Opioids in chronic nonmalignant pain

Opioid consumption is increasing worldwide (in both developed and underdeveloped regions) and, from 1990–2010 this increase was 1,100%. Many experts consider such a shift from undertreatment to overtreatment to be associated with increased inappropriate treatment, particularly in special populations (e.g. patients with chronic nonmalignant pain) and populations at increased risk of opioid-related side effects (e.g. elderly patients). However, the worldwide increase in opioid consumption is not driven solely by medical reasons. It is also driven by nonmedical reasons such as the economic development of certain countries, as measured by the World Health Organization (WHO) Human Development Index (HDI). With increasing HDI, opioid consumption (expressed as mg morphine equivalents [MEQs] per resident per year) has steadily increased in several WHO regions. In 1985, the WHO introduced an analgesic pain ladder approach for opioid prescribing for nonchronic, noncancer pain in underdeveloped countries. This approach was also adopted in industrialised regions and led to a marked increase in opioid prescribing over the next 2 years. Subsequently, opioid consumption again increased steadily in line with increasing HDI in almost all regions in the world (data for 2010 are shown in Figure 1).

These data suggest that opioid use is not related directly to pain prevalence, but may be more related to economic development. In Germany, HDI is 0.885 and opioid consumption is 376 mg MEQ per resident per year. Based on a population estimate of 82.3 million, this equates to annual MEQ consumption of 30.95 tonnes; this is sixth-ranked in the world. In Australia, HDI is 0.943, and opioid consumption is 352 mg MEQ per resident per year. Based on a population estimate of 22.3 million, this equates to annual MEQ consumption of 7.85 tonnes, which is seventh-ranked in the world. Corresponding figures for Canada, which is first-ranked, are HDI 0.888, and 753 mg MEQ per resident per year; this is twice as high as the figure for Germany and Australia. In the US, annual opioid consumption per capita is 693 mg MEQ, or an annual total of 215.1 MEQ tonnes for the entire country; the latter figure is more than twice the combined total (99.6 MEQ tonnes) for the other 9 top-ranked countries. In Australia and Germany, morphine prescribing has been decreasing since 2005; conversely, oxycodone prescribing has increased since introduction of the drug to the market (Figure 2).

Abbreviations used in this review:
BFI = Bax evil Function Index; CI = confidence interval; FDC = fixed-dose combination; FMRI = functional magnetic resonance imaging; GI = gastrointestinal; HDI = Human Development Index; MD = mean difference; MEQ = morphine equivalents; NSAID = nonsteroidal anti-inflammatory drug; OIBD = opioid induced bowel dysfunction; PR = prolonged release; QoL = quality of life; SBP = subacute back pain; SR = sustained-release; VAS = visual analogue scale; WHO = World Health Organization.

Figure 1. Increased opioid consumption in line with increased Human Development Index (2010 data).
LOG = logarithmic scale; MEQ = morphine equivalents.'
Oxycodone versus morphine

The above data raise the question of whether there is actually a scientific rationale for using oxycodone ahead of morphine. Indeed, the WHO stipulates that morphine is the ‘gold standard’ opioid, but from the scientific standpoint, clear reasons exist to prefer oxycodone over morphine:

