

## Narrative Review



## Oral Oxycodone for Acute Postoperative Pain: A Review of Clinical Trials

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**Background:** Opioids are the mainstay of pain management for acute postsurgical pain. Oral oxycodone is an opioid that can provide effective acute postoperative pain relief.

**Objectives:** To evaluate the use of oral oxycodone for acute postoperative pain management.

**Study Design:** This is a narrative review based on published articles searched in PubMed and Medline from 2003 to 2015 on oral oxycodone for acute postoperative pain management.

**Methods:** Clinical trials related to the use of oral oxycodone for acute postoperative pain management were searched via PubMed and Medline from 2003 to 2015. The search terms used were "oral strong opioids," "postsurgical," "postoperative," "post-surgical," and "post-operative." Treatment interventions were compared for analgesic efficacy, rescue medication use, side effects, recovery, length of hospital stay, and patient satisfaction.

**Results:** There were 26 clinical trials included in the review. Oral oxycodone showed superior postoperative analgesic efficacy compared with placebo in patients undergoing laparoscopic cholecystectomy, abdominal or pelvic surgery, bunionectomy, breast surgery, and spine surgery. When compared with intravenous opioids, oral oxycodone provided better or comparable pain relief following knee arthroplasty, spine surgery, caesarean section, laparoscopic colorectal surgery, and cardiac surgery. One study of dental postsurgery pain reported inferior pain control with oral oxycodone versus rofecoxib. (withdrawn from the US market due to cardiac safety concerns). In many studies, the demand for rescue analgesia and total opioid consumption were reduced in the oxycodone treatment arm. Patients receiving oral oxycodone experienced fewer opioid-related side effects than those on other opioids, and had a similar occurrence of postoperative nausea and vomiting as patients on placebo. Furthermore, oral oxycodone did not prolong hospital stay and was associated with lower drug costs compared with epidural and intravenous analgesics. Oxycodone administered as part of a multimodal analgesic regimen produced superior pain relief with fewer side effects and a reduced hospital stay.

**Limitation:** There is a limited number of randomized double blinded studies in individual surgical operations, thus making it more difficult to come up with definitive conclusions.

**Conclusion:** Oral oxycodone appears to offer safe and effective postoperative analgesia, and is a well-accepted and reasonable alternative to standard intravenous opioid analgesics.

**Key words:** Postoperative, pain, analgesia, oral oxycodone, opioid

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**E**ffective postoperative pain management is essential for minimizing discomfort and promoting early mobility and functional recovery of the surgical patient. Inadequate control of

acute postoperative pain may lead to delayed recovery and hospital discharge, diminished quality of life, and possible development of chronic pain, which can increase health care costs in the long run (1-3).

Ideally, postoperative pain management should aim to deliver adequate analgesia with minimal side effects. Opioids remain the mainstay of treatment for moderate to severe acute postoperative pain. In contrast to nonopioids, which demonstrate a “ceiling” analgesic effect, opioids provide greater efficacy as the dose is increased (4). However, the clinical utility of opioids is limited by their associated side effects, including respiratory depression, nausea, vomiting, pruritus, reduced bowel motility, and potential for dependence and addiction with long-term use (5).

Postoperative opioid analgesics may be administered by different routes, including oral, sublingual, rectal, parenteral (subcutaneous, intramuscular, intravenous), neuroaxial, and perineural means. Although the intravenous route may be appropriate in the immediate postsurgical period, oral analgesia is usually initiated once the patient is able to tolerate oral intake. Intravenous opioids, often administered as patient controlled analgesia (PCA), requires trained nursing staff and costly equipment (6). Furthermore, patients tied to the infusion pumps are restricted in their mobility. Therefore the oral route of administration is preferred because it is convenient, noninvasive, and cost-effective (7). It may also allow early discharge from the hospital after surgery.

