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POSITION PAPER

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

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Abstract

Background: Opioid use for chronic non-cancer pain (CNCP) is complex. In the absence of pan-European guidance on this issue, a position paper was commissioned by the European Pain Federation (EFIC).

*Developed by European Pain Federation. 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).

Methods: The clinical practice recommendations were developed by eight scientific societies and one patient self-help organization under the coordination of EFIC. A systematic literature search in MEDLINE (up until January 2020) was performed. Two categories of guidance are given: Evidence-based recommendations (supported by evidence from systematic reviews of randomized controlled trials or of observational studies) and Good Clinical Practice (GCP) statements (supported either by indirect evidence or by case-series, case-control studies and clinical experience). The GRADE system was applied to move from evidence to recommendations. The recommendations and GCP statements were developed by a multiprofessional task force (including nursing, service users, physicians, physiotherapy and psychology) and formal multistep procedures to reach a set of consensus recommendations. The clinical practice recommendations were reviewed by five external reviewers from North America and Europe and were also posted for public comment.

Results: The key clinical practice recommendations suggest: (a) first optimizing established non-pharmacological treatments and non-opioid analgesics and (b) considering opioid treatment if established non-pharmacological treatments or non-opioid analgesics are not effective and/or not tolerated and/or contraindicated. Evidence- and clinical consensus-based potential indications and contraindications for opioid treatment are presented. Eighteen GCP recommendations give guidance regarding clinical evaluation, as well as opioid treatment assessment, monitoring, continuation and discontinuation.

Conclusions: Opioids remain a treatment option for some selected patients with CNCP under careful surveillance.

Significance: In chronic pain, opioids are neither a universal cure nor a universally dangerous weapon. They should only be used for some selected chronic noncancer pain syndromes if established non-pharmacological and pharmacological treatment options have failed in supervised pain patients as part of a comprehensive, multi-modal, multidisciplinary approach to treatment. In this context alone, opioid therapy can be a useful tool in achieving and maintaining an optimal level of pain control in some patients.

1 | INTRODUCTION

In 2017, the European Pain Federation (EFIC) published a position paper on appropriate opioid use in chronic pain management (O'Brien et al., 2017). The position paper did not differentiate between management of chronic cancer and non-cancer pain (CNCP). The importance of opioids in the management of cancer pain and in palliative care is internationally accepted although the amount and quality of evidence around the use of opioids for treating cancer pain is disappointingly low (Wiffen et al., 2017).

The opioid crisis in North America (DeWeerdt, 2019) led to an update of the Canadian guideline on opioids for CNCP (Busse et al., 2017; Furlan et al., 2010) and to a guideline from the United States (US) Centers for Disease Control (CDC) (Dowell et al., 2016), which focused on harm reduction in relation to opioid prescribing for CNCP. Furthermore, several US authors have discussed their concerns that the opioid crisis reflects shortcomings of the North American health care systems (Dasgupta et al., 2018; Sullivan & Howe, 2013).

Although European countries are far from the opioid crisis in North America (Chenaf et al., 2019; Häuser et al., submitted; Kalkman et al., 2019; National Records of Scotland, 2018; Rosner et al., 2019), there are increasing concerns about the safety of long-term opioid therapy (LTOT) for patients with CNCP (Ballantyne, 2016). Therefore, EFIC commissioned a Task Force (TF) to update their position paper on appropriate opioid use specifically for CNCP and to separate it from cancer pain. In 2019, standards for the management of cancer-related pain across Europe from the EFIC Task Force on Cancer Pain were published (Bennett et al., 2019). By including other

European health professional societies, the paper was renamed as European Clinical Practice Recommendations (ECPRs).

This paper concerns opioids for CNCP and aims to promote the responsible use of opioids for CNCP by:

- discussing the role of opioids in the management of CNCP.
- identifying potential indications, contraindications and advice for discontinuation of opioids.
- providing recommendations for Good Clinical Practice (GCP; e.g. dosing; selection of opioids; monitoring side effects).
- discussing the role of opioids in specific patient populations.
- giving recommendations for the management of specific adverse events of opioids.

1.1 | Scope

The purpose of the ECPRs 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. The target audience includes:

- all health care professionals (physicians, psychologists, nurses, occupational therapists, physiotherapist, pharmacists) supporting patients with CNCP.
- those who take opioids (patients) and their significant others.
- those who create opioid prescribing policy.

These clinical practice recommendations discuss all oral and transdermal opioids which can be prescribed for chronic pain management in Europe (buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, polamidone, tilidine), including opioids with a two-way mode of action (tapentadol and tramadol). Combination products of opioids with other analgesics, such as paracetamol, are not covered. The ECPR is focused on LTOT for CNCP. Therefore, it does not address the management of acute or subacute pain (<4 weeks) treatment (including acute pain episodes of chronic diseases such as sickle cell disease), end of life care, or the use of opioids for non-painful conditions such as opioid use disorder.

Definitions of LTOT vary widely. Most studies define long-term as ≥12 weeks of opioid use (Karmali et al., 2020). Based on study duration of RCTs, we have made a classification for duration of opioid therapy for evidence-based recommendations for potential indication of opioids: short-term (4–12 weeks), intermediate-term (13–26 weeks), long-term (>26 weeks).

1.2 | Disclaimer

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.

The ECPRs do not represent a regulation of action or omission, which has been agreed by a legally legitimate institution, fixed in writing and published. It is not binding for the legal area of an institution and will not result in defined sanctions, if not followed. Recommendations only become clinically effective if the strength of recommendation is considered and integrated in individual patient care, including shared-decision making with patients. The decision as to whether a certain strength of recommendation should be followed must be made by physicians, considering the circumstances of individual patients and the available resources.

