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REVIEW

Oxycodone: a review of its use in the management of pain

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ABSTRACT

Background: Oxycodone is a strong opioid that acts at mu- and kappa-opioid receptors. It has pharmacological actions similar to strong opioids, but with a specific pharmacologic profile and greater analgesic potency to morphine. The efficacy of oxycodone in managing neuropathic and somatic pain, both of malignant and non-malignant origin, has been established in a wide range of settings.

Scope: This review aims to provide a comprehensive evaluation of oxycodone and its role within clinical settings in order to provide an evidence-based perspective on its use in the clinic. Literature searches using Medline, EMBASE and Cochrane Databases were used to compile data for review. The review provides information on the pharmacokinetics and pharmacodynamics of oxycodone and also profiles established clinical data in neuropathic and somatic pain as well as emerging data to support the use of oxycodone in visceral pain, which may be due to its interaction with kappa-opioid receptors. Oxycodone is available in a range of formulations for oral, intraspinal and parenteral administration.

Findings: The prolonged-release form of oxycodone offers a fast onset of analgesia, controlling pain for 12 hours and providing clinically meaningful relief of moderate to severe pain and improving quality of life across a broad spectrum of pain types.

Conclusions: Oxycodone provides significant pain relief. It has relevant points of difference from other opioids and as such may be a suitable alternative to morphine.

Introduction

The efficacy of opioids in the management of chronic cancer- and non-cancer-related pain is well known, leading guidelines to recommend their use in patients with persistent moderate-to-severe pain, particularly when other therapies have failed[1,2]. Despite these recommendations, however, many clinicians without specialist knowledge of pain management remain reluctant to prescribe opioids for chronic pain of non-malignant origin. Opioids have been classified by the World Health Organisation (WHO) as weak (e.g. codeine,

tramadol) and strong (e.g. oxycodone, morphine, hydromorphone, fentanyl and methadone), with strong opioids being recommended for use in patients with moderate-to-severe persistent pain, preferably given orally[1–3]. The question is, are there variations between the different opioids in their efficacy and tolerability with respect to treating moderate-to-severe pain? This narrative review provides an overview of the efficacy and tolerability of oxycodone across different pain types. Cancer pain is typically polymodal in type – it can be visceral, somatic or neuropathic – and these pain types are reviewed separately. It is intended to provide an insight into the clinical dataset of oxycodone across a broad range of chronic moderate-to-severe pain types and highlight the clinical efficacy for oxycodone that has been established over the last decade.

To compile this review the following search strategy was employed. Randomised trials of oxycodone in moderate-to-severe chronic neuropathic, somatic or cancer pain were identified by MEDLINE (1990–2007), EMBASE (1990–2007) and Cochrane Database searches were conducted up to February 2007. Additional reports were identified from the reference list of the retrieved papers, or from abstracts at key pain conferences from 2002 onwards that were deemed by the authors to add to the knowledge of severe pain, particularly in areas of pain that are poorly defined, in particular visceral pain. Where appropriate, reviews and meta-analyses from other authors have been included, and these are intended to exemplify key points or to add depth to the review of clinical studies. This review is essentially narrative in nature and has not been compiled using systematic criteria. The aim of this review is to provide a comprehensive overview of oxycodone and its use in moderate-to-severe pain. Search terms included 'oxycodone', 'neuropathic pain', 'somatic pain', 'visceral pain', 'cancer pain', 'post-operative pain', 'post-herpetic neuralgia', 'painful diabetic neuropathy', 'osteoarthritis', 'rheumatoid arthritis', 'surgery', 'pancreatitis', 'pelvic pain', 'knee-hip-replacement', 'non-malignant pain', 'back pain' and 'rehabilitation'. These search terms were combined in several search strings, for example 'somatic pain' AND 'oxycodone' AND 'low back pain'. All search strings contained oxycodone where appropriate, to ensure the clinical relevance of the material, the only exceptions to this being comparative data identified through pain types that were felt to add depth to the oxycodone data set. Source materials obtained through searches were reviewed by authors, and, where possible, all sources were included to ensure balance of content. Only human data are included in this review and, except for the studies in visceral pain, only human data from patients presenting with a pain pathology are included.

For clinical evaluation, reports were included in this review if they were randomised controlled trials (RCTs) which investigated the analgesic effects of oxycodone drugs in patients, with pain assessment as either the primary or a secondary outcome. In visceral pain, where data are currently limited, non-randomised studies of experimental pain were also included. Patients experienced a wide range of pain modalities from somatic pain e.g. joint pain, postoperative pain, cancer pain, back pain, neuropathic pain e.g. post-herpetic neuralgia and visceral pain e.g. pelvic pain. For discussion of oxycodone's pharmacokinetic and pharmacodynamic effects clinical studies were included where possible (e.g. effects of oxycodone in hepatic impairment), and in non-clinical instances all information available was included.

Information about the pain condition and number of patients studied, dosing regimen of oxycodone and comparator drug as appropriate, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals and adverse effects (minor and major) was taken from each report. A variety of outcome measures were used in the studies, the majority using standard subjective scales for pain intensity and/or pain relief. Eligibility was determined by reading each report identified by the search. All reports were read by all the authors and agreement was reached by discussion.

Background

Oxycodone (14-hydroxy-7,8-dihydrocodeine) – a semi-synthetic derivative of naturally occurring thebaine – is a strong opioid that is commonly used as an alternative to morphine. Oxycodone is similar to morphine in that it can be administered orally, rectally, intraspinally and parenterally. In this review the focus is the clinical efficacy of the oral formulation which is most widely used and studied. The main difference between the two opioids is the high oral bioavailability of oxycodone (> 60%). Mean estimates range from 42% to 87% while corresponding estimates for morphine range from 22% to 48%[4–7]. Comparisons of bioavailability of prolonged release (PR) oxycodone and PR morphine are match comparisons for bioavailability of conventional preparations of each drug. Oxycodone also differs from morphine in its metabolism; while morphine is metabolised via the enzyme UGT2B7, oxycodone undergoes hepatic metabolism primarily to noroxycodone via CYP3A4 and, to a much lesser extent, to oxymorphone via CYP2D6. Each of these metabolites may be further converted to noroxymorphone. Plasma concentrations of oxymorphone are negligible (approximately 2%) and it has been shown to not impact on the perceived pharmacodynamic effect of oxycodone[8]. Recent evidence suggests that central opioid effects are governed by oxycodone, with a negligible contribution

from its circulating metabolites[9]. The enzyme CYP2D6 is genetically polymorphic with 5–10% of the Caucasian population showing diminished CYP2D6 activity and poor metabolism, potentially leading to inter-individual variations in the efficacy of some drugs[10]. However, it is currently unclear whether variation in CYP2D6 activity influences the overall analgesic efficacy of oxycodone[5,9,11–13]. Clinical studies suggest that oxycodone has predictable pharmacokinetics[5,14], with no apparent dose ceiling and that it has an adverse effect profile in line with other opioids[15–17]. Oxycodone is generally indicated for the treatment of severe chronic pain requiring the use of a strong opioid, although indications vary between countries. It is available in a range of formulations which include intravenous ampoules for injection or infusion, immediate-release solution and capsules (all traded as OxyNorm; Napp Pharmaceuticals Ltd, Cambridge, UK) and a prolonged release (PR) preparation (OxyContin; Napp Pharmaceuticals Ltd) as well as combination formulations, for example with paracetamol (Percocet; Endo Pharmaceuticals, Chadds Ford, PA, USA). PR oxycodone has been shown to have a biphasic delivery system (Acrocontin; Napp Pharmaceuticals Ltd) providing a fast onset of analgesia within 1 hour and control of pain for a 12-hour dosing period[13,18]. It should be noted that as with many other opioids, oxycodone unfortunately also has a misuse potential. The abuse potential for oxycodone is similar to morphine. Most chronic non-malignant pain guidelines recommend the use of modified-release, rather than short-acting opioids in order to minimise the risk of tolerance and dependence[2]. However, concerns have been raised about abuse of, the 12 hour PR formulation of oxycodone (OxyContin). Taking broken, chewed or crushed PR oxycodone tablets leads to the rapid release and absorption of a potentially fatal dose of oxycodone. The ease of extraction of the active ingredient from this formulation has been suggested as a contributing factor to the rise in prolonged release oxycodone abuse rates which, in the USA, increased by almost 40% between 2002 and 2005[19].

The controlled release version of oxycodone has been favoured as the euphoric effect of an opioid can be achieved, but the prolonged action avoids the withdrawal effects associated with immediate release preparations or heroin[20].

