Recommendations of the updated LONTS guidelines

Long-term opioid therapy for chronic noncancer pain

In a representative sample of the German population aged ≥14 years taken in 2013, 7.4% of individuals fulfilled the criteria for chronic disabling noncancer pain [38]. Chronic noncancer pain (CNCP) is associated with high direct and indirect disease-related costs [38, 58]. In Germany, analgesics are frequently used in the long-term treatment (duration ≥3 months; [90]) of CNCP [58].

Data from German health insurance providers demonstrate an increase in the number of individual and long-term prescriptions of opioid-containing analgesics for CNCP patients during recent years [81, 95]. Furthermore, health insurance data indicate possible inappropriate treatment of fibromyalgia syndrome (FMS) and somatoform pain disorders with strong opioid-containing analgesics [37, 53, 95]. In contrast, it is possible that patients suffering from subgroups of CNCP that are in principle opioid-sensitive, e.g. neuropathic pain, are undertreated with opioid-containing analgesics.

Long-term application of opioid-containing analgesics in CNCP is debated at both the national and the international level. Several recommendations of the first version of these guidelines—which express a critical view of long-term therapy with opioid-containing analgesics [70]—were judged by the German Pain Association (“Deutsche Gesellschaft für Schmerzmedizin”) as expressions of “opioidphobia” that could harm patients and physicians [59]. The long-term efficacy and safety of opioid-containing analgesics in CNCP is controversially discussed in current US American reviews and guidelines [7, 45, 88].

A planned update of the guidelines was necessary according to Association of the Scientific Medical Societies in Germany (“Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften”, AWMF) regulations, and was deemed rational on the basis of the national and international controversy regarding the in-

*The authors thank the members of the consensus group for their contributions to the recommendation of the guidelines. The recommendations of the guideline authors express the ones of the consensus group.
dications, benefits and risks of opioid-containing analgesic treatment of CNCP.

Methods

For the planned update of the guidelines, the steering committee formulated the following key questions in a Delphi procedure:

a) Key questions answerable by meta-analyses of randomized controlled clinical trials (RCTs) and of RCTs of open-label extension studies:
   - For which chronic non-cancer pain syndromes is there evidence for the efficacy of long-term therapy with opioid-containing analgesics?
   - How efficacious (pain reduction, improvement in physical function) are opioid-containing analgesics in long-term application?
   - How well tolerated (RCT dropout rate due to adverse effects) are opioid-containing analgesics in long-term application?
   - How safe (rate of serious adverse events and mortalities) are opioid-containing analgesics in long-term application?
   - Are certain individual opioid-containing analgesics superior in terms of efficacy, tolerability and safety in particular chronic pain syndromes?
   - Do different application forms (oral vs. transdermal) of opioid-containing analgesics differ in terms of efficacy, tolerability and safety in particular chronic non-cancer pain syndromes?
   - Are opioid-containing analgesics superior to nonopioid analgesics in terms of efficacy, tolerability and safety in particular non-cancer pain syndromes?
   - By which procedures can patients who cannot be expected to experience long-term clinically relevant pain relief from opioid analgesics be identified early?
   - By which procedures can patients who can be expected to experience long-term clinically relevant pain relief from opioid analgesics be identified early?
   - After which treatment duration is a benefit and harm assessment advisable, as the rational basis for decisions regarding continuation or termination of the therapy?
   - Are patients on stable doses of opioid-containing analgesics safe to drive?

b) Key questions answerable by cohort studies:
   - How frequent are other relevant adverse effects of long-term use of opioid-containing analgesics (e.g. medication, death from overdose, endocrinological alterations, falls)?
   - Are patients on stable doses of opioid-containing analgesics be considered?
   - In which clinical constellations is there evidence for the context of long-term application of opioid-containing analgesics?

C) Key questions relating to the clinical practice of long-term application of opioid-containing analgesics that are answerable by expert consensus (clinical consensus point) and extrapolation from other guideline recommendations (international guidelines for opioid therapy, national guidelines on various chronic pain syndromes):
   - Which criteria are to be considered during the selection of drugs for long-term therapy of CNCP?
   - In which clinical constellations can long-term application of opioid-containing analgesics be considered?
   - In which clinical constellations is long-term application of opioid-containing analgesics inadvisable?
   - In which clinical constellations is a specialist psychotherapeutic diagnostic assessment advisable in the context of long-term application of opioid-containing analgesics?
   - Which diagnostic measures are recommended prior to commencing long-term application of opioid-containing analgesics?
   - What issues should treating physicians make patients aware of prior to commencing long-term application of opioid-containing analgesics?
   - Which criteria are to be considered during the selection of individual opioid-containing analgesics for long-term application?
   - How should opioid-containing analgesics for CNCP be titrated?
   - Which measures are recommended for the prophylaxis and treatment of adverse events?

Is rescue medication rational in the context of long-term application of opioid-containing analgesics?
Is it rational to make attempts to reduce medication in the context of long-term application of opioid-containing analgesics?
Are treatment pauses (“drug holidays”) rational in the context of long-term application of opioid-containing analgesics?
How should the efficacy and tolerability of long-term application of opioid-containing analgesics be assessed and documented?
Which measures should be taken in response to an increase in pain in the context of long-term application of opioid-containing analgesics?
In which clinical constellations should long-term use of opioid-containing analgesics be discontinued?
How can abuse (misuse) of opioid-containing analgesics be recognized?
Which prophylactic measures are rational for avoiding abuse of opioid-containing analgesics?
Which measures are rational in the context of abuse (misuse) of opioid-containing analgesics?
Which particular elements (e.g. selection of the preparation, dosage, control examinations) are to be considered in the context of long-term use of opioid-containing analgesics by special patient groups (children, adolescents, pregnant women, elderly patients, patients with current medication abuse behavior/medication dependence)?

The methodology of the literature search and literature analyses, as well as that of recommendations development is described in the guidelines methodology report.

Results

The core recommendations of the guidelines are marked in blue and italicized font.

I. Preamble

1. Clinical consensus point – definition of opioid-containing analgesics: for reasons of
linguistic simplicity, the term opioid-containing analgesics will be used in the guidelines. Strong consensus

Commentary. The guidelines make position statements on selective opioid antagonists combined/not combined with substances that reduce constipation and abuse. They also make statements regarding substances with mixed opioidergic and nonopioidergic mechanisms of action in comparison to placebo and non-opioid-containing analgesics. In the case of substances with mixed opioidergic and nonopioidergic mechanisms of action, the guidelines addressed the substances buprenorphine (an opioid with agonistic effects on the μ-receptor and antagonistic effects on the κ-receptor), tramadol (μ-opioid receptor agonist and inhibitor of norepinephrine and serotonin reuptake) and tapentadol (μ-receptor agonist and norepinephrine reuptake inhibitor). Additional substances with mixed opioidergic and nonopioidergic mechanisms of action (e.g. ketamine), were not addressed, since these are not used for long-term therapy in Germany.

The selective opioid agonist propoxyphene is not considered because the drug has been withdrawn from the market.

Mixed preparations of opioids and nonopioids (e.g. codeine + paracetamol) are not considered in the guideline meta-analyses. A qualitative analysis was conducted for an RCT with tramadol plus paracetamol in fibromyalgia syndrome.

2. Clinical consensus point – definition of long-term application: Long-term application of opioid-containing analgesics is assumed for a treatment duration >3 months. Strong consensus

Commentary. There is no uniformly used international definition of long-term therapy with opioid-containing analgesics. In its “clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain”, the American Pain Society defined long-term application opioids as “Use of opioids to treat chronic pain on a daily basis, or near daily, for at least 90 days and often indefinitely” [90].

In meta-analyses of RCTs, the following treatment durations were selected as criteria for longer-term therapy with opioid-containing analgesics: “short-term”: 4–12 weeks; “intermediate-term”: 13–26 weeks; “long-term” >26 weeks [15]. A therapeutic duration ≥26 weeks is referred to in the guideline text as long-term therapy. Very-short-term studies (<4 weeks; [15]) were not included in the meta-analyses. Treatment lasting <4 weeks is rather classified as acute therapy.

In the systematic reviews and meta-analyses performed for the guidelines, the duration of therapy is defined by the sum of the days of the titration and maintenance phases (for studies with a parallel or cross-over design) or the withdrawal phase, for studies with an enriched enrollment randomized withdrawal (EERW) design. Washout, unblinded start (run-in), tapering and follow-up times are not included in the study duration.

3. Consensus-based statement: The objective of the guideline update is promotion of responsible use of opioid-containing analgesics by physicians, other health care professionals involved in treatment and patients during long-term therapy of chronic noncancer pain by

- naming possible indications for and contraindications to treatment with opioid-containing analgesics,
- practice-orientated tips for administering and discontinuing therapy with opioid-containing analgesics.

Strong consensus

4. Consensus-based statement: The guidelines make position statements on indications and contraindications, as well as on administration of a 2-4 week therapy with opioid-containing analgesics. Regarding
the value of opioid-containing analgesics in comparison to other drug-based and non-drug-based treatment options in chronic pain syndromes, the guidelines refer to the German S3 guidelines for the corresponding clinical picture or, where these are not available, to international guidelines of a level corresponding to German S3 guidelines. Strong consensus.