- **Oxycodone has superior oral bioavailability to morphine (60–87% versus 30%).**
- **Morphine has active 3- and 6-glucuronide metabolites, which are potent μ-opioid receptor agonists. However, these metabolites have a significantly longer half-life than the parent compound. Therefore, patients who require a clear dose-response relationship, but who may experience problems with metabolite excretion (e.g. elderly patients with impaired renal function), may have side effects due to metabolite accumulation. Morphine is often inappropriate for the treatment of elderly patients or those with renal dysfunction.**
- **Oxycodone also has an active metabolite, oxymorphone, but this has a similar pharmacokinetic profile to that of the parent compound. Therefore, if oxycodone is selected appropriately and tailored to individual patient needs, the oxymorphone metabolite is unlikely to have a bearing on clinical use of the parent compound.**
- **Clear evidence now exists from animal and human studies that morphine and fentanyl may exacerbate immunosuppression, whereas oxycodone, buprenorphine and tapentadol do not.**
- **Both morphine and oxycodone are potent μ-opioid agonists, but oxycodone is also a κ-opioid agonist. Importantly, κ-receptors are distributed differently from μ-receptors and may respond in a different way to different pain types. Most κ-receptors are located in the gastrointestinal tract and abdominal space. Therefore, in patients with visceral pain unresponsive to morphine, it may be appropriate to switch to oxycodone.**
- **Morphine and oxycodone are potent analgesics, and clear dose-dependent activity exists for both compounds. Thus, equianalgesic activity might initially be expected for both compounds, yet several publications have documented differences in analgesic effects. This applies particularly for visceral pain syndromes or pain syndromes mediated at the supraspinal level.**
- **Oxycodone has a major advantage in that it can be administered as a fixed-dose combination (FDC) with naloxone to treat or even prevent opioid-induced bowel dysfunction (OIBD) or constipation.**

Trends in opioid prescription/perception

Traditionally, opioid analgesics were, and indeed still remain, the strongest analgesics available for management of acute (e.g. postsurgical, traumatic) pain. In 2013, Garimella & Cellini stated that “Despite years of advances in pain management, the mainstay of postoperative pain therapy in many settings is still opioids.”

In 2014, Raeder documented that “… opioids are still the most efficient, all-purpose analgesics we know;” and in 2016, major guidelines from a United States panel of interdisciplinary experts stated that “The panel recommends … opioids for postoperative analgesia … (strong recommendation, moderate quality evidence).”

However, a meta-analysis in 2016 reported that “There was [only] moderate-quality evidence that opioid analgesics reduce (chronic) low back pain in the short term; mean difference (MD) to placebo: −10.1 mm VAS (95% CI: −12.8 to −7.4).” Such a magnitude of treatment–placebo difference is clinically irrelevant for patients, which explains why opioids are so critically discussed in the setting of chronic nonmalignant pain. That said, could the issue be the selected patient population rather than the selected drug? Indeed, a 2016 Cochrane meta-analysis also concluded that “There is low-quality evidence that NSAIDs are more effective than placebo, with a mean difference in pain intensity score from baseline of −3.30 points (95% CI: −5.33 to −1.27) on a 0 to 100 mm VAS.” Other high-quality reviews reported that paracetamol or antidepressants were no better than placebo in the management of chronic lower back pain. Thus, a particularly important question to address is: Why is it that opioids are highly effective in acute/postsurgical pain, have moderate efficacy in subacute/recurrent pain, but have only limited efficacy in chronic pain states? There is no clear and easy answer to this question.

Our current understanding of nociceptive pathways is similar to, albeit somewhat more sophisticated than, the original model proposed by Descartes in 1633. That is, trauma occurs, receptors register the trauma and translate injury into a nervous signal (transduction), and the signal is then transmitted via nerve fibres to the spinal cord (transmission). In the spinal cord, peripheral neurons synapse with second-order neurons in the spinalthalamic, spinoreticular or spinomesencephalic pathways, which transmit signals to the midbrain and then connect with other neurons. Thus, via a process of translation, pain is perceived by patients (Figure 3).

Based on this model, many therapeutic strategies have been developed to prevent signal transduction, to treat peripheral or spinal transmission, or to interact with the translational process. Subsequently, the intensity of pain decreases, and pain perception is reduced with ongoing treatment. Intervention against this connectome has proved markedly effective in the management of acute, but not in all cases of chronic, pain. Indeed, many centres in the brain are involved in pain mediation, but also play a mediatory role in emotion, reward, fear, anxiety, and depression. This dynamic pain connectome might explain why some patients, during chronicity of their pain, may or may not respond to opioids.
The dynamic pain connectome

Emotion and reward centres

Interesting recent data emerged from a functional MRI (fMRI) study, in which 94 patients with subacute back pain had an fMRI pattern similar to that in healthy volunteers given a painful stimulus. Conversely, in 59 patients with chronic back pain, fMRI mappings indicated that pain processing occurred in totally different brain regions from those involved in subacute back pain; in chronic back pain, fMRI patterns were similar to those associated with emotion and reward centres in healthy volunteers. Thus, patients who develop chronic pain states, in which pain is processed via emotion and reward centres, will not respond to pharmacotherapy. Such patients must be identified and treated early before the chronic pain state develops.

