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Pain therapy – Are there new options on the horizon?

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A B S T R A C T

This article reviews the role of analgesic drugs with a particular emphasis on opioids. Opioids are the oldest and most potent drugs for the treatment of severe pain, but they are burdened by detrimental side effects such as respiratory depression, addiction, sedation, nausea, and constipation. Their clinical application is undisputed in acute (e.g., perioperative) and cancer pain, but their long-term use in chronic pain has met increasing scrutiny and has contributed to the current opioid crisis. We discuss epidemiological data, pharmacological principles, clinical applications, and research strategies aiming at novel opioids with reduced side effects.

The opioid epidemic

The treatment of pain remains a huge challenge in clinical medicine and public health [1,2]. Pain is the major symptom in rheumatoid (RA) and osteoarthritis (OA) [3,4]. Both are chronic conditions that are not linked to malignant disease, and pain can occur even in the absence of inflammatory signs (see chapter "Pain without inflammation"). Unfortunately, there is a lack of fundamental knowledge about the management of chronic noncancer pain. For example, the established use of opioids in acute and cancer pain was unjustly translated to chronic nonmalignant pain, and risks associated with opioid and nonsteroidal analgesic drugs (e.g., addiction, dependence, and cardiovascular complications), the bio-

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psycho-social characteristics of chronic pain, and nonpharmacologic approaches are unknown or misunderstood by many general practitioners and even specialists [5–10]. In addition, aggressive marketing of opioids despite lack of scientific evidence for long-term analgesic efficacy, as well as problems ensuing the legalization of cannabinoids, has contributed significantly [5,11–16]. The latter is supported by epidemiological studies indicating that cannabis use has escalated [17] and that it increases the risk of prescription opioid misuse [18]. In contrast to outdated beliefs, addiction is likely to play a key role in opioid misuse by chronic pain patients [5,6,10]. These and other factors have led to widespread misuse of opioid analgesics and to exponentially growing overdose deaths (the "opioid epidemic") in the USA [2,19,20].

There are clear signs that this problem is neither limited to opioids nor to the USA [5,20–24]. For example, the recent hype to legalize cannabinoids in the USA and other countries (e.g., Germany) also lacks scientific evidence for therapeutic efficacy and is largely driven by economic interests [11]. Based on data from 2007 to 2011, the prevalence of prescription opioid abuse per 1000 population was estimated as 1.37 for France, 1.10 for Germany, and 1.07 for the United Kingdom [25]. Data provided by the International Narcotics Control Board (INCB) indicate that the use of opioid analgesics (excluding tramadol) has doubled in North America (including Canada) and tripled in Europe and Oceania from 2001 to 2013 [22]. Measured in defined daily doses for statistical purposes (S-DDD), the consumption of opioids in Germany was approximately 23,000 and in North America was approximately 31,000 per million people between 2011 and 2013 [22]. In Germany, the use of opioid analgesics has steadily increased from 2000 to 2016, and opioids are mostly prescribed for chronic noncancer pain [26,27]. In 2015, the total opioid consumption in morphine equivalents (mg per capita; excluding tramadol and methadone) reached approximately 480 in Germany and 520 in USA (http://www.painpolicy.wisc.edu/home).

It is important to note that in many statistics, methadone and tramadol are allocated to distinct categories. This is because methadone is not only used to treat pain but also to treat addiction, and tramadol is not on the list of scheduled/controlled substances regulated by the INCB or by most countries (including Germany). The oral application of tramadol leads to the formation of a hepatic metabolite with high efficacy at mu-opioid receptors, thus resulting in similar abuse liability as other opioids [28,29]. Indeed, the abuse of tramadol has been on the rise for several years worldwide, particularly in the USA, Africa, and the Middle East [23,28–31]. It was proposed that this is due to its availability without prescription, easy illegal smuggling, and cheap prices [23,32]. Tramadol is also used to enhance sexual function and is even fed to farm animals to increase their work performance [23,28,33].