5. Evidence-based statement: Prescriptions of opioid-containing analgesics for patients with noncancer pain in Germany have increased during recent years. EL3b. Strong consensus

Commentary. Studies employing health insurance data indicate an increase in long-term prescrptions of opioids for patients with chronic noncancer pain (CNCP) in Germany during recent years. Among members of the Barmer Ersatzkasse BEK insurance scheme with noncancer diagnoses, the “defined daily dosages” (DDD) of weak opioids increased from 18,035,000 in 2006 to 19,744,000 in 2009 (+9.5%); for strong opioids from 9,363,000 to 12,647,000 in 2009 (+35.1%). The number of prescriptions for weak and strong opioids for more than one quarter rose from 1.99% (2006) to 2.11% (2009) among members of the BEK insurance scheme with noncancer diagnoses [95].

In analyses of data from the Allgemeinen Ortskrankenkasse AOK and the Kassenärztlichen Vereinigung Hessen health insurance providers, 5.3% of members with a noncancer diagnosis received at least one prescription for an opioid-containing analgesic in 2000; in 2010 this figure was 6.9%. Among these opioid-receiving CNCP patients, opioids were prescribed in each quarter of 2001 in 8.8% and in 2009 in 12.8%; the proportion of long-term treatments (>90 days with up to 30 days of interruptions to therapy) was 4.3% in 2001 and 7.5% in 2009 [81].

The number and the duration of prescriptions do not allow any conclusions to be made regarding possible under-, over- or inappropriate treatment.

6. Evidence-based statement: There are indications of inappropriate treatment with opioid-containing analgesics in individual clinical pictures in Germany. EL3b. Strong consensus

Commentary. No studies demonstrating undertreatment of CNCP in Germany are known to the authors. There are indications pointing to non-guideline-conform treatment with strong opioids in patients with functional/somatoform disorders in Germany. Among BEK members, 11% of patients with a fibromyalgia diagnosis (M 79.7) picked up prescriptions for narcotic strong-opioid analgesics in at least one quarter during the period 2008–2009. The S3 guidelines on fibromyalgia syndrome advise strong opioids [84]. Among member of the BEK/GEK (Gmünder Ersatzkasse) health insurance schemes, 23% with a somatoform pain disorder diagnosis received at least one prescription for strong opioids in 2009 [37]. The S3 guidelines on functional/somatoform physical symptoms advise strong opioids [23].

Patients with somatoform pain disorders or with a high psychosocial contribution to pain symptoms report high pain intensity and psychological strain. This can mislead treating physicians to prescribe opioids, which are considered to be the "strongest" painkillers [51].

According to a study conducted by the BARMER GEK health insurance provider, the prescription rate of WHO class II opioids for headache diagnoses made up 15.9% of all opioid prescriptions among members of the BARMER health insurance scheme from 2006 to 2010; for prescriptions of WHO class II opioids, this figure was 7.5% [95]. The Deutsche Migräne- and Kopfschmerzgesellschaft (German Migraine and Headache Society) guidelines advise opioid-containing analgesics for acute pain therapy, tension-type headaches and migraine recurrence prophylaxis [18, 19].

II. Possible indications for and contraindications to treatment with opioid-containing analgesics

Introductory remarks. The formulation “treatment option” in the following sections means that opioid-containing analgesics are one of the possible different types of therapy. The figures for therapy duration are based on the duration of the analyzed randomized trial. For long-term application (≥3 months), the authors refer to section II of these of these guidelines “Possible indications for and contraindications to treatment with opioid-containing analgesics”, recommendation number 8.

Possible indications

1. Evidence-based recommendation – diabetic polyneuropathy (ICD-10 G63.2*): Opioid-containing analgesics shall be offered as a treatment option for a duration of 4–12 weeks. EL1a, strong recommendation. Consensus

There are no grounds for a reduction in recommendation strength.

Commentary. RCTs with oxycodone, tapentadol and tramadol are available. Three studies with 380 patients and a parallel or cross-over design, and one study with 389 patients and an EERW design with study duration of 4–12 weeks have been performed. Opioid-containing analgesics were superior to placebo in terms of reduction of pain and perceived physical impairment, but inferior in terms of tolerability [85].

The national care guidelines ("Nationale Versorgungsleitlinie", NVL) on diabetic neuropathy in adults ("Neuropathie bei Diabetes im Erwachsenenalter") state: “No study demonstrates that particular substances with proven analgesic effects are first-choice treatment. Treatment algorithms based predominantly on expert consensus exist for the treatment of neuropathic pain. Most guidelines recommend that antidepressants or anticonvulsants be preferred, and that opioids only then be used if the aforementioned substance groups, either alone or in combination, have failed. There is as little evidence for this recommendation as for the decision to first apply an antidepressant or an anticonvulsant. Deviating from this, an opioid can also be given as the first-choice painkiller if a comorbidity (e.g. cardiac dysrhythmia, patient clearly over-weight) speaks against primary use of other (co)analgesics which, like TCAs or pregabalin, can cause weight gain or card-
ac dysrhythmia." The NVL recommends tricyclic antidepressants (TCAs), duloxetine and pregabalin as equally valuable drug-based treatment options. Methadone, morphine, oxycodone and tramadol are named as opioid-containing analgesics for which evidence from controlled studies is available [12].

The systematic literature search performed for the update of the LONTS found no RCTs that demonstrated significantly superior efficacy and tolerability of a particular substance class. In one RCT including patients with painful diabetic polyneuropathy and postherpetic neuralgia, no significant difference was found between morphine and gabapentin in terms of efficacy and tolerability [94].

A Cochrane review on oxycodone in neuropathic pain [31] published after the systematic literature search for the update of the LONTS included two oxycodone studies that were also included in the meta-analysis on neuropathic pain performed for the LONTS update [85]. The authors found oxycodone to be superior in terms of pain reduction, but inferior to placebo in terms of tolerability. The authors note that all studies had at least a high risk of systematic bias [31]. The results of the Cochrane review and those of the systematic review performed on neuropathic pain syndromes for the update of the LONTS pertaining to oxycodone are in agreement.

2. Evidence-based recommendation – postherpetic neuralgia (ICD-10 B02.2+): Opioid-containing analgesics can be offered as a treatment option for 4–12 weeks in a) Phantom pain (ICD-10 G54.6). EL2b, open recommendation. Strong consensus b) Pain following spinal cord injury. EL2b, open recommendation. Strong consensus c) Painful radiculopathy (ICD-10 M54.1). EL2b, open recommendation. Strong consensus d) Polyneuropathy of etiology other than diabetes or postherpetic neuralgia (e.g. HIV, drug-induced, alcoholic) (ICD-10 G63.-*): An individual attempt at therapy can be considered. EL5, open recommendation. Strong consensus

Explanation of the reasons for lowering the strength of the recommendation by two grades. Efficacy in terms of perceived physical impairment is not certain; <400 patients in the meta-analysis.

Commentary. Three RCTs with a parallel or cross-over design (morphine, oxycodone, tramadol) and 323 patients, with a median study duration of 6 (4–8) weeks are available. Opioid-containing analgesics were superior to placebo in terms of pain reduction, but not in terms of perceived physical impairment. Opioid-containing analgesics were inferior to placebo in terms of tolerability [87].

Direct comparisons of opioid-containing analgesics with non-opioid-containing analgesics (gabapentin, nortriptyline) revealed no differences in efficacy, safety or tolerability (see evidence-based statement on comparison of opioid- vs. non-opioid-containing analgesics [94]).

No German S3 guidelines on postherpetic neuralgia are available. In a review on postherpetic neuralgia guidelines, tricyclic antidepressants, gabapentin, pregabalin and lidocaine 5% plasters were named as first-line drug-based treatment options. Opioids, tramadol and capsaicin cream and plasters were named as second-line treatment options [34].

3. Evidence-based recommendation – other neuropathic pain syndromes of various etiologies: Opioid-containing analgesics can be offered as a treatment option for 4–12 weeks in a) Phantom pain (ICD-10 G54.6). EL2b, open recommendation. Strong consensus b) Pain following spinal cord injury. EL2b, open recommendation. Strong consensus c) Painful radiculopathy (ICD-10 M54.1). EL2b, open recommendation. Strong consensus d) Polyneuropathy of etiology other than diabetes or postherpetic neuralgia (e.g. HIV, drug-induced, alcoholic) (ICD-10 G63.-*): An individual attempt at therapy can be considered. EL5, open recommendation. Strong consensus

Explanation of the reasons for lowering the strength of the recommendation by one grade in phantom pain, pain following spinal cord injury and radiculopathy. Number of patients per disease in meta-analysis <400.

Commentary. One study with a median duration of 5 (4–6) weeks had been performed for each of the following: phantom pain, pain following spinal cord injury, painful radiculopathy and painful polyneuropathies of various etiologies. The number of patients per study was between 50 and 159. In the case of radiculopathy, no significant differences between morphine and placebo were found in terms of reduction of pain reduction and perceived physical impairment. In phantom pain (test substance: morphine) and pain following spinal cord injury (substance tested: tramadol), opioid-containing analgesics were superior to placebo in terms of pain reduction, but not in terms of perceived physical impairment. The rate of dropout due to adverse events was higher in the treatment groups than in the placebo group [85]. Despite the lack of superiority of morphine over placebo in the RCT on radiculopathy, an open recommendation was made. This open recommendation was made due to the fact that in several RCTs with opioid-containing analgesics in chronic back pain [66], in the RCT directly comparing opioid-containing analgesics [47] and in the open-label extension studies [39], patients with nociceptive/neuropathic (radicular) pain were also included, and these studies provided indications for the efficacy of opioid-containing analgesics.

No German S3 guidelines on phantom pain and nondiabetic polyneuropathies are available. The European Federation of Neurological Societies Task Force made no specific recommendations for these clinical pictures in its guidelines. Tramadol and other opioid-containing analgesics, tricyclic antidepressants, gabapentin, pregabalin and lidocaine 5% plasters were named as treatment options [8].

