European clinical practice recommendations on opioids for chronic noncancer pain – Part 2

*Special situations**

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European clinical practice recommendations on opioids for chronic noncancer pain – Part 2: Special situations*

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Abstract

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

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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 European Clinical Practice Recommendations give guidance for combination with other medications, the management of frequent (e.g. nausea, constipation) and rare (e.g. hyperalgesia) side effects, for special clinical populations (e.g. children and adolescents, pregnancy) and for special situations (e.g. liver cirrhosis).

Conclusion: If a trial with opioids for chronic noncancer pain is conducted, detailed knowledge and experience are needed to adapt the opioid treatment to a special patient group and/or clinical situation and to manage side effects effectively.

Significance: If a trial with opioids for chronic noncancer pain is conducted, detailed knowledge and experience are needed to adapt the opioid treatment to a special patient group and/or clinical situation and to manage side effects effectively. A collaboration of medical specialties and of all health care professionals is needed for some special populations and clinical situations.

1 | INTRODUCTION

Therapy with opioids for chronic non-cancer pain (CNCP) is associated with clinically meaningful side effects and risks. In randomized controlled trials, the dropout rates due to adverse events are higher than with placebo (Petzke et al., 2020; Sommer et al., 2020; Welsch et al., 2020). The most frequent side effects leading to discontinuation of opioids in RCTs for CNCP are gastrointestinal (e.g., nausea, constipation) and neurological (e.g. somnolence) side effects (Kalso et al., 2004). In observational studies, an increased risk of severe harms such as hypogonadism, opioid-use disorder or sleep-related breathing disorders have been described (Chou et al., 2020). The use of opioids for CNCP in special situations such as in children and adolescents (Cooper et al., 2017) is under debate.

In part I of the European Clinical Practice Recommendations for appropriate use of opioids for CNCP (Häuser et al., 2021), we have highlighted the need to monitor people prescribed with opioids for CNCP regularly to detect side effects of treatment. In part II we give guidance for the use of opioids in special clinical populations (e.g. children, pregnant women) and situations (e.g. liver and renal failure) and for the prevention and management of side effects.

2 | METHODS

The methods have been outlined in part I of the European Clinical Practice Recommendations for appropriate use of opioids for CNCP (Häuser et al., 2021). In short, 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.

3 | RESULTS

3.1 | Part 3: Special situations

3.1.1 | Differential indication of different opioids

3.1.1.1 Transdermal systems. *Transdermal systems with opioids should not be considered if there are* clinically meaningful *day and night variations in pain intensity*. Good clinical practice statement. Consensus (12/13; 7/8).

Comment: Transdermal opioid formulations can be used in patients with gastrointestinal disorders despite fluctuating pain intensity when absorption of oral formulations are considered troublesome.

3.1.1.2 Short- versus long acting oral opioids. *The decision to prescribe immediate-release- or extended release (long-acting) opioids can be considered based on the individual situation and clinical presentation (e.g., variability in time of pain).* Good clinical practice statement. Consensus (13/14; 8/9).

Comment: The Canadian guidelines recommend that clinicians can prescribe extended release opioids in patients with continuous pain (including pain at rest), both for comfort and simplicity of treatment. Activity-related pain may not require extended release release treatment and opioid therapy may be initiated with immediate - release alone (Busse et al., 2017). The CDC guidelines recommend starting opioid therapy with immediate-release opioids instead of extended-release/long-acting opioids (Dowell et al. 2016). The German guidelines recommend the use of long-acting opioids by a fixed schedule (Häuser et al., 2020). The French guideline does not comment on this topic (Moisset & Martinez, 2016).

A systematic review included 16 randomized trials and eight observational studies comparing long- and short-acting opioids. None of the randomized trials was rated as good quality. The authors concluded that there was insufficient evidence to determine whether long-acting opioids are more effective or safer than short-acting opioids (Chou et al., 2003). North American studies found signals that adverse events (e.g. unintentional overdose deaths, opioid control, concern of the patient) are more frequent with long-acting rather than short-acting opioids (Sullivan, 2014). There was no evidence to support that long-acting opioids were superior or inferior to short-acting ones in improving functional outcomes, reducing side effects or addiction.

3.1.1.3 Medication on-demand with immediate release opioids in the adjustment phase. *Demand medication with immediate release oral opioids can be considered to determine the optimal dose*. Good clinical practice statement. Strong Consensus (15/15; 10/10).

3.1.1.4 Ultra-short acting buccal or nasal opioids. *Ultra-short acting buccal or nasal opioids should not be considered for use as rescue medication*. Good clinical practice statement. Consensus (12/15; 9/10).

Comment: Based on clinical experience, the TF perceived a relevant risk of misuse of ultra-short acting opioids for CNCP. In addition, ultra-short acting buccal or nasal opioids are not approved for CNCP. In special circumstances (e.g., patients with gastrointestinal disorders with fluctuating absorption, vomiting) these substances can be considered.

3.1.2 | Combination with other centrally acting medications

3.1.2.1 Combination with benzodiazepines. *We suggest not prescribing opioids and benzodiazepines simultaneously*. Weak recommendation. Consensus (15/16; 10/11)

Rationale: Benzodiazepines and opioids both cause central nervous system depression and can decrease respiratory drive. Concurrent use is likely to put patients at greater risk for a potentially fatal overdose. Observational studies conducted in North America and Europe have demonstrated that concurrent benzodiazepine and opioid use increases the frequency of adverse events (Dowell et al., 2016).

Evidence summary

PICO: Population: Patients with chronic noncancer pain with opioid therapy, Intervention: Opioids and tranquilizer. Comparator: Opioids. Outcome: Serious adverse events.

Emergency room admissions for overdoses: In a US study of 315,428 privately insured persons aged 18–64 years (excluding past or present cancers) in the years 2001–2013, the combined use of opioids (at least one dose) and tranquilizers compared to mono-long-term therapy with opioids was associated with an increased risk of presentation in the emergency room or inpatient admission due to overdoses [adjusted odds ratio (OR) 1.81 (1.67 – 1.96) (Sun et al., 2017).

Abuse and dependence: In a retrospective cross-sectional study in 2014 including 69 German statutory health insurance funds with a total of 4,028,618 insured persons on LTOT for CNCP, hospital stays were associated with diagnoses of mental and behavioural disorders due to alcohol, opioids, tranquilizers and multiple substance use as well as intoxication by narcotics with the prescription of tranquilizers [OR 3.63; (3.03; 4.36)] (Häuser et al. 2018).

Deaths: In a US study with former members of the armed forces in the years 2004–2009, 2,400 deaths were described in connection with opioid medication and tranquilizers. The hazard ratio (HR) was 3.86 (3.49; 4.26, no absolute figures were given, Park et al., 2015).