Overall, these data indicate that the consumption and misuse of opioid analgesics have reached similar levels in USA, Europe, and other regions [5,30]. This is in contrast to claims that in Germany the risk of an opioid epidemic is comparatively low, purportedly due to, e.g., stricter prescription rules and absence of direct-to-consumer advertising [34]. However, according to German law, all patients have unlimited access to physicians and pharmacies of their choice, many opioid drugs are legitimately advertised among pharmacists and physicians, and opioids are promoted in the internet and other media. Thus, doctor- and pharmacy-shopping are common and enable easy circumvention of prescription restrictions. A recent survey suggested comparable conditions in the United States, the United Kingdom, France, and Australia [21].

Role of opioid therapy in musculoskeletal disorders

Although guidelines regarding the treatment of acute and cancer pain recommend opioids as a first line pharmacotherapy, current guidelines for noncancer pain (e.g., associated with RA and OA) caution against long-term treatment with opioids.

The current literature has the following features:

- it questions the efficacy of opioids for long-term treatment and emphasizes potential risks;
- it does not demonstrate that a high prescription rate for opioids correlates with increased pain control and improved functional outcome [35,36]; and

- it suggests that there is an association between the rise of prescriptions and the misuse of opioids (e.g., for emotional stabilization) [37–39].

Surveys revealed questionable attitudes of prescribers concerning opioid prescription in chronic noncancer pain [40,41]. In view of these obvious uncertainties, a number of guidelines for the rational use of opioids in noncancer pain have been published in the last several years. Most cited are the ones from France [42], Canada [43], Germany [44], and the US [45]. There are doubts about the impact of these guidelines on clinical practice [46]. The most important recommendations of these guidelines are summarized below, with special emphasis on chronic pain in RA or OA.

Analgesia

The analgesic efficacy of opioid monotherapy - with low- or high-potency opioids – is considered weak and not superior to nonopioid analgesics such as acetaminophen (paracetamol) or nonsteroidal anti-inflammatory drugs (NSAIDs).

- both opioids and nonopioids have a maximum analgesic efficacy of 10 on a 100 point Likert scale (after subtracting placebo effects). This is well below a clinically meaningful reduction of 20 units [47,48]
- in joint pain (e.g., RA and OA), neuropathic pain, and chronic nonspecific back pain, the median pain reduction may increase up to 25 points
- in a meta-analysis of studies including more than 10,000 patients, the calculated number needed to treat of 4 was similar between opioids, nonopioids, physical therapy, and psychotherapy [13]
- as in other chronic diseases with pain as the dominant symptom, pain may be "centrally driven" due to neuroplastic changes with subsequent development of hyperalgesia and multifocal pain. Therefore, ongoing OA may also be thought of as a "mixed" pain state with inflammatory (nociceptive) and centrally mediated (e.g., neuropathic) pain [49].

In several chronic inflammatory diseases, opioids have been studied when pain control was not achieved by disease modifying drugs, steroids, or other anti-inflammatory medications. For decades, oral NSAIDs, topical NSAIDs, acetaminophen, COX-2 inhibitors, and opioids have been drugs of choice in OA. A recent systematic review and meta-analysis evaluated the efficacy of these analgesics [50]. Topical NSAIDs produced more pain reduction than oral NSAIDs. The effects of all other drugs did not differ from earlier studies. Most importantly, pain relief by oral NSAIDs and opioids seems to be comparable in OA [51]. A consensus statement of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis consequently recommends opioids (e.g., sustained-release tramadol) as a "last step" only if topical and oral NSAIDs are inefficient [52]. The recent SPACE trial found no superiority of opioids over nonopioids for improving pain-related function over 12 months [53]. This is in accordance with the "NICE guidance" recommendations one decade ago [54]. In elderly patients with OA, long-term opioid therapy may increase the risk of fractures, mortality, and hospital admission in comparison to oral NSAIDs [44]. These side effects of opioids are dose-dependent. The risk of fractures in elderly patients correlated with a daily dose of more than 50 mg oral morphine equivalents [55].