2 | METHODS

2.1 | Task force membership

The TF included 17 members (6 female) from nine European countries (North, Central, East and South Europe and UK). Nine delegates were nominated by EFIC's board. The board selected delegates who advocate and who are critical with the use of opioids for CNCP. Seven delegates representing members of the European Pain Forum (https://europeanpainfederation.eu/advocacy/current-projects/european-pain-forum/) volunteered to contribute. These delegates were selected because of their clinical and/or scientific expertise. One delegate of the Pain Alliance Europe (PAE) participated as a patient representative. The TF included most health care professions (medicine, nursing, physiotherapy, psychology) caring for patients with chronic pain. The medical specialties of the physicians were anesthesiology, gastroenterology, general practice/family medicine, general internal medicine, neurology, pain medicine, palliative care, physical and rehabilitation medicine, psychiatry, psychosomatic medicine (see Table 1).

TABLE 1 Composition of the task force

TF member	Gender	Specialty	Country	Nominated by	Assessment of financial COIs related to the topic of the paper
Bannister, Kirsty	Female	Pharmacology	Great Britain	EFIC	None
Buchser, Eric	Male	Anesthesiology	Switzerland	European Society of Regional Anesthesia	None
Casale, Roberto	Male	Physical and Rehabilitation Medicine	Italy	European Society of Physical and Rehabilitation Medicine	None
Chenot, Jean- François	Male	General Practice/Family Medicine	Germany	EFIC	None
Chumbley, Gillian	Female	Nursing	Great Britain	EFIC	None
Doom, Geert	Male	Psychiatry	Belgium	European Psychiatric Association AND European Federation of Addiction Societies	None
Drewes, Asbjorn	Male	Internal Medicine/ Gastroenterology	Denmark	EFIC	moderate
Häuser, Winfried	Male	Internal Medicine, Psychosomatic Medicine	Germany	EFIC	None
Jutila, Liisa	Female	Patient representative	Finland	Pain Alliance Europe	None
Krcevski-Škvarč, Nevenka	Female	Palliative care medicine	Slovenia	EFIC	None
Morlion, Bart	Male	Anesthesiology	Belgium	EFIC	Moderate
O'Brien, Tony	Male	Palliative care medicine	Ireland	EFIC	Moderate
Pogatzki-Zahn, Esther	Female	Anesthesiology	Germany	European Society of Anaesthesiology	Moderate
Rakusa, Martin	Male	Neurology	Slovenia	European Academy of Neurology	None
Suarez -Serrano, Carmen	Female	Physiotherapy	Spain	European Region of the World Confederation of Physical Therapy	None
Tölle, Thomas	Male	Neurology	Germany	EFIC	Moderate
Vowles, Kevin	Male	Psychology	Great Britain	European Federation of Psychologists Associations	None

Abbreviation: EFIC, European Pain Federation.

2.2 | Managing conflicts of interest

All TF members declared any potential conflicts of interest (COIs) before the start of the update using the Form for Disclosure of Potential Conflicts of Interest from the International Committee of Medical Journal Editors (http://www.icmje.org/conflicts-of-interest/). Potential COIs were independently evaluated by two representatives of EFIC (Sam Kynman, Executive Director and Prof. Hans Georg Kress, Chair of Ethics Committee), who did not participate in the development of this paper. Discrepancies were resolved by consensus. The degree of financial COIs with pharmaceutical companies producing opioids was classified into none, slight, moderate, high, defined as follows:

- None: No interaction.
- Slight: Only honoraria for lectures.
- Moderate: Advisory board; study support.
- High: Patent; employee of a pharmaceutical company.

Twelve members of the TF had no COIs, including the three TF chairs (Häuser, Krcevski-Škvarč, & Vowles). Five members had moderate financial COIs (Drewes, Morlion, O'Brien, Pogatzky-Zahn, Tölle).

Secretarial support for the drafting of this position paper came from EFIC. The funding of EFIC is detailed in its most recent annual reports which can be found on the EFIC website https://europeanpainfederation.eu/how-we-work/annual-report/. The funding of PAE is detailed in https://pae-eu.eu/activities/.

2.3 | Key questions

The key questions to be addressed were defined by a Delphi round of theTF. Four recent national (Canada, France, Germany, USA; Busse et al., 2017; Dowell et al., 2016; Moisset & Martinez, 2016; Häuser et al., 2020) guidelines on opioids for CNCP were provided to the members of the TF by the evidence synthesis team to inform the process. The key questions are outlined in Supplementary Material 1.

2.4 | Search strategy

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. The evidence synthesis team (Häuser, Welsch) conducted the searches. 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.

2.5 | Summary of evidence

The patient representative was involved in defining the key questions, providing recommendations and good clinical practice statements, and the evaluation of the patient version of the clinical practice recommendations.

The evidence synthesis team created evidence summaries based on the selected systematic reviews. The selection of outcomes of interest was based on the recommendations of the ACTINPAIN writing group of the International Association for the Study of Pain's (IASP) Special Interest Group on Systematic Reviews in Pain Relief (Moore et al., 2010) and the guideline on the clinical development of medicinal products intended for the treatment of pain of the European Medicines Agency (2017). These outcomes included:

1. Pain relief from baseline of 30% or greater
2. Patient global impression to be much or very much improved
3. Disability
4. Drop out rates to adverse events
5. Serious adverse events
6. Death
7. Non-medical use/dependence

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).

2.5.1 | Patient preferences

Pain Alliance Europe (PAE) conducted a survey with some member countries (Spain, Romania, Belgium, UK, Sweden

and Finland) on the importance of potential positive and negative effects taking a new medication for the chronic pain management from 22 May to 2 June 2020. The potential positive and negative effects of medications (related to opioids) were selected by three TF members (two physicians, one patient representative). In total, 131 PAE members participated (78% females). The details of the patient survey are outlined in Supplementary Material 2. Important or very important positive and negative effects were rated as follows:

- Positive effects
  a. Pain relief of 50% or more: 74% of the respondents.
  b. Pain relief of 30% or more: 92% of the respondents.
  c. Improvement of daily functioning: 91%.
  d. Improvement of sleep: 82%.