Oxycodone is a semisynthetic opioid analgesic derived from the opium alkaloid thebaine. Unlike morphine, which is a  $\mu$ -opioid receptor agonist, oxycodone induces analgesia by primarily acting as a  $\kappa$ -opioid receptor agonist with a relatively low affinity for  $\mu$ -opioid receptors (8,9). There are several advantages to oxycodone versus morphine for postoperative pain management. The oral bioavailability of oxycodone is 60% compared with 15–30% for oral morphine (10,11). Oxycodone is transported more efficiently across the blood-brain barrier (BBB) than morphine, making it twice as potent as morphine (12,13). Oxycodone has been shown to be more effective than morphine in blocking visceral pain, an added benefit when treating postsurgical pain with a significant visceral pain component (14). Furthermore, less nausea, hallucinations and pruritus have been reported with oxycodone compared with morphine (15). Oxycodone is available as immediate-release (IR) and controlled-release (CR) formulations, the latter designed to deliver sustained analgesic effect with less frequent dosing (every 12 hours). Additionally, CR oxycodone provides fast onset of pain relief similar to that of the IR formulation (16).

High levels of postoperative pain are typically re-

ported in several surgical disciplines, including upper abdominal surgery, orthopaedics, spinal surgery, and cardiothoracic surgery (17,18). Some minor procedures such as tonsillectomy and knee arthroscopy can also result in high pain scores (17,19). Although the value of oral oxycodone for pain control has been investigated in various postsurgical settings (20–22), there is no comprehensive systematic review that assesses its efficacy and safety in individual surgical disciplines. We present here an overview of published clinical trials that used oral oxycodone for pain relief after different surgical interventions.

## **METHODS**

We conducted a literature search in PubMed and Medline to identify eligible studies published in the English language from 2003 through 2015. The reference lists of papers were also searched for other suitable studies. The initial search included the key words “oral strong opioids” (i.e., oxycodone, hydromorphone, methadone, buprenorphine and oxymorphone), “post-surgical,” “postoperative,” “post-surgical,” and “post-operative.” This original search yielded 126 results, of which 70 pertained to oral oxycodone. The inclusion criteria for this review were “studies that used oral oxycodone only” or “studies with oral oxycodone as part of a multimodal regimen.” Studies that reported the use of intravenous oxycodone were excluded from the analysis.

Data were extracted from each study that met the selection criteria to allow qualitative comparisons of interventions. The outcome measures chosen for comparison were analgesic efficacy (pain scores), changes in rescue medication use (reported in terms of amount of medication, proportion of patients who required rescue analgesia or time to first rescue analgesic), dose, side effects, postoperative recovery, patient satisfaction, and the health-related cost.

## **RESULTS**

### **Characteristics of Clinical Trials**

There were 26 clinical trials that fulfilled the inclusion criteria and were included in the review (Table 1). Thirteen studies had a randomized double-blind trial design and 10 of these had a placebo control arm. There were 17 randomized trials with an active comparator. Three studies were designed to compare a prospective cohort with a retrospective historical cohort. One open-label study compared results from 2 prospective cohorts.