In a prospective observational study with a 1-year follow-up with US American senior citizens' home residents, 478 deaths related to overdose (0.022% per year for 2,182,374 people) were found. Death rates due to overdoses were 10 times higher (7.0 [6.3, 7.8] per 10,000 person-years) under a combination therapy of opioids and benzodiazepines than under opioids alone (0.7 [0.6, 0.9] per 10,000 person-years, no absolute numbers given) (Dasgupta et al., 2016).

In a study in US veterans, the association between guideline-equitable long-term opioid therapy and 1-year mortality was investigated. The mortality rate was elevated when co-medicated with opioids and benzodiazepines (HR 1.39 [1.12, 1.66]). A decrease in mortality was found with concomitant psychotherapy (HR 0.62; [0.51, 0.71]) and physical rehabilitation (HR 0.81 [0.67, 0.98]). A decrease in mortality was also found in cases of substance dependence when addiction therapy was used (HR 0.47 [0.32, 0.68]) (Gaither et al., 2016).

In a retrospective US cohort study, the risk of overdose death was particularly high for opioids combined with benzodiazepines and skeletal muscle relaxants (aHR, 12.6; 95% CI: 8.9, 17.9). Even at opioid doses 1–19 mg MEQ/d, patients using sedative-hypnotics concurrently had 5.6 times the risk than patients without sedative-hypnotics (aHR, 5.6; 95% CI: 1.6, 19.3) (Garg et al., 2017).

The significance of the studies is limited by the retrospective nature of most studies and possible conflicting variables (e.g., confounding by indication). In patients who are already treated by opioids combined with tranquilizers, a careful tapering should be conducted.

3.1.2.2 Combination with gabapentinoids. *We suggest that care be exercised in relation to combination therapy with opioids and gabapentinoids due to potential risks of respiratory depression and opioid overdose*. Weak recommendation. Consensus (13/14;8/9).

Rationale: Gabapentinoids and opioids both cause central nervous system depression and may decrease respiratory drive (McAnally et al., 2020). Concurrent use is likely to put patients at greater risk for a potentially fatal overdose. Observational studies conducted in Canada have found increased mortality when opioids were combined with gabapentinoids compared to opioids alone.

Evidence summary

PICO: Population: Patients with chronic noncancer pain with opioid therapy Intervention: Opioids and Gabapentinoids. Comparator: Opioids. Outcome: Serious adverse events.

There is only one RCT in CNCP which demonstrated the superiority of a combination of morphine plus gabapentin versus single therapy for painful diabetic neuropathy or postherpetic neuralgia (Gilron et al., 2005). A systematic review identified only seven eligible RCTs with different combinations for neuropathic pain. Combination therapy received an inconclusive GRADE recommendation due to conflicting findings (Finnerup et al., 2015). However, the combination of opioids with other classes of analgesics are frequently used in routine clinical care. The Canadian Health Authority, Health Canada, in a communication dated 17 September 2019, drew the attention of Canadian citizens to the increased risk of opioid overdoses and other serious side effects when taking pregabalin or gabapentin at the same time (Health Canada, 2019). In a Canadian population-based nested case–control study (case–control study in which cases and controls were drawn from the population of a cohort study), which considered data from 1997 to 2013, the mortality of patients on combination therapy of opioids and gabapentin was increased compared with opioid monotherapy: [OR 1.99 (1.61–2.47)] (Gomes et al. 2017].

The US Food and Drug Administration (FDA), in a communication of 19 December 2019, pointed out the risk of respiratory depression and fatal opioid overdose when opioids are combined with pregabalin and gabapentin (Food & Drug Admininstration, 2019).

The British Medicines and Healthcare products Regulatory Agency recommended to carefully observe patients for signs of CNS depression when prescribing gabapentin in patients who require concomitant treatment with opioid medicines (Medicines & Healthcare products Regulatory Agency, 2017).

Reports from North America need to be scrutinized in light of the opioid epidemic. In addition, the significance of the studies is limited by the retrospective nature and possible conflicting variables (e.g., confounding by indication).

3.1.2.3 Serotonin syndrome. *Physicians prescribing opioids should consider paying special attention to the occurrence of a serotonin-syndrome if fentanyl, methadone, oxycodone, tapentadol and tramadol are combined with medications with other serotonergic medication*. Good clinical practice statement. Strong Consensus (15/15; 10/10).

Comment: Symptoms can range from mild to fatal and classically include altered mental status, autonomic dysfunction and neuromuscular excitation. Several criteria exist for making this clinical diagnosis, but the Hunter criteria are generally accepted as the most accurate. The diagnosis can be made in patients with a history of exposure to a serotonergic drug plus one or more of the following: spontaneous clonus, inducible clonus with agitation and diaphoresis, ocular clonus with agitation and diaphoresis, tremor and hyperreflexia, hypertonia, temperature over 38°C with ocular or inducible clonus (Simon & Keenaghan, 2019).

Serotonergic medications include SSRI, SNRI, tricyclic agents, MAO-inhibitors, NaSSA (Mirtazapine), St. John's word, L-Tryptophan, Lithium, triptanes (Baldo, 2018).

3.1.2.4 Anticholinergic syndrome. *Physicians prescribing opioids should pay special attention to the occurrence of anticholinergic syndrome if opioids are combined with antidepressants and neuroleptics*. Good clinical practice statement. Strong Consensus (15/15; 10/10).

Comment

Peripheral anticholinergic syndrome: constipation, urinary retention, tachycardia, hypertension, mydriasis, dry skin and mucous membranes.

Central anticholinergic syndrome: decrease in vigilance, aggressiveness, agitation, hallucinations, coma, dizziness and dysarthria.

Older patients in particular are sensitive to anticholinergic side effects.

Anticholinergic medications include: Antihistamines (Diphenhydramine, Doxylamine, Promethazine, Chlorpheniramine, Cyproheptadine); antitussives (Dextromethorphan); antidepressants (tricyclic antidepressants Amitriptyline, Imipramine, Doxepin); antipsychotics (Chlorpromazine, Droperidol, Haloperidol, Quetiapine, Olanzapine); anticonvulsants (Carbamazepine); antiemetics/travel sickness (scopolamine); and topical ophthalmoplegics (Cyclopentolate, Homatropine) (Kiesel et al., 2018).

3.1.2.5 QT-prolongation. *Physicians prescribing opioids should consider obtaining an ECG with assessment of the QT interval prior to starting a prescription with methadone, oxycodone (>100 mg/d) and tramadol in patients with cardiovascular diseases or patients taking medications with known effect on the QT interval. In patients with prolonged QT interval, the prescription of these opioids should be considered to be avoided*. Good clinical practice statement. Consensus/strong Consensus (14/15; 10/10).

