Taylor & Francis
Taylor & Francis Group

Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: www.informahealthcare.com/journals/icmo20

Opioids: a two-faced Janus

Karsten Ahlbeck

To cite this article: Karsten Ahlbeck (2011) Opioids: a two-faced Janus, Current Medical Research and Opinion, 27:2, 439-448, DOI: 10.1185/03007995.2010.545379

To link to this article: https://doi.org/10.1185/03007995.2010.545379

CMRO

Current Medical Research & Opinion Vol. 27, No. 2, 2011, 439–448

0300-7995
doi:10.1185/03007995.2010.545379

Article FT-0163.R1/545379

Review
Opioids: a two-faced Janus

Karsten Ahlbeck
Karolinska University Hospital, Stockholm, Sweden

Address for correspondence:
Karsten Ahlbeck MD, Department of Anesthesiology, Surgical Services and Intensive Care, Karolinska University Hospital, Solna SE-171 76, Stockholm, Sweden.
Tel.: +46 708 103407; Fax: +46 708 103749; karsten@narkos.se

Key words:
Adverse effects – Analgesia – Opiates – Opioids – Pain – Quality of life

Accepted: 2 December 2010; published online: 3 January 2011
Citation: Curr Med Res Opin 2011; 27:439–48

Abstract

Background:
Long-term pain is a debilitating condition that is costly to treat and has a significant impact on patient quality of life. Classical opioids have been used for the treatment of pain for centuries and are one of the most effective drug classes available for acute severe pain and long-term pain. However, concerns regarding adverse effects, tolerance to analgesic effects and the potential for addiction have resulted in a reluctance to prescribe and use opioids for the management of long-term non-cancer pain. Adverse events, including gastrointestinal side effects such as constipation, nausea and vomiting, and central nervous system side effects such as sedation are responsible for as many as one in five patients discontinuing opioid treatment, often leading to inadequate pain relief and poor patient quality of life. Therefore, new analgesic therapies are needed that are associated with fewer adverse effects, whilst providing sustainable pain relief for patients with long-term pain.

Objective and methods:
To provide an overview of the historical development, uses, mechanisms of action, receptor affinities and side-effect profiles of classical opioids. In addition, recent developments and novel approaches for long-term, severe pain treatment are also reviewed.

Results:
A number of treatment strategies were identified: co-administration with opioid-sparing analgesics to reduce side effects and/or risk of dependence, the use of peripheral opioid antagonists and novel delivery mechanisms to reduce side effects, the development of non-opioid agents that reduce side effects and enhance analgesia such as glial cell modulators, and the development of novel agents with combined μ-receptor and monoaminergic activity within the same molecule.

Conclusions:
Despite these recent advances, there have been very few completely novel drug developments. Hence, there remains a continuing need for innovative therapeutic strategies for the treatment of long-term pain. The most promising alternatives appear to be the use of traditional opioids together with peripheral opioid antagonists, combining opioids with glial cell modulators, and the use of novel agents with μ-receptor agonist and noradrenaline reuptake inhibitor activity within the same molecule (MOR-NRI compounds).

Introduction

Long-term, severe pain is a debilitating condition, which can have a significant effect on patients' quality of life (QoL) and their ability to work. For example, a survey of 46,394 patients suffering from long-term pain from 15 European countries and Israel showed that moderate-to-severe long-term pain affected 19% of adults. Moreover, in-depth interviews with 4839 of respondents with long-term pain revealed that 21% of patients had depression, 61% were less able or unable to work from outside of their home, 19% had lost their job and 13% had changed their job because of their pain[1]. The QoL of the patient should be an important consideration in pain clinics, since pain severity alone is often a poor predictor of

low level life satisfaction and QoL can be as important to the patient as a decrease in pain severity[2].

Long-term pain can be costly to treat and generates a significant burden on healthcare systems[1,3,4]. In particular, treatment of long-term pain requires an interdisciplinary approach, which can lead to high costs[5]. It is important to treat pain efficiently and as early as possible because there is less chance of a patient developing long-term pain if treated well in the early stages of acute pain. For example, a study of acute low-back pain patients at high risk of their pain becoming a long-term disability found that those patients assigned to an early intervention programme had fewer incidences of long-term pain disability, medication use and healthcare utilisation compared with those patients who did not receive early intervention. Moreover, early intervention was associated with greater cost savings[6]. One in five adults suffers from long-term pain and this high prevalence together with the related socio-economic consequences has meant that it is increasingly recognised as a significant health care problem[4].

Classical opioids are a mainstay for the treatment of long-term, severe pain; primarily pain in cancer but in selected cases also non-cancer pain, such as neuropathic pain and low-back pain[7]. The term 'opioids' describes drugs whose action is mediated via binding at the opioid receptors distributed throughout the brain, spinal cord, peripheral nervous system, skin and joints[8]. Opioids mimic some of the pharmacological properties of natural opiates found endogenously within the human body.

Despite the fact that opioids are among the most powerful analgesics available for the treatment of most types of severe pain, their clinical utility is limited by the trade-off between efficacy and side effects, which can be divided into peripheral effects (constipation, urinary retention, hives, bronchospasm) and central effects (nausea, sedation, dizziness, respiratory depression, hypotension, miosis, cough suppression) and can adversely affect quality of life[9]. Despite these side-effects, strategies involving careful titration, patient information and relevant medication to treat opioid-related side effects can be used to successfully manage chronic pain.