PR oxycodone has also shown to be abused. A survey recently published, the National Household Survey on Drug Abuse (NHSDA)[21], collected data from a broad population spectrum (n = 70 000) to obtain self-reports of illicit/non-medical, as well as medically appropriate drug use. The survey has been conducted intermittently since 1971 and annually since 1990, so that trends in drug use are apparent and the methodology repeatedly validated. PR oxycodone data are available for 1999, 2000 and 2001 and these data have been computed into estimates of the number of non-medical uses in the context of non-medical use of any prescription analgesic and non-medical use of any oxycodone containing medication. Across the 3-years in question, non-medical use of PR oxycodone did increase (1999 = 3.6%, 2000 = 6.6%, 2001 = 12.2%) and this was statistically significant ($p < 0.05$), a trend that is in common with all different analgesics in the same time period. For example, the combination of acetaminophen (paracetamol) and hydromorphone rose in the same period from approximately 30% to more almost 45% ($p < 0.05$). It was clear from this survey that users who misuse PR oxycodone were typically younger than those who use it appropriately, were typically twice as more likely to use other analgesic drugs inappropriately, were 1.7 times as likely to have used cocaine, 2.8 times as likely to have used heroin and 3.6 times more likely to have used needles to inject drugs of abuse[21]. Usually, exposure to other drugs, either illicit use or misuse of prescription medication took place before misuse of PR oxycodone, suggesting that abusers progressed to using PR oxycodone, often progressing from 'gateway' drugs such as marijuana. These data indicate that 0.1–0.2% of new users report non-medical use of PR oxycodone per year, a pattern that is observed with most other prescription analgesics. This suggests that while PR oxycodone misuse is a concern, it forms part of an overall larger problem of prescription analgesic abuse. Further, these data suggest that fear among clinicians to prescribe PR oxycodone to patients, and fear among patients in pain that taking PR oxycodone will lead to addiction is largely unwarranted, as non-medical use of PR oxycodone typically occurs in a person with a history of substantial drug abuse i.e. of the 91.2% of those who reported using PR oxycodone for non-medical use 70.3% also reported using cocaine or heroin. However, within this survey it is unknown how many of those reporting non-medical use of PR oxycodone had also been prescribed the drug legitimately, although the average age of misusers was 34 years and that of medically appropriate users more than 50 years. The NHDSA survey does exclude elements of the US population including homeless people not using shelters, active military personnel and residents of institutions such as prisons or hospitals. Also, the actual numbers of patients reporting non-medical use of PR oxycodone were low, so that small variations in these numbers may create dramatic changes in observed rates[20]. Most data relating to abuse or misuse of PR oxycodone are derived from North America and similar European data appear to be lacking. As the route of misuse is typically through snorting a crushed tablet or administration of dissolved tablets intravenously or intramuscularly[20], there are moves to develop strong opioid analgesics

with the added benefit of reduced abuse potential through combination with opioid antagonists.

Hepatic and renal failure

Oxycodone and its metabolites are excreted primarily by the kidney, with up to 19% of oxycodone eliminated, unchanged, in the urine[22]. In patients with mild-to-moderate hepatic dysfunction or mild-to-severe renal dysfunction, peak plasma oxycodone and noroxycodone concentrations are higher than in normal subjects[23,24]. In end stage renal failure, the half-life of oxycodone is significantly increased[16,25]; clearance may also be decreased in patients with hepatic insufficiency[25].

Receptor pharmacology

When given parenterally, oxycodone's analgesic potency is comparable to, or marginally less than that of morphine[26]. Animal data suggest that the antinociceptive effects of oxycodone are mediated by μ- and possibly κ-opioid receptors, as demonstrated by selective antagonism by norbinaltorphimine, in contrast to morphine which interacts primarily with μ-opioid analgesic receptors[27,28]. These data are supported by radioligand binding and behavioural studies in rats with neuropathic pain that has recently emerged[29]. In this study rats with chronic constriction injury (CCI) of the sciatic nerve or those with streptozotocin (STZ) induced diabetes were given either morphine or oxycodone intravenously or subcutaneously. In the CCI model the effects of oxycodone, but not morphine were abolished by norbinaltorphimine, further oxycodone provided long-term antinociception in STZ-diabetic rats (maintained over 24 weeks) compared with morphine where antinociceptive effects were abolished by 12 weeks[29]. Centrally, oxycodone was shown to bind preferentially to κ-receptors, specifically the κ_{2b}-opioid receptor and with lower affinity to μ-opioid receptors[29]. These data suggest that the antinociceptive profile of oxycodone and morphine are different when assessed in rat models of neuropathic pain[29]. However, data in rodents demonstrate that only a low degree of cross tolerance (≈ 24%) is observed after intravenous (IV) oxycodone administration to morphine-tolerant rats, whereas IV morphine showed a high degree of cross-tolerance (≈ 71%) in rats rendered tolerant to oxycodone[30].

κ-opioid receptors have been implicated in the aetiology of visceral pain in animal models[31]. Studies in mice lacking κ-opioid receptors show them to be more vulnerable to visceral inflammation and hence visceral pain[32]. In human experimental studies, subjects received multimodal pain stimulation to the oesophagus (pressure, heat and electrical) to achieve both pain detection and tolerance thresholds[33]. The effects of opioid administration (oxycodone and morphine) were explored and it was observed that oxycodone was superior to morphine in extending stimulus intensities for both mechanical ($p < 0.001$) and electrical (single stimulus $p = 0.002$; repeated stimulus $p < 0.001$). However, it is not known if the efficacy of oxycodone was due to a kappa agonistic effect[33]. This study was an experimental study in human volunteers, which has limitations over a randomised clinical study but does give an insight into the potential for oxycodone in visceral pain, which bears out anecdotal impressions. These data have also been substantiated in a further study in chronic pancreatitis where oxycodone and morphine were shown to have differential effects, with oxycodone more effective than morphine[34] (this study is reviewed in further detail later in this review). Furthermore, cross-talk between μ- and κ-receptors plays a role in how nociception is mediated[35]. Other exciting data are also emerging, currently only in human cell lines, suggesting that physical interaction between these receptors may play a role in pain control[36].

Gender, age and immunosuppression

Gender and age in adults have been shown to have no significant effects on the analgesic efficacy of oxycodone[16]. Oxycodone is not generally indicated in patients under the age of 18 years due to the lack of studies in this population, although in some markets the opioid may be used in individuals over the age of 12[22].

Opioid use has long been linked to immunosuppression and arises due to a complex relationship between opioids and the immune system, which has been reviewed extensively elsewhere[37]. The site of immunosuppressive opioid activity has been shown to be the periaqueductal grey, and while it is not yet clear which opioid receptors are of key involvement in immunosuppression it is thought that μ-opioid receptors play a role[37]. Different opioids have varying effects with respect to immunosuppression and this appears to be due to opioid-receptor affinity and molecular structure[37]. Opioids with a high affinity for μ-opioid receptors have significant immunosuppressive effects whereas those with pure κ- or δ-opioid receptor affinity do not[37,38]. Animal data suggests that oxycodone and hydromorphone induces less immunosuppression than morphine[39].

Efficacy in neuropathic pain

The efficacy of oxycodone in neuropathic pain (NP) is well established, with randomised clinical studies reporting that the drug provided better pain relief and greater improvements in quality of life scores than placebo[40–42] (Table 1) and these are reviewed

by Eisenberg *et al.*[43], and supported by observational studies[44] and individual case studies[45]. Studies involving 603 patients with NP have found that PR oxycodone (mean dose 40 mg/day) resulted in a decrease in mean pain intensity (0–10 scale) from 6 to under 3 after 3 weeks of treatment, while functional impairment, quality of life and performance scores also improved substantially[44]. The analgesic effect of PR oxycodone on evoked pain has been investigated in two trials[40,42]. In both studies, PR oxycodone (mean daily doses of up to 45 mg and 40 mg, respectively) was significantly superior to placebo in reducing allodynia, categorized as skin pain ($p = 0.0004$ and $p = 0.0001$). In both studies visual analogue scale (VAS) scores significantly improved in patients receiving oxycodone compared with those receiving placebo ($p = 0.001$). In the later study from 2003[42], VAS scores improved from 67.0 ± 14.9 to 21.8 ± 20.7 compared with placebo, where only an improvement of 18.4 mm was observed. The limitations of this study are clearly the small patient numbers involved (< 50) and the ability of both clinicians and patients to correctly guess the active treatment phase due to side effect profile, although the authors attest that the maintenance of concealment

Table 1. *Overview of randomized controlled trials comparing the analgesic efficacy of prolonged-release oxycodone with placebo in chronic pain of non-malignant origin*