Comment: Available data indicate that some opioids such as methadone are high-risk even at low doses, and have the potential for a dose-dependent prolongation of the QT interval and development of ventricular tachycardia (Krantz et al., 2003). Some opioids such as tramadol and oxycodone are intermediate risk medications and may develop long QT interval and ventricular tachycardia in high doses. Some other opioids such as morphine and buprenorphine are low-risk medications and do not produce QT interval prolongation in at least in routine doses (Behzadi et al., 2018). Therapeutic and supratherapeutic doses of tapentadol do not affect the QT/QTc interval in healthy subjects (Oh et al., 2010).

3.1.3 | Special patient groups

3.1.3.1 People aged ≥65 years. *Physicians prescribing opioids should consider starting with a low dose, increasing the dose slowly (if needed), and close monitoring of efficacy and tolerability*. Good clinical practice statement. Strong Consensus (15/15; 10/10).

Comment: Age-related pharmacodynamic and pharmacokinetic changes lead to a longer duration of action of opioids in old age. For these reasons, it is recommended to start opioid therapy with an approximately 25%–50% dose reduction compared to younger patients and to increase the dose more slowly (Busse et al., 2017).

A systematic review of 23 placebo-controlled RCTs with patient populations with chronic musculoskeletal pain and an average age >60 years found low average effects of opioids on pain and disability. Termination rates with opioids were four times higher than with other analgesics (Megale et al., 2018).

Maximum starting dose should be 30 mg MEQ/d.

3.1.3.2 Frailty and/or multi-morbidity. *Physicians prescribing opioids should consider starting with a low dose, increasing the dose slowly (if needed), and close monitoring of efficacy and tolerability*. Good clinical practice statement. Strong Consensus (16/16; 11/11).

Comment: The maximum starting dose should be 30 mg MEQ/d. For details see Abdulla et al. (2013).

3.1.3.3 Neurodegenerative diseases (including cognitive impairment). *Physicians prescribing opioids should consider starting with a low dose, increasing the dose slowly (if needed), and close monitoring of efficacy and tolerability*. Good clinical practice statement. Consensus/strong consensus (15/16; 11/11).

Comment: A systematic review of case–control studies on neuropsychological effects of LTOT for CNCP found that opioids reduce attention when compared with treatments not targeted on the CNS. If opioids are used together with antidepressants and/or anticonvulsants, this effect increases (Allegri et al., 2019).

There is currently a lack of evidence to support safety evaluations of commonly used analgesics in patients with dementia (Erdal et al. 2019). In a placebo-controlled RCT in patients with advanced dementia and depression, transdermal buprenorphine had a significantly higher risk of discontinuation compared with placebo in people with advanced dementia and depression, mainly due to psychiatric and neurological adverse events. Daytime activity dropped significantly during the first week of treatment. Concomitant use of antidepressants further reduced the tolerability of buprenorphine (Erdal et al., 2018).

3.1.3.4 Current severe affective disorder and/or suicidal ideation (F32-34). *Physicians prescribing opioids should consider not starting opioid prescription when there is current severe affective disorder and/or suicidal ideation*. Good clinical practice statement. Strong Consensus (16/16; 11/11).

Comment: Long-term opioid therapy increases the risk of incident, recurrent and treatment-resistant depression.

Depressed patients may tend to overuse opioids because they use them to treat insomnia and stress. Depression also seems to increase the risk of abuse or nonmedical use of prescription opioids among adults and adolescents (Sullivan, 2018). Therefore, current severe affective disorder and/or suicidal ideation should be successfully treated by psychiatric- psychotherapeutic interventions before initiating opioid therapy.

3.1.3.5 Children and adolescents. *Opioids should be considered for use only in exceptional cases and in specialized centres for pain therapy in children and adolescents*. Good clinical practice statement. Strong Consensus (15/15; 10/10).

Comment: There are no RCTs of opioids for CNCP in children and adolescents available (Cooper et al., 2017). Our statement is based on the potential risks of opioids (e.g., opioid use disorder, endocrinological changes).

3.1.3.6 Pregnancy and medically indicated opioid therapy. *Opioid therapy can be considered for the termination in a stepwise fashion if pregnancy occurs during ongoing therapy with opioids*. Good clinical practice statement. Consensus (12/14; 8/9).

Comment: The database for the use of opioids (and other analgesics) in pregnancy is limited. Only paracetamol is generally allowed in pregnancy in all trimesters. For all opioids, an insufficient experience is reported in www.embryotox.de. For treatment during pregnancy, morphine, tramadol, buprenorphine (50–300 systematically evaluated pregnancies) are most likely to be recommended, without fundamental reservations against other opioids (fentanyl, oxycodone, hydromorphone). There is little experience with tilidine/naloxone (<50 pregnancies) and no experience with tapentadol (Australian Government, 2020).

In breastfeeding women, the ultra-rapid conversion of codeine to morphine can result in high and unsafe levels of morphine in blood and breast milk. The U.S. Food and Drug Administration has strengthened the label warning to state that breastfeeding is not recommended while using medicines containing codeine or tramadol because of the potential for serious adverse effects in the infant due to opioid overdose (Food & Drug Admininstration, 2019).

In the case of discontinuation, withdrawal symptoms should be avoided as this is associated with an increased risk of premature labour and miscarriage or premature birth. Care in opioid weaning should be exercised as opioid withdrawal can precipitate premature delivery (Reddy et al., 2017).

In the case of an indicated analgesia that cannot be achieved otherwise, it may be necessary to continue therapy with opioid analgesics during pregnancy. The delivery should then take place in a stage I/II perinatal centre, as neonatal abstinence syndrome (NAS) is very likely in the newborn (Reddy et al., 2017).

3.1.3.7 Pregnancy and abuse/dependence of opioids prescribed for medical reasons. *Methadone/polamidon or buprenorphine as medication-assisted therapy should be considered for use in close cooperation of obstetricians/gynecologists, pain physicians and mental health care specialists*. Good clinical practice statement. Strong Consensus (13/13; 8/8).

Comment: The World Health Organization (2014) support methadone and buprenorphine as medication treatment options for pregnant women with opioid use disorder. However, recent studies indicate that buprenorphine has advantages over methadone (Rausgaard et al., 2020).

3.1.3.8 Breastfeeding and abuse/dependence of opioids prescribed for medical reasons. *Methadone/polamidon or buprenorphine as medication-assisted therapy should be considered to use in close cooperation of obstetricians/gynecologists, pain physicians and mental health care specialists to enable breastfeeding as an integral component of the early management of neonatal abstinence syndrome*. Good clinical practice statement. Strong Consensus (13/13; 8/8).