- Negative effects
  a. Somnolence: 66%.
  b. "Addiction": 58%.
  c. Sexual problems: 45%.

In addition, a search in PubMed ['patient preferences' AND 'opioids' AND 'CNCP') in 6 February 2020 produced 6 hits. We found one systematic review, which ranked pain relief, nausea and vomiting as highly significant negative 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 two studies that evaluated addiction, found it less important to patients than pain relief (Goshua et al., 2018).

2.6 | Development of recommendations and GCP statements

This paper includes two categories of guidance: Evidence-based recommendations (supported by evidence from systematic reviews of RCTs or of observational studies) and GCP statements (supported by either indirect evidence or by single RCTs, case-series, case-control studies or clinical experience). We applied the GRADE system to move from evidence to recommendations if systematic reviews with GRADE ratings were available (Andrews et al., 2013). We used UptoDate rating of quality of evidence, if systematic reviews with GRADE ratings were not available (see Table 2). All members of the TF completed the Uptodate® Grading tutorial (https://www.uptodate.com/home/grading-tutorial#).

Evidence-based recommendations could be made 'for' or 'against'. The strength of a recommendation could be 'strong' or 'weak' (see Table 3). For a strong recommendation, we noted, 'We recommend'. For a weak recommendation, we noted, 'We suggest'. Similarly, GCP statements could be made 'for' or 'against' with the terms 'should be considered' (valid for nearly all patients) and 'can be considered' (valid for the majority of patients) (see Table 3).

The TF is aware that there are controversies or disparities in interpretation of the evidence (e.g. of the RCTs for CLBP).

TABLE 2 Rating of the quality of supporting evidence according to UptoDate®

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

TABLE 3 How to use and understand the recommendations and good clinical practice statement of the position paper

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.

Therefore, our evidence-based recommendations are based on clinical experience, too.

2.7 | Consensus-finding procedure

The evidence-based recommendations and GCP statements were initially prepared by the three chairs of the TF (Häuser, Krcevski-Skvarc, & Vowles). These were then discussed, modified and finalized by the TF in seven Delphi rounds. The individual members of the TF then voted online from 1 to 12 June 2020. The group held a final web-based consensus conference on 13 June 2020. All TF members participated in the online voting and all but one in the web-based consensus-conference. In this conference, all statements and recommendations which did not reach a consensus of >90% in the online vote were discussed and modified if necessary with the aim to increase the strength of consensus. For both voting procedures TF members had three options: Agree, disagree or abstention (due to lack of expertise). Abstention votes were not included in calculations regarding the strength of consensus.

Strength of consensus was classified as follows: strong consensus: >95% agreement; consensus: 75%–95% agreement; majority: 50%–75% agreement; no consensus: ≤50% agreement.

The strength of consensus was assessed in two ways: With and without the votes of the members with moderate COIs. In the document, the strength of consensus for every recommendation and clinical practice statement is reported as follows in brackets: (votes of all TF members; votes of all TF members without COIs).

2.8 | External reviews

The draft ECPR document was sent to five individuals with expertise in opioids for chronic pain, each of whom provided an open review. These individuals included Jane Ballantyne (USA), Andrea Furlan (Canada), Cathy Stannard (UK), Rainer Sabatowski (Germany) and Mark Sullivan (USA). These experts were asked to identify any omissions of important topics, comment regarding evidence-based recommendations or GCPs, provide alternative suggestions if necessary, and comment on methods where important. The heads of the TF drafted replies to the reviewers and suggested changes to evidence-based recommendations, GCP statements and comments in consensus. All suggestions for modifications of this paper were discussed by the TF.

Based on the comments of the reviewers, five GCP statements (two on the role of opioids; one on short- versus long acting opioids; one on intake scheme; one on opioid-induced hyperalgesia) were changed with regards to content. One new GCP statement on opioid tapering was added. A Delphi round of the TF to assess the strength of consensus of these five modified GCP statements was conducted. The wording of the strength of recommendation for GCP statements was changed. The wording, but not the content, of eleven GCP statements was changed. Twenty-seven comments were also expanded. In the sections 'background, scope, disclaimer' six amendments were made.

Twelve public comments (11 from health care professionals, one from a pharmaceutical company producing an opioid) were received. All public commentators declared their financial conflicts of interest (available on request): All comments were reviewed and answered by the TF chairs based on consensus. The answers were discussed by the TF members. Seventeen comments were modified (wording, supplements) based on the comments of the health professionals. Based on the comment of the pharmaceutical company, one supplement was made in the section scope and ten comments were modified (wording, supplements). We followed one of six suggestions of the company, to mention their product in the comment.

The changes in the ECPRs based on the comments of the reviewers and the public commentators can be provided on request.

2.9 | Final approval

This ECPRs were approved by the board of EFIC and the boards of nine participating member societies of the Pain Forumn and the European Pain Alliance.

2.10 | Publication and dissemination

The ECPRs were submitted to the European Journal of Pain in two parts. Part one covers the role of opioids in the management of CNCP, potential indications and contraindications, and GCP of opioid use. Part two covers special situations, including non-medical use and dependence (Krcevski-Škvarc et al., 2021). A short version for health care professionals will be designed by the TF and be available on the webpage of EFIC. A version for lay persons of the position paper will be developed with PAE.

3 | RESULTS

3.1 | Good clinical practice statements and recommendations

3.1.1 | Part 1: Role of opioids in the management of chronic noncancer pain

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).