Reference	*n*	Duration of treatment	Pain origin	Drug	Mean dose	Mean pain endpoint scores	*p*-value*
Neuropathic pain							
Gimbel *et al.*[41]	159	6 weeks	Diabetic neuropathy	PR oxycodone	10 mg/12 h	4.1†	0.002
				Placebo		5.3†	
Watson *et al.*[42]	36	4 weeks	Diabetic neuropathy	PR oxycodone	Up to 40 mg/12 h	21.8‡	0.0001
				Active placebo (benztropine)	Up to 1 mg/12 h	48.6‡	
Watson and Babul[40]	50	4 weeks	Post-herpetic neuralgia	PR oxycodone	Up to 45 mg/12 h	2.9§	0.001
				Placebo		1.8§	
Somatic pain							
Zautra *et al.*[56]	104	2 weeks	Osteoarthritis	PR oxycodone	Up to 120 mg/day	4.96**	< 0.001
				Placebo		6.34**	
Markenson *et al.*[55]	107	90 days	Osteoarthritis	PR oxycodone	Up to 120 mg/day	4.9††	< 0.024
				Placebo		6.0††	
Reuben *et al.*[66]	55	1 hour pre-operatively	Ambulatory laparoscopic tubal ligation surgery	PR oxycodone	10 mg	3.0‡‡	< 0.001
				Placebo		4.0‡‡	
Cheville *et al.*[67]	59	NR	Unilateral total knee arthroplasty	PR oxycodone	Up to 30 mg/12 h	4.8§§	0.012
				Placebo		5.9§§	
Visceral pain							
Sunshine *et al.*[84]	182	NR	Abdominal/ gynaecological surgery	PR oxycodone	10 mg	2.40***	≤ 0.05
					20 mg	3.17***	≤ 0.05
					30 mg	3.13***	≤ 0.05
				IR oxycodone	15 mg	2.90***	≤ 0.05
				IR oxycodone/ acetaminophen	10 mg/650 mg	3.37***	≤ 0.05
				Placebo		1.76***	

*vs. placebo
†Numerical scale (0 = no pain, 10 = as bad as you can imagine)
‡Visual analogue scale (0–100 mm)
§Mean weekly pain relief score (0 = pain worse; 5 = complete relief)
**24 hour pain (0 = no pain; 10 = as bad as you can imagine)
††Mean Brief Pain Inventory scores for average pain (rating of pain, interference and function)
‡‡VAS pain score 24 hours after surgery (0–10 no pain to worst pain ever)
§§Overall pain relief (VAS 0–100)
***Overall pain relief (patient rating)
IR = immediate release; NR = not reported; PR = prolonged release; VAS = visual analogue scale

is more important in preventing bias than a patient's ability to guess the treatment phase. In both studies[40,42] the assessment of evoked pain was based upon patients self reports of 'skin pain' rather than upon quantitative testing of specific sensations. In the later study[42] the stimulation of pain is outlined (e.g., heat, cold or mechanical), but in the earlier study the authors do not outline the nature of the non-painful stimuli. These findings are supported by a recent systematic review that examines the results from short- and intermediate-term treatment of NP with opioids[43]. In this instance the reviewers concluded that opioids were significantly superior to placebo in evoked neuropathic pain[43].

Number needed to treat (NNT) is a treatment-specific measurement used for the comparison of relative efficacy and provides, currently, the best way to compare therapies. NNT values for individual compounds are evaluated by a comparison against placebo. In a recent analysis of neuropathic pain and common medications used to alleviate pain, NNT was defined as the number of patients needed to treat with a certain drug to obtain one patient with 50% pain relief. If 50% pain relief could not be obtained, then the number of patients reporting good pain relief was used to obtain an NNT[46]. This analysis showed that combined NNTs for tricyclic antidepressants are 3.3, for anticonvulsants such as gabapentin and carbamazepine 4.2, N-methyl D-aspartate (NMDA) antagonists 7.6 and opioids 2.5 (Table 2). For PR oxycodone, specifically, the NNT has been calculated to be 2.6 (confidence interval [CI] 1.9–4.1), comparable to the NNT for morphine of 2.5 (CI 1.9–3.4)[46].

Post-herpetic neuralgia

The efficacy of oxycodone in relieving pain in post-herpetic neuralgia has been studied in a placebo-controlled, crossover study in which patients (n = 50) were randomised to PR oxycodone (up to 30 mg/12 h) or placebo for 4 weeks[40]. Oxycodone resulted in both a significant increase in mean weekly pain relief scores (2.9 vs. 1.8; p = 0.001; [0 = pain worse, 5 = complete relief]) and reductions in weekly pain intensity scores (34 vs. 55; p = 0.0001 [VAS 0–100 mm, 0 = no pain, 100 = unbearable pain]) than placebo (Figure 1A). Further, masked patient preference also scored significantly better in the oxycodone group (67% vs. 11%; p = 0.001). In this study, long-term extension data are not available, so it cannot be known if these effects were maintained beyond the study period. Similarly, any adaptations or tolerance to side effects associated with oxycodone such as nausea and vomiting were not observed due to the short duration of this study. This is a similar reduction in pain score to that provided by other analgesics such as gabapentin i.e. 2–3 point decrease on a 0–10 VAS[47].

Diabetic neuropathy

The management of pain in patients with diabetic neuropathy remains unsatisfactory for many patients; however, a recent study suggests that oxycodone provides effective pain relief in this population[41]. In this multicentre, double-blind trial, patients with moderate-to-severe pain from diabetic neuropathy were randomized to receive 10 mg PR oxycodone (n = 77) or placebo (n = 82) every 12 hours for 6 weeks, with this dose being increased up to 60 mg every 12 hours if needed. At an average dose of 37 mg/12 h, PR oxycodone was found to provide more analgesia than placebo (p = 0.002); average daily pain intensities (0 = no pain; 10 = as bad as you can imagine) were rated as 4.1 for PR oxycodone versus 5.3 for placebo, with PR oxycodone-treated patients also reporting improvements in sleep (3.6 vs. 5.3, $p < 0.001$ [0 = pain does not interfere; 10 = completely interferes]) and satisfaction with therapy (3.4 vs. 2.4, $p < 0.001$

Table 2. *Combined numbers needed to treated with 95% CI (numbers in parentheses) to obtain more than one patient with > 50% pain relief. Reproduced with permission from Finnerup* et al.[46]

Drug	Neuropathic pain*	Central pain	Peripheral pain	Painful polyneuropathy	PHN	TGN
Antidepressants†	3.3 (2.9–3.8)	3.1 (2.7–3.7)	3.1 (2.7–3.7)	3.3 (2.7–4.1)	2.8 (2.2–3.8)	ND
Anticonvulsants	4.2 (3.8–4.8)	ns	4.1 (3.6–4.8)	3.9 (3.3–4.7)	4.4 (3.6–5.6)	1.7 (1.4–2.2)
Opioids	2.5 (2.0–3.2)	ND	2.7 (2.1–3.6)	2.6 (1.7–6.0)	2.6 (2.0–3.8)	ND
NMDA antagonists	7.6 (4.4–27.0)	ND	5.5 (3.4–14.0)	2.9 (1.8–6.6)	ns	ND

*Heterogeneous neuropathic pain

†i.e. SSRIs, TCAs, SNRIs, DNRIs

CI = confidence interval; DNRI = dopamine noradrenaline reuptake inhibitor; ND = no studies done; NMDA = N-methyl D-aspartate; NNT = number needed to treat; ns = not significant; PHN = post-herpetic neuralgia; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRI = serotonin selective reuptake inhibitor; TCA = tricyclic antidepressant; TGN = Trigeminal neuralgia

[1 = not satisfied; 6 = totally satisfied]) compared with placebo (Figure 1B). Adverse events in the PR oxycodone group were typical of opioids, and there was no evidence of tolerance or physical dependence during the study, although this study was of short duration with a treatment period of only a maximum of 6 weeks. A further possible limitation in this setting is the unblinded nature of investigators with respect to adverse events which could introduce bias, although the primary efficacy variable was captured by patient diaries, it is possible that the nature of opioid-induced side effects such as constipation, nausea and vomiting could lead to unintentional recognition of treatment arm.

Further evidence for the efficacy of PR oxycodone in painful diabetic neuropathy has been provided by a 4-week study in 36 patients with at least moderate pain for at least 3 months[42]. PR oxycodone (up to 40 mg/12 h) resulted in VAS (21.8 vs. 48.6; $p = 0.0001$), ordinal pain scores (1.2 vs. 2.0; $p = 0.0001$) and better pain relief (1.7 vs. 2.8; $p = 0.0005$) than active placebo (benztropine) during the last week of treatment (Figure 1C), with 88% of patients preferring this therapy over placebo ($p = 0.0001$)[42].

Gabapentin also appears to be effective in this setting; Cochrane reviews of drugs used for diabetic neuropathy have calculated the NNT for antidepressants to be 1.3 for this type of pain versus 2.9 for gabapentin[48,49]. However, there is evidence to suggest that the analgesic effects of gabapentin are improved by addition of an opioid, with the combination synergising to provide better analgesia at lower doses than the single agents[50].