Other problems associated with classical opioid use include tolerability, tolerance to analgesic effects and dependency[7,10]. This is particularly problematic in complex pain conditions, such as low-back pain, where treatment often involves targeting both the nociceptive and neuropathic pain systems. Opioids have limited efficacy in treating neuropathic pain and higher doses of opioid and/or combination therapy are often required for these conditions[11]. High doses of opioids can lead to both tolerance-associated hyperalgesia (an increased sensitivity to pain), putting patients at risk of suffering from insufficient analgesia, and debilitating side effects, especially after repeated administration for the treatment of long-term pain. In response to this tolerance-associated hyperalgesia, the dose of the opioid is increased which in turn can increase side effects. An increase in side effects may then lead to a decrease in analgesic dose resulting in the patient experiencing more pain. This creates a vicious circle of insufficient analgesia and side effects, both of which can lead to low patient compliance and treatment discontinuation[12–14]. These problems can lead to a reluctance to prescribe them, particularly for non-cancer pain[7,9,15]. Overly restrictive laws and regulations may also impede the use of opioids in some countries[16]. Further limitations of classical opioids include the need for dose titration, treatment reliability and patient satisfaction, needs and worries[12,13,17,18].

These limitations highlight the need for new treatments for long-term pain with strong efficacy comparable to classical potent opioids, but with fewer adverse effects. Although there have been some recent developments in terms of delivery mechanisms and combination therapies to attempt to mitigate side effects, there is room for more improvement at the molecular level.

This review will provide an overview of the historical development of classical opioids and their use, outlining the mechanism of action of opioids, and the target receptor subtypes. Differences in commonly used potent opioids will be outlined, with specific reference to chemical structures, receptor affinities and side-effect profiles. Finally, recent developments in treatments for long-term, severe pain (opioid and non-opioid) will be highlighted, including a discussion of tapentadol as an example of one type of novel approach.

History of classical opioids development and usage

Naturally occurring opioids, derived from the opium poppy, have been used in pain management for thousands of years, and today opioids continue to be one of the most commonly prescribed treatments for pain. Opioids can broadly be separated into four different classes: the endogenous opioids, which are produced naturally in the body (namely, dynorphins, enkephalins, endorphins, endomorphins and nociceptin/orphanin); the natural opioids, alkaloids extracted from the resin of the opium poppy (e.g. morphine, codeine, thebaine and noscapine; sometimes also entitled opiates); semi-synthetic opioids, created from natural opioids (e.g. diamorphine, oxymorphone, oxycodone, buprenorphine); and fully synthetic opioids (e.g. methadone and pethidine)[19]. The natural opioid morphine was first extracted from the opium poppy at the beginning of the 19th century, and in the 20th century synthetic opioids were developed, both of which had a dramatic effect on the increased use of opioids in pain management.

Although the development of opioids was important for many forms of acute and chronic pain, there was growing concern throughout the majority of the 20th century that the use of opioids in the treatment of long-term pain was to be avoided owing to the adverse effect of addiction and diminishing efficacy over time, due to tolerance development[19]. However, the use of classical opioids for the treatment of pain has steadily been increasing and classical opioids are now commonly used in the treatment of acute and long-term cancer pain, as well as long-term non-cancer pain[7,20]. The use of opioids has often been considered as the last option available to patients suffering from long-term pain, and they have been used very restrictively for the elderly due to increased adverse effects and impaired elimination. However, the recently published American Geriatric Society (AGS) guidelines state that in properly selected patients, opioid analgesics constitute an indispensable treatment in non-cancer pain and AGS conclude that "all patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy"[21], demonstrating their continued clinical utility in pain management. This is important because early, effective treatment of several different acute pain conditions can prevent them developing into chronic pain conditions[6].

Despite the increased use of classical opioids in the treatment of long-term pain, there remains a need for evidence-based and/or patient need-based prescribing guidelines, to ensure that patients receive optimal analgesia. Evidence suggests that physicians' prescribing practices are more likely to be influenced by habit or tradition, rather than by the needs of the individual patient[22,23]. For example, although the natural opioid morphine and the semi-synthetic opioid oxycodone have equivalent analgesic efficacy[24], oxycodone is often prescribed, despite being more costly and having no obvious clinical advantage[25]. So-called equipotent doses between opioids are mainly based on single-dose studies on specific pain types, making their relevance for an individual patient doubtful, especially in long-term opioid use.

The pain system

Although there are many causes of long-term pain, it is typically described as nociceptive – where pain receptors are activated following tissue injury – or neuropathic, with pain arising as a direct consequence of a lesion or disease affecting the somatosensory system[26].

Both acute and long-term pain are induced by mechanisms involving the peripheral and central nervous system. However, pain experienced by patients can also involve a complex interaction of molecular signals, including neurotransmitters, peptides, cytokines and hormones[27]. Thus, the pain system is a complex interaction of different molecular mechanisms and pathways involving various cellular, protein and phospholipid components. In this way, the pain system can be compared with the coagulation system in terms of its complexity and the integration of different activating signals. There is one major difference though: we are quite familiar with the pro- and antithrombotic properties of the coagulation system, with the possibility of interaction through pharmaceutical compounds within the cascade to correct a defect. Within the pain system, we do not fully appreciate the pro- and anti-nociceptive properties and do not yet fully know how to interact pharmaceutically within the 'pain cascade'. Long-term pain in particular is often a heterogeneous condition involving many different processes and a neuropathic pain component is often involved, for example in chronic back pain, resulting in more severe, complex, and costly treatment[28]. Moreover, psychological factors can exacerbate chronic pain. Fear of pain (catastrophising) and avoidance of pain-inducing movement (kinaesiophobia) have been shown to exacerbate chronic back pain[29], and negative affect, such as anger and sadness, may act as risk factors for pain amplification[30]. Therefore, in order to treat patients with long-term pain effectively, it is important to adopt a biopsychosocial model, targeting nociceptive, neuropathic and psychological mechanisms.