In longitudinal studies, Hashmi et al. also showed that patients with subacute back pain who recovered within 1 year of treatment had improved scores for pain and reward, whereas scores for emotion were not markedly altered. Conversely, in patients with persistent subacute back pain, scores for pain and reward improved, but scores for emotion significantly deteriorated (Figure 4). Thus, chronic nociceptive or neuropathic pain was propagated by neuronal circuitry (i.e. emotional pathways) other than specific pain pathways.

Figure 3. The dynamic pain connectome.

Figure 4. Involvement of pain, emotion and reward neuronal circuits: in patients who recover from subacute back pain (SBPr); or in patients for whom subacute back pain persists (SBPp).
General considerations about opioids in chronic pain
The discussion above outlines that opioid therapy should be accurately tailored to meet the needs of individual patients. Traditionally, the WHO pain-relief 'ladder' was used to try to appropriately tailor treatment. This was based on the rather simplistic consideration of what has already been given to a patient, how does it work, and what is next on the 3-step ladder? That is, treatment starts with non-opioids and then progresses to low-potency opioids and then high-potency opioids. While this approach helped establish opioids in underdeveloped countries, it has limited application based on our current understanding of opioid efficacy and the pathophysiologic background of pain.

Today, evidence-based guidelines about opioid use are followed. However, Abdel Shaheed et al. recently conducted a meta-analysis and reported that opioids versus placebo produced only a modest and clinically insignificant analgesic effect (~10.1VAS score reduction) against certain pain types, including musculoskeletal pain; of course, muscular pain would not be expected to respond to opioids in the first place. Thus, although the evidence-based approach is better than the WHO pain ladder, it is not ideal.

In future, pain-management strategies will likely be based on the following question: Do the current pathophysiological mechanisms underlying the distinct pain type/syndrome of a particular patient respond to analgesics (e.g. opioids)? Clear distinction is therefore needed between pain mechanisms such as nociceptive or neuropathic inputs, pain due to anxiety, depression, emotion or fear, or pain processed by the reward system. In these respects, it is currently difficult to translate data from fMRI mapping into therapeutic targeting strategies for various pain types based on patient-reported outcomes.

In 2015, a large survey of German physicians was conducted to assess opioid-related effects in daily clinical practice. The physicians surveyed reported that opioids produced a good or adequate response (based on different definitions of efficacy) in approximately two-thirds of patients with refractory chronic lower back pain: that is, 67.5% of patients had a >50% decrease in pain intensity; 64.8% had a >50% improvement in pain-related disability in daily life; and 64.6% had a significant improvement in pain-related quality of life (QoL). Importantly, 54% of patients were also able to start, for the first time, nonpharmacological therapy for lower back pain. The proportions of patients with opioid-related adverse events (AEs) are shown in Figure 5. Regarding constipation, the occurrence concurs with the rate reported (15–81%) in randomised, controlled trials in opioid-treated patients with chronic nonmalignant pain; the rate varied depending on duration of treatment.