Efficacy in somatic pain

The effectiveness of oxycodone in relieving somatic pain (SP) is well documented, with evidence provided from studies conducted in osteoarthritis (OA), back pain and pre- and post-operative pain.

Joint pain – osteoarthritis-related and rheumatic pain

The analgesia conferred by PR oxycodone treatment in moderate-to-severe OA pain has been evaluated in a 2-week placebo-controlled trial followed by an open-label extension phase for up to 18 months[51]. In this study patients received placebo ($n = 45$), PR oxycodone 10 mg b.i.d. ($n = 44$) or PR oxycodone 20 mg b.i.d. ($n = 44$). Use of PR oxycodone at either dose was effective in reducing mean pain scores compared with placebo. Indeed, PR oxycodone (20 mg) was superior to placebo in reducing pain intensity ($p < 0.05$) and improving the mood, sleep and enjoyment of life of

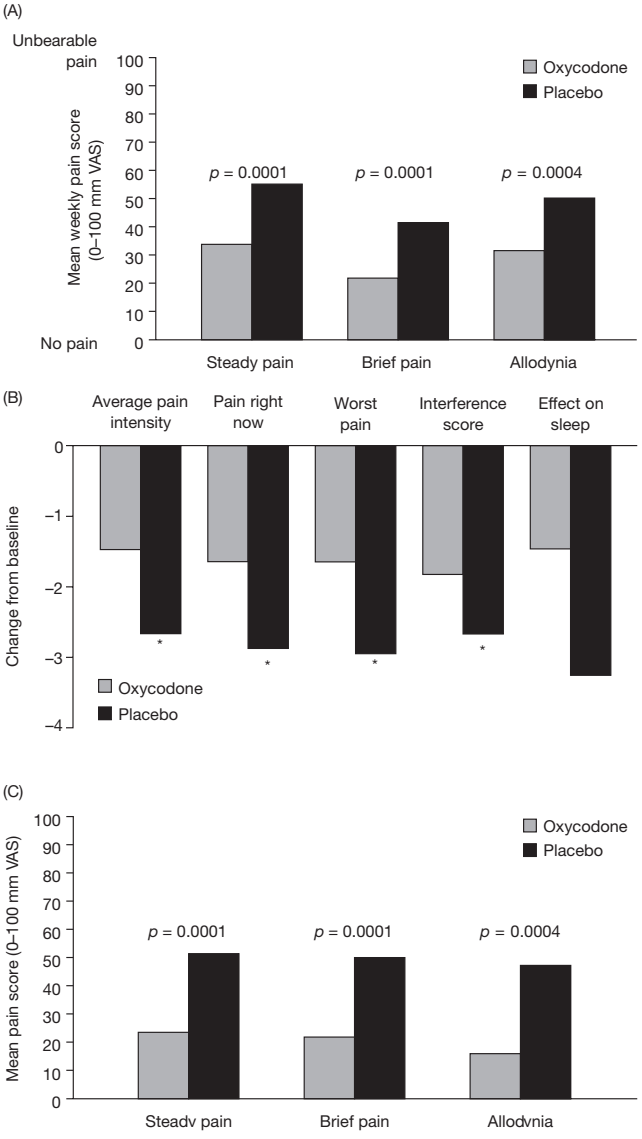

Figure 1. *Outcome in pain scores in (A) post-herpetic neuralgia and (B and C) diabetic neuropathy for patients receiving prolonged-release (PR) oxycodone or placebo*

(A) Patients received 30 mg/12 h of PR oxycodone or placebo for 4 weeks. (B) Patients received an average dose of 37 mg/12 h (dose range 10–60 mg) PR oxycodone for 6 weeks. (C) Patients received PR oxycodone, up to 40 mg/12 h for 4 weeks. Across the three studies patients receiving PR oxycodone achieved significantly better pain relief compared with placebo. Reproduced with permission from Watson and Babul[40], Gimbel et al.[41] and Watson *et al.*[42]. *$p < 0.05$ vs. placebo

133 patients with moderate-to severe OA-related pain randomised for treatment[51]. In many clinical trials a 20% average reduction in baseline pain intensity is considered clinically meaningful. In this study, PR oxycodone achieved this goal within 1 day and 10 mg oxycodone within 2 days; patients receiving placebo never reached a clinically meaningful reduction in pain intensity. Analgesia was maintained in the

long-term and the daily dose of oxycodone remained stable at around 40 mg/day after titration, with pain considered to be controlled below a 'moderate' level throughout the extension phase. Withdrawal of PR oxycodone demonstrated an increase in pain intensity (increase from 1.7 to 2.3–2.5 on a four-point scale) that more than 80% of patients rated as unacceptable. In this study few patients (n = 17) withdrew due to ineffective treatment in both the active treatment arms, a number that was higher in the placebo arm (n = 22). Consequently, the number of completers in this study was high (45 across the two active arms). The efficacy of long-term opioid treatment in the management of chronic rheumatic disease pain is further supported by a 3-year retrospective analysis of 644 patients receiving either opioids (oxycodone and/or codeine; doses were converted to equivalents of 30 mg codeine) or non-opioid prescriptions (control group) for rheumatic diseases[52]. This study was the first description of opioid use in a large cohort of patients with rheumatic disease, and indicated that patients may benefit from opioid use. Prolonged opioid treatment was found to be effective in reducing the severity of pain with only mild side effects. Furthermore, doses were stable for prolonged periods of time with increases attributable to worsening of the condition rather than tolerance. However, in this study the long- or short-term opioid using groups were based on retrospective prescription data, known to have limitations, since filled prescriptions do not always correlate with actual drug consumption by patients. Also, pain results were based on qualitative reports by patients within rheumatology clinics, who may not be wholly representative of patients who are often treated in the primary care setting.

In a separate study, oxycodone therapy, regardless of formulation (either immediate or prolonged release), has been shown to provide better pain control in OA and improvements in functional parameters such as sleep compared with placebo[53]. In this study, pain was measured on a 0–3 scale (0 = none, 3 = severe) and sleep on a 0–5 scale (1 = very poor, 5 = excellent). Oxycodone was provided at a similar dose for each formulation (PR = mean dose oxycodone, 39.9 mg/day; immediate-release [IR] oxycodone-acetaminophen [paracetamol] combination, mean dose oxycodone, 40.3 mg/day). In this study, patients were titrated with IR oxycodone to a pain level determined to be less than 'moderate' by patients over 4 weeks and then randomised to a treatment arm. Pain intensities post-randomisation were then evaluated for a further 4 weeks. Oxycodone reduced pain intensity from 2.44 to 1.38 (p = 0.0001) and improved the quality of sleep from 2.58 to 3.57 (p = 0.0001)[53]. With respect to pain there were no significant differences between PR oxycodone and IR oxycodone, however while quality of sleep was significantly better with active treatment than placebo, scores remained significantly higher in the PR oxycodone group compared with the IR oxycodone-acetaminophen (paracetamol) group (p = 0.0001)[53]. Adverse events observed were typical of opioids, and as there was no wash-out phase between the titration phase on IR oxycodone and the randomisation phase, some adverse events may be attributable to the titration phase medication. The authors of this study note, that long-term use of opioids suggests that 16 weeks of titration are needed to stabilize the dose of oxycodone and that the 30-day titration phase in this study may be inadequate in length to achieve stable dosing. Further, the short duration of the treatment phase may make extrapolations to long-term use challenging. Another study of oxycodone in OA, demonstrated that it significantly reduced pain intensity (reductions in Brief Pain Inventory from 6.9 to 5.1; $p < 0.05$ and change in VAS of 20.6 mm; $p < 0.05$) and significantly improved functional parameters such as sleep (baseline = 6.4, stable dosing score/day 15 = 3.0) (stable dosing being defined as titration until pain level and dose were stable for 48 hours), mood (baseline = 5.9, stable dosing score/day 15 = 3.8), normal work (baseline = 6.9, stable dosing score/day 15 = 5.2) and life enjoyment (baseline = 6.5, stable dosing score/day 15 = 4.1) ($p < 0.05$)[54]. No significant changes in either pain or functional status were observed for patients receiving placebo[54]. These early data have been corroborated by a later study by Markenson *et al.*[55]. In this study, 107 patients received 90-day PR oxycodone or placebo plus acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) as required. PR oxycodone (up to 120 mg/day) produced significant pain control and improvement in physical functioning in patients with OA with persistent moderate-to-severe pain uncontrolled by standard therapy (NSAIDs, acetaminophen and/or short-acting opioids). Mean Brief Pain Inventory scores at day 90 for average pain (4.9 vs. 6.0; $p < 0.024$), pain right now (4.4 vs. 5.7; $p < 0.008$) and worst pain (5.5 vs. 6.6; $p < 0.020$) were significantly lower for PR oxycodone compared with placebo, with 38% of PR oxycodone patients achieving at least 30% pain relief after 90 days versus 18% of those receiving placebo (p = 0.031). This study is strengthened by the number of parameters used to evaluate pain, including the standardized and validated Brief Pain Inventory tool and multiple outcome domains as determined by IMMPACT (Initiative on Methods, Measurement and Pain Assessment in Clinical Trials) such as pain reduction, physical functioning and patient disposition. Further, in this study the patient population was well-defined, meeting OA criteria defined by the American College of Rheumatology, and was appropriately powered to limit possible confounders. The authors do

note, however, that as there were no measures to blind either investigators or patients with respect to adverse events, many of which are easily identifiable for patients receiving opioids, some element of bias could have been introduced. Also the investigators question the possible limitation that including a placebo cohort could have on these study data, even though patients receiving placebo were required to receive NSAIDs or paracetamol at maximum doses[55].