Opioids and opioid receptors

Classical opioids work by binding to opioid receptors which are found principally in the CNS and gastrointestinal tract. There are four major opioid receptors: the classical μ (mu), κ (kappa) and δ (delta)[31–33], and the non-classical nociceptin receptor NOP[34]. For each of these there are also subtypes (μ_1, μ_2, κ_1, κ_2, κ_3, δ_1, δ_2 and orl_1) which have been suggested, but not confirmed, based on evidence from functional studies[35]. The opioid receptors are transmembrane spanning G-protein coupled receptors which act on GABAergic neurotransmission, and are activated under natural conditions by the endogenous opioids[36].

The different classes of opioid receptors are associated with distinct neurological responses, with those involved in pain modulation found in both the CNS and the peripheral nervous system[35,37,38]. The μ-opioid receptors mediate spinal and supraspinal analgesia, reduced gastrointestinal tract motility, respiratory depression, euphoria and sedation. The κ- and δ-opioid receptors have also been implicated in spinal and supraspinal analgesia. In addition to these effects, the κ-opioid receptors mediate peripheral analgesia, sedation, respiratory depression, dyspnoea and dysphoria. In contrast to the μ- and κ-opioid receptors, much less is known about the δ-opioid receptors, which

are located within the brain and are thought to play a role in psychomimetic and dysphoric effects[37]. It is important to recognise that the endogenous opioid system affects several physiological systems including reward systems, the immune system, learning, memory functions and stress response, demonstrating how complex the effects of long-term opioid treatment can be.

The different opioid receptors have important implications for the use of opioids in pain management. Whether the opioid is an opioid receptor agonist or antagonist, together with both the type of receptor to which it binds and the extent of receptor binding, will affect how effective and how well tolerated the different opioids are in the treatment of pain (Table 1)[38,39]. Despite the presence of these different opioid receptor classes, opioid drugs predominantly mediate their analgesic effects through activation of μ-opioid receptors[19].

Side effects and tolerance

The analgesic effect of opioids may be accompanied by undesired side effects caused by activation of opioid receptors involved in other functions. Opioids have a small therapeutic range where small changes in plasma concentration can produce large changes in effect. The most common adverse effects of opioids include gastrointestinal effects (constipation, nausea and vomiting) and sedation[40,41].

Inhibition of gut motility is mediated by inhibition of both peripheral and central μ- and κ-opioid receptors and can lead to constipation[42]. The precise mechanism of opioid-induced nausea and vomiting is not known; however, the vomiting centre in the medulla oblongata of the brain is known to co-ordinate stimuli that lead to these effects. The gastrointestinal tract, the vestibular apparatus, the cerebral cortex and the chemoreceptor trigger zone (CTZ) all feed information to this centre and opioid-mediated nausea and vomiting may be caused by stimulation of the neurones in the CTZ, inhibition of gut motility, stimulation of the vestibular apparatus or by reducing the inhibitory input into this region[43].

In addition to side effects concerning the gastrointestinal tract, opioids can adversely affect the CNS through lowering the level of consciousness, disturbing cognition and motor coordination, and by causing toxic effects on neurons. Sedation is a common effect of opioids, possibly due to a decrease in central cholinergic activity or neurotoxic metabolites[44]. In the treatment of long-term pain, neurotoxicity is of particular concern because it is increasingly reported with prolonged administration of high-dose opioids[41]. For example, although the precise underlying mechanisms of development of hyperalgesia are still unclear, one possible contributing factor may be its occurrence as a result of the neurotoxic action of opioids, through apoptosis of GABAergic cells in the spinal cord dorsal horn, neuroexcitatory effects of glucuronide metabolites and NMDA receptor agonism[45,46].

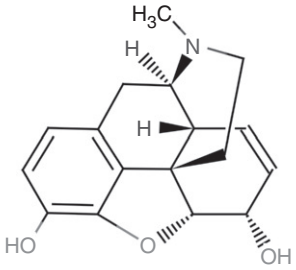
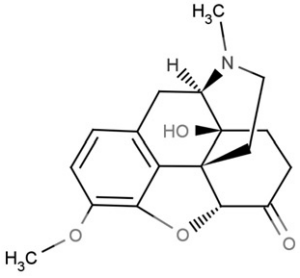
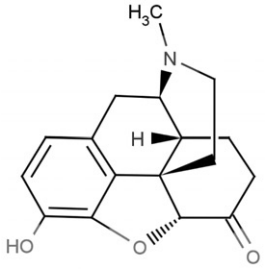
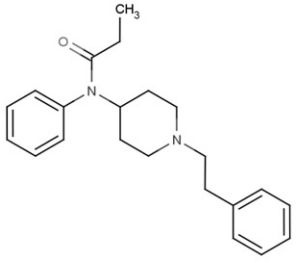
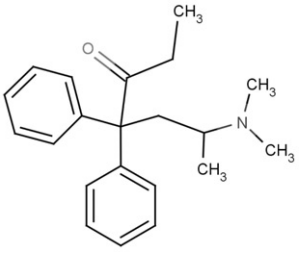
The opioid effects on the CNS can also lead to the development of analgesic tolerance, often associated with hyperalgesia[44]. Analgesic tolerance to the effects of opioids is reported in approximately 15% of patients[41], although the incidence is probably different depending on the patient population and substance used, and is characterised by a shortened duration of action and decreased analgesia despite increases in dose. Although the precise mechanism by which analgesic tolerance develops is unclear, it is thought to involve modulation of the opioid receptors and NMDA receptor activation[41].