The S3 guidelines on epidural spinal cord stimulation make the following recommendation: if attempts at multimodal conservative treatment of failed back surgery syndrome with radiculopathy remain unsuccessful, treatment with epidural spinal cord stimulation combined with continued intensive physical therapy should be offered [20].

Controlled studies on opioid-containing analgesics in polyneuropathies of etiologies other than diabetes or postherpetic neuralgia (e.g. HIV, drug-induced, alcoholic) were not identified by the systematic literature search.
Evidence-based recommendation – chronic osteoarthritis pain (ICD-10 M15–M19): Opioid-containing analgesics can be offered as a treatment option for a duration of 4–12 weeks. ELJa, open recommendation. Strong consensus

Explanation of the reasons for lowering the strength of the recommendation by two grades. No superiority over placebo in terms of 50% pain reduction; unfavorable risk-benefit ratio in comparison to nonsteroidal antiinflammatories (NSARs) during the study period (see evidence-based statement on comparison of opioid- vs. non-opioid-containing analgesics; [94]).

Commentary. Sixteen RCTs with a parallel or cross-over design and four RCTs with an EERW design, with a total of 8545 patients had been performed. Seven RCTs had a study duration >12 weeks (range: 13–24 weeks). The substances tested were buprenorphine, codeine, fentanyl, hydromorphone, morphine, oxycodone, oxymorphone, tapentadol and tramadol. Opioid-containing analgesics were superior to placebo in terms of reduction of pain and perceived physical impairment, but inferior in terms of tolerability [79].

In direct comparisons, NSARs were superior to tramadol in terms of efficacy (pain intensity, perceived physical impairment; [94]). In a retrospective cohort study of geriatric patients with osteoarthritis and rheumatoid arthritis, taking of opioids but not of NSAR/c Coxibs was associated with an increased mortality risk [83]. It is possible that these study results are distorted due to taking of freely purchasable NSARs and more severely ill patients in the opioid group.

In clinical practice, treatment with NSARs is frequently contraindicated by a patient’s comorbidities (e.g. cardiovascular disease, renal insufficiency, history of ulcers) [5]. The German S3 guidelines on coxarthrosis name physiotherapy (recommendation grade C) as an additional treatment option in coxarthrosis. Opioid-containing analgesics can be used in cases of severe pain [21].

Evidence-based recommendation – chronic back pain: Opioid-containing analgesics can be offered as a treatment option for 4–12 weeks. ELJa, open recommendation. Strong consensus

Explanation of the reasons for lowering the strength of the recommendation by two grades. Limited relevance of several effect sizes [66]. Better risk–benefit ratio of non-drug-based procedures [40, 93].

Commentary. Eleven RCTs with 4575 participants had been performed with buprenorphine, hydromorphone, morphine, oxycodone, tapentadol and tramadol (six RCTs with a parallel or cross-over design and four RCT with an EERW design). Three RCTs had a study duration of >12 weeks (range: 13–15 weeks). Opioid-containing analgesics were superior to placebo in terms of reduction of pain and perceived physical impairment, but inferior in terms of tolerability [66]. The diagnostic classification of back pain etiology in the eleven RCTs excluded specific causes in most studies.

In a direct comparison, a cyclooxygenase (COX) 2 inhibitor was superior to tramadol in terms of efficacy and tolerability. In two studies lasting 6 weeks, celecoxib 200 mg and tramadol 100 mg/d were administered to 796 and 802 patients, respectively. Celecoxib was superior to tramadol in terms of the frequency of 30% pain reduction (study 1: 63.2% vs. 49.9%; study 2: 64.1% vs. 55.1%) and in terms of the rate of dropout due to adverse events (study 1: 1.2% vs. 13.4%; study 2: 1.0% vs. 10.6%) [62].

A systematic review of 61 RCTs with 6390 patients demonstrated a reduction in pain and perceived physical impairment brought about by medical exercise therapy during follow-up [40]. A systematic review of 18 RCTs demonstrated positive effects of multimodal rehabilitation treatment on perceived physical impairment and return to work [93].

The risk difference (to placebo) for the rate of 50% pain reduction was 5%, and was as such below the a priori defined limit of 10% for a relevant difference in studies with a parallel and cross-over design. In terms of the frequency of reports of pronounced or very pronounced global improvement, no significant differences to placebo were found in studies with parallel and cross-over designs. The a priori defined standardized mean difference (SMD) limit of ≥0.2 (to placebo) was reached for perceived physical impairment in studies with parallel and cross-over designs (SMD: −0.22 [−0.31; −0.12]; p<0.0001). However, two studies without a significant difference to placebo could not be included in the meta-analysis because means and standard deviations were not reported. The SMD is thus very probably <0.2 [66].

The NVL guidelines on back pain make no clear recommendation on longer-term (≥4 weeks) treatment with opioid-containing analgesics. These guidelines recommend reevaluation of treatment with opioid-containing analgesics after 4 weeks at the latest in the case of acute nonspecific pain, and after 3 months at the latest in chronic nonspecific back pain. If the desired pain reduction/improvement in function is not observed, continuation of treatment with opioid-containing analgesics is contraindicated. The NVL guidelines strongly recommend multimodal programs in situations where drug-based, physical and physiotherapeutic approaches have been insufficiently effective [13].

The S3 guidelines recommend epidural spinal cord stimulation in failed back surgery syndrome with predominant radicular pain where conservative procedures have failed and psychological contraindications are excluded [20].

Evidence-based recommendation – rheumatoid arthritis (ICD-10 M06–): Opioid-containing analgesics can be offered as an option for symptomatic treatment of pain for a limited period of time (up to 6 weeks). ELJb, open recommendation. Consensus

Explanation of the reasons for lowering the strength of the recommendation by one grade. Number of patients in the study<400.

Commentary. In one RCT lasting 6 weeks, 20 rheumatoid arthritis patients were treated with tilidine/naloxone for 6 weeks. At the end of therapy, 11 patients in the treatment group reported a lower pain intensity than the 8 patients in the placebo group (p=0.05; no intention-to-
treat analysis). In the tilidine group, 5 patients discontinued therapy prematurely (2 due to insufficient effect, 3 due to adverse events). In the placebo group, 2 patients discontinued therapy prematurely due to insufficient effect. Since the study had <20 patients per study arm [11], it was not included in the meta-analyses performed for the update of the LONTS.

A Cochrane review pooled seven studies together (dextropropoxyphene, codeine, tramadol, tilidine, pentazocine, morphine, either as monotherapy or combined with nonopioid analgesics). Study duration was between 1 and 6 weeks. The only study with a duration ≥4 weeks was the aforementioned study with tilidine. Opioids were superior to placebo in terms of the frequency of reports of general condition to be much or very much improved (three studies, 324 participants: relative risk, RR: 1.44; 95% CI: 1.03; 2.03). Opioid-containing analgesics and placebo did not differ in terms of tolerability. The RR for dropout due to adverse events was 2.67 (three studies, 331 participants; 95% CI: 0.52; 13.75). One study compared codeine/paracetamol with diclofenac and found no significant differences in efficacy and tolerability [96].

The S3 guidelines on management of early rheumatoid arthritis (RA) recommend application of NSARs for symptomatic treatment of pain. Application of opioid-containing analgesics for symptomatic treatment of pain in RA patients should represent the exceptional case, particularly among patients in early stages of disease. The indication should only be established after exhaustion of all other named treatment options. In exceptional cases and where NSARs are contraindicated, application of opioid-containing analgesics may be justified even in patients in early stages of disease [24].

7. Evidence-based recommendation – long-term therapy (≥6 months): Opioid-containing analgesics can be offered as a long-term treatment option in patients with chronic back pain, chronic osteoarthritis pain and chronic neuropathic pain (polyneuropathies of various etiologies, postherpetic neuralgia), who have experienced a clinically relevant reduction in pain and/or perceived physical impairment from treatment administered for a limited period (4–6 weeks), with absent or mild adverse events. EL3a, open recommendation. Strong consensus

Commentary. This recommendation is based on two randomized open studies of ≥52 weeks in which two opioids were compared [2, 97] and one meta-analysis of eleven open-label extension studies of RCTs with a duration of at least 2 weeks. The studies were performed with buprenorphine, fentanyl, hydromorphone, morphine, oxycodone, oxymorphone, tapentadol and tramadol [39].

In one of the open controlled studies, 675 patients with chronic back pain (nociceptive, neuropathic, mixed nociceptive/neuropathic) received transdermal fentanyl or oral morphine for 13 months. Of patients in the fentanyl group, 37% (40%) reported a 50% reduction in pain at rest (during movement) at the end of treatment, as did 37% (50%) of the patients in the morphine group. Physical function (SF-36, physical functioning) improved significantly on average in both groups (p<0.0001; from 29 to 37 on a scale of 0 to 100, where “0” represents the worst score and “100” the best). The rate of dropout due to adverse events was 37% for fentanyl and 31% for morphine. No mortalities or cases of dependence behavior were observed [2].

In a 52-week open controlled study, 1117 patients with chronic back or osteoarthritis pain received either tapentadol or oxycodone. The average mean (standard error) pain intensities in the tapentadol and oxycodone groups at the start of the study were 7.6 (0.05) and 7.6 (0.11), respectively. These values fell to 4.4 (0.09) and 4.5 (0.17), respectively, at the end of the study. Of patients in the tapentadol group, 48.1% (394/819) reported global condition to be much or very much improved, whereas this figure was 41.2% (73/177) for patients in the oxycodone group. The rate of dropout due to adverse events was 23% in der tapentadol group and 37% in the oxycodone group. No mortalities or cases of dependence behavior were observed [97].