A recent study in 104 patients with moderate-to-severe OA rated current pain intensity and average level of pain on a 0 to 10 scale (0 = no pain; 10 = pain as bad as you can imagine) in a daily diary which were averaged to provide composite indices of pain[56]. Significant reductions in pain parameters were observed compared with placebo. Specifically, PROC MIXED multilevel analyses, a statistical analysis that can evaluate multi-level datasets including both fixed and random parameters to explore longitudinal data through time, have shown significant reductions in pain compared with placebo ($Z = -1.45$, $p < 0.001$, where Z equals the extent of change), improvements in coping efficacy ($Z = 0.46$, $p < 0.006$) and reductions in helplessness ($Z = -0.69$, $p < 0.05$) and passive coping ($Z = -0.45$, $p < 0.055$) following 2-week treatment with PR oxycodone (up to 120 mg/day) when compared with placebo[56]. The design of this study follows that set by Markenson *et al.*[55] and provides an insight not into pain reduction but the impact that reducing pain can have (i.e. the ability of patients to cope, feel less helpless and improved self-belief). However, the interpretation of the causal order and strength of meditational relationships does need to be approached with some caution as they are based on the modelling of observational data rather than experimental manipulation of a parameter. There is also potentially an element of unblindedness in this study as it is clear that many placebo treated participants discontinued early for reasons of lack of effectiveness, suggesting their realisation of placebo treatment. Long-term detailed analysis of patients was also not possible due to the appearance of side effects associated with opioid therapy and this serves to highlight the benefits of therapy effectiveness are weighed against side effects on the individual.

Low back pain

Seven-day treatment with PR oxycodone (10 mg) given every 12 hours has been shown to provide comparable efficacy to IR oxycodone (5 mg) given four times daily in patients with persistent low back pain, despite prior analgesic therapy[57]. Pain intensity (0 = none, 1 = slight, 2 = moderate, 3 = severe) decreased from moderate-to-severe at baseline to slight at the end of titration with both formulations (average daily doses 40 mg and 38 mg, respectively) and no significant differences between formulations were observed for any parameter. Although the short duration of this study could not address long-term opioid issues common in treating chronic non-cancer pain, in particular adverse events such as constipation, which in patients treated longer-term is an anticipated side effect that does not develop tolerance. In addition, an oxycodone/acetaminophen formulation has been shown to be effective in the treatment of low back pain; the majority of patients (67%) reported significant pain relief as measured with the Brief Pain Inventory ($p < 0.0005$) and improvements in mean pain score from baseline 34.5% ± 23.6% to 63.6% ± 23.1% at 4 weeks, with a three times daily dosing frequency or less (mean dose 8.2/325 mg t.i.d.), suggesting that this formulation can provide meaningful pain relief with around-the-clock dosing[58]. In this study, patients also achieved significant improvements in quality of life measures as measured by the Brief Pain Inventory where overall scores improved from 39.9 ± 13.4 to 21.1 ± 13.8, and the North American Spine Society Lumbar Spine Questionnaire ($p < 0.0001$)[58]. In this study, investigators also evaluated the impact of treatment on the neuropathic component of low back pain, using the Neuropathic Pain Scale (NPS). Even on this scale, active treatment with oxycodone/acetaminophen (paracetamol) demonstrated significant reductions in the combined severity of four pain descriptors – sharp, hot, dull and deep pain ($p = 0.007$) with scores changing from a baseline of 58.6 to 45.2 at the end of treatment. This study was a prospective open-label trial and so subject to potential bias as a result. It also did not include a placebo or comparator arm and the number of patients treated was relatively small. However, the aim of the study was to demonstrate preliminarily the effectiveness of oxycodone/acetaminophen and the data obtained highlight that further rigorous studies are warranted.

Two recent observational studies have also shown improved efficacy of PR oxycodone over standard analgesics[59,60] in chronic low back pain (CLBP) and lumbar root compression syndrome. In the first study in CLBP, 3-week treatment with PR oxycodone (mean dose 31.2 mg/day) in conjunction with multidisciplinary rehabilitation was given to patients with a baseline pain intensity ≥ 50 mm VAS despite pharmacotherapy. Patients were randomised to receive either rehabilitation therapy (standard therapy) or rehabilitation therapy plus oxycodone (modified therapy)[59]. Modified therapy demonstrated improvements in pain relief of 50% in 71% of patients receiving oxycodone compared to those on rehabilitation alone (55%), and complete pain relief was achieved in 27% of patients with oxycodone

compared to 5% on standard rehabilitation therapy. A further 55% patients reported that their employability was completely/almost completely regained versus 17% in the standard group, receiving the centres' conventional analgesic medication, which included non-opioids (e.g. paracetamol, metamizol, ibuprofen), WHO-II weak opioids (e.g. tramadol), WHO-III strong opioids (either oral or transdermal) and/or additional analgesic medications (e.g. antidepressants, anticonvulsants, glucocorticoids) (Figure 2). In comparison to other studies the NNT is approximately the same[46,59]. Patients' expectations towards rehabilitation were fulfilled or exceeded in 61% of those receiving PR oxycodone compared with 32% receiving standard treatments. This study highlights the complexity of pain, particularly low back pain, where successful rehabilitation requires a multidisciplinary approach addressing pharmacotherapy, physical, psychological, social and occupational factors. This study, while not double blinded or randomised, highlights that a modified multidisciplinary rehabilitation approach which includes WHO Step III opioids may be beneficial.

In the second study[60], analgesics were classified in groups according to the WHO classification (WHO step I, II and III)[61], with PR oxycodone (a Step III analgesic) analysed separately. PR oxycodone (20–60 mg) reduced the intensity of back and nerve root pain (51.3%) compared with other analgesics (Step III, 22.6%; Step II, 33.5%; Step I, 37.1%) or no analgesics (9.1%) and improved the feasibility of orthopaedic therapy (45.7%) compared with comparators (tolperisone, ibuprofen, metamizole, acetaminophen, celecoxib, rofecoxib, tramadol and buprenorphine); WHO Step III, 25.0%; Step II, 21.9%; Step I, 31.3%[60]. This study is small, and short (only 14 day treatment period) and demonstrates that a WHO Step III opioid can provide effective pain relief compared with other analgesic options on the ladder. Larger, controlled studies of a longer duration, ideally with an extension phase are clearly warranted.

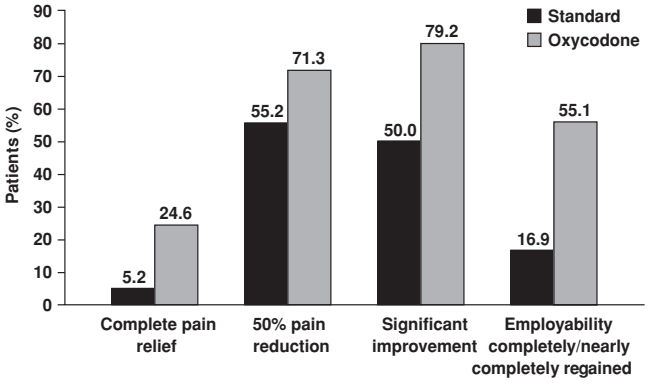

Figure 2. *Outcome of patients suffering from moderate-to-severe chronic low back pain following 3-week treatment with prolonged-release oxycodone (mean dose 31.2 mg/day) or standard analgesics. Reproduced with permission from Überall* et al.[59]

In a recent meta-analysis[62] of effectiveness and side effects of opioids for chronic non-cancer pain including back pain, OA and neuropathic pain, strong opioids (both morphine and oxycodone), were more effective than placebo for both pain and functional outcomes in patients with nociceptive or neuropathic pain or fibromyalgia, and were also superior to naproxen (oxycodone = 54.9 ± 15.87 vs. naproxen = 65.5 ± 19.05; standardised mean difference [SMD] –0.58 [–1.42, 0.26] on a 0–100 VAS) and nortriptyline (morphine = 4.4 ± 2.4 versus nortriptyline = 5.1 ± 2.3, SMD –0.30 [–0.65, 0.06] on a 0–10 numerical rating scale). Among the side effects observed, only constipation and nausea were reported to be clinically and statistically significant with risk differences observed of 9% (CI 1–17%) and 14% (CI 4–25%)[62]. Meta-analyses such as these demonstrate the analgesic efficacy of opioids[62], and the use of oxycodone specifically in these pain modalities has been shown here. Reports in the literature, either case reports[63], meta-analyses[64] or open-label follow-up studies[51,52] do indicate that patients can achieve effective analgesia and improved functioning long-term. However, the impracticability of conducting controlled trials over prolonged periods means that short-term data predominate and long-term data remain limited such that questions concerning the impact of opioids in terms of efficacy and side effects, such as sexual dysfunction, immunosuppression and tolerance remain to be answered.