Before initiating opioid treatment, the prescribing physician must determine the pain mechanism and establish its sensitivity to opioids. Although opioids may provide analgesia for patients with long-term pain, the adverse effects associated with their use can lead to patients discontinuing treatment. Opioid rotation is used commonly in the clinic to avoid further adverse effects, although the scientific basis for this is lacking[47]. A recent systematic review of 17 trials involving non-cancer pain patients taking opioids demonstrated that adverse events were a key reason for discontinuation[18]. This is in agreement with other reviews, which have shown that up to one in five patients discontinue therapy due to adverse events[13]. However, despite the undesired side effects associated with opioid use, there is evidence that patients can develop coping strategies to balance the relationship between pain relief and side effects, with patients accepting more pain for a reduction in sedation and nausea[48]. These results highlight that there remains a need for new therapies with good analgesic effects, but with better tolerability profiles to ensure that patients experience minimal side effects without compromising their pain relief[49].

Dependency

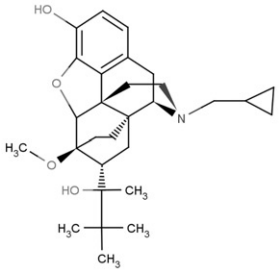
One of the main concerns of physicians when prescribing opioids is that the daily doses used for pain relief may predispose patients to drug dependence. In the context of analgesic pharmacotherapy, physical dependency is a state where the body becomes physiologically dependent on the drug such that without the drug pain recurs. For opioids, physical dependency usually also involves withdrawal symptoms if the drug is discontinued abruptly. Addiction is a state of physical and psychological dependency where the patient develops drug-seeking behaviour and continuous use despite negative consequences of use. Tolerance represents the need to increase opioid dosage to obtain the same effect of pain relief.

Table 1. Efficacy and adverse effects of classical strong opioids.

Agent	Structure[a]	Opioid receptor bound	Adverse effects	Type of pain treated
Morphine[35]		μ-opioid receptor agonist, with some activity at κ- and δ-opioid receptors	Typical of opioid analgesics[b] Also adverse events associated with excess histamine release Active metabolite (M6G)	Relief of moderate-to-severe pain, particularly that associated with cancer, myocardial infarction and surgery
Oxycodone[35]		μ-opioid receptor agonist, with some evidence of activity at κ-opioid receptors	Typical of opioid analgesics[b]	Moderate-to-severe pain
Hydromorphone[35]		μ- and δ-opioid receptor agonist	Typical of opioid analgesics[b]	Useful alternative to morphine in the treatment of moderate-to-severe pain
Fentanyl[35]		μ-opioid receptor agonist	Typical of opioid analgesics[b] Patch formulations have been associated with local skin reactions Complicated pharmacokinetics	Adjunct to general anaesthesia and as an anaesthetic for induction and maintenance Patch formulation primarily for moderate to severe pain
Methadone[35]		μ-opioid receptor agonist	Typical of opioid analgesics[b] QT prolongation and torsades de pointes have been reported Injection-site pain Complicated pharmacokinetics	Substitution therapy for treatment of opioid dependence Pain sustained by NMDA receptor activity Moderate-to-severe pain

(*continued*)

Table 1. Continued.

Agent	Structure[a]	Opioid receptor bound	Adverse effects	Type of pain treated
Buprenorphine[35]		Partial agonist at μ-opioid receptors (although analgesic effect in humans is equivalent to full agonist activity) and κ-opioid receptor antagonist	Typical of opioid analgesics[b]; can be used in patients with renal impairment without dose adjustment Patch formulations have been associated with local skin reactions	Relief of moderate-to-severe pain Also used as substitution therapy for treatment of opioid dependence

[a]Images from the National Library of Medicine within the public domain (URL: http://chem.sis.nlm.nih.gov/chemidplus/).
[b]Adverse effects typical of opioid analgesics, the most common of which include nausea, vomiting, constipation, drowsiness and confusion. More serious effects that are seen at higher doses include respiratory depression.

Certain population subgroups, such as those with a history of drug abuse, are at higher risk of opioid addiction[50]. Dependency problems are more commonly associated with non-cancer pain[51–53]; however, a recent systematic review of clinical trials involving patients with long-term non-cancer pain receiving opioids showed that signs of dependence and misuse were relatively low and reported in 0.05% and 0.43% of patients, respectively[18]. An initial assessment of a patient's risk of opioid dependency should be made before therapy begins, and regular monitoring and the use of screening instruments, such as the *Opioid Risk Tool*, the *Screener and Opioid Assessment for Patients with Pain-Revised* and the *Screening Instrument for Substance Abuse Potential*, during treatment can be successfully used to balance the efficacy of opioids whilst minimising the risk of dependence[54–56]. Slow-release formulations are most often preferable, but regardless of the opioid used in the treatment of long-term pain, increased communication between patients and their physician about dependency concerns and unmet needs can greatly improve pain management[57]. An agreement between the patient and the treating physician should be made before treatment begins to ensure that lack of either pain relief or increased QoL results in discontinuation of the opioid treatment.