## Oral Oxycodone for Postoperative Pain

Table 1. *Characteristics of clinical trials.*

| Author(s)<br>(Year)                    | Surgery type  | Study design   | Drugs administered (n)   | Dosage and frequency   | Rescue medication  |
|--|---|--|--|--|--|
| Fanelli et al<br>(2008) (23)           | Laparoscopic cholecystectomy                                  | Randomized, double-blind                               | CR oxycodone (25)<br>Placebo (25)  | 10 mg ≥ 60 y or 20 mg < 60 y;<br>1 h before surgery and 12 h after the first dose<br>1 h before surgery and 12 h after the first dose                        | Tramadol   |
| Jokela et al<br>(2007) (24)            | Gynecological laparoscopic surgery                            | Randomized, double-blind                               | CR oxycodone (29)<br>Placebo (29)  | 15 mg 1 h before surgery<br>1 h before surgery   | Fentanyl<br>Normal-release oxycodone                         |
| Ho (2008)<br>(25)                      | Laparoscopic colorectal surgery                               | Open-label, prospective cohort                         | CR oxycodone (14)<br>PCA morphine (9)  | 10–30 mg, day 1 & day 2 after surgery<br>8–28 mg, day 1; 4–31 mg day 2 after surgery   | IR oxycodone   |
| Santoso et al<br>(2014) (26)           | Abdominal hysterectomy with lymphadenectomy                   | Prospective cohort vs retrospective historical control | Oxycodone (multimodal) (105)<br>PCA morphine (113)   | 10 mg every 6 h as needed<br>2 mg every 10 min as needed for the first night postoperatively   | Not specified  |
| Singla et al<br>(2005) (27)            | Abdominal or pelvic surgery                                   | Randomized, double-blind                               | Oxycodone/ibuprofen (168)<br>Ibuprofen (174)<br>Oxycodone (52)<br>Placebo (60)   | 5 mg/400 mg<br>400 mg<br>5 mg<br>(all study medications given as single dose between 14 and 48 h after surgery)  | Oxycodone/<br>acetaminophen<br>Hydrocodone/<br>acetaminophen |
| Kerpsack and Fankhauser<br>(2005) (28) | Primary total joint arthroplasty                              | Prospective cohort vs retrospective historical control | CR oxycodone (57)<br>Oxycodone/acetaminophen (59)  | 20–40 mg as needed for 48 h post surgery<br>10 mg oxycodone with acetaminophen every 4 h for 48 h post surgery   | Oxycodone<br>Hydromorphone                                   |
| Richards et al<br>(2013) (29)          | Total knee arthroplasty                                       | Randomized, open-label                                 | Flexible dose morphine/oxycodone (14)<br>Fixed dose morphine/oxycodone (15)<br>Oxycodone/acetaminophen (15)  | 3 mg/2 mg to 24 mg/16 mg every 4 to 6 h<br>3 mg/2 mg every 4 to 6 h<br>5 mg/325 mg every 4 to 6 h<br>(all study treatments started on the day after surgery) | Supplemental acetaminophen                                   |
| Lamplot et al<br>(2014) (30)           | Total knee arthroplasty                                       | Randomized, controlled                                 | Oxycodone (multimodal) (19)<br>PCA hydromorphone (17)  | Oxycodone 10 mg every 12 h (plus tramadol, ketorolac, hydrocodone and hydromorphone)<br>1 mg IV as needed  | Hydrocodone<br>Hydromorphone                                 |
| Stessel et al<br>(2014) (31)           | Ambulatory knee arthroscopy or inguinal hernia repair surgery | Randomized, controlled                                 | Group 1 Acetaminophen/naproxen (PCM/NAPR) (35)<br>Group 2 Acetaminophen/CR oxycodone for 24 h (PCM/Oxy24h) (35)<br>Group 3 Acetaminophen/CR oxycodone for 48 h (PCM/Oxy48h) (35) | Naproxen 500 mg twice a day for 48 h<br>CR oxycodone 10 mg twice a day for 24 h<br>CR oxycodone 10 mg twice a day for 48 h                                   | Naproxen   |
| Woods et al<br>(2006) (32)             | Anterior cruciate ligament reconstruction                     | Randomized, controlled                                 | Block group:<br>Ropivacaine + oral hydrocodone (45)<br>Injection group:<br>Bupivacaine/morphine + oral oxycodone (45)  | 0.2% at 4 mL/h + 5 mg<br>20 mL of 0.5%/10 mg + 5 mg  | Hydromorphone  |

Table 1 (cont.). Characteristics of clinical trials.