Physical performance and quality of life

Besides pain reduction, the improvement of physical function and quality of life are the most important treatment goals in patients with chronic noncancer pain [48]. However,

- there is no evidence that opioids have a positive effect on quality of life in those patients; and
- there is only weak evidence that opioids improve physical function or quality of sleep.

In light of the low efficacy of opioids in analgesia and physical function, particular pain syndromes and contraindications have to be identified and evaluated prior to the initiation of long-term opioid therapy (Table 1).

Side effects

Typical side effects of NSAIDs (gastrointestinal, renal, and cardiovascular) [56] are not observed with opioid therapy. However, in contrast to common beliefs, patients undergoing long-term opioid treatment are vulnerable to dose-dependent serious adverse events [57]. Side effects such as the risk of falls, cognitive impairment, insomnia, and depressive disorders have to be taken into account [58,59]. The dropout rate of patients due to side effects or insufficient analgesic efficacy is approximately 30% in published opioid studies and exceeds the dropout rate of nonopioid analgesics (approximately 25%). The dropout rate did not differ between so-called "low-potency" (e.g., tramadol and codeine) and "high-potency" opioids (e.g., morphine, oxycodone, and fentanyl). It may be concluded that opioids in general – in equipotent doses – display no relevant substance-specific differences regarding efficacy or side effects. There may be interindividual differences though. For example, in male patients, relevant endocrinological changes have been found. Testosterone levels have to be evaluated after more than three months of opioid therapy [60,61]. Opioids often impair driving ability at the beginning of therapy, but stable opioid doses do not seem to interfere with driving in most patients [62,63].

Risk of opioid abuse

Long-term treatment with opioids may induce abuse and dependence, even in patients treated according to the abovementioned guidelines [38]. Not all of these patients should be considered "addicted", as typical abuse characteristics such as continuous or unauthorized dose escalations and incompliance with therapeutic plans are often absent. The phenomena of addiction/abuse, dependence, and tolerance may overlap and are interindividually heterogeneous [37,64]. Assessment for risk factors may lower the risk for misuse and abuse (Table 2) [65,66].

Initiation of opioid therapy

A therapeutic trial with opioids is not justifiable by proven superiority of opioids over other therapeutic options but may be based on the individual patient's history and risk profile. Opioids may be *one* element of an interdisciplinary multimodal treatment approach (Table 3).

Table 1
Exclusion criteria for the use of opioids in patients with chronic noncancer pain. In patients with psychiatric comorbidities, opioids may be prescribed if multimodal assessment has identified pain management as priority.

Types of pain NOT recommended for long-term opioid therapy
• primary headache syndromes
• functional cardiac, gastrointestinal, urological, and gynecologic disorders
• somatoform and other predominantly psychologically triggered pain disorders
• predominantly attack-like pain with pain-free intervals
• pain syndromes with changing clinical course
Patient characteristics as contraindications for long-term opioid therapy
• allergy and intolerance
• (planned) pregnancy and lactation period
• psychological instability, high-grade affective disorder, and suicidal risk
• high-grade obstructive sleep apnea syndrome
• harmful substance abuse, drug dependence, and diversion of controlled substances
• inadequate use of opioids
• limited supervision of drug ingestion, e.g., in patients with cognitive impairment
• poor compliance with the treatment plan
• psychosocial factors, e.g., lawsuits for litigation or early retirement

Table 2
Risk factors for opioid abuse.

Psychosocial and psychological risk factors
• major social challenges
• psychiatric comorbidities
• history of abuse and dependence on psychotropic substances
• maladaptive coping strategies
• young age and male sex
Opioid-specific risk factors
• "high-potency" opioids
• immediate-release opioids
Iatrogenic factors
• insufficient patient education prior to the initiation of opioid therapy
• monodisciplinary evaluation and reevaluation of psychosocial risk factors
• inadequate monitoring of therapeutic outcome and patient compliance

Table 3
Patient instructions and information prior to starting opioid therapy.