New developments

Maintaining patient QoL and functionality whilst continuing to provide effective analgesia continues to be an unmet need of patients with long-term pain, with up to 40% of patients from the European pain survey reporting inadequate management of their pain. Moreover, a third of respondents were not taking any pain medication and 14% of these cases were because they discontinued earlier treatment owing to side effects[1]. Both new treatment strategies to improve tolerability to classical opioids (opioid-sparing analgesics, co-administered peripheral opioid antagonists, and alternative delivery mechanisms) and the development of novel non-classical opioids with intrinsic sustained efficacy and reduced side effect profiles, may help to improve the care received by patients with long-term pain.

Opioid sparing drug regimens: combination of substances

Opioid-sparing drug regimens, where a non-opioid analgesic is given in addition to an opioid, can be used to help reduce the total dose of opioids as a result of analgesic synergy between the opioid and non-opioid agents. This technique has proved particularly useful in patients with neuropathic pain[58], where agents such as controlled-release oxycodone and pregabalin have been used in free combination[59]. Some other examples include the use of oxycodone and paracetamol in fixed-dose combination for moderate-to-severe chronic pain[60]; and ketamine[61], gabapentin or pregabalin[62] for post-operative pain. However, the use of two different substance classes in this way can lead to risks associated with drug–drug interactions as well as additional side effects. Careful adjustment and monitoring of both substances is, therefore, required to ensure that efficacy is maintained whilst alleviating side effects[63].

Peripheral opioid antagonists

The development of peripheral opioid receptor antagonists have been designed to reduce opioid-induced bowel dysfunction by targeting opioid receptors in the gastrointestinal tract, whilst preserving the central opioid receptor activity of concurrently administered opioid analgesics. Early preclinical and clinical studies of two such agents, alvimopan and methylnaltrexone, demonstrated that both of these agents were better than placebo at reducing the

increased gastrointestinal transit time and constipation caused by opioid treatment[64]. Moreover, they were associated with fewer adverse events compared with classical opioids, while preserving opioid-induced analgesia. A subcutaneous formulation of methylnaltrexone has now been approved in Europe, Australia, Chile, Venezuela, Canada and the US for the treatment of opioid-induced constipation, while alvimopan is not FDA-indicated for the treatment of opioid-induced constipation due to safety concerns after a phase III study[65]. A similar effect of ameliorating opioid-induced bowel dysfunction in patients with severe long-term pain has been observed with treatment of oral prolonged-release oxycodone/naloxone, which combines a strong opioid receptor agonist with naloxone, which serves as a peripherally acting opioid receptor antagonist when given as an oral formulation[66–68]. However, the strategy of peripheral opioid antagonism may be less useful in chronic pain conditions with a marked inflammatory component, such as rheumatoid arthritis, where opioids have been shown to provide analgesia and anti-inflammatory effects through interaction with peripherally expressed κ-opioid receptors[69,70].

Drug delivery mechanisms

In addition to the use of opioid sparing drug regimens/combinations and peripherally acting opioid antagonists, there have also been new developments in delivery mechanisms of classical opioids to improve tolerability. Controlled transdermal delivery (in the form of patches) of fentanyl and buprenorphine have been associated with a lower incidence of constipation (compared with systemic morphine) and in the case of transdermal buprenorphine, CNS side effects (compared with other classical opioids)[71–75].

Novel molecular developments

Evidence is accumulating for the role of glial cell activation in pain modulation, including neuropathic pain states, secondary to the release of neuroexcitatory and proinflammatory mediators[76]. The identification that opioids can induce glial cell activation via nonstereoselective binding to toll-like receptor 4 (TLR4) as a mechanism for opioid-induced undesired effects such as tolerance, withdrawal, respiratory depression and hyperalgesia[77,78], has led to interest in the development of glial cell modulators for the reduction of opioid-induced side effects and enhancement of opioid-induced analgesia[79]. One such agent, ibudilast (AV-411), which suppresses glial cell activity and has TLR4 activity, is in clinical development for the treatment of neuropathic pain and for the enhancement of opioid analgesia on the basis of preclinical data showing efficacy in rat models of neuropathic pain, enhancement of morphine activity and reduction in morphine tolerance and withdrawal[80]. Other agents that improve the efficacy of opioids in animal models include minocycline, propentofylline (SLC022), interleukins, soluble tumour necrosis factor receptor, and TLR4 antagonists[80].

Respiratory depression is one of the most feared opioid-related side effects and can limit opioid effectiveness, particularly in the postoperative setting. Whilst respiratory depression can be effectively treated by the opioid antagonists naloxone and naltrexone, analgesic efficacy is also reduced. Agents such as the α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid (AMPA) receptor agonists (ampakines) and minocycline have been shown to suppress opioid-induced respiratory depression without affecting analgesic efficacy[81,82]. Serotonin (5-hydroxy tryptamine,5-HT) agonists, by virtue of the role of 5-HT neurones in the maintenance of respiratory drive, have also been evaluated for the suppression of opioid-induced respiratory depression, but not found to be effective[82].