Post-operative pain

Oral PR oxycodone is not recommended for the first 24-hours post-operatively[22]; however, IV oxycodone is used as part of a patient-controlled analgesia (PCA) regimen within this period and the IR-formulation is also indicated for post-operative use[65]. Nevertheless, studies are available that report the efficacy of oral PR oxycodone in the postoperative setting[66–70] for example anterior cruciate ligament surgery[66]. PR oxycodone has also been shown to provide effective analgesia during rehabilitation following total knee arthroplasty[67,68]. PR oxycodone-treated patients (up to 30 mg/12 h) reported significantly less pain (VAS, 4.8 vs. 5.9; $p = 0.012$) and greater knee movement and quadriceps strength versus placebo, with patients being discharged an average of 2.3 days earlier than placebo-treated patients[67]. In a second study, PR oxycodone significantly improved time for patients to achieve active flexion range of motion (ROM) of ≥ 90° ($p = 0.051$), sleep scores ($p = 0.001$) and reduced pain scores compared with an oxycodone/acetaminophen formulation ($p < 0.001$) concluding that PR oxycodone can facilitate shorter

functional recovery[68]. Limitations of these studies are several. All are of short duration as they explore the role of oxycodone in an acute setting rather than long-term chronic pain; they typically review, in the case of arthroplasty for example, the impact of oxycodone on inpatients and do not follow those patients discharged directly to home[67] and so may reflect a patient population in greater pain.

The post-operative analgesia of PR oxycodone (10 mg/12 h) has also been compared with IV tramadol/metamizol (100 mg/1 g every 4 hours), that is step II of the WHO 3-step ladder, after retinal surgery[69]. Patients in the PR oxycodone group had significantly lower pain scores at rest and 16 hours post-surgery (VAS 0 mm versus 5, $p = 0.03$) and 24 hours (VAS 0 mm versus 2, $p = 0.029$) although there was no significant difference in the area under the curve (AUC) for pain scores; quality of analgesia over time was also significantly higher in the oxycodone group compared with the tramadol/metamizol group (AUC defined as pain score over time was 69.8 ± 9.8 vs. 53.2 ± 17.5; $p = 0.001$)[69]. This study assumed analgesia in both groups to be equally effective and so focused on the incidence of post-operative nausea and vomiting (PONV), a particular challenge for eye surgery and found that patients treated with oxycodone had a better outcome with respect to PONV than those treated with tramadol[69]. The efficacy of PR oxycodone (10 mg) has also been compared with controlled-release (CR) tramadol (100 mg) following orthopaedic surgery[70]. The pain relief provided by PR oxycodone and CR tramadol were comparable in this study (median pain scores 20 and 18, respectively); however, CR tramadol-treated patients experienced significantly more nausea (15% vs. 6%; $p = 0.011$) and emesis ($n = 15$ vs. $n = 0$; $p = 0.013$) than those receiving PR oxycodone. Clearly, in this study all patients suffered from acute nociceptive pain, so results are not necessarily translatable to the moderate-to-severe chronic pain population.

Post-operative oral oxycodone has been compared with standard analgesia, including epidural anaesthesia, in two recent studies[71,72]. In the first study, 3-week treatment with PR oxycodone (up to 40 mg/12 h) was found to be as effective as standard therapy (including acetaminophen (paracetamol) plus codeine and oxycodone/acetaminophen combinations) demonstrated in a separate study in treating postoperative pain after knee or hip replacement[71]. However, patients in the PR oxycodone group recorded lower mean pain intensity scores at the time of discharge from hospital than those in the standard therapy group (VAS, 20.2 vs. 27.7, respectively; $p = 0.021$). Furthermore, the length of hospital stay was shorter (5.5 vs. 6.4 days; $p < 0.001$) and analgesic administration in hospital used less frequently in the PR oxycodone group (number of analgesic doses on days 2–6: 2.1 vs. 3.5; $p < 0.05$). However, outcome differences may reflect the comparison of two separate studies being conducted, one with oxycodone and one with standard therapy, rather than a prospective direct comparator study. Both studies used different rescue medication and criteria for hospital discharge was not formalised within the protocol and may produce results that need to be treated with caution. In another small study aimed to evaluate patient outcome following oral oxycodone or invasive epidural anaesthesia (EDA) in patients receiving analgesia after radical retropubic prostatectomy, oral oxycodone (20 mg) provided pain relief that was comparable with a similar side effect profile but was substantially cheaper than EDA (€9 versus €121) and enabled earlier mobilisation of patients (60% of oxycodone patients mobile on day 1 versus 30% of EDA-treated patients, $p < 0.06$) – leading the authors to conclude that treatment with oxycodone was preferable to EDA with ropivacaine (2 mg/ml, 4–12 ml/h)[72]. Although not currently a licensed indication, one study has reported that PR oxycodone provides effective analgesia in paediatric patients (10–19 years) after spinal fusion surgery; mean pain decreased from 4.2 to 3.7 (0–10 scale) when patients were converted to PR oxycodone (mean initial dose 1.24 mg/kg per day) from parenteral morphine equivalents ($p = 0.533$)[73]. However, the reduction is less than one point on the VAS scale and it is, therefore, questionable whether it is clinically meaningful. Side effects were observed to be lower with PR oxycodone compared with PCA (by 12.6%, from 56.5% of patients to 43.9%), and were as expected e.g. nausea and vomiting. It should be noted, however, that PR oxycodone is contraindicated in the first 24 hours post-operatively[22].

Efficacy in visceral pain

Visceral pain places a considerable burden on society and is one of the most common forms of pain[74,75] and includes pain such as myocardial ischaemia from atherosclerosis, urinary colic, irritable bowel syndrome, pancreatitis etc[74]. Indeed, the leading gastrointestinal complaint leading to visit to a clinician is pain – accounting for 12.2 million visits in the USA in 2000[76]. Similarly, chronic pelvic pain has an annual prevalence of 38/1000 women in the UK, which is comparable to that of asthma (37/1000) and back pain (41/1000)[77]. A further Canadian study has demonstrated, via a survey, that 5.2% of the Canadian population suffer from one or more lower gastrointestinal symptoms, including pain, bloating etc. for 12 weeks or more[78]. These symptoms cause a high burden on work performance

and patients seeking professional consultations are frequently dissatisfied with treatment (up to 75%)[78].

The need to improve the characterisation and treatment of visceral pain has led to the development of human experimental pain models, which offer the possibility of exploring the pain system under controlled conditions[79,80]. In these models pain is evoked via an oesophageal probe that can measure different pain modalities e.g. mechanical, thermal or chemical thus stimulating different groups of pain afferents[34,79–81]. These models are likely to be a valuable tool to differentiate visceral pain from other forms of pain and enable effective pain management strategies to be undertaken in the future. However, it should be remembered that while models provide a controlled experimental environment, and can provide valuable data in visceral pain, they are not wholly representative of clinical scenarios in visceral pain.