| Author(s)<br>(Year)          | Surgery type                                      | Study design   | Drugs administered (n)   | Dosage and frequency  | Rescue medication   |
|------------------------------|---|--|--|---|---|
| Daniels et al (2011) (33)    | Bunionectomy                                      | Randomized, double-blind                               | Oxycodone HCl/niacin (135)<br>Oxycodone HCl/niacin (134)<br>Placebo (136)  | 2x5/30 mg every 6 h for 48 h<br>2x7.5/30 mg every 6 h for 48 h<br>2 tablets every 6 h for 48 h<br>(study medication was taken within 6 h of surgery)  | Ketorolac<br>tromethamine   |
| Daniels et al (2009) (34)    | Primary unilateral first metatarsal bunionectomy  | Randomized, double-blind                               | Oxycodone HCl IR (279)<br>Tapentadol IR (275)<br>Tapentadol IR (278)<br>Placebo (69)   | 10 mg every 4–6 h for 72 h<br>50 mg every 4–6 h for 72 h<br>75 mg every 4–6 h for 72 h<br>Every 4–6 h for 72 h  | Acetaminophen   |
| Stegmann et al (2008) (35)   | Unilateral metatarsal bunionectomy with osteotomy | Randomized, double-blind                               | Oxycodone HCl IR (67)<br>Tapentadol IR (67)<br>Tapentadol IR (68)<br>Placebo (67)  | 10 mg every 4–6 h for 72 h<br>50 mg every 4–6 h for 72 h<br>100 mg every 4–6 h for 72 h<br>Every 4–6 h for 72 h<br>(study medication was started 1 day after surgery)   | Acetaminophen<br>Ibuprofen or<br>ketorolac<br>Acetaminophen plus<br>hydrocodone |
| Blumenthal et al (2007) (21) | Elective lumbar discectomy                        | Randomized, double-blind                               | CR oxycodone (20)<br>Placebo (20)  | 20 mg every 12 h<br>Every 12 h<br>(study medication was given from the evening before surgery until the second postoperative morning)   | Not specified   |
| Rajpal et al (2010) (36)     | Spine surgery                                     | Prospective cohort vs retrospective historical control | CR Oxycodone (multimodal) (100)<br>IV PCA morphine or hydromorphone (100)  | Preoperative/intraoperative period:<br>CR oxycodone 20 mg (plus gabapentin, acetaminophen, dolasetron)<br>Postoperative period (through third day):<br>CR oxycodone 10–20 mg BID (plus gabapentin, acetaminophen)<br>1–2 mg or 0.2–0.4 mg, respectively, with a 6–10 min lockout interval between doses | Parenteral opioids  |
| Kampe et al (2004) (22)      | Breast surgery for cancer                         | Randomized, double-blind                               | CR oxycodone (20)<br>Placebo (20)  | 20 mg at 1 h pre-op and 12 h later<br>At 1 h preop and 12 h later   | Piritramide   |
| Kampe et al (2009) (37)      | Breast surgery for cancer                         | Randomized, double-blind                               | CR oxycodone (26)<br>CR tramadol (27)  | 20 mg at 30 min preop and 12 h later<br>200 mg at 30 min preop and 12 h later   | Acetaminophen   |
| Davis et al (2006) (38)      | Caesarean   | Randomized, controlled                                 | Oxycodone/acetaminophen (oral analgesic) (46)<br>IV PCA morphine (47)  | 2x5/325 mg every 3 h for first 12 h, thereafter, 1 to 2 tablets every 4 h as needed<br>1 mg/h + 1 mg on demand for first 12 h, thereafter, PCA discontinued and 1 to 2 oxycodone/acetaminophen tablets every 4 h as needed  | Meperidine  |
| Dieterich et al (2012) (39)  | Caesarean   | Randomized, controlled                                 | Oxycodone (113)<br>PCA piritramide (126)   | 20 mg at 2 h and 12 h after surgery<br>2 mg/mL 0.9% saline, discontinued at 24 h  | Ibuprofen<br>Acetaminophen  |
| Niklasson et al (2015) (40)  | Caesarean   | Randomized, open-label                                 | Oxycodone (38)<br>IV morphine/oral codeine (39)<br>Both treatment groups received adjunctive ibuprofen/acetaminophen throughout the 48-h study period. | 20 mg at 0 h; thereafter, 10 mg every 12 h for minimum 48 h.<br>10 mg/mL morphine for 24 h; thereafter, 2x30 mg codeine every 6 h for minimum 48 h.   | Ibuprofen<br>Acetaminophen<br>IR oxycodone<br>-oxycodone group only             |