Eleven open-label extension studies of placebo-controlled RCTs with 2445 participants with nociceptive pain (back pain, osteoarthritis) and neuropathic pain (radiculopathy, polyneuropathy) were included in the meta-analysis. Median study duration was 26 (26–108) weeks. Four studies investigated oxycodone, two tramadol, and buprenorphine, hydromorphone, morphine, oxymorphone and tapentadol were each investigated in one study. Of the patients randomized at the start of the study, 28.5% finished the open-label phase; 49.9% discontinued the open-label phase prematurely due to insufficient pain relief and 16.8% discontinued the open-label phase prematurely due to adverse events. During the open-label phase, 0.08% of patients died. Only one study systematically investigated opioid abuse: in the opinion of the study director, 5.7% of patients fulfilled the criteria for opioid abuse, whereas in the opinion of independent experts, 2.6% of the patients fulfilled these criteria [39].

8. Evidence-based statement: For other diseases with the cardinal symptom chronic pain, no placebo-controlled RCTs with a study duration ≥4 weeks and ≥20 patients per study arm or recommendations from German guidelines on symptomatic treatment of pain were found. Strong consensus

Commentary. In a 12-week study of 306 restless legs syndrome patients who had not responded to previous treatment with dopamine agonists or who had experienced only a partial response; or in whom intolerance or contraindications to dopamine agonists were present, oxycodone/naloxone was superior to placebo in terms of pain reduction (a secondary therapeutic goal) [89].

Consensus-based recommendation – individual therapeutic approach: For all other types of chronic noncancer pain (see below), treatment with opioid-containing analgesics is to be considered an individual therapeutic approach, due to insufficient data. Possible indications for short-term (4–12 weeks) and long-term (>26 weeks) treatment with opioid containing analgesics are:

9. Certain types of secondary headache (e.g. in the case of vascular diseases and nonvascular intercranial disorders) (ICD-10 G44.8). Consensus
10. Chronic pain associated with manifest osteoporosis (vertebral fractures) (ICD-10 M80.-). Strong consensus

11. Chronic pain associated with other inflammatory rheumatic diseases apart from rheumatoid arthritis (e.g. in systemic lupus erythematosus, spondylarthritides) (ICD-10 M45–M49). Strong consensus

12. Chronic postoperative pain (e.g. post-thoracotomy, poststernotomy, postmastectomy pain syndrome, following abdominal and hernia surgery, following facial surgery). Strong consensus

13. Chronic pain in the extremities associated with ischemic and inflammatory arterial occlusive disease (ICD-10 I70–I79). Strong consensus

14. Chronic pain associated with decubitus grades 3 and 4 (ICD-10 L89.2- and L89.3-). Strong consensus

15. Chronic pain associated with fixed contracture in patients in care. Consensus

16. Central (cerebral) neuropathic pain (e.g. following thalamus infarction, multiple sclerosis). Strong consensus

17. Chronic complex regional pain syndrome (CRPS) types I and II. Strong consensus

Commentary. The abovementioned indications have not been proven by controlled studies; nor are there clear indications of damage or negative effects; nor are there negative statements in other guidelines. The statements regarding the practice of opioid therapy explained in part III are particularly valid for an individual treatment approach.

For treatment of pain in dementia patients, we would refer to the literature [17, 80].

Contraindications

18. Evidence-based statement – primary headaches (ICD-10 G43.x, G44.0, G44.2, G44.8; headache without accompanying structural lesion): All primary headaches should not be treated with opioid-containing analgesics. EL3b, negative recommendation. Strong consensus

Reasons for raising the grade of the negative recommendation. Negative risk–benefit ratio of opioid-containing analgesics; ethical obligations.

Commentary. The S1 guidelines on migraine states in a commentary that tramadol in combination with paracetamol has shown efficacy in the treatment of acute migraine attacks. However, opioid-containing analgesics and tranquilizers should not be used to treat migraine attacks. Opioid-containing analgesics have limited efficacy, frequently cause vomiting, have a high potential for dependence development and underuse of medication leads to headache relatively quickly [18].

The S1 guidelines on tension-type headache states in a commentary that retrospective analyses of patients with chronic daily headaches who received opioid-containing analgesics showed that the majority of patients discontinued treatment, due to lack of efficacy or intolerable adverse events of opioid-containing analgesics, or because of increased use of medication. However, it is possible that a small subgroup exists who did profit from lasting benefits of this treatment. Due to their high potential for causing dependence development and indications of further chronicization of headaches during treatment with opioid-containing analgesics in the sense of medication-induced headaches, the guideline committee considers the use of opioid-containing analgesics for treatment of headaches to be strictly not indicated [19].

19. Clinical consensus point: Pain associated with functional/somatoform disorders (ICD-10 F45.-) should not be treated with opioid-containing analgesics. Strong consensus

Commentary. The S3 guidelines on irritable bowel syndrome (IBS) make a negative recommendation for opioid-containing analgesics for the treatment of IBS. A recommendation is made for antidepressants (tricyclic antidepressants and serotonin reuptake inhibitors, SSRI), spasmyloytics and dietary fiber [48].

The S3 guidelines on FMS make a strong negative recommendation for strong opioids. In terms of drug-based treatments, amitriptyline and—in the case of depression and anxiety disorder comorbidities—duloxetine are recommended [84].

The S2k guidelines on lower abdominal pain in women state in a commentary that treatment with opioid-containing analgesics should not take place. Antidepressant medication may be rational; particularly where a psychological comorbidity is present [22].

The S3 guidelines on nonspecific/functional/somatoform physical symptoms recommend that in patients treated with opioid-containing analgesics, an attempt be made at withdrawal [23].

20. Evidence-based recommendation – fibromyalgia syndrome (ICD-10 M79.7)

a) Opioid-containing analgesics should not be offered as a treatment option in fibromyalgia syndrome. EL4a, negative recommendation. Strong consensus

b) Tramadol and tramadol paracetamol can be considered as a treatment option for a limited period of time (4–12 weeks). EL2b, open recommendation. Consensus

Commentary. No controlled studies with opioid-containing analgesics without inhibition of norepinephrine and serotonin are available. In one case series, 16 patients received transdermal fentanyl 75 mg/h for 72 h, over a period of 4–8 weeks. No significant reduction in pain or limitations to quality of life could be identified. All patients reported adverse events (confusion, nausea, vomiting). Out of 16 patients, 7 discontinued treatment prematurely [14]. In a prospective cohort study conducted in a Canadian pain center, 151 patients with and without opioid treatment were monitored for a follow-up period of 2 years. Pain intensity and perceived physical impairment improved in patients with and without opioid treatment. Patients with opioid treatment were more frequently unemployed at the end of the study than patients without opioids [27].

In a 1-year US cohort study with 1700 FMS patients, three groups were differentiated on the basis of their medication...
at the start of the study: without opioids; with tramadol; and with opioids without tramadol. At the end of the study, patients in the no opioid and tramadol groups had more favorable results for most outcome variables (pain intensity, health-related quality of life, psychological wellbeing, sleep quality) than did the opioid group [64]. Both the German and the Canadian guidelines made a negative recommendation for strong opioids in FMS. The German FMS guidelines make a strong recommendation for moderate aerobic exercise, cognitive behavioral therapy, meditative exercise therapy (tai-chi, yoga), multimodal therapy (combination of exercise therapy with cognitive behavioral therapy or relaxation techniques) and low-intensity strength training [1].

One placebo-controlled RCT with tramadol, an EERW design and 69 patients was performed over a period of 6 weeks [75]. One placebo-controlled RCT with a parallel design was performed with tramadol/paracetamol in 315 patients over a period of 12 weeks [9]. Tramadol and tramadol/paracetamol were superior to placebo in terms of pain reduction and the frequency of pronounced pain reduction (“a lot of pain relief”). Tramadol/paracetamol was superior to placebo in terms of reduction of perceived physical impairment. Tramadol and tramadol/paracetamol led to increased rates of dropout due to adverse events compared to placebo.

The positive effect of tramadol is possibly due to inhibition of norepinephrine and serotonin uptake. Norepinephrine/serotonin reuptake inhibitors are superior to placebo in terms of pain reduction in FMS [36].

In FMS there is a more favorable risk–benefit ratio, as well as evidence of a sustained positive affect, for aerobic training [35] and cognitive behavioral training [10] performed after completion of treatment.

21. Clinical consensus point: Chronic pain as a (cardinal) symptom of psychiatric disorders (e.g. depression, ICD-10 F43.2, F32, F33; sustained somatoform pain disorder, ICD-10 F45.40; generalized anxiety disorder, ICD-10 F41.1; postraumatic stress disorder, ICD-10 F43.1) should not be treated with opioid containing analgesics. Consensus.

Commentary. In both outpatient (general practitioners and specialist physicians) and inpatient care, some patients with psychiatric disorders place chronic pain and not psychological symptoms at the forefront when describing their symptoms. A psychiatric disorder as the cause of chronic pain can often only be identified by extensive investigation (e.g. by a specialist psychiatric and psychotherapeutic physician, a physician specialized in psychosomatic medicine, psychosomatic psychotherapists) and/or case course (e.g. remission of pain following psychiatric-psychotherapeutic treatment of a depressive disorder).

22. Evidence-based recommendation – chronic pancreatitis (ICD-10 K86.-): Opioid-containing analgesics should not be offered as a treatment option for ≥4 weeks. EL2b, negative recommendation. Strong consensus.