Comment: Optimization of non-pharmacological therapies should include interdisciplinary multimodal pain therapy (Kaiser et al., 2017) – if available – and – in selected patients – invasive procedures such as neuromodulation.

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).

Rationale: We are not aware of any interdisciplinary evidence-based guideline which recommends opioids as a first line treatment for any type of CNCP. Non-pharmacological therapies such as exercise and psychological therapies have been recommended as first line therapies for common CNCP syndromes such as low back (Oliveira et al., 2018) or osteoarthritis pain (Gay et al., 2016). Although non-pharmacological approaches for chronic pain have only small effect sizes with NNTs ranging from 4 to above 10 (Skelly et al., 2018), they should be optimized first given that the efficacy of drug therapies for CNCP syndromes such as low back pain is limited too and associated with potentially significant side effects. Anticonvulsants have been recommended as first line therapy for neuropathic pain (Finnerup et al., 2015). Potential serious adverse events such as overdose death and addiction by opioids (Busse et al., 2012), gastrointestinal bleeding (Castellsague et al., 2012) and cardiovascular events by NSAIDs (Bally et al., 2017), non-medical use of gabapentinoids (Schjerning et al., 2016), and liver failure by antidepressants (Darr & Sussman, 2020) must be considered.

Evidence summary (for details see Supplementary Material 3): PICO (Patient, Intervention, Comparator, Outcome): What is the efficacy, tolerability and safety of opioids compared to non-opioid analgesics for CNCP in RCTs of at least 4 weeks duration?

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 CNCP, 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)

Comment: There is marked inter-individual variation in response/tolerability of all analgesics including various opioids that is not predicatable prospectively. A number of factors may influence the clinician's choice of opioid when initiating treatment including:

- Clinician's preference, often based on familiarity, availability and cost
- Required route of delivery – e.g. oral (preferrred) but in some instances a transdermal delivery may be selected for ease of administration and reducing oral medication burden etc.

- Comorbidities of the patient (see section on special situations)

4. Potential indications

Preliminary remarks:

a. All potential indication cited below should only be considered in the view of the recommendations on the role of opioids in the management of CNCP.
b. CNCP is a descriptive term which covers many painful medical conditions which vary in clinical presentation and underlying pathophysiological mechanisms, including the absence of identifiable underlying mechanism. The IASP-WHO joint task force which developed the new concepts of the chronic pain classification system has suggested a distinction between chronic primary pain (disease of its own right) and chronic secondary pain (pain as a symptom of an underlying disease). The main pathophysiological mechanism of primary pain syndromes is nociplastic pain and of chronic secondary pain syndromes nociceptive and/or neuropathic pain (Nicholas et al., 2019; Treede et al., 2019; Trouvin & Perrot, 2019). Nociplastic pain is defined by p*ain* that (1) arises from altered nociception despite no (2) clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or (3) evidence for disease or lesion of the somatosensory system causing the pain (Kosek et al., 2016).

The distinction between primary and secondary pain can be an oversimplification. In some patients with chronic secondary pain, such as osteoarthritis or post-injury pain, nociplastic mechanisms play a role (Moore et al., 2020; Woolf, 1983). Ongoing nociceptive input, for example, by low grade joint inflammation, may play a role in so-called secondary (comorbid) fibromyalgia (Fitzcharles et al., 2018) which is regarded to be a prototype of a nociplastic pain syndrome (Nicholas et al., 2019).

Because of the diversity of CNCP syndromes, the updated position paper follows the approach of the French and German guideline (Häuser et al., 2020; Moisset & Martinez, 2016), to split CNCP into different clinical entities with regards to potential indications and contraindications of opioids.

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

Evidence summary (for details see Supplementary Material 4):

PICO: What is the efficacy, tolerability and safety of opioids compared to placebo in patients of any age with CNCP?

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) (Supplementary Materials 1 and 2).

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.

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

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

Preliminary remark: A risk benefit analysis before embarking opioid therapy for the diagnoses listed below is necessary.

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.

Rationale: Opioids achieve improvements of pain and function compared to placebo at the cost of a lower tolerability in chronic low back and osteoarthritis pain and in some neuropathic pain syndromes. In the context of RCTs and close clinical surveillance, opioids can be considered reasonably safe.

For all other medical conditions with nociceptive and/or neuropathic pain mechanisms, the evidence for the use of opioids is based on single RCTs for some neuropathic pain syndromes and on clinical experience for all other medical conditions.

Evidence summary (see Supplementary Material 5):

5. Potential contraindications: Opioids should not be considered for primary pain syndromes. Good clinical practice statement

Rationale: For primary pain syndromes: (a) Our systematic search found only one RCT each with tramadol (Russell et al., 2000) and tramadol/paracetamol (Bennett et al., 2003) for a nociplastic pain syndrome (FMS). Tramadol has an additional mode of action (serotonine and noradrenaline reuptake inhibitor) which might explain the efficacy found (Walitt et al., 2016). (b) Cohort studies have demonstrated that opioid use is associated with a negative clinical outcome in migraine (Ashina, 2019; Minen et al., 2014) and fibromyalgia (Fitzcharles et al., 2013). (c) Guidelines discourage the use of opioids, for example for IBS (Drossman, 2019), fibromyalgia (MacFarlane et al., 2017) or migraine (American Headache Society, 2019). (d) Patients with primary pain syndromes may be less responsive to opioids due to higher endogenous opioid levels and more susceptible to worsening of hyperalgesia by opioids (Toubia & Khalife, 2019).

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)

6. Controversial issues

The TF could not reach consensus regarding the potential indications or contraindications of opioids for pain management in chronic pancreatitis and chronic inflammatory bowel disease (mainly Crohn's disease). There was a consensus that opioids should only be used in selected patients after interdisciplinary specialist assessment as part of a multimodal treatment approach and with close surveillance.