• define realistic treatment goals for opioid therapy (e.g., "pain-free" is not realistic)
• plan a time-limited trial to evaluate efficacy and side effects
• ensure active participation in adjuvant therapies within a multimodal treatment approach
• educate about physical and psychological dependence, the risk of withdrawal, potential interactions with other medications or comorbidity
• instruct about the dosing scheme and the obligation to follow the instructions
• ensure mandatory reevaluation appointments in regular intervals
• discontinue therapy when treatment goals are not reached or noncompliance appears
• interdict opioid prescriptions from other healthcare providers

Although there is consent about the necessity of regular reevaluation visits, there are no recommendations about the time intervals between visits [66]. Opioids should be prescribed as slow release formulations or transdermal systems with a fixed dosing scheme. Buccal and intranasal opioids are not recommended. Opioid therapy should start with an individual dose titration over a limited time span of, e.g., two to three weeks to reach an individually effective and tolerable dose. Immediate-release opioids may be used as demand medication to find the therapeutic dose. After completion of the titration period, immediate-release opioids should be terminated or strictly limited. Besides the individual tolerance to typical opioid side effects, particular opioid drugs may be indicated for some patient groups with organ insufficiency, higher age, or certain co-medications [67–69]. To exploit positive patient expectations as a context factor for enhanced efficacy, patient preferences for particular compounds should be explored. There is no evidence supporting the routine combination of opioids with nonopioids such as anticonvulsants or antidepressants. Such compounds may be added in patients with mixed pain (e.g., nociceptive/neuropathic pain) [70].

Patient reevaluation

Analgesic efficacy of opioid treatment longer than three months has been suggested only by uncontrolled observational studies [13]. For structured regular visits, the following interview contents should be considered (the so called "5 A") (Table 4) [65,66,71].

Current research strategies

As mentioned above, chronic pain (particularly noncancer pain, e.g., associated with arthritis) should never be treated with drugs alone, but should be managed in the context of an interdisciplinary team approach. Nonetheless, the search continues for novel analgesics and formulations to reduce adverse side effects (reviewed in Ref. [72]). In the case of opioids, previously developed selective agonists for delta- or kappa-opioid receptors were troubled by unacceptable side effects (e.g., convulsions and dysphoria) [73,74]. Thus, alternative strategies are being pursued.

Table 4
Structured therapy evaluation using the "5 A".

Analgesia
continuous meaningful reduction of pain intensity without dose escalations
Activity
physical performance including activities of daily life, homework, days of sick-leave, sleep quality, libido, and social contacts
Adverse Effects
side-effects and their management
Aberrant Behavior
indicators for misuse or abuse, e.g., unauthorized dose escalations, incompliance regarding regular dose reduction testing, opioid use for nonanalgesia symptoms such as sleep or restlessness, multiple prescribers, uncontrolled use of alcohol or benzodiazepines, and increasing psychosocial stress factors
Affect
symptoms of depressive or anxiety disorder and decreasing emotional capacity

Abuse-deterrent formulations

One approach was the development of "abuse-deterrent" formulations, e.g., by increasing resistance to crushing, chewing, or dissolving, or by adding antagonists or other aversive ingredients. However, the active agents still retain euphoric or respiratory depressant properties. Indeed, the dissemination of such formulations has spawned sophisticated ways of defeating them, and has led to increasing heroin use and death rates. Thus, prevention of abuse will not be achieved by pharmaceutical strategies alone but must include psychosocial and other (e.g., regulatory and educational) approaches [72,75,76].

Augmenting endogenous opioid mechanisms

Endogenous opioid peptides are susceptible to rapid enzymatic degradation by aminopeptidase N and neutral endopeptidase (enkephalinases). Preventing this degradation by inhibitors (in the CNS or in peripheral tissues) has been shown to produce analgesic effects in many animal models and in some human trials [77–79]. This strategy avoids unphysiologically high concentrations of exogenous agonists at (ubiquitously distributed) receptors and, thus, diminishes the risk for development of receptor downregulation, tolerance, desensitization, off-site, or paradoxical excitatory effects [78]. Another interesting strategy is based on vaccination-induced recruitment of opioid peptide-producing lymphocytes to inflamed tissue [80].