Commentary. The German guidelines on chronic pancreatitis recommend symptomatic treatment of pain according to the WHO grading system [54]. However, there are indications that opioid-containing analgesics are not effective in the treatment of chronic pancreatitis. In an open randomized cross-over study, 18 patients with chronic pancreatitis were treated for 4 weeks with either fentanyl (average study dose 36 µg/d) or delayed release morphine (average study dose 128 mg/d). All patients had been pretreated with opioid-containing analgesics (no doses reported). No washout phase was included. Neither drug led to a significant pre–post reduction in pain intensity or improvement in physical function. Two patients withdrew from the study due to adverse events [60].

A sustained reduction in pain can be achieved in a proportion of patients by surgical and interventional endoscopic procedures [54]. In a 3-week placebo-controlled RCT with 64 patients, use of pregabalin was more frequently associated with effective pain reduction than use of placebo (36% vs. 24%, p<0.02). There were no differences in terms of physical function and safety [63].

23. Evidence-based recommendation – chronic inflammatory bowel diseases (ICD-10 K50.- und K51.-): Opioid-containing analgesics should not be offered as a treatment option for ≥4 weeks. EL3b. Strong consensus.

Commentary. No controlled studies are available on symptomatic treatment of pain with analogues in the chronic inflammatory bowel diseases ulcerative colitis and Crohn’s disease. The German guidelines recommend metamizole, paracetamol or opioids for a limited period of time (no exact duration given) for symptomatic treatment of acute-phase pain. Longer-term (no exact duration given) application of opioids for symptomatic treatment of pain is not recommended, due to the associated risks [43]. In a retrospective and embedded cohort study with 4856 patients, use of narcotics was an independent predictor of pneumonia (OR: 2.28; 95% CI: 2.09–2.48; [50]).

24. Consensus-based recommendation – irresponsible use of opioid-containing analgesics: In cases of current harmful use of prescription drugs or their transfer to an unauthorized person and/or serious doubts concerning responsible use of opioid-containing analgesics (e.g. uncontrolled taking of medication and/or sustained lack of readiness or inability to adhere to the treatment plan), no treatment should be initiated. Strong consensus.

25. Consensus-based recommendation – severe affective disorder (ICD-10 F32–34) and/or suicidality (ICD-10 R45.8): In case of severe affective disorder and/or suicidality, treatment with opioid-containing analgesics should not be initiated. Strong consensus.

III. Practical aspects of opioid treatment

Introductory remarks. One quality criterion of guidelines is the provision of materials that facilitate easy implementation of the guideline recommendations in daily clinical practice. These materials should be simple and—wherever possible—available at minimal costs [3]. Therefore, for several of the following recommenda-
tions, so-called practice tools for treating physicians are detailed. These practice tools were suggested by members of the steering and consensus committees.

A. Measures prior to inducing treatment with opioid-containing analgesics

1. Clinical consensus point – participatory decision making: In the context of participatory decision making, the possible risks and benefits of treatment with opioid-containing analgesics compared to other drug-based and non-drug-based treatment options should be discussed with the patient. Strong consensus

Commentary. Relevant individual risks should be detailed during the informative discussion with the patient, e.g. risk of falls and confusion in older patients or loss of libido in younger patients.

2. Clinical consensus point – choice of pharmacotherapy: Selection of the pharmacotherapy should consider the chronic pain syndrome in question, the patient’s comorbidities, contraindications, the patient’s preferences, benefits and harmful effects of previous treatments, as well as the risk–benefit profiles of drug-based and non-drug-based treatment alternatives. Strong consensus

Commentary. In the case of the decision being made for drug-based symptomatic treatment of pain, the following aspects can be considered when addressing the question of whether to use an opioid-containing or a non-opioid-containing painkiller (the statements relate to the correspondingly investigated study period):

a) In osteoarthritis pain, NSARs are superior to the opioid-containing analgesic tramadol in terms of reduction of pain and perceived physical impairment. NSARs are better tolerated in osteoarthritis pain than the opioid-containing analgesic tramadol. In terms of safety, there are no significant differences between the opioid-containing analgesic tramadol and non-opioid-containing analgesics in osteoarthritis pain [94].

b) In neuropathic pain syndromes, there is no difference between opioid-containing analgesics and non-opioid-containing analgesics (anticonvulsants, antidepressants) in terms of reduction of pain and perceived physical impairment. In neuropathic pain, non-opioid-containing analgesics are better tolerated than opioid-containing analgesics. In terms of safety, there are no significant differences between opioid-containing analgesics and non-opioid-containing analgesics in neuropathic pain [94].

Ten RCTs with 3046 participants were included in a meta-analysis of direct comparisons between opioid-containing vs. non-opioid-containing painkillers. Median study duration was 6 weeks (minimum 4, maximum 12 weeks). Tramadol was compared to NSAR in chronic osteoarthritis pain in five studies and to flupirtine in chronic back pain in one study. In various neuropathic pain syndromes, morphine was compared to antidepressants in two studies, to the anticonvulsant gabapentin in one study and to the antiarrhythmic agent mexiletine in one study. In neuropathic pain there were no differences between the substance classes in terms of reduction of pain and perceived physical impairment. The rate of dropout due to adverse events was higher for opioid-containing analgesics. In chronic osteoarthritis pain, NSARs and flupirtine were superior to tramadol in terms of pain reduction, perceived physical impairment and tolerability (dropout rate due to adverse events) [94].

According to a “Rote-Hand-Brief” from 15.07.2014, flupirtine is only indicated for treatment of acute pain in adults, due to its potential hepatotoxicity. Flupirtine may only be applied in cases where treatment with other analgesics (e.g. NSARs, weak opioids) is contraindicated. The duration of flupirtine application must not exceed 2 weeks [4].

In light of current debate on the cardiovascular and gastrointestinal safety of NSARs, their long-term administration for osteoarthritis pain is problematic in this patient group [5].

3. Clinical consensus point – monotherapy with opioid-containing analgesics. Treatment with opioid-containing analgesics alone should not be performed in chronic non-cancer pain syndromes. Self-help programs and physical and/or psychotherapeutic methods and/or psychotherapeutic methods (including patient education) and/or lifestyle modifications should complement drug-based pain therapy. Strong consensus

Commentary. The choice of non-drug-based treatment should concord to existing German guidelines for the corresponding disease with cardinal symptom chronic pain.

4. Clinical consensus point – case history and clinical status: General case history, dependence- and pain-related case history, as well as the physical and psychological status of the patient should be determined and documented. Strong consensus

Commentary. General case history:

- Past medical history and surgery, comorbidities, allergies, psychiatric disorders including substance abuse or dependence
- Thorough history of medication (including drug interactions and adverse events, taking habits)
- Careful physical examination including a functional musculoskeletal examination; neurological and, where appropriate, neurophysiological examination
- Evaluation of current level of function
- Where appropriate, diagnostic nerve blocks; where appropriate, urine and other laboratory tests to assess non-reported use of illegal substances, alcohol and medication
- Where appropriate, special diagnostic procedures relating to diseases and states that could represent limitations to the application of opioid-containing analgesics
- Establishment that pain is a type of CNCP in which the application of opioid-containing analgesics can be considered
Pain-related case history:
- Pain intensity described on a numerical or visual analog scale, with reports on “momentary pain”, “least and most severe pain during the past week” and “average pain during the past week(s)”
- Type of pain and possible underlying diseases
- Location, duration, variability and character of pain
- Causes of pain as presumed by the patient
- Adjustment to past medication (pain intensity after use, duration of pain relief, all adverse events)
- Manifestations of pain in behavior and expression of the patient
- Evaluation of the social environment, family, social amplifiers, pension application situation, employment situation etc.
- Stress/strain resulting from pain
- Evaluation of pain-related functional impairments
- Current professional activities and hazards at work
- Current and past drug-based and other pain treatments
- Expectations of pain treatment

Evaluation of level of function:
- Cognitive function (alertness, concentration, memory)
- Professional activities or ability to work
- Vitality, maintenance of social contacts
- Sleep
- Mobility
- Sexual function
- Self-mindfulness
- Housework, hobbies, activities

Practice tools:
- German version of the Brief Pain Inventory (BPI)
- Recommendations for assessment of elderly patients in German-speaking territories

5. Clinical consensus point – psychosocial case history: Documentation of psychosocial case history and screening for current and/or past psychiatric disorders should be performed by the treating physician. Consensus

Commentary. The psychosocial case history should assess current psychosocial stresses and strains (e.g. work, family). Screening for psychiatric disorders should assess increased depression, anxiety, the burden of physical symptoms and substance abuse.

A multimodal pain therapy treatment necessitates interdisciplinary diagnostic assessment within at least two specialist areas. One specialist area is obligatorily a psychiatric or psychosomatic or psychological-psychotherapeutic discipline (see “Operationen- und Prozedurenschlüssel”, OPS 8.91x [25]).

Practice tools:
- Screening instrument for anxiety and depression PHQ 4 (German)
  http://commons.wikimedia.org/wiki/File:PHQ-4.TIF
- Screening for alcohol dependence:
  a) Audit-C questionnaire (German),
  http://www.bundesaerztekammer.de/downloads/AlkAUDITCFragebogen.pdf
  b) CAGE-Test (German), http://www.zuefam.ch/pdf/cagetest.pdf
- Geriatric depression scale (German)

6. Clinical consensus point – specialist psychotherapeutic consolidation examination: In the case of indications of a mental disorder, the patient should be presented to a physician specialized in psychiatry and psychotherapy or psychosomatic medicine and psychotherapy or a medical or psychological psychotherapist. Strong consensus

Commentary. Diagnostic assessment of psychiatric disorders can also be performed by general practitioners with competence in basic psychosomatic care.