Chronic pancreatitis: In one RCT comparing morphine and fentanyl, both medications did not significantly reduce pain and disability (Niemann et al., 2000). In US cohort studies, opioid use was associated with opioid use disorder (Bilal et al., 2019). According to the clinical experience, up to 25% of patients can experience pain relief associated with opioid use (Drewes et al., 2017). Therefore, opioids can be used in selected patients under close surveillance for restricted time following the same recommendations as used for other pain syndromes. As many patients have postprandial pain or intermittent worsening of the background pain, treatment with immediate release opioids for shorter periods is likely better than controlled release opioids that may carry a higher risk of dependency. However, about 50% of patients have a history of alcohol use disorder (Olesen et al., 2019) and about 20% continue to have excess alcohol consumption (Olesen

et al., 2020). This subgroup of patients may have a high potential for substance use disorders and opioids – if prescripbed – shall be used with high level of control and attention.

Inflammatory bowel diseases: Long-lasting pain is seldom a problem in patients with ulcerative colitis unless severe complications occur, but patients with Crohn's disease may suffer from severe chronic pain due to inflammation, strictures and stenosis of the gut. In a US cohort study, patients reported the same intensity of abdominal pain with and without opioids (Coates et al., 2020), but this may reflect confounding by indication as opioids are likely administered to patients with most pain and the study had a retrospective design. In a British retrospective cohort study, mortality was increased in case of high or moderate morphine dosage compared to propensity matched controls (Burr et al., 2018). The problems with visceral pain and opioids are mainly related to their side-effects on the gut and problems with motility, fluid transport and sphincter function (Farmer et al., 2019). This is often a major problem in patients with Crohn's disease where strictures and stenosis of the gut may worsen the opioid induced side effects. To summarize, opioids can be considered for short-term treatment of pain in case of acute flare-ups in patients with Crohn's disease, but long-term opioid use may be associated with poor outcomes. The guideline of the British Society of Gastroenterology discourages the use of opioids for pain management in inflammatory bowel diseases (Lamb et al., 2019).

3.1.2 | Part 2: Good clinical practice

1. Measures prior to opioid initiation

1.1 Case history and clinical status*:* General case history (including previous substance use disorder), pain-related case history and the physical and psychological status of the patient should be considered and documented. Good clinical practice statement. Strong Consensus (17/17; 17/17).

Practice tool (Facultative): Brief Pain Inventory Short Version: http://www.npcrc.org/files/news/briefpain_short.pdf

1.2 Screening for mental disorders: The physician who is thinking about opioid prescribing should consider documentation of psychosocial case history and screening for current and/or past psychiatric disorders. Good clinical practice statement. Strong Consensus (17/17; 17/17).

Practice tool (Facultative): Patient Health Questionnaire 4. https://www.oregonpainguidance.org/app/content/uploads/2016/05/PHQ-4.pdf

1.3 Mental health care examination: In the case of indications of a mental disorder (depressive and anxiety disorders, substance use disorder) it should be considered to offer the patient a consultation with a mental health care specialist depending on local resources and tradition. Good clinical practice statement. Strong Consensus (17/17; 17/17).

Rationale: Mental health disorders increase the risk of abuse of prescribed opioids (Cragg et al., 2019).

1.4 Therapeutic goals. Physicians prescribing opioids should consider setting individual and realistic therapeutic goals together with the patient. Good clinical practice statement. Strong Consensus (17/17; 17/17).

Rationale: The definition of therapeutic goals includes the consideration of the patients belief system regarding the efficacy of opioids. Patients with CNCP may have unrealistic expectations for medication-based pain relief, for example, complete pain relief. From a medical point of view, reasonable therapeutic goals (= therapeutic response) are individually meaningful improvements in everyday function (e.g. return to work, 'being able to mow the lawn again', 'be able to take care of oneself again'). Goals may also include pain relief of 30% or greater, although pain reduction as a therapeutic goal has been the topic of some debate (Ballantyne & Sullivan, 2015).

1.5 Patient information: Physicians prescribing opioids should consider providing patients with information by means of documented oral or written communication, including information on traffic and workplace aspects relevant to the patient (and potentially to the family and/or caregiver). Good clinical practice statement. Strong Consensus (17/17; 17/17).

Comment*:* Information is likely to work best is it is easily understood by patients and brief.

Patient information may include:

- Instructions relating to exact timing and dosage of medication; duration of action of the medication; instructions to follow in case of a missed dose
- Indications of interactions with other medications including over- the – counter medication and illicit substances
- Prophylactic treatment of adverse medication reactions, such as constipation
- Cessation of alcohol or sedative consumption without prior discussion with the physician
- Patient responsibilities, such as good adherence to the treatment plan, regular feedback to the treating physician; for example, in the form of a pain journal
- Safe storage of opioids
- Instructions on how to safely dispose of opioids not used by the patient in accordance with the relevant legal regulations on narcotics
- Legal aspect pertaining to distribution of opioid-containing medications
- Taking opioid-containing medications abroad
- Possible negative influence on the ability to drive, as well as on activities in the workplace (e.g. work with machines, control activities), and during leisure time (e.g. housework, gardening, sport)
- Potential short- and long-term harms

Comment: Patients should be informed that driving under stable doses of opioids may not be impaired in general and that patient's has the responsibility checking himself a priori, if he feels fit for driving or not. Information on the impact of impairment due to other health-related conditions (such as mental diseases, motor function impairment) and co-medication (such as benzodiazepines, antidepressive medications) must also be provided. Meta-analysis of experimental studies have shown that there are many factors influencing the degree of impairment caused by medication consumption (e.g. active agent, galenics, route of administration, dose, time of administration, time period between administration and performance requirement, compliance and disposition of the patient as well as concomitant use of additional medications) (Ramaekers et al., 2006).