Comment: Neonatal abstinence syndrome is a neurological condition resulting from prenatal exposure to opioids. The sudden cessation of opioids in neonates can lead to withdrawal symptoms affecting the neurological, respiratory and gastrointestinal systems. With rare exception, breastfeeding is the optimal way to feed infants and has special benefits for women and infants with perinatal opioid exposure. Infants breastfed and/or fed their mother's own breastmilk experience less severe opioid withdrawal symptoms, have shorter hospital stays, and are less likely to be treated with medication for withdrawal (Wu & Carre, 2018).

3.1.3.9 Current substance abuse and dependence (alcohol, cannabinoids, opioids, cocaine, tranquilizer, others). *An indicated therapy with opioids should only be considered to be conducted in close collaboration with an addiction mental health care specialist*. Good clinical practice statement. Strong Consensus (17/17; 12/12).

3.1.3.10 Homeless and Vulnerably Housed Persons. *Physicians should consider providing homeless persons with access to pain management programs including supervised access to opioids – if indicated*. Good Clinical Practice Statement. Strong Consensus (17/17; 12/12).

Comment: A coordinated, inter-agency and multifaceted approach is required to address the underlying structural, cultural and societal factors that contribute to homelessness and its stigmatization. In the interim, we need to develop more tailored and accessible services to ensure that the homeless in our societies receive better health care, including pain management. This will require the provision of supervised access to opioid analgesics for carefully selected and supervised persons in a way that minimizes potential harm. In particular, robust strategies to minimize the risk of medication misuse and diversion must be in place (Magwood et al., 2020).

3.1.3.11 Prisoners: *Physicians should consider providing persons in custodial settings with access to pain management programs including supervised access to opioids – if indicated.*

Good Clinical Practice Statement. Strong Consensus (17/17; 12/12).

Comment: Prisoner feedback identifies four areas of concern:

1. Delays in accessing treatment.
2. Prisoners reported that healthcare staff are not perceived as caring and do not always appear to take prisoners' reports of pain seriously.
3. Inconsistencies in approaches adopted by different clinicians, particularly when prisoners are moved from one custodial setting to another.
4. A perceived reluctance to prescribe opioids when simple non-opioid analgesics prove ineffective.

In prisons, there are additional risks associated with the use of controlled medications including a high prevalence of mental health problems, medication dependence and the potential for diversion and misuse. In circumstances where an appropriate physician evaluation has occurred and the physician is satisfied that a trial of opioid medication is indicated, such therapy may be warranted and appropriate. As in all circumstances where opioids are prescribed, each patient must be kept under close clinical surveillance and every precaution must be taken to ensure the safe-keeping and security of prescribed medications.

In prisons, the issue of opioid diversion or abuse is particularly problematic and may result in harm to the individual prisoner or other inmates. In July 2014, the Prison Healthcare Board and the National Offender Management Service in the UK developed a national prison pain management formulary. When implemented across a national prison service, such a formulary supported (Bradshaw et al., 2017):

- Greater consistency in evidence-based prescribing
- Greater consistency when patients transfer from one custodial setting to another
- Reassurance to the prescribing clinician that the formulary incorporates evidence-based guidance with due regard to the known risks associated with the clinical setting
- Greater transparency and standardization on the use of prescribed medicines as part of pain care pathways in custodial settings

A prison formulary provides a rational, evidence-based approach to the use of analgesic medications for people in prisons (Health & Justice Clinical Reference Group NHS England, 2017).

3.1.4 | Comorbidities

3.1.4.1 Renal impairment: *In case of advanced renal insufficiency* (CKD 4: eGFR < 30 ml/min), *buprenorphine, fentanyl or hydromorphone should be considered as preferred. Other opioids can be used carefully, but dose education and careful observation are required*. Good clinical practice statement. Strong Consensus (14/14; 9/9).

Comment: In the few available studies, no clear benefits of certain opioids in cases of impaired renal function can be deduced. Recommendations for the use of specific opioids are based mainly on theoretical pharmacokinetic considerations (Mallappallil et al., 2017).

eGFR 30–89 ml/min: All opioids can be used with consideration of reduced dose or frequency. Dose titration should start with lower doses than usual, but should be based on clinical efficacy. Every opioid should be titrated individually, dosing of opioids in renal impairment should be guided by the clinical effect and side effects, not only by biochemistry. Dose reduction or extended dose interval is recommended for transdermal fentanyl, hydromorphone, morphine, oxycodone, tilidine and tramadol. In the case of tapentadol, a dose adjustment is not necessary in the case of slightly or moderately impaired renal function. For severely impaired renal function, use is not recommended due to the lack of data. No dose reduction necessary: Buprenorphine transdermal.

eGFR < 30 ml/min: Buprenorphine, fentanyl or hydromorphone should be preferred.

Haemodialysis: Buprenorphine, fentanyl or hydromorphone should be preferred. Hydromorphone morphine and tramadol are dialysable. Buprenorphine, fentanyl and methadone are not dialysable (King et al., 2011).

Practice tool: Online tool for dose adjustment in renal failure of the Pharmacology Department of the University of Heidelberg: http://dosing.de/

3.1.4.2 *Liver cirrhosis: Opioids can be considered when carefully used, but dose reduction and careful observation is needed*. Good clinical practice statement. Strong Consensus (14/14; 9/9).

Comment: In the few available studies, no clear benefits of certain opioids in cases of impaired liver function can be deduced. Recommendations for the use of specific opioids are therefore based mainly on theoretical pharmacokinetic considerations. Every opioid should be titrated individually, dosing of opioids in hepatic impairment should be guided by the clinical effect and side effects, not only by biochemistry. Opioids can be given in patients with liver cirrhosis under close surveillance with cautiously increasing dosage (risk of triggering hepatic encephalopathy, major adverse effects or opioid overdose). Particular attention should be paid to the prevention of constipation in these patients. Note for the dose recommendations for opioids in liver cirrhosis below that due to shunts, changes in first pass metabolism, albumin binding etc. that cannot be easily quantified, dosages are highly individual and adverse effects unpredictable Donbe.

Dose recommendations for opioids in liver cirrhosis (modified according to Weersink et al., 2018).

Medication	Child A	Child B	Child C
Buprenorphine	No dose adjustment needed	Start with half of usual dose	Start with half of usual dose
Fentanyl	Start with half of usual dose	Start with half of usual dose	Start with half of usual dose
Hydromorphone	Start with a quarter of usual dose	Start with a quarter of usual dose	Start with a quarter of usual dose
Morphine	Start with half of usual dose	Start with half of usual dose	Start with a quarter of usual dose
Oxycodone	Start with a quarter of usual dose	Start with a quarter of usual dose	Start with a quarter of usual dose; double interval between dosages
Tapentadol	No dose adjustment needed	Start with 50 mg, maximum 150 mg/d	Not recommended
Tramadol	Start with 50 mg, maximum 200 mg/d	Start with 25 mg, maximum 100 mg/d	Start with 25 mg, maximum 100 mg/d

3.1.4.3 Short bowel syndrome: *Liquids, capsules and uncoated tablets or transdermal applications can be considered as preferred over oral modified-release formulations (slow-release, controlled-release or sustained-release) opioids*. Good clinical practice statement. Strong Consensus (13/13; 8/8).

