consensus      |
| Chronic pelvic pain by extensive adhesions and/or advanced endometriosis       | 5                          | Open                       | Consensus             |

Table 3
Contraindications for opioids.

| Medical condition                                                                 | Level of evidence (Oxford) | Strength of recommendation | Strength of consensus |
|-----------------------------------------------------------------------------------|----------------------------|-----------------------------|-----------------------|
| Primary headache                                                                  | 3b                         | Strong against              | Strong                |
| Functional disorders (eg, fibromyalgia syndrome*, irritable bowel syndrome)       | 5                          | Strong against              | Strong                |
| Chronic pain as a major manifestation of a mental disorder (atypical depression, persistent somatoform pain disorder, generalized anxiety disorder, and posttraumatic stress disorder) | 5                          | Strong against              | Consensus             |
| Chronic pancreatitis†                                                            | 2b                         | Against                     | Strong                |
| Chronic inflammatory bowel disease†                                              | 3b                         | Against                     | Strong                |
| Comorbid severe affective disorder and/or suicidality                            | 5                          | Strong against              | Strong                |
| Current medication abuse or passing on of medications to unauthorized persons, and/or serious doubt concerning responsible use of opioid analgesics (eg, uncontrolled taking of medications and/or unwillingness or inability to adhere to the dosing schedule) | 5                          | Strong against              | Strong                |
| Current or planned pregnancy                                                      | 5                          | Strong against              | Strong                |

* Except tramadol for fibromyalgia syndrome (minority vote of the German Association of Rheumatology, and the German Pain Society).
† Treatment for a limited time (<4 weeks) is possible during an acute episode.
opioids do not generally provide superior pain relief compared to anticonvulsants and antidepressants for neuropathic pain,13 or compared to NSAIDs for chronic low back27 and OA pain.18

Furthermore, in considering the efficacy of long-term opioid therapy (>1 year) for improving chronic pain and function, the U.S. guidelines concluded that the current evidence is insufficient.5,10 However, to the best of our knowledge, this statement is also valid for all nonopioid analgesics including antidepresants and anticonvulsants. The evidence available does not allow conclusions about which of the major drug classes are most effective and safest for long-term treatment of CNCP. Evidence-based alternatives for neuropathic pain are antidepressants and anticonvulsants, with many potential and relevant side effects.13 The risks of NSAIDs used for musculoskeletal pain such as myocardial infarction2 and gastrointestinal bleeding42 are well known. In addition, long-term treatment with NSAIDs is contraindicated in patients with heart, hepatic, and renal failure.42 Paracetamol is ineffective in the treatment of low back pain and provides minimal short-term benefit for people with OA.27 Despite the many limitations of opioids, they may be the best available and potentially efficacious drug for older patients with chronic musculoskeletal pain with co morbid medical diseases. In Germany, 2/3 of long-term opioid prescriptions (at least one prescription in 3 consecutive quarters each) are for people aged older than 60 years, most of whom had more than one major medical disease.22,28

Opioid therapy is associated with increased risks such as hypogonadism, breathing-related disorders (worsening of sleep-apnoea syndrome), falls, and delirium in the elderly. These risks have been addressed by both the Canadian4 and German23 guidelines. Opioid use disorder is a major topic in all 3 guidelines. In collaboration with the psychiatric medical associations, the German guidelines provided diagnostic criteria and pathways for treatment that is adapted for the German healthcare system.

There were also relevant differences between the Canadian and U.S. guidelines compared to the German guideline: The number of medical associations involved was greatest in the German guideline. The German guideline included representatives of multiple medical associations, including primary care physicians as well as nonphysician associations (nurses, pharmacists, and psychologists), and patient associations. All contributed to the strength of consensus and had the opportunity to formulate a minority vote on disputed statements (Table 3).23

For the assessment of long-term efficacy and safety, the German guidelines also analysed open-label extension studies of RCTs with opioids in CNCP. These type of studies are a requirement by the European Medicines Agency for the approval of a drug.12 In addition, the evidence-based recommendations for potential indication in the German guideline made a distinction between short-term (4–12 weeks), intermediate-term (13–26 weeks), and long-term therapy (>26 weeks) (E-Table 4–11, available as supplemental digital content at http://links.lww.com/PR9/A72).

The German guideline included and defined both evidence- and consensus-based indications and contraindications for opioids. The definition of specific contraindications had previously been incorporated in the first update of the German guideline. This addition was triggered by the emerging negative North American experience with the objective to prevent uncritical use of opioids and avert a potential opioid epidemic in Germany.23 Prescription of high doses of opioids to patients with poorly defined chronic pain syndromes was a factor driving the opioid crisis in North America. This was further compounded by patient characteristics that included physical and psychological trauma, social disadvantage, and hopelessness that served as a trigger for reports of pain intensity prompting prescriptions of more opioids.8,9 In addition, exclusion criteria of RCTs of opioid use in CNCP often precluded entry of patients with mental comorbidities such as a history of substance abuse and depression, conditions that are prevalent in routine clinical care in the United States.34 According to the German guideline, patients with these comorbidities should only be treated with opioids in the setting of a supported indication for opioid use and ideally in collaboration with a psychiatrist. Finally, the German guidelines recommended consideration of a trial of dose reduction and/or taper after 6 months of sustained response to validate further long-term treatment.20,23

7. Conclusions

The current guidelines for opioids for CNCP aim to destroy the myth that opioids are the most powerful and effective drugs for treatment of CNCP. By highlighting the importance of non-pharmacological therapies, current pain-related guidelines have reduced the focus on pharmacological treatments of CNCP. However, nonpharmacological therapies (physiotherapy and psychological therapies, with the exception of lifestyle changes) are not universally available for many patients worldwide, and may only be partially effective.

In patients who do not respond to nonopioid drugs or with contraindications for use of these drugs, opioids remain a valuable treatment option, if they help to improve and/or maintain quality of life, as well as functional and social participation.

Opioid therapy is associated with potential relevant harms. A close monitoring of the patient is necessary to balance the benefits and harms in the individual patient at regular intervals. National healthcare systems also differ in the availability of regular patient–physician appointments to adequately review the effects of opioid therapy.

National guidelines on opioids for CNCP must consider the strength, limitations, and potential pitfalls of the respective national healthcare systems. The risks for misdirected use of current recommendations in populations outside the scope of the respective guidelines should be kept in mind.11

Disclosures

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A72.
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