7. Clinical consensus point – therapeutic goals. Together with the patient, individual and realistic therapeutic goals should be set. Strong consensus

Commentary. Patients with CNCP often have high expectations for drug-based pain relief. In a survey of patients at a US pain clinic, 52 chronic back pain patients named 58% pain reduction (to 2.2 on an 11-point scale) and a 68% reduction in perceived physical impairments (to 1.8 on an 11-point scale) as criteria for successful treatment [61].

From a medical point of view, reasonable therapeutic goals (= therapeutic response) are a reduction in pain of at least 30% and/or individually appropriate improvements in everyday function (e.g. return to work, “being able to mow the lawn again”, “be able to take care of oneself again”; [26]).

8. Clinical consensus point – patient information: Patients should be provided 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). Strong consensus

Commentary. Contents of the patient information:

General aspects:
- Goals and expectations of the treatment
- Treatment alternatives and complimentary measures
- Dependence of therapeutic success on the individual case
- Requirement for continual reassessment of treatment
- Requirement that the opioid-containing medication be prescribed by a single physician and the exact regulations governing any locum representation that may become necessary
- Instructions relating to exact taking and dosage of medication
- Indications of interactions with other medications
- Prophylactic treatment of adverse drug reactions, e.g. constipation
- Ban on consumption of alcohol or sedatives without prior discussion with the physician
Patients’ responsibilities: adherence to the treatment plan, regular feedback to the treating physician; e.g. in the form of a pain journal

Safe storage of the opioid-containing medication

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

Consequences of nonadherence

Taking opioid-containing medications abroad

Risks and adverse events:

Information on adverse drug reactions that can either occur temporarily or only in the context of prolonged application, including: the risk of physical dependence and development of an addictive disorder, constipation, nausea, sedation, pruritus, vertigo, vomiting, reduced cognitive performance, fatigue, xerostomia, increased sweating, headache, reduced ability to express changes in emotion, loss of sexual desire, effects on the pituitary–gonadal axis

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)

Practice tools:

Information leaflet on opioid treatment (German)


9. Clinical consensus point – safety of driving while taking opioids: In a documented process, the physician should fully inform patient on traffic- and workplace-relevant aspects of the therapy before commencing treatment with opioid-containing analgesics. Strong consensus

Commentary. Detailed literature [52, 77, 78].

Practice tools:

Information leaflet on driving safety while taking opioids (German)


10. Clinical consensus point – titration and driving safety: Patients should be made aware that they should not drive during the titration phase or when their dose is changed. Strong consensus

Practice tools:

Information leaflet on driving safety while taking during opioids (German)


II. Clinical consensus point – titration or changes to dose and the workplace: Possible hazards at the workplace should be considered. Strong consensus

Commentary. If professional activities are associated with an increased or unclear hazard potential, it can be considered whether to involve the company-supervising occupational health practitioner (company physician) to advise and support the employee.

12. Clinical consensus point – other centrally acting substances: Hypnotics and tranquilizers should be reduced or discontinued before commencing treatment with opioid-containing substances. Consensus

Commentary. This recommendation was also made by the Canadian practice guidelines [29].

B. Performing treatment with opioid-containing substances

13. Evidence-based recommendation – differential indication of individual opioid-containing analgesics: No recommendation for preference of oral or transdermal application routes of opioid-containing analgesics can be made. EL1a, strong consensus

Commentary. This recommendation was also made by the Canadian practice guidelines [29].

Three RCTs with 1400 patients were included in a meta-analysis of direct comparisons of the application routes of opioid-containing analgesics. In two studies, transdermal fentanyl was compared with oral morphine and one study compared transdermal buprenorphine with oral tramadol. The indications for opioid therapy were chronic back pain, chronic osteoarthritis pain and chronic neuropathic pain. There were no significant differences between the preparations and their application forms in terms of pain reduction, perceived physical impairments, rate of dropout due to adverse events or frequency of severe adverse events [47].

1. Evidence-based recommendation – differential indication of individual opioid-containing analgesics: No recommendation for preference of a particular opioid-containing analgesic can be made. EL1a, strong consensus

Commentary. This recommendation was also made by the Canadian practice guidelines [29].
Fentanyl patches are the most frequently prescribed strong opioid in Germany. However, when prescribing and handling these, recommendations for safe application are not always observed: as such, fentanyl patches are often used in opioid-naïve patients, and by prescription of excessive doses at baseline, patients can be put at risk—particularly elderly patients and those with comorbidities [6]. Despite contraindications, fentanyl patches are also prescribed for acute pain and only a quarter of these patients have diseases necessitating transdermal application of pain killers, such as dysphagia. This was demonstrated by an analysis of health insurance data from 2004 to 2006 [30].

In the guideline committee’s opinion, there is no CNCP indication for with only transdermal systems should be applied.

15. Clinical consensus point – differential indication of opioid-containing analgesics: When selecting the opioid-containing analgesic and its application route, the patient’s comorbidities, contraindications to transdermal systems or oral intake and the adverse events profile of the opioid-containing analgesic should be considered, as should be the patient’s preferences. Strong consensus

Commentary.

a) In a network analysis, patients with chronic pain (CNCP and cancer pain) reported less gastrointestinal adverse events (nausea, constipation) with tapentadol compared to fentanyl, hydromorphone, morphine and oxymorphone [73] or tramadol [55]. Patients with 300 mg/d tramadol reported less drowsiness than patients with 200–500 mg/d tapentadol [55].

b) Despite considerable data on treatment of chronic back and osteoarthritis pain, the individual response of a patient to drug-based treatment cannot be predicted. Clinical experience shows that there are considerable inter- and intraindividual differences in the effectiveness and tolerability of different opioid-containing analgesics.

c) Buprenorphine, codeine, dihydrocodeine, fentanyl, oxycodone and tramadol have the potential to interact with selected medications (see practice tools) on the basis of their affinity for cytochrome P<sub>450</sub> isoenzyme 3A4. Codeine and tramadol have the potential to interact with CYP2D6. Where CYP2D6 is inhibited or genetically inactive (“poor metabolizer”), the effect of tramadol is reduced and that of codeine absent (see practice tools). With tapentadol and tramadol, their serotonergic properties—with the possibility of serotonin syndrome and the risk of seizures—are to be considered [67, 68]. The clinical relevance of the drug interactions of opioids has not yet been clarified. Possible clinically relevant interactions are: diltiazem with fentanyl and oxycodone; fluconazole with fentanyl and oxycodone; clarithromycin with oxycodone [65].

Practice tools:

- Opioid-containing analgesics in renal insufficiency patients (German) http://www.dgss.org/fileadmin/pdf/LONTS_Praaxiswerkzeug_01.pdf
- Opioid-containing analgesics in renal insufficiency patients (German) http://www.dgss.org/fileadmin/pdf/LONTS_Praaxiswerkzeug_02.pdf
- Drug Commission of the German Medical Association (DCGMA) advice on the use of fentanyl-patches (German) http://www.dgss.org/fileadmin/pdf/LONTS_Praaxiswerkzeug_06.pdf
- Cytochrome P<sub>450</sub>-associated interactions of low-potency opioids (German) http://www.dgss.org/fileadmin/pdf/LONTS_Praaxiswerkzeug_11.pdf
- Cytochrome P<sub>450</sub>-associated interactions of high-potency opioids (German) http://www.dgss.org/fileadmin/pdf/LONTS_Praaxiswerkzeug_12.pdf

16. Clinical consensus point—short-acting vs. long-acting preparations: Preparations with delayed galenic formulation or longer-lasting action should be used. Consensus

Commentary. It is assumed that taking delayed-release preparations according to a strict application scheme is associated with better pain control and adherence to treatment, as well as with a reduced risk of falls and development of dependence. However, these assumptions have not been proven in studies with high methodological quality. When deciding whether to apply a short-acting or a long-acting opioid-containing analgesic, the individual efficacy and tolerability of the particular galenics should be considered [16, 69].

17. Clinical consensus point – taking schedule: Opioid-containing analgesics should be taken according to a strict time schedule (which depends on the duration of effectiveness of the particular preparation). Strong consensus

18. Consensus-based recommendation – preparation substitution: In the case of stable medication settings, a change to a preparation with other pharmacokinetic and dynamic characteristics should only be made in consultation with the treating physician and after fully informing the patient. Strong consensus

Commentary. The question of whether the available galenic formulations of opioid-containing analgesics differ in their pharmacokinetic and dynamic properties requires further studies [91].

In the opinion of the patients’ representatives within the guideline committee members, in the case of stable medication settings, a change to a substitute preparation should only be made in consultation with the treating physician and pharmacist, and after fully informing the patient. Only if the treating physician approves this substitution may this change be made.

19. Clinical consensus point – titration: treatment should be initiated with low doses. Strong consensus

20. Clinical consensus point – titration: Depending on effectiveness and tolerability, the dose should be increased in a stepwise manner, in order to reach the individual therapeutic goal. Strong consensus

21. Clinical consensus point – nonretarded opioid-containing analgesics as rescue medication during the titration phase: During the titration phase, nonretarded opioid
containing analgesics may be used as rescue medication to establish the optimal dose. Strong consensus

**Commentary.** It should, however, be noted that certain fast-acting opioid preparations—particularly transmucosal or intranasal fentanyl preparations—are approved exclusively for countering cancer breakthrough pain.