1.6 Titration and driving safety: Physicians prescribing opioids should consider informing patient of national legal regulations regarding driving during the titration phase or when their dose is changed and to document the information in the chart. Good clinical practice statement. Strong Consensus (17/17; 17/17).

Comment*:* Titration/opioid initiation phase including dose change (upwards, downwards) or opioid switching are the most vulnerable phases of functional/cognitive impairment due to opioid treatment (Bruera et al., 1989; Ramaekers et al., 2006).

2. Treatment with opioids

2.1 Number of prescribing physicians: Physicians prescribing opioids can consider opioid prescriptions only by one physician at a time when possible or by a physician of the same clinical team or a nominee if the designated prescriber is on leave. Strong Consensus (16/16;11/11).

Comment: Prescription by multiple physicians is associated with abuse and dependence of prescribed opioids (Cragg et al., 2019).

2.2 Titration: Physicians prescribing opioids should consider initiating treatment with low doses (<50 mg morphine equivalent/d). Good clinical practice statement. Consensus/strong Consensus (15/16;11/11).

Comment: There are different practice tools available for calculating morphine milligram equivalents (MME). They differ in the dosages of MME based on single dose studies in healthy individuals and can vary considerably. Therefore, these practice tools should be used as a guide only. When changing from one opioid to another, conversion ratios should always be used cautiously.

Practice tool*:* Calculating morphine milligram equivalents.

https://www.cdc.gov/drugoverdose/training/dosing/

app: http://www.opioidcalculator.com.au/

2.3 Titration: Physicians prescribing opioids should consider increasing doses in a stepwise manner in order to reach the individual therapeutic goal- depending on effectiveness and tolerability. Good clinical practice statement. Strong Consensus (16/16;11/11).

Comment: A stepwise manner could be 25% increase within 3–8 days.

2.4 Treatment responders and optimal dose: Physicians and patients should consider that an optimal dose is one which achieves the predefined therapeutic goals with simultaneous minimal or tolerable adverse events (=treatment responder). Good clinical practice statement. Strong Consensus (17/17;12/12).

Comment: An optimal dose is reached when an increase does not lead to any pain reduction or functional improvement.

2.5 Maximum dosage: We suggest exceeding a dose of >90 mg/d oral MME in exceptional cases only. Weak recommendation. Consensus/strong Consensus (14/17; 12/12)

Rationale: Observational studies conducted in North America provide evidence of a progressive increase in the likelihood of unintentional non-fatal overdose or death as the prescribed dose of opioids increases. These serious outcomes are rare in those prescribed less than 50 MEQ/d, but increase in those prescribed doses of 50–90 MEQ/d, and though still rare, are further increased in those prescribed doses over 90 MEQ/d (Busse et al., 2017).

Evidence summary:

PICO

Population: Patients with chronic noncancer pain beginning opioid therapy Intervention: Limit opioid dose to a particular maximum dose. Comparator: No maximum opioid dose.

Meta-regression of within-trial comparisons of different doses of opioids found moderate-quality evidence against a dose-response effect for pain relief or functional recovery (Busse et al. 2017).

The daily dosages in the long-term open label extensions studies were as follows: Buprenorphine transdermal (5–40 μg/h; average 14 μg/h); Hydromorphone (8–32 mg/d; average 17 mg/d); Morphine (Maximum 90 mg/d, half of the patients used <60 mg/d); Oxycodone: 20–140 mg/d (mean dosages in studies 44 mg/d); Tapentadol (100–500 mg/d; average 368 mg/d) (Bialas et al., 2020).

There is likely a dose-dependent increase in the risk of non-fatal opioid overdose: 0.2% for <20 mg MED/day; 0.7% for 50–99 mg MED/day; and 1.8% for ≥100 mg MED/day. There is an increased risk of fatal opioid overdose with higher doses: 0.1% for <20 mg MED/day; 0.14% for 20–49 mg MED/day; 0.18% for 50–99 mg MED/day; and 0.23% for ≥100 mg MED/day (Busse et al., 2017). Confounding by indication (more severe cases receive higher dosages of opioids) have to be taken into account in the studies showing a dose-dependent increase of risks (Ranapurwala et al., 2019).

Based on these data, current guidelines recommend a clinical re-evaluation of the following dosage are exceeded: France and Germany: >120 mg MEQ/d (France: Specialist consultation >150 mg MEQ/d) (Häuser et al., 2020; Moisset & Martinez, 2016) and USA and Canada >90 MEQ/d (Busse et al., 2017; Dowell et al., 2016).

There is wide variability in patient response to pain medications, which may be related to pain origin, pain sensitivity, cultural differences, weight, age and prior use of opiates, as well as genetic polymorphisms. Medication-metabolizing enzymes are commonly influenced by genetic variations. The CYP450 enzymes, CYP3A4 (fentanyl) and CYP2D6 (codeine, hydrocodone, oxycodone, tramadol) are involved in the metabolism of opioids (Agarwal et al., 2017). Some patients (e.g. rapid metabolizers) might require higher dosages of opioids than the ones recommended by the guidelines.

This recommendation does not address or suggest discontinuation of opioids already prescribed at higher dosages nor to justify abruptly stopping opioid prescriptions or coverage.

2.6 Opioid rotation. In case of inadequate pain relief or intolerable opioid-related toxicity/adverse effects, a switch to an alternative opioid (opioid rotation) should be considered. Good clinical practice statement. Consensus/strong Consensus (14/15; 10/10).

Comment: The evidence to support the practice of opioid switching is largely anecdotal or based on observational and uncontrolled studies (Treillet et al., 2018). For details of opioid rotation see Figure 1 and Supplementary Material 6.