Comment: Patients with short bowel syndrome (SBS) may be at risk for impaired absorption of oral medications. Most medications are absorbed in the stomach and proximal small bowel, and thus their effect is preserved. Enteric-coated medications and timed/delayed-release medications, in contrast, may not be absorbed properly and should generally be avoided. When feasible, alternative methods for medication delivery (e.g., liquid, transdermal, suppositories) should be used and medication levels should be monitored (UptoDate, 2020).

Patients with less than 2 meters of the gut are at risk of short bowel syndrome, which can result in compromised absorption of opioids. On the other hand, opioids are also prescribed as antidiarrhoeal agents by gastroenterologists in short bowel syndrome to treat hypermobility.

Preference should be given to dispersible formulations if they are available. Formulations such as liquids, capsules and uncoated tablets are likely to be better absorbed. It may be necessary to avoid oral modified-release formulations (slow-release, controlled-release or sustained-release) opioids. If a solid dose form of an opioid is to be altered, there is a potential for a shift in side effects and efficacy.

A common strategy to improve medication bioavailability in short bowel syndrome is to increase the prescribed dose – even beyond that 'recommended'. The effect can be monitored by evaluating the balance between analgesia and side effects. Careful monitoring for systemic side effects such as drowsiness, sedation and respiratory depression, especially during the initiation and dose titration phase, are crucial to minimize the risks associated with oral opioids in short bowel syndrome.

Patients with a colostomy are unlikely to suffer significant problems with opioid absorption as opioids are absorbed in the stomach and proximal small intestine. Normal doses and formulations can be used for most patients. In patients with small intestinal stomas (jejunostomy or ileostomy), the ability to use medications normally is largely dependent on the residual length of the small intestine and more dispersible formulations are likely to be better absorbed.

Methadone has some unique pharmacokinetic properties which makes it a valuable option in short bowel syndrome. It is a very lipophilic medication and oral methadone has a bioavailability of nearly 80% of the administered dose compared to 26% for morphine. It is absorbed rapidly from the stomach, and most absorption occurs before transiting beyond the stomach.

3.1.5 | Management of complications

3.1.5.1 Constipation: *Treatment with laxatives should be considered prophylactically in most patients*. Good clinical practice statement. Consensus (14/15; 9/10)

Comment: About 60%–80% of patients in opioid therapy suffer from side effects from the gut. Constipation is the predominant complaint, but nausea (partly a central side effect), vomiting, abdominal pain, and distension etc. are also frequently seen (Farmer et al., 2019). A decision regarding the use of prophylactic therapy for constipation and other opioid-related side effects in the gut is necessary and must be made in each individual case depending on the symptoms. It is a common mistake to define constipation as number of bowel movements, but straining, gas production, hard consistency of stools and abdominal discomfort are more frequent symptoms that need to be taken into consideration. A decision about a prophylactic laxative therapy, if necessary, must be made in each case and depending on the defecation pattern of the patient. In patients with a pre-existing constipation (tendency), the prophylactic administration of laxatives is recommended. In many patients, the administration of laxatives may be necessary during the entire duration of therapy with opioid-containing analgesics. According to the clinical experience of the TF, the constipation-promoting effect of opioids may vary between patients.

The preference of a specific medication (including peripherally acting opioid antagonists for prophylaxis and therapy of opioid-induced constipation) is not possible due to variation in practice between countries. Suggestions for

a stepwise medication (including peripherally acting opioid antagonists) approach can be found in the literature (e.g., Farmer et al., 2019).

3.1.5.2 Nausea and vomiting: *An antiemetic treatment can be considered in some patients at the beginning of the therapy. After about 2–4 weeks, discontinuation of antiemetic therapy should be considered*. Good clinical practice statement. Strong Consensus (15/15; 10/10).

Comment: According to the clinical experience of the TF, the emetic effect of opioids may vary between patients. Opioid-induced nausea and vomiting are experienced by up to 40% of pain patients with no history of emesis. However, because this is an inconsistent consequence of opioid therapy, prophylactic antiemetics are generally not prescribed. In most patients, tolerance to the emetic effect of opioids develops after 2–4 weeks, routine administration of antiemetics is not necessary.

There are no controlled studies on the use of antiemetics for the treatment of opioid-induced nausea in CNCP. The preference of a specific medication for prophylaxis and therapy of opioid-induced constipation is not possible due to variation in practice between countries. Antihistamines, neuroleptics, prokinetics and setrons (5-HT3 receptor antagonists) may be used.

3.1.5.3 Psychiatric side effects: *If somnolence, delirium, hallucinations, nightmares, persistent anxiety/depression suicidal ideation occur*, *dosages should be considered for reduction as much as possible or therapy should be considered to be switched to another opioid*. Good clinical practice statement. Strong Consensus (15/15; 10/10).

Comment: For details see Sivanesan et al., 2016. Psychiatric consultation should be considered.

3.1.5.4 Myoclonic movements: *If myoclonic movements occur*, *dosages should be considered for reduction as much as possible or therapy should be considered to be switched to another opioid*. Good clinical practice statement. Strong Consensus (16/16;11/11).

Comment: Myocloni mainly occur by a glucuronide metabolite of morphine and hydromorphone accumulation in renal impairment (Mercadante, 1998).

3.1.5.5 Increase of pain severity. *In case of an increase of pain severity, a clinical assessment should be considered to differentiate between progression of the disease, tolerance and opioid-induced hyperalgesia*. Good clinical practice statement. Strong Consensus (15/15; 10/10).

Comment: It is important to identify different reasons for increase of pain intensity prior to a change in management plan:

Progression of the disease: In some CNCP syndromes, the clinical picture can deteriorate, which in turn can lead to an increase in nociception. For example, in the case of osteoarthritis, the movement-dependent pain can be increased with damage of the joint cartilage.

Tolerance: Tolerance to opioid analgesia may develop after ongoing exposure to the drug. The same dose of drug administered over time produces less analgesic effect. The rate of onset and extent of tolerance development is variable depending on the individual drug and patient characteristics (Colvin et al., 2019).

Opioid-induced hyperalgesia (OIH): There are no internationally accepted and/or validated criteria to diagnose. OIH can be considered present when symptoms worsen even with an increase in opioid dose (and worsening in disease/tolerance have been excluded) and when these symptoms and signs are present:

(i) increased nociception over time
(ii) tendency to spread to other areas
(iii) hyperalgesia to external stimuli (Colvin et al. 2019).