In one such model of experimental pain in skin, muscles and oesophagus the analgesic effects of equipotent doses of oxycodone (15 mg) and morphine (30 mg), and placebo were compared in healthy volunteers. Oxycodone and morphine were found to provide a significantly better analgesic effect than placebo in all tissues ($p < 0.001$)[33] as measured by peak tolerance threshold (PTT). IR oxycodone and IR morphine were equipotent in skin and muscle. In the oesophagus both morphine and oxycodone significantly altered PTT for mechanical and electrical stimulation; changes in PTT of 101.3 for mechanical stimulation ($p < 0.001$), thermal stimulation 9.5 ($p < 0.001$) and 20.1 ($p < 0.001$) for repeated electrical stimulation were observed[33]. However, *post hoc* analyses indicated that oxycodone was significantly more effective at attenuating thermal or mechanical pain in the oesophagus than morphine ($p < 0.05$), but was comparable to morphine with respect to electrical stimulation ($p > 0.05$). In patients with chronic pancreatitis the same experimental protocol was applied[34]. Oxycodone demonstrated significant attenuation of pain compared with both morphine and placebo in mechanical muscular pain as measured by increases in the PTT ($F = 11.0$, $p < 0.001$), and increased the pain detection threshold in the oesophagus for thermal (heat) pain ($F = 9.5$, $p < 0.001$); oxycodone and morphine were equally both superior to placebo in attenuating mechanical oesophageal pain to increase the PTT ($F = 8.6$, $p < 0.001$) (Figures 3A and 3B). These data suggested that opioids may have differential analgesic profiles, which, if known, can be of value in treating patients with severe visceral pain. One hypothesis proposed to explain the superior effect of oxycodone in human experimental visceral pain is that it could act via the κ-opioid receptor, since κ-receptors on peripheral sensory nerves in the gut and in the dorsal horn of the spinal cord play an important role in the mediation of the visceral pain system[27,33,34]. The finding may also be explained by a differential interaction with different sub-classes of the μ-receptor[82,83]. In patients, chronic visceral pain may lead to a central up-regulation of κ-opioid receptors in the spinal cord and the brain[33,34]. Hence, this may mask the visceral specific effects on the peripheral afferents and explain the superiority of oxycodone across all tissues.

Abdominal and gynaecological post-operative pain

Several studies have compared the analgesic effects of oxycodone with those of morphine in relieving post-operative pain from visceral origin[7,13,84]. In one study comparing IV oxycodone and IV morphine (0.05 mg/kg for both) after major abdominal surgery, pain relief was achieved faster (28 vs. 46 min; $p < 0.05$) and lasted longer (39 vs. 27 min; not significant) with IV oxycodone than morphine[7]. Furthermore, morphine caused more sedation and a significantly greater

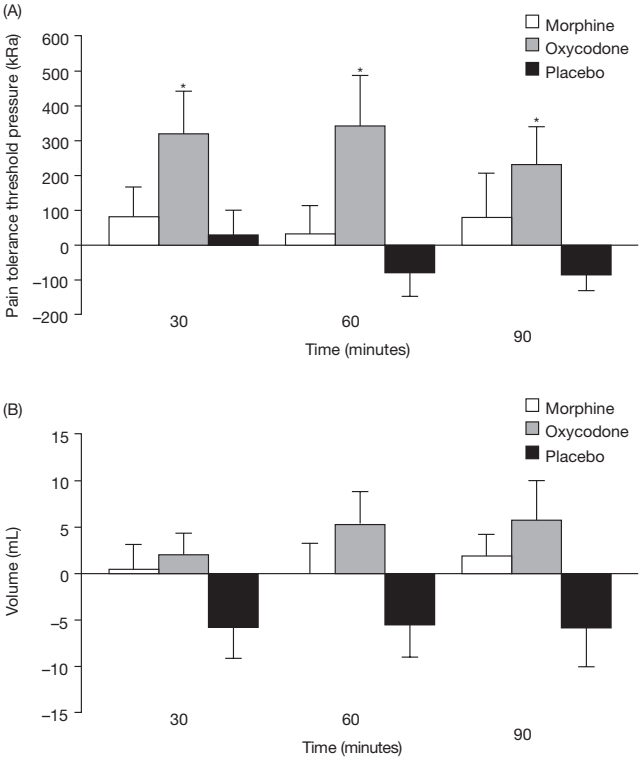

Figure 3. *Change in mechanical pain tolerance threshold intensities (± standard error of mean) from baseline in patients with chronic pancreatitis 30, 60 and 90 minutes after administration of morphine, 30 mg, oxycodone, 15 mg or placebo. (A) Mechanical stimulation of the muscle (pain tolerance thresholds, kPa). (B) Mechanical distension of the oesophagus (pain tolerance threshold, volume (mL)). Reproduced with permission from Staahl* et al.[34]. *p < 0.05 *vs. morphine and placebo*

decrease in mean arterial pressure than oxycodone ($p < 0.05$). In a second study, PR oxycodone (20 mg or 40 mg) provided comparable post-operative pain relief to CR morphine (45 mg or 90 mg) following hysterectomy, but was 1.8 times more potent than morphine for total effect (95% CI; 1.09–2.42) as calculated from measurements of the sum of the pain intensity differences (SPID)[13].

PR oxycodone (10, 20 and 30 mg) has been compared with IR oxycodone (15 mg), an IR oxycodone/acetaminophen combination (10/650 mg) and placebo in 182 patients after abdominal or gynaecological surgery[84]. Patients were randomised to receive a single dose IR oxycodone, PR oxycodone or IR oxycodone and acetaminophen (paracetamol), pain intensity was rated on a four-point scale and pain relief was evaluated on a five point verbal rating scale (0 = no pain relief; 5 = complete pain relief) and VAS 0–100 mm. In these patients oxycodone, regardless of formulation, was significantly more effective than placebo with respect to sum of the pain intensity differences ($p \leq 0.05$), total pain relief ($p \leq 0.05$), peak pain intensity difference ($p \leq 0.05$) and peak pain relief ($p \leq 0.05$). All three doses of PR oxycodone provided extended pain relief (12 hours) compared with IR oxycodone and IR oxycodone plus acetaminophen (paracetamol) where analgesia lasted between 6 and 8 hours[84].

Efficacy in cancer pain

Morphine is the strong opioid of choice for the treatment of moderate-to-severe cancer pain according to guidelines from the WHO[61,85]. This recommendation was derived by virtue of availability, familiarity to clinicians, established effectiveness and simplicity of administration and relative inexpensive cost, although it is clear that oxycodone is now very widely used for pain management[86].

Oxycodone has a similar efficacy to morphine and hydromorphone[87], supporting its use as an opioid for cancer-related pain (Table 3) as demonstrated in a recent meta-analysis. In this review there was no evidence that tolerability or mean pain scores differed between oxycodone and control drugs (oral morphine and oral hydromorphone; pooled standardized mean difference, 0.04; 95% CI –0.29 to 0.36), which prompted the authors to indicate that morphine and oxycodone were equally effective and that patients do not need to be automatically switched to oxycodone[87]. The authors do outline however, that this meta-analysis did contain only 160 patients, that the confidence interval for oxycodone data were narrow and that a clinically meaningful difference was not obtained in the studies evaluated – highlighting perhaps the limited systematic data available in cancer pain. As a result, the data do need to be treated with an element of caution. This is coupled to the potential for bias within the studies evaluated, as blinding was not apparent in many or could not be guaranteed to be successful[87]. Limitations are compounded by the short duration of studies, with attrition rates often driven by a need to minimize patient losses due to worsening disease, thus meaning that long-term data of efficacy or adverse events are not available. It is often assumed that all cancer pain can be relieved with morphine, but it is known that the clinical response to morphine is highly variable with approximately 10–30% of patients unable to tolerate mainly due to adverse side-effects; treatment with other opioids is required to optimise the balance between adequate pain relief and side effect profile[88]. Patients who do not respond or who have intolerance to morphine have been shown to be successfully converted to oxycodone. In a prospective evaluation of 186 patients, 138 responded well to morphine, whereas 48 patients were switched to oxycodone, the most common reasons being inadequate pain relief (30.5%), confusion and drowsiness (47.4%), nightmares (16.5%) and nausea (7.2%)[88]. Of the 64 patients switched, 47 had good clinical benefits (good analgesia with minimal side effects) when switched to oxycodone. The remainder of the patients required switching to other alternative opioids such as fentanyl and methadone. It should be noted that this study lacks cross-over data from oxycodone to morphine and so correlations for this comparison cannot be evaluated.