In contrast to the approaches designed to mitigate the adverse effects of classical opioids outlined above, novel non-classical molecules with similar efficacy but reduced side effects are in clinical development. One such example is tapentadol, a novel centrally acting analgesic combining two mechanisms of action, μ-opioid receptor agonism and noradrenaline reuptake inhibition, in a single molecule[83,84]. Preclinical studies of tapentadol have shown that it is effective at relieving pain in a number of different pain models including nociceptive, inflammatory, visceral, mono- and polyneuropathic models. A role of noradrenaline in the analgesic efficacy was directly demonstrated in some of the models[84]. The two different mechanisms of action of tapentadol are thought to provide an opioid-sparing effect for patients, thereby reducing opioid-related side effects. The analgesic efficacy is only two to three times lower than that of morphine despite a 50-fold lower affinity for the μ-opioid receptor[84,85]. In contrast to combining two separate drugs with different mode of action, the combination of two analgesic mechanisms in one drug has the added benefit of allowing the targeting of different pain systems without disruption of efficacy owing to problems with drug–drug interactions. Clinical studies have confirmed the preclinical findings that tapentadol provides effective relief of nociceptive and neuropathic pain and is associated with a lower incidence of adverse events compared with oxycodone, leading to a lower treatment discontinuation rate[84,85].

Conclusions

Classical opioids are important in the management of long-term pain and have the potential for wider use amongst the general population in carefully selected

patients. Current management of patients with long-term pain using opioids is often limited by side effects, which can lead to insufficient pain relief and patient discontinuation of treatment. Dependency on opioids, particularly in non-cancer pain, is an adverse effect frequently feared by the patient and physician; however, this can often be avoided by maintaining regular physician–patient contact, which has the added benefit of making treatment more effective. Treatment of long-term pain with classical opioids should not be completely avoided, although the choice of opioid used for treatment should be considered carefully and be based on sound scientific knowledge rather than physician preferences or local prescribing traditions. There remains a need to improve the balance between the efficacy and side effects of analgesics used in the treatment of long-term pain, so that patients receive adequate pain relief in addition to improvements in QoL. A variety of agents are in development without intrinsic opioid activity that reduce opioid-related side effects and enhance opioid analgesia, the most promising of which appear to be the glial cell modulators and ampakines. In addition, tapentadol, a new compound with combined opioidergic and monoaminergic activity within the same molecule has recently been registered, representing a new drug class (MOR-NRI), having similar efficacy to classical opioids, but being associated with fewer and less severe side effects. Innovative treatments with these properties would hopefully reduce the number of treatment discontinuations, which would in turn improve patient QoL. Several clinical studies of new treatments for long-term pain are currently taking place, and the results of these trials are eagerly awaited for the future of long-term pain management.

Transparency

Declaration of funding
Grünenthal GmbH funded this paper.

Declaration of financial/other relationships
K.A. has disclosed that he is a member of the Advisory Board on Change Pain and a clinical investigator of tapentadol, for Grünenthal GmbH. He has given lectures in pain management sponsored by Grünenthal Sweden AB. No honorarium was provided for the writing of this review.

Acknowledgement
Medical writing assistance was provided by Fiona Murray-Zmijewski (Wolters Kluwer) and was funded by Grünenthal GmbH.

References

1. Breivik H, Collett B, Ventafridda V, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006;10:287-333
2. Silvemark AJ, Kallmen H, Portala K, et al. Life satisfaction in patients with long-term non-malignant pain – relating LiSat-11 to the Multidimensional Pain Inventory (MPI). Health Qual Life Outcomes 2008;6:70
3. Blyth FM, March LM, Brnabic AJ, et al. Chronic pain and frequent use of health care. Pain 2004;111:51-8
4. International Association for the Study of Pain, European Federation of IASP Chapters. Unrelieved pain is a major global healthcare problem (IASP EFIC Factsheet 4A). 2005. Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Home&section=2004_2005_Right_to_Pain_Relief&template=/CM/ContentDisplay.cfm&ContentFileID=311 [Last accessed 15 October 2010]
5. Gardea MA, Gatchel RJ. Interdisciplinary treatment of chronic pain. Curr Rev Pain 2000;4:18-23
6. Gatchel RJ, Polatin PB, Noe C, et al. Treatment- and cost-effectiveness of early intervention for acute low-back pain patients: a one-year prospective study. J Occup Rehabil 2003;13:1-9
7. Ballantyne JC, Mao J. Opioid therapy for chronic pain. N Engl J Med 2003;349:1943-53
8. Hall EJ, Sykes NP. Analgesia for patients with advanced disease: I. Postgrad Med J 2004;80:148-54
9. McNicol E, Horowicz-Mehler N, Fisk RA, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. J Pain 2003;4:231-56
10. Collett BJ. Opioid tolerance: the clinical perspective. Br J Anaesth 1998;81:58-68
11. Baron R. Neuropathic pain: a clinical perspective. Handb Exp Pharmacol 2009:3-30
12. Kalso E, Edwards JE, Moore RA, et al. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain 2004;112:372-80
13. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. Arthritis Res Ther 2005;7:R1046-51
14. Ollat H, Cesaro P. Pharmacology of neuropathic pain. Clin Neuropharmacol 1995;18:391-404
15. Turk DC. Clinicians' attitudes about prolonged use of opioids and the issue of patient heterogeneity. J Pain Symptom Manag 1996;11:218-30
16. World Health Organization. Achieving Balance in National Opioids Control Policy. Guidelines for Assessment. 2000. Available at: http://www.painpolicy.wisc.edu/publicat/00whoabi/00whoabi.htm [Last accessed 15 October 2010]
17. Chou R, Clark E, Helfand M. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review. J Pain Symptom Manag 2003;26:1026-48
18. Noble M, Tregear SJ, Treadwell JR, et al. Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. J Pain Symptom Manag 2008;35:214-28
19. Rosenblum A, Marsch LA, Joseph H, et al. Opioids and the treatment of chronic pain: controversies, current status, and future directions. Exp Clin Psychopharmacol 2008;16:405-16
20. Pergolizzi J, Boger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain Pract 2008;8:287-313
21. American Geriatrics Society. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc 2009;57:1331-46
22. Heins A, Grammas M, Heins JK, et al. Determinants of variation in analgesic and opioid prescribing practice in an emergency department. J Opioid Manag 2006;2:335-40
23. Victor TW, Alvarez NA, Gould E. Opioid prescribing practices in chronic pain management: guidelines do not sufficiently influence clinical practice. J Pain 2009;10:1051-7
24. Reid CM, Martin RM, Sterne JA, et al. Oxycodone for cancer-related pain: meta-analysis of randomized controlled trials. Arch Intern Med 2006;166:837-43