Suggested Clinical Criteria for Diagnosing OIH (Eisenberg et al., 2015):

- Increased pain intensity during ongoing opioid treatment.
- No evidence for underlying disease progression.
- No evidence for either clinical or pharmacological opioid withdrawal (i.e., symptoms and signs of opioid withdrawal; increased pain as a result of the end of previous opioid dose effect).
- No evidence for opioid tolerance: to be tested clinically by decreased pain in response to an adequate opioid rescue dose.
- Decrease in pain intensity in response to a reduction in opioid dose (gradual dose reduction might be required to avoid abstinence syndrome).
- No evidence for addictive behaviour.

OIH can be differentiated from worsening in disease and tolerance by reducing dose and monitoring response (Colvin et al., 2019).

3.1.5.6 Opioid induced hyperalgesia. *Opioids should be considered for reduction as much as possible*. Good clinical practice statement. Strong Consensus (15/15; 10/10)

Comment: For details see Bannister (2015).

3.1.5.7 Tolerance. *In case of tolerance development, a dose increase (bearing in mind guidance on opioid dose limits), opioid switch or opioid withdrawal should be considered*. Good clinical practice statement. Strong Consensus (15/15; 10/10).

Comment: In the context of LTOT, there may be a reduction in analgesic effectiveness (tolerance). As a rule, no more than two opioid changes should be carried out with tolerance development. Continued tolerance development with a repeated need for dose adjustment even after opioid changes is not useful for obtaining a clinically relevant effect (responder). Instead of a further opioid rotation, a stepwise opioid reduction or opioid withdrawal should be performed.

3.1.5.8 Pruritus. *Opioid dosages should be considered for reduction as much as possible or switch to another opioid should be considered*. Good clinical practice statement. Strong Consensus (15/15; 10/10).

Comment: For details see Reich and Szepietowski (2010).

3.1.5.9 Urinary retention. *Opioid dosages should be considered for reduction as much as possible or switch to another opioid should be considered*. Good clinical practice statement. Strong Consensus (16/16; 11/11).

Comment: More details in Verhamme et al. (2008).

3.1.5.10 Hypogonadism. *A screening for hypogonadism can be considered. These treatment options can to be considered: decreasing dosages (if applicable), opioid rotation and hormone replacement*. Good clinical practice statement. Strong Consensus (14/14;9/9).

Comment: Long-term opioid therapy can lead to central hypogonadism in women and in men. Clinically, patients with opioid-induced hypogonadism mainly suffer from sexual dysfunction and infertility (Antony et al., 2020). The prevalence of patients with opioid-induced hypogonadism ranges from 19% to 86%, depending on the criteria for diagnosis of hypogonadism (Coluzzi et al., 2018).

The evaluation of serum testosterone levels can be considered in male LTOT opioid users. Testosterone can be replaced, in both men and women, as a transdermal patch, gel or by injection based on the clinical profile of individual and shared decision making on the potential benefits and harms of testosterone therapy (Coluzzi et al., 2018; Seyfried & Hester, 2012). Careful monitoring is required as side-effects include site reactions, polycythaemia and increased risk of prostate cancer in men and menstrual irregularities and hirsutism in women. Oestrogen replacement therapy is best monitored by a gynaecologist (Seyfried & Hester, 2012).

3.1.5.11 Sleep-related breath disorders. *Opioid treatment should be considered for discontinuation if sleep-disordered breathing occurs and does not improve despite optimization of breathing therapy and/or reduction or cessation of other medications with negatively affect respiration (hypnotics, antipsychotics) - if possible*. Good clinical practice statement. Strong Consensus (15/15; 10/10).

Comment: Opioids are associated with several types of sleep-disordered breathing, including sleep-related hypoventilation, central sleep apnoea (CSA) and obstructive sleep apnoea (OSA) (Rosen et al., 2019). The risk increases with simultaneous intake of tranquilizers/hypnotics and morphine equivalence doses of ≥200 mg/d (Correa et al., 2015). Opioids should only be started in patients with sleep-related breathing disorders after very carefully balancing potential benefits and risks.

Adaptive servoventilation and bilevel positive airway pressure ventilation were effective according to some reports in CSA (Correa et al., 2015). Opioid withdrawal improves the symptoms of sleep-disordered breathing (Schwarzer et al., 2015).

3.1.5.12 Problematic use of prescribed opioids

3.1.5.12.1 Terms and criteria. *There is no universally accepted terminology and diagnostic criteria available which capture all aspects of problematic use of opioids prescribed for CNCP*. Good clinical practice statement. Consensus (13/14; 8/9).

Comment: A systematic review of the Analgesic, Anesthetic and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION) public-private partnership with the US FDA and the American Pain Society (APS) found that the existing terms of misuse, abuse, dependence, addiction, aberrant medication behaviour, etc. from consensus efforts, review articles, and major institutions and agencies are often defined inconsistently and idiosyncratically (Smith et al., 2013). The terms 'aberrant medication behaviour, abuse and addiction might be pejorative or stigmatizing in some contexts. The terms 'Using medication not as prescribed or intended,' non-medical use, substance use disorder/dependence are considered to be more appropriate (Scholten et al., 2017).

The International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual (DSM) are commonly used in illicit substance use research and clinical practice. Of importance, the ICD 10 and DSM classification systems were not designed specifically to address the pharmaceutical medication use in patients using medications under medical supervision. In the field of prescribed pain medicine, however, they remain controversial (Campbell et al.2016), particularly as issues of tolerance and withdrawal, which are often used as key criteria for substance use disorders, are to be expected with prolonged use of prescribed opioids. Purely physical symptoms are insufficient for a diagnosis of dependence.

The diagnostic criteria of DSM-5 (American Psychiatric Association (APA), 2013) have been frequently used to assess problematic use of opioids prescribed for chronic pain in pain medicine (Vowles et al. 2015). APA explicitly states that these criteria are not appropriate for individuals taking opioids under appropriate medical supervision. In rendering a diagnosis of opioid use disorder (OUD), the criteria tolerance and withdrawal are not considered met if the individual is prescribed an opioid by a licensed clinician (Supplementary Material 1, box 1). Questions have been raised about the validity of the new definition, the adequacy of field testing, the potential cultural and social biases embodied in the new approach, and the clinical and epidemiological effects of the lowered diagnostic thresholds (Degenhardt et al., 2015).