Constipation

Constipation is intrinsically related to analgesic efficacy, since both are mediated by activation of μ-opioid receptors. In the gastrointestinal (GI) tract, such receptor activation leads to uncoupling of physiological and autonomic intestinal motility processes, which are needed for laxatives to exert their pharmacological effects. Moreover, this uncoupling leads to downregulation of intestinal secretions (including that of digestive enzymes), increased fluid absorption, increased sphincteric tone, and dysregulation of autonomic opening processes. So, constipation is just the tip of the iceberg, and many other GI effects may also be reported by opioid-treated patients, including anorexia, nausea and vomiting, gastro-oesophageal reflux, malabsorption, maldigestion, prolonged GI transit time, palpitations, colic, pain, stool impaction, incomplete evacuation, and paradoxical diarrhoea. For these reasons, the principal consideration is now opioid-induced bowel dysfunction (OIBD) rather than constipation per se.

Although significant evidence exists that laxatives are effective in the management of constipation unrelated to opioid therapy, there is virtually no scientific evidence that laxatives are effective in OIBD. Conversely, substantial high-quality evidence now exists of the efficacy of μ-opioid antagonists (e.g. naloxone) in OIBD management.

Data from the German Pain Registry
Analysis of post hoc data from the German Pain Registry for 300 randomly selected patients with morphine-treated refractory chronic lower back pain revealed that 65.0% of patients attained a VAS pain score of <30 mm after 12 weeks. However, at week 12, 69.3% of patients had a Bowel Function Index (BFI) VAS score of >30 mm, which indicates opioid-induced constipation. Altogether, therefore, the benefits of treatment were outweighed by the risks of constipation. The same benefit–risk profile was evident for oxycodone, whereas AEs were considerably less frequent for oxycodone/naloxone than the other two opioids (Figure 6).

Figure 5. Opioid-related adverse events in daily clinical practice.
In this box-and-whisker diagram, the bottom and top of the blue boxes indicate the first and third quartiles; the white vertical lines inside the blue boxes indicate median values; and the whiskers show 2.5% and 97.5% percentiles. Values shown on the right-hand side of the figure are average reporting rates.

Figure 6. Post hoc analysis of data from the German Pain Registry: incidence of adverse events. MEQ = morphine equivalents.
Another analysis used strict combined criteria to define a response (primary outcome) to oxycodone/naloxone, oxycodone, or morphine:23
1. No AE-related treatment discontinuation.
2. An increase in BFI of ≥50% versus baseline.
3. Lower back pain VAS increase of ≥50% versus baseline.
4. Functionality improvement ≥50% versus baseline.
5. QoL improvement ≥50% versus baseline.

The primary outcome was attained by significantly more patients treated with the FDC rather than oxycodone or morphine (22.2% vs 6.3–9.3%; p<0.001). For a secondary outcome, which comprised endpoints (1) and (2), plus (3), (4) or (5), the response rate was 71.5% versus 41.1–51.0% (p<0.001; Figure 7).23

There are two possible reasons why the FDC of oxycodone/naloxone was more effective than oxycodone or morphine monotherapy in this study:

1. The pre-hepatic action of sustained-release (SR) naloxone may prevent or reduce the development of OIBD and OIBD-related GI side effects.
2. Improved GI function may lead to enhanced absorption of SR oxycodone and, subsequently, to greater systemic or central plasma concentrations.

Ultra-low dosages of SR naloxone may enhance the analgesic activity of opioid agonists by preventing the G protein coupling switch (from Gαs to Gβ).24

Figure 7. German Pain Registry data: clinical efficacy of oxycodone/naloxone (OXN) relative to morphine (MOR) and oxycodone (OXY) in patients with lower back pain.23

AE = adverse event; BFI = Bowel Function Index; LBPIX = Lower Back Pain Index; MEQ = morphine equivalents; ns = not significant; QoL = quality of life.

Oxycodone/naloxone versus tapentadol in chronic lower back pain with a neuropathic component

A phase 3b/4, open-label study compared the efficacy of prolonged-release (PR) oxycodone/naloxone with that of PR tapentadol in patients with severe chronic lower back pain and a neuropathic component (Pain Detect Questionnaire score ≥13).25

The primary study endpoint was change in average pain intensity from randomisation to end of the 12-week treatment period (3-week titration, 9-week maintenance phase). Although the 3-week titration period was probably too short for a potent opioid such as oxycodone/naloxone, pain intensity scores were statistically and clinically significantly reduced from baseline to week 12 in both treatment groups (Figure 8).