2.7 Indication for potential long-term opioid therapy: A therapy lasting >3 months should only be considered in treatment responders (as defined in Part 2, Section 1.4 above). Good clinical practice statement. Consensus/Strong Consensus (16/17; 12/12).

Comment: The decision to continue or stop opioid therapy should occur at 1 month in the majority of patients. In some patients, this decision may occur up to 3 months following opioid initiation, for example, in case of a very slow increase in dosage over time.

3. Monitoring and documentation of treatment

3.1 Regular monitoring of treatment: During LTOT, prescribing physicians should consider to review the following at regular intervals (at least once every three months): (1) whether therapeutic goals continue to be met, (2) whether there are indications of adverse events (e.g. loss of libido or psychological changes such as loss of interest, hypomnesis or falls), or (3) evidence of opioid use disorder or non-medical use. Good clinical practice statement. Strong Consensus (17/17; 12/12).

3.2 Urine drug screening: Urine drug screening should be considered when there is suspected non-medical use of prescribed opioids and/or illicit drug use. Good clinical practice statement. Strong Consensus (17/17; 12/12).

Comment: Consider screening for the following substances: Amphetamines, methamphetamines, benzodiazepines, barbiturates, marijuana, cocaine and phencyclidine.

4. Discontinuation of treatment with opioids

4.1 Discontinuation of an opioid trial (<12 weeks): If the individual therapeutic goals are not met during the titration phase (maximum 12 weeks) or after rotation to another opioid or if insufficiently treatable or intolerable adverse events occur (in the opinion of patient or physician), treatment with opioid-containing analgesics should be considered for discontinuation in a stepwise manner. Good clinical practice statement. Strong Consensus (17/17; 12/12).

4.2 Discontinuation of treatment >12 weeks

Long-term treatment should be considered for discontinuation in a stepwise manner if:

1. The individual therapeutic goals are no longer achieved, or insufficiently treatable or intolerable adverse events occur (in the opinion of patient or physician),
2. The individual therapeutic goals are achieved by other medical, physiotherapeutic, physical or psychotherapeutic treatments.
3. The person prescribed with opioids refuse urine tests for medications in case of suspected non-medical use of prescribed opioids.
4. The person prescribed opioids diverts or uses the opioids in a non-medical manner despite complementary treatment from a dependence specialist.

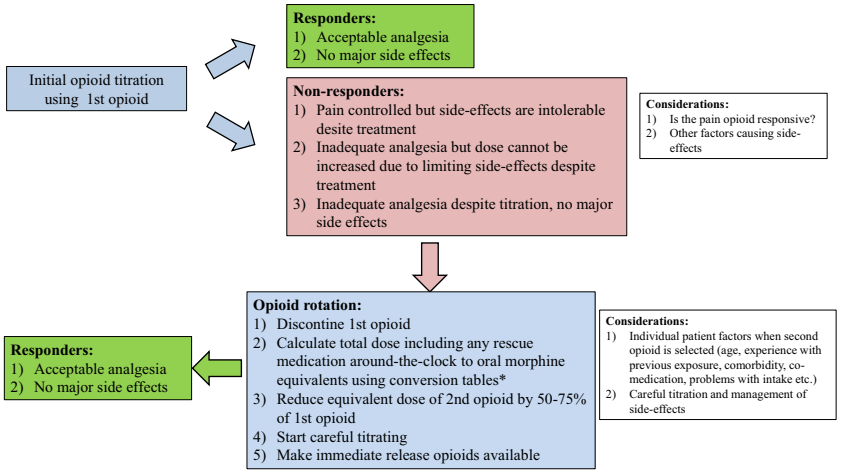

FIGURE 1 Opioid rotation (modified from Drewes et al. 2013)

Good clinical practice statement. Strong Consensus (17/17; 12/12).

4.2 Medication reduction

After 6 months of opioid treatment with a good response, a dose reduction can be considered with the patient, to assess the indication for continued treatment and the response to the non-pharmacological treatments (e.g. multimodal therapy) that are being used in parallel. Good clinical practice statement. Strong Consensus (17/17; 12/12).

The main recommendations for good clinical practice are summarized in Table 4.

TABLE 4 Opioids for chronic noncancer pain – a summary

1. Comprehensive clinical evaluation
   a. Medical and psychosocial history
   b. Medical and if necessary psychological and physiotherapeutic examination
   c. Technical examinations
   d. Interdisciplinary assessment if needed
2. Start treatment
   a. Education
   b. Non-pharmacological therapies
   c. Non-opioids if needed
3. Consider a trial with opioids if
   a. There is a relative indication for opioids for the type of the pain syndrome of the patient and
   b. non-pharmacological treatment and non-opioid analgesics are
   (i) Not effective and/or
   (ii) Not tolerated and/or
   (iii) Contraindicated
4. Shared decision making with patients
   a. Assess individual benefit risk-ratio
   b. Consider patient's treatment preferences
   c. Obtain informed consent and agreement
   d. Establish individual and realistic treatment goals (sustained improvement of daily functioning, pain reduction)
5. Initial dose adjustment phase (8–12 weeks)
   a. Start slow, go slow
   b. Monitor and treat side effects if needed
   c. Find the optimal dosage (predefined treatment goals met; no or tolerable/manageable side effects)
   d. Discontinue if
   (i) Predefined treatment goals not reached
   (ii) Intolerable/manageable side effects
   (iii) Non-medical use of prescribed opioids
6. Long-term opioid therapy (>12 weeks)
   a. Regular assessments (at least every 3 months)
   b. Assess four A's: Activity, analgesia, aberrant behaviour, adverse effects
   c. Promote non-pharmacological therapies
   d. Continue if
   (i) Stable dosage
   (ii) Sustained improvement of daily functioning and pain reduction
   (iii) tolerable/manageable side effects
   (iv) No signals of non-medical use of prescribed opioids
   e. Discuss tapering/drug holiday after 6 months with the patient
   f. Discontinue if
   (i) Dose escalation
   (ii) Loss of improvement of daily functioning and of pain reduction
   (iii) tolerable/manageable side effects
   (iv) Signals of non-medical use of prescribed opioids

4 | DISCUSSION

We discuss some similarities and differences between the existing guidelines, including those from Canada, the US CDC and the European clinical practice recommendations.