Allosteric modulators

Allosteric modulators of opioid receptors were shown to influence the affinity and/or efficacy of orthosteric ligands *in vitro*, but evidence for *in vivo* efficacy is lacking so far [81]. Nonetheless, this concept is intriguing because positive allosteric modulators may enhance the activity of endogenous opioid peptides which are elevated during stress and pain. This activity would be confined to opioid receptors that are exposed to released endogenous opioids and would thereby avoid side effects (similar to the concept of enkephalinase inhibitors) [78,81].

Bivalent ligands

Opioid receptors (and other GPCR) can form dimers or oligomers (i.e., two or more monomers physically interacting with each other). A number of bivalent ligands incorporating distinct pharmacophores for two receptors are being investigated [72,82]. The underlying idea is that the combination of agonist and antagonist properties at different opioid or nonopioid receptors may reduce side effects. However, previous clinical studies have demonstrated that such compounds typically exhibit ceiling effects for analgesia and may elicit a withdrawal syndrome when administered together with a pure agonist [83].

Biased signaling

The concept of biased signaling (i.e., preferential activation of distinct intracellular pathways) has generated considerable excitement [72,82,84–87]. Opioid agonists that primarily activate G-proteins rather than arrestins were sought for, based on the hypothesis that arrestin binding promotes side effects, while G-protein activation underlies analgesic effects [84,86,87]. However, upon systemic administration of opioid agonists, G-protein activation occurs not only in nociceptive neurons (which promote pain) but also in neurons driving respiration, arousal, and intestinal peristalsis [88–91]. Thus, an opioid agonist that (*via* G-proteins) effectively reduces electrical excitation of sensory neurons (an essential prerequisite for analgesia) will likewise (*via* G-proteins) inhibit the above mentioned neurons and thereby produce respiratory depression, sedation, and constipation [88–91]. Recent studies directly demonstrated opioid receptor activation in the brain [87,92], nausea, vomiting [92], and respiratory depression [93] induced by purported biased agonists. In both animal [94] and human [95] trials, prototype-biased agonists produced similar side effects as conventional opioids.

Peripherally restricted opioid agonists

Targeting peripheral opioid receptors became an area of renewed interest. Although earlier attempts to demonstrate peripheral opioid analgesia in healthy tissue failed, potent antinociception was consistently detected in models of nerve damage and inflammatory pain (reviewed in Ref. [96]), in keeping with the notion that injury and inflammation unmask peripheral opioid effects. In addition, awareness increased that many acute and chronic pain syndromes crucially depend on the stimulation of peripheral sensory neurons [1,97,98], and that adverse effects of conventional opioids or of nonsteroidal analgesics [72,99] may be avoided.

Peripheral opioid receptors mediate a substantial proportion of analgesia produced by conventional opioids (reviewed in Ref. [100]). Clinical trials suggested that about half of the analgesic effect produced by systemic opioids is mediated outside the central nervous system [101]. The most extensively studied regimen is the intraarticular administration of low doses of morphine [102–104]. Meta-analyses showed that it produces postoperative pain relief of similar efficacy to local anesthetics [105], and no significant adverse effects have been reported so far [103,106].

Different strategies to obtain peripherally restricted opioids were pursued. A common approach is the development of hydrophilic substances with minimal capability to cross the blood-brain barrier (reviewed in Ref. [96]). In collaboration with chemists, we used a cleavable linker to attach morphine to a polyglycerol-based nanocarrier [107]. Preclinical experiments showed that this construct exclusively activated peripheral opioid receptors to produce analgesia in injured tissue without evoking sedation or constipation [107].