The Pain and Opioid IN Treatment (POINT) cohort was a 2 - year prospective cohort study of 1514 people prescribed opioids for their chronic pain who were recruited in 2012–13 from community-based pharmacies across Australia. After giving patients the Composite International Diagnostic Interview about their opioid use, patients were categorized as having opioid use disorders by ICD-10, the ICD-11

(Supplementary Material 1, box 2), DSM-IV and DSM-5. Classification of problematic pharmaceutical opioid use varied across editions of ICD and DSM. The much lower levels of agreement between DSM-5 and other definitions than between other definitions might be attributed to DSM-5 containing an increased number of criteria and treating dependence and problematic use as a continuum. The more parsimonious ICD-11 dependence definition showed excellent model fit and excellent agreement with previous classificatory systems (Degenhardt et al., 2015).

Recently, Ballantyne et al. (2019) have suggested a new category of problematic use of prescribed opioids, called Opioid Dependence. They argue that some patients with chronic pain on LTOT can develop a complex refractory dependence syndrome which inhibits tapering of opioids (Supplementary Material 1, box 3). These patients do not fit into DSM-5 criteria of OUD. The authors do not report how many of these criteria must be met to diagnose an Opioid Dependence.

One major component of the opioid crisis in North America was problematic use of prescribed opioids associated with mortality. Recently, the rise in opioid prescribing is causing increasing concern in Europe (Kalkman et al., 2019, 2020). The prevalence rates of opioid misuse and dependence vary widely depending on the setting, country and the criteria and methods of assessment used: Some reviews have found wide variability in rates of opioid misuse and harmful opioid use in patients with opioids prescribed for chronic pain (Minozzi et al., 2013; Voon et al., 2017; Vowles et al., 2015). Many of these same reviews also highlighted significant heterogeneity in this literature and some methodological shortcomings (e.g., Voon et al., 2017; Vowles et al., 2015). For example, a systematic review found rates of misuse averaged between 21% and 29% (range, 95% confidence interval [CI]: 13%–38%) and rates of addiction averaged between 8% and 12% (range, 95% CI: 3%–17%) in patients with opioids prescribed for chronic pain (Vowles et al., 2015). In addition, 36 of 38 studies included in the review were conducted in the United States, with only two studies conducted in Europe. The prevalence rate of abuse was 0.08%–0.3% in a prospective study in a Norwegian database and of addiction was 14.4%–19.3% in a cross-sectional study in a Danish pain clinic (Vowles et al., 2015).

A systematic review on predictors of misuse among patients with outpatient opioid prescriptions found that the following factors were associated with the development of misuse: any current or previous substance use (odds ratio [OR] 3.55; 95% confidence interval [CI] 2.62–4.82), any mental health diagnosis (OR 2.45; 95% CI 1.91–3.15), younger age (OR 2.19; 95% CI 1.81–2.64) and male sex (OR 1.23; 95% CI 1.10–1.36) (Cragg et al., 2019).

3.1.5.12.2 There is a transition of patient behaviour between intended use, unintended use/consumption (misuse), harmful use (abuse) and dependent ('addicted') use of opioids prescribed for medical reasons. Good clinical practice statement. Strong Consensus (13/14; 8/9).

Comment

Example definitions:

- Intended use: Prescription and use of opioids for indications mentioned in this position paper (e.g., post-zoster neuralgia).
- Misuse (improper prescription by a physician): prescription of opioids for contraindications mentioned in this paper (e.g., primary headaches).
- Misuse (Improper use by physician and/or patient): prescribing (physician) and taking opioids (patient) prescribed for the intended purpose despite lack of efficacy for potential indications mentioned in this paper.
- Abuse (non.medical use): use of opioids by patients for psychotropic purposes (e.g., sedation).
- Dependence: boiling out of a fentanyl patch for intravenous injection for intoxication purposes.

3.1.5.12.3 Screening. *Screening instruments such as the Current Opioid Misuse Measure (COMM®) or the short version COMM-9 can be considered to screen for abuse of prescribed opioids*. Good clinical practice statement. Strong Consensus (14/14; 9/9).

Comment: The Current Opioid Misuse Measure (COMM®) is a commonly used self-report 17-items instrument to identify and monitor aberrant opioid-related behaviour in people with chronic pain on opioid therapy (Butler et al. 2010). A validated German version is available (Just et al., 2018). A validated English short version with 9-items is available (McCaffrey et al., 2019).

Practice tool: Current Opioid Misuse Measure (COMM®) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2955853/

3.1.5.12.4 Diagnosis. Additional clinical criteria (see table 5) to DSM-5 opioid use disorder criteria and/or the ICD 11 opioid dependence criteria can be considered for use to evaluate for opioid use disorder. Good clinical practice statement. Strong Consensus (13/13; 8/8).

Comment: For additional criteria see Table 1

3.1.5.12.5 Management. *A collaboration with an opioid use disorder treatment specialist in case of problematic use of opioids prescribed for chronic pain should be considered if available*. Good clinical practice statement. Strong Consensus (17/17; 12/12).

3.1.5.12.6 Treatment options for opioid use disorder. These treatment options can be considered in the view of the local resources and national legislation

- *Opioid tapering [outpatient, inpatient (e.g., pain or addiction/psychiatric department)]*
- *Continuation of therapy with a stable opioid dose to sustain pain relief or minimize withdrawal symptoms. Also*

TABLE 1 Non-specific signals for misuse, abuse and dependence (Häuser et al., 2020)

Non-specific signals for misuse
- Ingestion despite low to no efficacy
- Changing pain localization, multilocular spread (generalisation) of pain, transformation to primary pain under ongoing therapy
- Opioid-induced hyperalgesia (tendency to spread pain, increase in pain sensitivity and opioid resistance)

Non-specific signals of abuse/dependence:
- High at rest pain and discrepancy between pain indication and behaviour
- Demanding a specific opioid, especially short-acting and/or fast acting opioids
- Opioid use mainly for symptom relief other than pain (distress, anxiety, fear, depression, sleep disturbance)
- Unconcerted increases in dosage
- Urging an increase in dose without improving symptoms/function or despite an increase in side effects
- Repeated unreliability (unpunctuality, non-appearance) or lack of compliance
- Concealed use of substances with addictive potential (discrepancies in drug monitoring)
- Urging the prescription of more psychotropic substances
- Change of the agreed intake intervals, independent adjustment as required
- Defence against changes in therapy
- Changes in character under therapy (e.g. impulse control disorders) and other new psychiatric symptoms
- Misuse of other substances for psychotropic purposes
- Increase of irritability, depression, anxiety, nightmares under therapy

Signals of psychological dependence:
- Persistent resistance to changes in medication despite
- Ineffectiveness and/or symptoms of a medically undesirable psychotropic effect (euphoria, sedation, anxiety relief)
- Psychotropic (mostly dose-dependent) side effects (fatigue, listlessness, concentration disorders)
- Injection of oral/transdermal administration forms
- Intravenous and oral application of transdermal systems
- Forged prescriptions
- Steal/Borrow Opioids
- Implausible hoarding of prescribed opioids
- Concealed/denied reference by other doctors
- Illicit use of other psychotropic substances including other opioids
- Frequent loss of prescriptions
- Requiring a parenteral route of administration
- Trade of opioids with third parties
- Loss of control (e.g. repeated episodes of dosage increases or increasingly needs-based intake despite clear agreement/warning, clear immediate negative consequences of taking medication in the private and social environment)
- Compulsory use

consider psychological therapies, and/or regular urine drug testing (or other specimen) to exclude use of other opioids and or other psychoactive substances.