Scope and audience: All existing guidelines aim to promote responsible prescribing of opioids to promote the safety of people with chronic pain. All papers covers CNCP, although the title of the CDC guideline is 'chronic pain'. The Canadian and CDC guidelines are valid for adults with CNCP, while the European recommendations also include children and adolescents. The Canadian guidelines were revised and the CDC guidelines were developed to reduce the opioid epidemic in Canada and USA. The European recommendations were drafted to help prevent a prescription opioid epidemic in Europe. The target audience of the CDC guidelines are primary care clinicians, while the Canadian and European recommendations are targeted to all health care professionals involved in the care of people with CNCP.

Composition of the guideline panel: The Canadian guideline was an investigator-initiated study. The US and European papers were developed by an umbrella organisation (CDC and EFIC, respectively). All guidelines/position papers were produced by a group of medical experts of different specialties. The European TF included other health professionals (e.g. nursing, clinical psychology). Canada and Europe included a patient representative in the steering committee and several measures of patient engagement. Canada and Europe included experts who viewed opioids as having an important role and several who viewed the practice with skepticism.

Engagement of other organisations and reviews: The Canadian guideline group included the input of two Canadian medical associations for clinical practice statements. CDC invited federal partners and stakeholders to comment. The European recommendations were approved by scientific organizations of different health care professionals. All guidelines/recommendations were open to public comments. The European recommendations invited European as well as North American medical experts to review.

Managing conflicts of interest: All papers required a conflict of interest statement of all members of the guideline panel. CDC excluded experts who had a financial or promotional relationship with a company that made a product that might be affected by the guideline. The potential impact of financial COIs in European recommendations can be

concluded from the strength of consensus separately assessed for the whole guideline group and the ones without financial COIs. CDC reviewed potential nonfinancial conflicts carefully (e.g. intellectual property, travel, public statements or positions such as congressional testimony) to determine if the activities would have a direct and predictable effect on the recommendation.

Methods: All guidelines/recommendations conducted systematic searches of literature, performed meta-analyses of randomized placebo-controlled trials with opioids and rated the quality of evidence. The European guidelines assessed the strength of consensus on recommendations and clinical practice statements of the TF. EFIC's strong consensus for GCP and lack of strong consensus on most potential indications and contraindications reflect the different clinical background and experience with opioids for CNCP of the TF members. All guidelines/recommendations used GRADE to rate the quality of evidence for evidence-based recommendations. The majority of the European guidances for clinicians were based on a selective search of literature and expert consensus.

Overall content: Canada produced 10, CDC 12 and Europe six evidence-based recommendations. Canada offered 10 evidence – based expert guidances and Europe 60 good clinical practice statements.

Role of opioids in the management of CNCP: All guidelines/recommendations recommended to start a trial with opioids only if non-pharmacological and non-opioid medications have failed. The European recommendations specified that established (guideline-recommended) treatments should have failed. The belief that opioids are the most powerful medication against CNCP have not been supported by any of the three guidelines, which demonstrated that opioids and non-opioid analgesics are equally effective in reducing pain (with small effect sizes). Therefore, the World Health Organization's analgesic 'ladder' for cancer-pain treatment, which placed nonsteroidal anti-inflammatory drugs (NSAIDs) on the bottom rung for mild pain and opioids on higher rungs for persistent moderate-to severe pain, is not supported in CNCP.

In contrast to the North American guidelines, the European recommendations gave different recommendations for different types of CNCP, for example, not to treat primary chronic pain syndromes with opioids. Prescription of high doses of opioids to patients with primary pain syndromes might have been a factor driving the opioid crisis in North America. Inclusion of patients with physical and psychological trauma, social disadvantage, and hopelessness that can enhance reports of pain intensity may have also resulted in prescription of more opioids (Dasgupta et al., 2018; deWeerdt, 2019; Petzke et al., 2020).

All three papers defined stopping rules for opioid therapy.

5 | CONCLUSIONS

Opioids are not a panacea for all types of CNCP, and must only be used in selected and supervised pain patients as part of a comprehensive, multi-modal, multi-disciplinary approach to treatment. In this context alone, opioid therapy can be a useful tool in achieving and maintaining an optimal level of pain control in selected patients. Misplaced barriers to access (e.g. payers restricting reimbursement or requiring previous authorizations that lead to lengthy delays) can lead to unnecessary suffering, just as overly-zealous prescription of opioids can lead to unnecessary suffering.

As recently stated by Barnett (2020), "the opioid-prescribing debate seems hopelessly polarized: either opioids are industrially sponsored weapons of mass addiction or they're a misunderstood last hope for alleviating suffering. The optimal use of medications lies between these two poles."

Opioids are a two edged sword. Used inappropriately (wrong indication, inappropriate monitoring of positive and negative effects, inadequate management of side effects) they can be associated with relevant harms to the patient. Therefore, the European Pain Federation calls for continuous medical education on the correct use of opioids in multiprofessional and multi-modal therapeutic approaches. We also call for enhancing access to, and funding for, comprehensive pain treatment services and therapies and increasing funds for robust research in pain treatment.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

WH performed the search of literature. All authors participated in developing the clinical practice recommendations. NKS, KV and WH wrote the manuscript. All authors discussed and commented on the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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