25. Wiffen PJ, McQuay HJ. Oral morphine for cancer pain. Cochrane Database Syst Rev 2007:CD003868
26. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008; 70:1630-5
27. Chapman CR, Tuckett RP, Song CW. Pain and stress in a systems perspective: reciprocal neural, endocrine, and immune interactions. J Pain 2008;9: 122-45
28. Schmidt CO, Schweikert B, Wenig CM, et al. Modelling the prevalence and cost of back pain with neuropathic components in the general population. Eur J Pain 2009;13:1030-5
29. Picavet HS, Vlaeyen JW, Schouten JS. Pain catastrophizing and kinesiophobia: predictors of chronic low back pain. Am J Epidemiol 2002;156:1028-34
30. van Middendorp H, Lumley MA, Jacobs JW, et al. The effects of anger and sadness on clinical pain reports and experimentally-induced pain thresholds in women with and without fibromyalgia. Arthritis Care Res (Hoboken) 2010; 62:1370-6
31. Chen Y, Mestek A, Liu J, et al. Molecular cloning and functional expression of a mu-opioid receptor from rat brain. Mol Pharmacol 1993;44:8-12
32. Martin WR, Eades CG, Thompson JA, et al. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J Pharmacol Exp Ther 1976;197:517-32
33. Nicholson B. Responsible prescribing of opioids for the management of chronic pain. Drugs 2003;63:17-32
34. Mollereau C, Mouledous L. Tissue distribution of the opioid receptor-like (ORL1) receptor. Peptides 2000;21:907-17
35. Gutstein H, Akil H. Opioid analgesics. In: Brunton L, Lazo J, Parker K (eds). Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th edn. New York: McGraw-Hill, 2006:547-90
36. Law PY, Wong YH, Loh HH. Molecular mechanisms and regulation of opioid receptor signaling. Annu Rev Pharmacol Toxicol 2000;40:389-430
37. Lomberk G, Cruciani R, Urrutia R. Primers on molecular pathways – pain and opioid receptors, I. Pancreatology 2008;8:544-5
38. Sweetman S. Martindale. The Complete Drug Reference, 36th edn. London: Pharmaceutical Press, 2009
39. Corbett AD, Henderson G, McKnight AT, et al. 75 years of opioid research: the exciting but vain quest for the Holy Grail. Br J Pharmacol 2006;147(Suppl. 1): S153-62
40. Argoff CE, Silvershein DI. A comparison of long- and short-acting opioids for the treatment of chronic noncancer pain: tailoring therapy to meet patient needs. Mayo Clin Proc 2009;84:602-12
41. Vella-Brincat J, Macleod AD. Adverse effects of opioids on the central nervous systems of palliative care patients. J Pain Palliat Care Pharmacother 2007; 21:15-25
42. Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. Drugs 2003;63:649-71
43. Herndon CM, Jackson 2nd KC, Hallin PA. Management of opioid-induced gastrointestinal effects in patients receiving palliative care. Pharmacotherapy 2002;22:240-50
44. Harris JD. Management of expected and unexpected opioid-related side effects. Clin J Pain 2008;24(Suppl. 10):S8-S13
45. Mao J, Sung B, Ji RR, Lim G. Neuronal apoptosis associated with morphine tolerance: evidence for an opioid-induced neurotoxic mechanism. J Neurosci 2002;22:7650-61
46. Mercadante S, Ferrera P, Villari P, et al. Hyperalgesia: an emerging iatrogenic syndrome. J Pain Symptom Manag 2003;26:769-75
47. Quigley C. Opioid switching to improve pain relief and drug tolerability. Cochrane Database Syst Rev 2004:CD004847
48. Blake S, Ruel B, Seamark C, et al. Experiences of patients requiring strong opioid drugs for chronic non-cancer pain: a patient-initiated study. Br J Gen Pract 2007;57:101-8
49. Manchikanti L, Manchikanti KN, Pampati V, et al. Prevalence of side effects of prolonged low or moderate dose opioid therapy with concomitant benzodiazepine and/or antidepressant therapy in chronic non-cancer pain. Pain Physician 2009;12:259-67
50. Portenoy RK, Farrar JT, Backonja MM, et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. Clin J Pain 2007;23:287-99
51. Edlund MJ, Steffick D, Hudson T, et al. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. Pain 2007;129:355-62
52. Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. BMC Health Serv Res 2006;6:46
53. Reid MC, Engles-Horton LL, Weber MB, et al. Use of opioid medications for chronic noncancer pain syndromes in primary care. J Gen Intern Med 2002;17:173-9
54. Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. Pain Med 2005;6:107-12
55. Passik SD. Issues in long-term opioid therapy: unmet needs, risks, and solutions. Mayo Clin Proc 2009;84:593-601
56. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. Pain Med 2005; 6:432-42
57. McCarberg BH, Nicholson BD, Todd KH, et al. The impact of pain on quality of life and the unmet needs of pain management: results from pain sufferers and physicians participating in an Internet survey. Am J Ther 2008;15:312-20
58. Davis MP, Walsh D, Lagman R, et al. Controversies in pharmacotherapy of pain management. Lancet Oncol 2005;6:696-704
59. Gatti A, Sabato AF, Occhioni R, et al. Controlled-release oxycodone and pregabalin in the treatment of neuropathic pain: results of a multicenter Italian study. Eur Neurol 2009;61:129-37
60. Gatti A, Sabato E, Di Paolo AR, et al. Oxycodone/paracetamol: a low-dose synergic combination useful in different types of pain. Clin Drug Investig 2010;30(Suppl. 2):3-14
61. Bell RF, Dahl JB, Moore RA, et al. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev 2006:CD004603
62. Dauri M, Faria S, Gatti A, et al. Gabapentin and pregabalin for the acute postoperative pain management. A systematic-narrative review of the recent clinical evidences. Curr Drug Targets 2009;10:716-33
63. Geppetti P, Benemei S. Pain treatment with opioids: achieving the minimal effective and the minimal interacting dose. Clin Drug Investig 2009;29 (Suppl. 1):3-16
64. DeHaven-Hudkins DL, DeHaven RN, Little PJ, et al. The involvement of the mu-opioid receptor in gastrointestinal pathophysiology: therapeutic opportunities for antagonism at this receptor. Pharmacol Ther 2008; 117:162-87
65. Becker G, Blum HE. Novel opioid antagonists for opioid-induced bowel dysfunction and postoperative ileus. Lancet 2009;373:1198-206
66. Lowenstein O, Leyendecker P, Hopp M, et al. Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: a randomised controlled trial. Expert Opin Pharmacother 2009;10:531-43
67. Nadstawek J, Leyendecker P, Hopp M, et al. Patient assessment of a novel therapeutic approach for the treatment of severe, chronic pain. Int J Clin Pract 2008;62:1159-67
68. Vondrackova D, Leyendecker P, Meissner W, et al. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. J Pain 2008;9:1144-54
69. Stein C, Lang LJ. Peripheral mechanisms of opioid analgesia. Curr Opin Pharmacol 2009;9:3-8
70. Walker JS. Anti-inflammatory effects of opioids. Adv Exp Med Biol 2003;521: 148-60
71. Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. J Pain Symptom Manag 1997; 13:254-61
72. Allan L, Richarz U, Simpson K, et al. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naive patients with chronic low back pain. Spine (Phila Pa 1976) 2005;30:2484-90