- *Buprenorphine or methadone/polamidon therapy with psychological therapies – if available- with regular urine drug testing (or other specimen) to exclude the use of other opioid and or other psychoactive substances*

Good clinical practice statement. Strong Consensus (14/14; 9/9).

Comment: For patients with prescription opioid use disorder, long-term maintenance of opioid agonists is associated with less prescription opioid use and better adherence to medication and psychological therapies for opioid dependence compared with opioid taper or psychological treatments alone. Methadone maintenance was not associated with differences in therapeutic efficacy compared with buprenorphine maintenance treatment. Evidence quality was low to moderate (Nielsen et al., 2016). There is some evidence that psychological therapies can aid in reducing both pain interference and opioid misuse in those who are using opioids in a harmful manner (Garland et al., 2019; Vowles et al., 2019).

Multi-substance dependence (e.g., Benzodiazepines, illegal medications together with prescription opioids) is not an indication for a pain specialist, but for specialist addiction treatment.

3.1.5.12.7 Opioid tapering: Cessation of opioids should be considered to be done gradually. In particular, dose reduction should be slow after a long period of opioid administration and/or when it concerns long-acting opioids. Good clinical practice statement. Strong consensus (16/16; 11/11).

Comment: The CDC guidelines state that a decrease of 10% per month is a reasonable starting point if patients have taken opioids for a year or longer. A decrease of 10% per week may work for some patients who have taken opioids for a shorter time (weeks to months) (CDC, no date).

Practice tools: Opioid tapering for inpatients (see Supplementary Material 2) and opioid tapering for outpatients (see CDC, no date).

3.1.5.12.8 Medication support of opioid tapering. Opioid tapering can be considered to be done with or without medication support (e.g., tricyclic antidepressants, gabapentinoids, clonidine). Good clinical practice statement. Consensus (13/14; 8/9).

3.1.6 | Prevention of non-medical use of prescribed opioids

3.1.6.1. Acute pain therapy after surgical and interventional procedures. *Acute pain therapy by opioids after surgical and interventional procedures should be considered to be tailored and discontinued as soon as clinically indicated*. Good clinical practice statement. Strong Consensus (16/16; 11/11).

Comment: Part of the opioid epidemic in the US is attributed to the continuation of opioid treatment started in hospitals for acute pain (Mir et al., 2019). Multimodal pain management including regional anaesthesia techniques should be used perioperatively to avoid or decrease the need of opioids of patients who might be on preoperative opioids. At discharge, if opioids are still required, they should be prescribed with tailored approaches (Hill et al. 2017). Communication between hospitals and the community/primary healthcare team is very important. In individual cases, if opioids are still needed after the usual period of postoperative or interventional pain, interdisciplinary non-opioid interventions should be initiated.

3.1.6.2 Other measures. *We suggest these measures to identify and prevent abuse and misuse of prescribed opioids: risk-screening tools, controlled-substance agreements and compliance monitoring. Weak recommendation*. Strong Consensus (16/16; 11/11).

Comment

Evidence summary

PICO: Population: Patients with chronic noncancer pain with opioid therapy. Intervention: Measures to identify and prevent abuse and misuse of prescribed opioids. Comparator: No measures and/or treatment as usual. Outcome: Non-medical use of prescribed opioids.

A systematic review (search of literature May 1, 2007-January 18, 2013) found weak to moderate evidence supports the value of thorough patient assessment, risk-screening tools, controlled-substance agreements, careful dose titration, opioid dose ceilings, compliance monitoring and adherence to practice guidelines. Moderate to strong evidence suggests that prescribing tamper-resistant opioids may help prevent non-medical use but may also have the unintended consequence of prompting a migration of users to other marketed opioids, heroin or other substances. Similarly, preliminary evidence suggests that although recent regulatory and legal efforts may reduce non-medical use, they also impose barriers to the legitimate treatment of pain (Argoff et al., 2014).

A systematic review found that the following factors associated with the development of non-medical use: any current or previous substance use (OR 3.55; 95% confidence interval [CI] 2.62, 4.82), any mental health diagnosis (OR 2.45; 95% CI 1.91, 3.15), younger age (OR 2.19; 95% CI 1.81, 2.64) and male sex (OR 1.23; 95% CI 1.10, 1.36) (Cragg et al., 2019). We recommend a careful review of the indication for opioid treatment in these patients and, in opioids are prescribed, close monitoring of patients.

4 | DISCUSSION

We discuss some similarities and differences between the existing guidelines, including those from Canada (Busse et al., 2017), the United States Centers for Disease Control (US CDC; Dowell et al., 2016) and the European clinical practice recommendations.

The Canadian and US CDC guidelines are focussed on the prevention and treatment of opioid use disorder. The recommendations to manage prescription opioid disorder of people with chronic pain are similar between the three guidelines. Some North American recommendations such as the prescription of tamper-resistant formulations to prevent from oral to nasal or intravenous injection or of naloxone to patients receiving opioids who are identified as at risk due to high dose, medical history, or comorbidities to treat overdosages cannot be found in the European Clinical Practice Recommendations because these treatment options are not available in most European countries.

All guidelines recommend avoiding prescribing opioids and tranquilizers/sedatives simultaneously and give guidance on the management of sleep-related breathing disorders. Statements for special patients' populations (seniors, pregnancy, mental health conditions) can be found in the US CDC and European guidelines.

The European Clinical Practice Recommendations give guidance for the management of frequent (e.g. nausea, constipation) and rare (e.g. hyperalgesia) side effects, for special clinical populations (e.g. children and adolescents, prisoners) and for special situations (e.g. liver cirrhosis, short bowel syndrome) highlighting the aspiration of the project to assist primary care physicians and specialists.

5 | CONCLUSIONS

If a trial with opioids is conducted, detailed knowledge and experience are needed to adapt the opioid treatment to a special patient group and/or clinical situation and to manage side effects effectively. Therefore, the European Pain Federation calls for continuous medical education on the correct use of opioids. Collaboration of medical specialties and all health

care professionals is needed for some special populations and clinical situations.

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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, 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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