22. Clinical consensus point – treatment responders and optimal dose: An optimal dose is one which achieves the predefined therapeutic goals with simultaneous minimal or tolerable adverse events. Strong consensus

**Commentary.** In the clinical experience of the guideline committee, whether a response (attainment of the individual therapeutic goals) to treatment and acceptable tolerability (= treatment response) are present can be judged after 4–6 weeks.

In medical terms, a treatment response is at least 30% pain reduction and/or improvements in physical function in daily life (e.g. return to work, “able to mow the lawn again”). During the further course of treatment, a good treatment response is characterized by no or minimal tolerance development and no or only minimal dose increases during a period of several months.

23. Clinical consensus point – maximum doses: A dose of >120 mg/d oral morphine equivalents should only be exceeded in exceptional cases. Strong consensus

**Commentary.** Cohort studies conducted in the USA indicate an increase in complications associated with daily doses >120 mg morphine equivalents [28].

The average daily doses in long-term open-label studies of RCTs were 14 μg/h buprenorphine transdermal, 35–50 mg oxycodone oral, 360 mg tapentadol oral and 300 mg tramadol oral [39]. In a 1-year nonblinded comparison study, the average end dose of transdermal fentanyl was 50 μg/h and that of oral morphine 80 mg/d [2].

24. Clinical consensus point – maximum doses: Before increasing the dose to >120 mg/d oral morphine equivalents, the indications for treatment with opioid-containing analgesics, as well as other treatment options and possible abusive use of the prescribed drug are to be checked. Strong consensus

**Commentary.** Before increasing the dose to >120 mg/d oral morphine equivalents, the following questions must be answered: is there evidence of relevant tolerance development? Are there indications of development of opioid dependence? Are there other indications of possible abuse of the prescribed drug? Would the patient agree to a trial discontinuation of opioid therapy? Are there any treatment alternatives?

25. Clinical consensus point: A therapy lasting >3 months should only be performed in treatment responders. Strong consensus

26. Clinical consensus point – rescue medication with opioid-containing analgesics – long-term therapy: During long-term treatment, opioid-containing analgesics should not be used as rescue medication. Strong consensus

**Commentary.** In individual situations (e.g. planned increased physical strain in chronic osteoarthritis pain), a one-time prophylactically increased dose of a delayed-release opioid-containing analgesic and/or a short-acting opioid-containing analgesic to be taken as required can be considered.

27. Clinical consensus point – treatment of nausea and vomiting: Antiemetic treatment can be administered at the start of therapy. After 2–4 weeks, the indications for discontinuation of antiemetic treatment should be assessed. Strong consensus

**Commentary.** Most patients develop tolerance to the emetic effects of opioid-containing analgesics after 2–4 weeks [82].

**Practice tools:**
- Antiemetics in opioid-induced nausea (German) http://www.dgss.org/fileadmin/pdf/LONTS_Praxiswerkzeug_08.pdf

28. Clinical consensus point – treatment of constipation: In most patients, treatment of constipation with laxatives should be initiated prophylactically. In many patients, use of laxatives can be necessary throughout the entire treatment period. Strong consensus

**Commentary.** The decision between prophylactic and as-required treatment with laxatives is to be made on an individual basis and depends on the patient’s defecation pattern. In patients who already have (or tend toward) constipation, prophylactic administration of laxatives is rational [57]. There are inadequate data on efficacy and adverse events of laxatives in opioid-induced constipation [76].

**Practice tools:**
- Treatment of opioid-induced constipation (German) http://www.dgss.org/fileadmin/pdf/LONTS_Praxiswerkzeug_08.pdf

29. Clinical consensus point – procedure in the case of reduced effectiveness: In the instance of reduced effectiveness, the case must be reevaluated. Strong consensus

**Commentary.** Differential diagnoses in the case of reduced effectiveness (Tab. 1):
- Disease progression
- Tolerance development
- Opioid-induced hyperalgesia
- Misuse, abuse or substance dependence

30. Clinical consensus point – tolerance development: In the case of tolerance development, the dose can be increased, the opioid can be changed or opioids can be withdrawn. Strong consensus

**Commentary.** The guideline committee recommends that, in general, the opioid not be changed more than twice in cases of tolerance development.

**Practice tools:**
- Change of opioid (German) http://www.dgss.org/fileadmin/pdf/LONTS_Praxiswerkzeug_09.pdf
During long-term therapy (e.g. with opioids), a reduction in analgesic effectiveness may be observed. The presumed cause is relocation of opioid receptors from the cell surface into the cell interior (receptor internalization), where they are no longer available to the analgesic effect.

In isolated cases, neurotoxic adverse events of opioid treatment have been reported. These neurotoxic adverse events manifested as hyperalgesia, sometimes with other neurological (allodynia, myoclonus) and psychiatric (hallucinations, nightmares) symptoms.

In some diseases (similar to the situation of cancerous disease) the clinical picture can worsen, which, in turn, can lead to increased noiception. This can, e.g. in osteoarthritis with progressive wear of the articular cartilage, massively accentuate motion-dependent pain.

In the case of misuse or abuse of opioid-containing analgesics: In the case of persistent reduction or discontinuation, the psychological dependence is mainly characterized by the desire for regular use (craving).

In the case of longer-term abuse, physical and/or psychological dependence on the abused substance develops. While the physical dependence principally manifests as withdrawal symptoms following sudden reduction or discontinuation, the psychological dependence is mainly characterized by the desire for regular use (craving).

a) Pain relief achieved (e.g. pain journal)

b) Functional status and quality of life, particularly frequently during the titration phase
c) Development of a divergent substance-related behavior
d) Illegal distribution or procurement of opioid-containing analgesics
e) Comprehensive assessment of pain relief and improvements in quality of life and functional status, as well as the behavioral, emotional and cognitive changes resulting from these effects

Practice tools:
- Documentation of progression, Brief Pain Inventory (BPI; German) http://www.npcrc.org/files/news/briefpain_short.pdf

In order to ensure adherence, seek further support from the patient's environment.

Transfer of the patient to a dependence specialist.

Discontinuation of long-term application by qualified withdrawal.

Explanation: dependence specialists: physicians with qualifications in addiction medicine primary care, psychiatric and psychotherapeutic physicians, psychologists and social workers in drug counseling services.

D. Discontinuation of treatment with opioid-containing analgesics

35. Clinical consensus point – discontinuation of a treatment attempt: If the individual therapeutic goals are not reached during the titration phase (maximum 12 weeks), or (in the view of the patient and/or the physician) insufficiently treatable or intolerable adverse events occur, treatment with opioid-containing analgesics should be discontinued in a stepwise manner. Strong consensus

36. Clinical consensus point – discontinuation of treatment >12 weeks

a) If the individual therapeutic goals are no longer achieved, or (in the view of the patient and/or the physician) insufficiently treatable or intolerable adverse events occur, treatment with opioid-containing analgesics should be discontinued in a stepwise manner. Strong consensus

b) If the individual therapeutic goals are achieved by other medical (e.g. surgery, radiation therapy, sufficient treatment of the underlying condition), psychotherapeutic, physical or psychotherapeutic measures, treatment with opioid-containing analgesics should be
**Schwerpunkt**

**discontinued in a stepwise manner. Strong consensus**

c) If the patient uses the prescribed opioid-containing analgesic in an abusive manner despite complementary treatment from a dependence specialist, treatment with opioid-containing analgesics should be discontinued in a stepwise manner. Strong consensus

**Commentary.** Indications of possible misuse/abuse:
- Signs that the patient is increasingly unable to cope with the demands of work, family and the social environment
- Repeated implausible failure to attend appointments
- Increasing lack of participation in other therapeutic measures (e.g., physiotherapy)
- Unwillingness to change the method of treatment (dosage, preparation) although negative physiological and psychological effects of the medication are evident
- Reports of unintended psychological effects (euphoric, sedative etc.)
- Nonprescribed use of medication to treat other symptoms
- Deviations from the taking schedule, e.g. nonprescribed dose increases
- Increased craving for short-acting opioids
- Repeated losing of prescriptions
- “Borrowing” of opioid-containing analgesics from fellow patients, acquaintances or family members
- Attempts to acquire prescriptions from other physicians, in clinics or emergency departments, without informing the treating physician
- Procurement or distribution of opioid-containing analgesics outside of the medical context
- Hoarding of medication during phases of less severe pain
- Expressed desire for preparations for which the possibility of unintended use is stated
- Request for dose increases or premature restocking of tablets, although sufficient pain relief has been achieved
- Use of prescription drugs in an unintended manner (e.g. injection of oral preparations or slitting open delayed-release preparations)
- Aggressive demands for stronger medication
- Abuse of alcohol or illegal drugs
- Urine test positive for nonprescribed opioids, sedatives, hypnotics or illegal drugs
- Distribution or sale of opioids to third parties, falsification of prescriptions, stealing or borrowing of medication [87]

37. Clinical consensus point – drug holiday: After 6 months, the possibility of dose reduction and/or a trial discontinuation should be discussed with patients with a treatment response, in order to assess the indication for continuation of treatment and the response to the non-drug-based therapeutic measures initiated in parallel (e.g. multimodal therapy). Strong consensus

**Commentary.** The reasons for this recommendation are:
a) Spontaneous improvements in symptoms (natural disease course) are described for some CNCP symptoms, e.g. chronic back pain [44] and postherpetic neuralgia [71].
b) It is possible that the therapeutic goals can be achieved by the physical treatments and/or psychotherapeutic procedures initiated in parallel, and that an opioid-containing analgesic is no longer necessary.
c) Randomized, placebo-controlled studies in CNCP were performed up to a maximum of 24 weeks.