73. Donner B, Zenz M, Tryba M, et al. Direct conversion from oral morphine to transdermal fentanyl: a multicenter study in patients with cancer pain. Pain 1996;64:527-34
74. Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. Eur J Pain 2009;13:219-30
75. Shipton EA. Safety and tolerability of buprenorphine. In: Budd K, Raffa R (eds). Buprenorphine – The Unique Opioid Analgesic. Stuttgart: Thieme Verlag KG, 2005:92-101
76. Watkins LR, Hutchinson MR, Rice KC, et al. The 'toll' of opioid-induced glial activation: improving the clinical efficacy of opioids by targeting glia. Trends Pharmacol Sci 2009;30:581-91
77. Hutchinson MR, Bland ST, Johnson KW, et al. Opioid-induced glial activation: mechanisms of activation and implications for opioid analgesia, dependence, and reward. Scientific World Journal 2007;7:98-111
78. Hutchinson MR, Zhang Y, Shridhar M, et al. Evidence that opioids may have toll-like receptor 4 and MD-2 effects. Brain Behav Immun 2010;24:83-95
79. Hameed H, Hameed M, Christo PJ. The effect of morphine on glial cells as a potential therapeutic target for pharmacological development of analgesic drugs. Curr Pain Headache Rep 2010;14:96-104
80. Ledeboer A, Hutchinson MR, Watkins LR, et al. Ibudilast (AV-411). A new class therapeutic candidate for neuropathic pain and opioid withdrawal syndromes. Expert Opin Investig Drugs 2007;16:935-50
81. Oertel BG, Felden L, Tran PV, et al. Selective antagonism of opioid-induced ventilatory depression by an ampakine molecule in humans without loss of opioid analgesia. Clin Pharmacol Ther 2010;87:204-11
82. Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. Anesthesiology 2010;112:226-38
83. Hartrick CT. Tapentadol immediate release for the relief of moderate-to-severe acute pain. Expert Opin Pharmacother 2009;10:2687-96
84. Tzschentke TM, Jahnel U, Kogel B, et al. Tapentadol hydrochloride: A next-generation, centrally acting analgesic with two mechanisms of action in a single molecule. Drugs Today (Barc) 2009;45:483-96
85. Tzschentke TM, Christoph T, Kogel B, et al. (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel mu-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. J Pharmacol Exp Ther 2007;323:265-76