PR oxycodone has been shown to provide equivalent analgesic efficacy to CR morphine[5,89,90] and CR hydromorphone[91] in patients with chronic cancer-related pain (Table 3). The incidence of adverse events was similar between patients receiving PR oxycodone and morphine or hydromorphone in these studies. The most common events being constipation (oxycodone 21–66%, morphine 19–52%), sedation (oxycodone 15–59%, morphine 19–66%) and nausea (oxycodone 4–51%, morphine 15–59%)[5,90,92] though hallucinations were experienced by two morphine- and two hydromorphone-treated patients[91], and nightmares were experienced by three morphine-treated patients[90] versus no incidences of hallucinations or nightmares in patients receiving PR oxycodone. In one study ($n = 26$) comparing a combination of PR oxycodone and IR morphine with standard administration of morphine in advanced cancer patients, rescue morphine analgesic consumption was 38% higher in patients receiving only morphine versus those receiving the combination of both morphine and oxycodone[92]. In all these studies, the duration of active treatment was short (ranging from 3 to 14 days), and so data reflect the analgesic efficacy of oxycodone, but extrapolations to long-term

Table 3. Overview of studies comparing the analgesic efficacy of prolonged-release oxycodone with controlled-release morphine or hydromorphone in the relief of chronic cancer-related pain

Reference	Design	Drug	Mean dose	Mean pain scores at the end of treatment
Heiskanen and Kalso[90]	Open-label, randomized titration phase + double-blind, randomized, 2-way, 3–6 day crossover; $n = 45$	PR oxycodone CR morphine	123 mg/day 180 mg/day	0.99* 0.77*
Hagen and Babul[91]	Double-blind, 2-way, 7-day cross-over; $n = 31$	PR oxycodone CR hydromorphone	124 mg/day 30 mg/day	28.0† 30.6†
Mucci-LoRusso *et al.*[5]	Randomized, double-blind study for up to 12 days; $n = 52$	PR oxycodone CR morphine	101 mg/day 140 mg/day	1.3‡ 1.0‡
Bruera *et al.*[89]	Randomized 7-day study; $n = 32$	PR oxycodone CR morphine	46.5 mg/12 h 72.6 mg/12 h	24.3† 22.9†

*VRSpi, verbal rating scale pain intensity (mean daily pain intensity on a four-point verbal rating scale)

†Visual analogue scale (0–100 mm)

‡0 = none; 3 = severe

CR = oxycodone with controlled release; PR = prolonged release

efficacy and the incidence and impact of adverse events are difficult.

The analgesia provided by PR oxycodone in cancer pain has also been compared with that of IR oxycodone, with both formulations demonstrating equivalent efficacy in terms of pain relief and comparable side effect profiles[93–95]. In one study, PR oxycodone (mean dose 114 mg/day) was associated with fewer adverse events than IR oxycodone (mean dose 127 mg/day; 109 vs. 186 events; $p = 0.006$)[93], while a further study suggested both formulations provide stable pain control within similar timeframes[94]. In both these studies, the timeframe for treatment was short either 5 days[93] or 21 days[94].

One longer-term study of the use of PR oxycodone (mean dose 112.7 mg/day) for the treatment of cancer pain ($n = 87$) has demonstrated that the drug can successfully manage cancer-related pain over a 12-week period providing mean pain intensity scores of 1.6 ± 0.1[96]. Patients were allocated in this open label study to receive PR oxycodone, plus IR oxycodone as needed for breakthrough pain. Pain was measured using a categorical four-point scale (CAT) which does exhibit good correlation with VAS and numerical rating scales (NRS), but can exaggerate pain intensity as the correlation to standard scales is not linear. Tolerance to side effects did develop but this was complicated by patients' worsening disease state. Further, more than half of treated patients did not titrate their oxycodone dosing when indicated due to several reasons, including lack of awareness by healthcare professional, patient preference or patient avoidance of side effects[96]. A total of 51% of patients completed the study, with opioid-related side-effects decreasing from 55% of patients in week 1 to 13% of patients in week 12 ($p = 0.0002$), even despite stable pain control and an increasing total daily PR oxycodone (up to 120 mg/day). Constipation was however, actively managed with co-medication (laxatives etc.) and tolerance to nausea was observed within the same period (22.5 reducing to 2.5%, $p = 0.013$)[96]. A further study has evaluated the use of PR oxycodone in cancer pain at a starting dose of 5 mg every 12 hours with a mean age of 69.1 years; 90% (18/20) of patients attained stable and adequate pain control, with two-thirds of these (12/18) requiring no dose titration[97]. This study was an open label, dose titration study to evaluate the new low dose of PR oxycodone in a Japanese population. The 5 mg dose of PR oxycodone offers a lower starting dose which may be particularly useful in patients who may be more sensitive to opioid analgesics[97]. However, these data have not been subsequently validated in a broader cancer population encompassing a spectrum of ethnic groups.

Tolerability

The side-effect profile of oxycodone is comparable to that of other opioids, with the most common side effects reported being constipation, sedation and nausea[90]. However, fewer hallucinations have been reported with PR oxycodone (mean doses 101 and 124 mg/day, respectively) (0–2 patients) than either CR morphine (mean dose 140 mg/day) (five patients)[5,92] and CR hydromorphone (mean dose 30 mg/day) (two patients)[91] in patients with cancer-related pain. Furthermore, patients who do not respond or who have intolerance to morphine can be successfully converted to PR oxycodone[88]. In addition, PR oxycodone-treated

patients (mean dose 39.9 mg/day) have been reported to experience less nausea and vomiting then those receiving morphine (14 patients versus 19 patients)[98] or an IR oxycodone/acetaminophen (paracetamol) combination (mean dose 40.3 mg/day) (n = 5 [15%] versus n = 14 [38%])[53]. PR oxycodone (10 mg) has also been shown to be better tolerated than tramadol (100 mg) in post-operative pain therapy in relation to nausea, emesis and central effects such as sedation, insomnia, myoclonus and nightmares[70]. In common with other opioids, oxycodone is associated with constipation, and a recent meta-analysis in non-cancer pain places this occurrence at approximately 16%[62]. These data are supported by a systematic review of opioid-induced side effects across a range of pain types (cancer and non-cancer pain) of Step III opioids which illustrates that constipation occurs at a rate of approximately 15% (95% CI 14–16)[99]. Constipation results from a series of opioid induced effects on the gut, including decreased neural input as opioids bind to μ- and κ-receptors and inhibit acetylcholine release, delayed transit of food through the gut and altered propulsion in the form of stimulated contractions of the gut and increased fluid absorption within the gut increasing the dryness of faecal matter[100]. Constipation in patients is characterised by a constellation of symptoms including hard dry stools, straining, incomplete evacuation, bloating, abdominal distension and increased gastro-oesophageal reflux acting as a barrier to effective pain management, limiting therapy or prompting discontinuation[100]. Constipation is often managed with prophylactic laxative therapy, but evidence is emerging that oral opioid antagonists which have limited access to the blood brain barrier may be useful to block peripheral μ-opioid receptors, preventing constipation without affecting analgesia. Opioid antagonists that are emerging as useful agents include methylnatrexone[101], alvimopan[102] and naloxone[103]. Several commercial products are either in development or have recently become available.

Interestingly, some opioid-related adverse events, such as nausea, pruritus and somnolence, are reported to diminish during PR oxycodone therapy, despite increasing total daily doses (mean dose 112.7 mg/day[96] or starting doses of 10 mg[57] or 20 mg[51]). The favourable adverse event profile associated with oxycodone may be related to the observation that the drug does not contain any clinically active metabolites[16,104].

Conclusions

The efficacy of oxycodone in managing neuropathic and somatic pain – both in cancer- and non-cancer related pain – has been established in a wide range of settings, with evidence showing that PR oxycodone provides clinically meaningful relief of moderate-to-severe pain. Similarly, data are emerging that support the use of oxycodone in visceral pain – a challenging condition that affects many patients, albeit at this point in human experimental models[33]. One theory for the efficacy of oxycodone in neuropathic and visceral pain is its activity at κ-opioid receptors although further data are required to fully support this position[28,33].

Oxycodone has a similar adverse event profile to morphine but a more favourable pharmacokinetic profile[15–17]. Although morphine has been the standard opioid analgesic in the management of moderate-to-severe pain for many years, according to opioid consumption across the world oxycodone is the most widely used in the treatment of severe pain[86]. Large scale comparative trials with morphine are lacking, and quantification of morphine-induced adverse events in comparison with other agents has yet to be carried out. Evidence is now accumulating to suggest that oxycodone provides significant benefits for patients across a broad spectrum of pain types: somatic, neuropathic, visceral and cancer pain. Importantly, evidence is accumulating to suggest that oxycodone provides significant pain relief that may be more acceptable to patients[88] than morphine, and has relevant points of difference with other opioids – the most marked being its effect at κ-opioid receptors and the impact this has been shown to have[27,28,31,32,34], for example in visceral pain and receptor cross-talk linked to increased nociception.

We now have a greater number of strong analgesics in our armamentarium. Several studies show inter-individual variation to different opioids, although at present we cannot predetermine which patients will do well on which opioid. There are pain research activities at all levels – genetics, metabonomics, proteomics, molecular physiology, pharmacology and brain imaging. As more evidence becomes available it has become apparent that although strong opioids are efficacious in terms of pain control, greater attention needs to be focused on the side effect profiles of these drugs and the different individual responses to them. Increasing our understanding of the molecular basis underlying opioid effects on individual patients has the potential to help us identify the right opioid for each pain scenario and each patient, avoiding delay in achieving pain control with minimal side effect.

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