Improvement in the primary study endpoint was statistically significantly greater in the tapentadol than oxycodone/naloxone group (–3.7 vs –2.7 points; p=0.003). However, this between-treatment difference was not clinically relevant. Furthermore, the trial was substantially flawed in that the pre-defined statistical analysis plan stated that ≥96 patients per group were needed for the primary endpoint analysis: however, after the 3-week titration period, only 62 patients in the FDC group were still receiving treatment; and at completion of the 9-week maintenance phase, only 48 patients in the FDC group and 86 in the tapentadol group were still receiving treatment. This is an extraordinarily high drop-out rate for an open-label study of a potent opioid and was probably attributable to an inadequate titration phase: that is, forced titration and the need to attain predefined treatment goals before progressing were probably inappropriate for opioid therapy, which needs to be individually tailored.25

A real-life study using data from the German Pain Registry was a blinded endpoint analysis of routine data from 12-week, prospective, open-label observations and compared oxycodone/naloxone with tapentadol in 201 patients with chronic lower back pain with a neuropathic component.26 After the 12-week study phase, significantly more patients treated with oxycodone/naloxone than tapentadol had achieved the combined primary study endpoint (no discontinuation due to AEs; no CNS-related AEs; no constipation; and ≥30% improvements from baseline in pain, function, and QoL; 58.9% vs 25.6% of patients; p=0.014). The increase in proportion of patients with a VAS pain score ≥30 mm was 71.9% in the FDC group, compared with 61.6% in the tapentadol group. Furthermore, the proportion of patients with a VAS pain score ≥50 mm was significantly greater in the FDC than tapentadol group (p=0.031); the same was true for a VAS pain score ≥70 mm (p<0.001). Side-effect profiles were similar in the two study groups.25
Based on these two divergent studies, Dr Uebelhart’s recommendations are:

- Tapentadol is preferred for patients with a definite neuropathic pain syndrome (e.g., patients with diabetic neuropathy or postherpetic neuralgia and high Pain Detect Questionnaire scores). This is particularly relevant if patients have low average pain intensity over 24 hours, but transient exacerbations of pain or sharp, lancinating pain attacks.

- Oxycodone/naloxone is preferred for patients with chronic lower back pain and higher average pain intensity over 24 hours without acute exacerbations, yet with some neuropathic component.

- Depending on individual response, patients may be switched to another treatment.

Take home messages

Opioid analgesics still have a definitive place in the treatment of chronic nonmalignant pain, although opioid therapy should always be embedded in a multimodal treatment approach that includes other pharmacological and nonpharmacological measures.

- If multimodal treatment is adopted, approximately two-thirds of opioid-treated patients with chronic nonmalignant pain will experience clinically relevant improvements in pain, pain-related disability in daily life, and quality of life.

- Constipation is a frequent and distressing complication of potent opioid analgesic therapy, and affects approximately 50–70% of opioid-treated patients in daily practice. OIBD may develop as an independent comorbidity in patients with chronic nonmalignant pain and may affect the success of treatment regarding pain, functionality, and quality of life.

- Conventional measures (e.g. laxatives) for the prevention and treatment of OIBD are often recommended first-line, despite only limited evidence of efficacy. Indeed, laxatives are unlikely to be effective in OIBD because opioids lead to upregulation of physiological and autonomic intestinal motility processes. Peripherally acting opioid antagonists (ideally in a FDC with SR opioid) are unequivocally superior to laxatives for the prevention and treatment of OIBD.

- Opioid analgesics are effective in the treatment of refractory neuropathic pain. However, because of their side-effect profile and safety considerations, they are typically recommended only as third-line agents in this setting. Safety can be improved if opioids are carefully titrated, as part of a multimodal strategy, to meet the needs of individual patients.

References