In a recent cooperative project with mathematicians, we pursued a pharmacodynamic concept that is independent of pharmacokinetic issues such as barrier permeability but relies on acidosis in damaged tissue. We hypothesized that opioid receptors and ligands exhibit different conformation dynamics in inflamed tissue compared to noninflamed (brain and intestinal wall) [108,109]. Novel methods of computer simulations indicated that opioid ligands assume a more stable binding position at low pH than at physiological pH, suggesting that agonists have an enhanced potential to activate the receptor under acidic (inflamed) conditions. Based on these *in silico* studies, a prototype (NFEPP) was designed that selectively activated peripheral opioid receptors and induced analgesia in injured tissue (at low pH), while typical adverse effects (respiratory depression, reward, sedation, motor disturbance, and constipation) elicited in noninjured environments (at normal pH in brain or intestinal wall) were absent [110,111]. These results were attributed to acidosis-induced conformational alterations of peripheral opioid receptors and to the low acid dissociation constant of NFEPP ($pK_a = 6.8$). The latter property precludes protonation of a tertiary amine in the ligand (an essential prerequisite for activation of opioid receptors) in noninflamed tissues [110,112]. This is unique because conventional opioid agonists have pK_a values above 7.5 and are therefore protonated and capable of activating opioid receptors at both low and normal pH values [112]. Importantly, both NFEPP and PG-M produced analgesic effects of similar magnitude to conventional opioids [107,110,111]. These findings await further toxicological evaluation and confirmation in clinical trials.

Summary

- The epidemic of opioid misuse has taught us that there is a lack of fundamental knowledge about the characteristics and management of chronic pain, that conflicts of interest and validity of models must be considered in the context of drug development, and that novel analgesics with less abuse liability are badly needed.
- Long-term prescription of opioids for chronic inflammatory pain beyond three months is indicated only in well-selected individual patients due to weak evidence for opioid efficacy.
- Opioids may be a therapeutic option for short-term management of acute inflammatory pain or acute exacerbations of chronic inflammatory pain. Patients with myofascial, inflammatory, or certain neuropathic pain syndromes may be responders. There is no evidence that long-term treatment with opioids for rheumatic and musculoskeletal pain differs from other pain syndromes.
- Long-term therapy with opioids should be used only within a multimodal pain management approach.
- Due to insufficient evidence for adequate identification of responders, long-term opioid treatment is always considered an individual therapeutic trial.
- Long-term benefits regarding analgesia and functional improvement have to be monitored.
- The risk-benefit ratio of opioids and NSAIDs seems to be comparable.
- To ensure maximum patient safety and avoid overtreatment with opioids, a structured and strict patient stratification and monitoring system has to be applied.
- Presently, the most promising perspectives for novel drugs appear to be augmenting endogenous opioid actions and selectively targeting pathological conformations of peripheral opioid receptors.

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Conflicts of interest

C.S. is listed as inventor on US Patent 9133120 B2. A.K. serves on advisory boards of Pfizer and Grünenthal and has received honoraria for lectures from Janssen, Pfizer, and Grünenthal.

Practice points

- Long-term prescription of opioids for chronic inflammatory pain beyond three months is indicated only in well-selected individual patients due to weak evidence for analgesic efficacy.
- Opioids may be a therapeutic option for short-term management of acute inflammatory pain or acute exacerbations of chronic inflammatory pain. There is no evidence that long-term treatment with opioids for rheumatic and musculoskeletal pain differs from other chronic noncancer pain syndromes.
- Long-term therapy with opioids should be used only within a multimodal pain management approach based on the bio-psycho-social concept of chronic pain.
- Due to insufficient evidence for adequate identification of responders, long-term opioid treatment is always considered an individual therapeutic trial.
- Long-term benefits regarding analgesia and functional improvement have to be monitored.
- The risk-benefit ratio of opioids and NSAIDs seems to be comparable.
- To ensure maximum patient safety and avoid overtreatment with opioids, a structured and strict patient stratification and monitoring system has to be applied.

Research agenda

The most promising perspectives for novel analgesic drugs appear to be augmenting endogenous opioid actions and selectively targeting pathological conformations of peripheral opioid receptors. More rigorously controlled studies demonstrating the beneficial effects of multimodal therapeutic programs based on the bio-psycho-social concept of chronic pain are needed.

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