38. Clinical consensus point. If the patient exhibits opioid-associated psychological abnormalities, the following options are available:
- Reduction of the opioid dose
- Change of opioid
- Stepwise discontinuation of treatment with opioid-containing analgesics

**Strong consensus**

39. Evidence-based recommendation – opioid withdrawal as a therapeutic measure: In patients with persistent severe pain and/or impairments during long-term use of opioid-containing analgesics, opioid withdrawal within the context of a multimodal treatment program can be considered. EL4b. Strong consensus

**Commentary.** Cohort studies conducted in German pain centers were able to demonstrate a reduction in pain and perceived impairments achieved by opioid withdrawal within the context of a multimodal treatment program [46, 92].

40. Clinical consensus point – practical aspects of discontinuing treatment: Long-term treatment with opioid-containing analgesics should be discontinued in a stepwise manner. Drug-based, physiotherapeutic and psychotherapeutic complementary treatments should be considered. Strong consensus

**Commentary.** When discontinuing application of opioid-containing analgesics, withdrawal symptoms can arise.

Before discontinuation, evaluation of treatment, comorbidities, psychological state and other relevant factors should be complete.

The patient and the patient’s family should be educated in advance on the withdrawal process and the frequently occurring withdrawal symptoms.

Contact with the patient should be maintained until completion of withdraw-
In order to reduce withdrawal symptoms, withdrawal of opioid treatment should involve stepwise reductions of the daily dose accompanied by support measures (e.g. application of clonidine or doxepin). A patient requires approximately 80–90% of the previous day’s dose in order to avoid withdrawal symptoms. The longer the duration of opioid treatment, the slower the withdrawal process should be.

The decision of whether to perform withdrawal on an outpatient or an inpatient basis is to be made individually.

Following their application for several months, it may be necessary for withdrawal of opioid-containing analgesics or withdrawal of the dependent patient to take place in an acute hospital.

If sudden withdrawal, e.g. due to allergies or intolerance, is necessary, this should take place on an inpatient basis in an acute hospital.

The measures and decision-making processes pertaining to establishment of indications, the application and possible discontinuation of treatment with opioid-containing analgesics are summarized as an algorithm (Fig. 1).

E. Special patient groups

41. Clinical consensus point – elderly patients: Treatment should be initiated with a low dose. The dose should be increased slowly. Frequent assessments of effectiveness and tolerability should be performed. Strong consensus

Commentary. Age-dependent pharmacodynamic and pharmacokinetic changes lead to a longer duration of opioid action in elderly patients. For these reasons, amongst others, it is recommended that opioid treatment be initiated with a dose reduced by approximately 25–50% compared to younger patients and that the dose be increase more slowly [29].

Practice tools:
- Medication potentially inadequate for older persons: the PRISCUS list (German)
  http://www.aerzteblatt.de/archiv/literatur/77776

42. Clinical consensus point – children and adolescents: Treatment with opioid-containing analgesics should only be performed in exceptional cases. Treatment should be performed in specialized centers/by specialized pediatricians. Strong consensus

Commentary. Detailed literature [32].

43. Clinical consensus point – pregnant women: In the case of a planned pregnancy, prior discontinuation of treatment with opioid-containing analgesics should be strongly advised. If pregnancy occurs during therapy with opioid-containing analgesics, discontinuation of treatment should be strived for. Strong consensus

Commentary. In the case of withdrawal treatment, withdrawal symptoms should be avoided, since these are associated with an increased risk of premature contractions and spontaneous abortion or premature births. In isolated cases (prob-
problems during withdrawal treatment), opioid substitution therapy can also be considered. Should it be necessary to continue treatment with opioid-containing analgesics during the pregnancy, the delivery should be performed in a level I/II perinatal center, since it is possible that the newborn will exhibit postpartal withdrawal symptoms [41, 42, 86].

44. Clinical consensus point – patients with comorbid mental disorders: Treatment should be initiated with a low dose. The dose should be increased slowly. Frequent assessments of effectiveness and tolerability should be performed. Complementary specialist psychotherapeutic treatment should be considered. Strong consensus

45. Clinical consensus point – patients with current substance dependence: Treatment should be performed in tight collaboration between physicians and psychological psychotherapists with competencies in dependence medicine. Strong consensus

Commentary. Patients with a possible indication for the application of opioids due to pain, who simultaneously have a current substance dependency, represent an interdisciplinary challenge. This situation renders tight collaboration necessary in the selection, induction, application and integration of pain and dependence medicine treatment options. A purely drug-based therapeutic approach is generally not indicated. There are no current German evidence-based recommendations or guidelines pertaining to this context; existing guidelines describe general main features of the treatment [33, 87].

For the special case of patients with an indication for the application of opioids due to pain, who simultaneously have a current substance dependency, the recommendations from the German Medical Association on substitution therapy and the Narcotic Drugs Prescription Ordinance (Betäubungsmittel-Verschreibungsverordnung, BtMVV) regulations from 20. January, 1998 (BGBI. I S. 74, 80), last changed 20. July, 2012 (BGBl. I S. 1639), on prescription of opioids in the presence of both indications are to be considered. Direct collaboration and agreement between pain therapists and the physician administering substitution therapy is thus generally necessary. Taking into account alternative pain medicine (application of nonopioid and other analgesics; physiotherapeutic, psychological and multimodal treatment approaches) and dependence medicine (withdrawal treatment, psychosocial counseling) treatment options, an individually appropriate treatment with opioids for pain management and substitution can be considered.

Discussion

In light of the differing interests of the persons involved in the guidelines (patients and caregivers; physicians and psychologists; general practitioners and specialists; practice physicians and clinicians), the strong consensus—which was arrived at for almost all recommendations—is particularly noteworthy.

In the opinion of the steering committee, the following research desiderata exist:

- In order to address the question of long-term efficacy and safety, analyses of routine health insurance data and (currently nonexistent) registers of patients with chronic pain are probably more significant than further placebo-controlled RCTs. Subgroup analyses (e.g. elderly patients and adolescents) are required.
- Routine health insurance data can also deliver indications of inappropriate treatment (e.g. frequency of non-guideline-conform prescription of opioid-containing painkillers) and the frequency of abusive use.
- Indications that other, particularly activating- and acceptance-oriented types of treatment (particularly multimodal pain therapy), possibly have a small therapeutic effect during opioid application should also be investigated in cohort studies.
- Clinical investigation of the question of benefits and adverse events in a comparison of “opioids according to a time schedule (time contingent)” vs. “opioids as required”—within the context of a sufficiently statistically powered study with suitable design—is rational.

- Head-to-head comparisons of different opioids, of opioids with other classes of analgesics and of opioids with psychological approaches in longer-term RCTs (e.g. 26 weeks), with follow-ups after 1–2 years (“comparative effectiveness research”), are necessary. Network meta-analyses represent another possibility for performing indirect comparisons between individual opioid-containing analgesics, between opioid-containing analgesics and other classes of analgesics and between opioid-containing analgesics and psychological approaches [55].
- Standardized collection of data on subjective adverse events such as nausea, constipation, vertigo and obtundation is necessary, in order to be able to evaluate the adverse events profile of the individual substances in direct and indirect comparisons in a more valid manner [72].
- Development of a validated German screening instrument for abuse of and dependence on substances, other than alcohol, which are able to cause physical dependence, is desirable.

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Compliance with ethical guidelines

Conflict of interest. W. Häuser received honoraria for educational lectures from Abbott, Janssen-Cilag, MSD Sharp & Dohme and Pfizer, as well as one honorarium for consulting services (study design) from Daiichi Sankyo. G. Lindena is director of the CLARA institute for clinical research (which takes over projects and generates income), and director and partner of the Berlin-Brandenburger Rückenheilanstalt (BBR); she has received honoraria for educational lectures as part of the aforementioned projects and received financial support for different applications related to these projects, with no (pharmaceutical) industry-sponsored projects during the past 3 years. C. Maifer received honoraria for consulting services from Pfizer and Mundipharma, as well as for educational lectures from Pfizer, Mundipharma, MSD, Lilly and Grünenthal. L. Radbruch serves on the AOK Vita advisory board. R. Sabatowski has act-
ed as consultant for Cephalon and Janssen-Cilag. He has received fees for the preparation of specialist training courses for MSD and Grünenthal. The University Pain Center Dresden has received payments from Grünenthal, Astellas and Allergan for conducting commissioned clinical studies. M. Schärer served on advisory boards for Change Pain, Grünenthal and Developh. M. Schilitenwolf provided advisory services for Daiichi Sankyo regarding design of an RCT with anticonvulsants in FMS; he gave a lecture for MSD and non-product related talks for Pfizer; he received third-party funds support from Phillips for a licensing study RCT. T. Tölle serves on advisory boards for Lilly, Astellas, Pfizer, Esteve and Grünenthal; he has held lectures and training activities for Lilly, Astellas, Mundipharma, Grünenthal, Hexal, Janssen-Cilag and Pfizer; he is subproject director in the “Neuropain” European research project from Pfizer, NY, with 12 other European partners; he is subproject director in the IMI European research project that is cofinanced by the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA). F. Petzke received honoraria for advisory services from Grünenthal, Epiomics Spine and Janssen-Cilag, and study support (third-party funds) and reimbursement of travel expenses from Janssen-Cilag, F. Back, P. Engeser, G. Hege-Scheuing, M. Hüpke, H. Norda, M. Schäfer, H. Sorgatz, A. Willweber-Strumpf and T. Tölle.

The accompanying manuscript does not include studies on humans or animals.

References