Table 1 (cont.). *Characteristics of clinical trials.*

| Author(s)<br>(Year)          | Surgery type                     | Study design             | Drugs administered (n)  | Dosage and frequency  | Rescue medication   |
|------------------------------|----------------------------------|--------------------------|---|---|---|
| McDonnell et al (2010) (41)  | Caesarean                        | Randomized, double-blind | Oxycodone (55)<br>Intrathecal morphine (56)                       | 20 mg SR at 0 h; thereafter, 10 mg IR every 6 h for 24 h<br>100 µg at spinal anaesthesia  | IR oxycodone<br>Tramadol                                    |
| Ruetzler et al (2014) (20)   | Elective cardiac surgery         | Randomized, controlled   | Oral opioid (Oxycodone/naloxone) (24)<br>IV PCA morphine (26)     | 18 mg oxycodone every 12 h + 5 mg per 30 min as needed<br>0.3 mg/h  | Supplemental oxycodone or morphine in the respective groups |
| Hohwu et al (2006) (42)      | Radical retropubic prostatectomy | Randomized, controlled   | Oxycodone - multimodal (20)<br>Epidural - ropivacaine (20)        | Oxycodone 10 mg every 12 h (plus bupivacaine, paracetamol, morphine on demand)<br>2 mg/mL; 4–12 mL/h (plus paracetamol, morphine on demand) | Morphine  |
| Kaufmann et al (2004) (43)   | Retinal surgery                  | Randomized, double-blind | CR oxycodone (16)<br>IV Tramadol/metamizol (TM) (19)              | 10 mg post-op and 10 mg after 12 h<br>100 mg/1 g every 4 h up to 24 h post-op   | Piritramide   |
| Korn et al (2004) (44)       | Dental surgery                   | Randomized, double-blind | Oxycodone/acetaminophen (91)<br>Rofecoxib (90)<br>Placebo (31)    | 5/325 mg<br>50 mg<br>(study medication was given to patients experiencing moderate to severe postoperative pain)                            | Acetaminophen plus hydrocodone bitartrate                   |
| Gammaitoni et al (2003) (45) | Dental surgery                   | Randomized, double-blind | Oxycodone/acetaminophen (59)<br>CR oxycodone (61)<br>Placebo (30) | 10/325 mg<br>20 mg<br>(study medication was given to patients experiencing moderate to severe postoperative pain)                           | Not specified   |

CR, controlled-release; IR, immediate release; PCA, patient controlled analgesia; SR, sustained-release

## Main Findings by Surgical Setting

### Abdominal Surgery

#### Laparoscopic abdominal surgery

Fanelli and colleagues (23) investigated the preoperative administration of CR oxycodone as a transition opioid from an intraoperative remifentanyl infusion for pain control after laparoscopic cholecystectomy (Table 2). Compared with placebo, CR oxycodone treatment (10 mg ≥ 60 years old or 20 mg < 60 years old, one hour before surgery and 12 hours after first administration) resulted in a 50% or greater reduction in pain scores, more than 50% reduction in rescue analgesic (tramadol) use, and a shorter time to discharge from the recovery room and from the surgical ward. There were no differences between the 2 groups in postoperative complication rates (shivering, postoperative nausea and vomiting [PONV] and pruritus). Jokela and colleagues (24) also compared the effect of preoperative CR oxycodone treatment (15 mg one hour before surgery) versus placebo on postoperative analgesia in gynecological laparoscopic surgery. The 2 study groups did not differ

in their visual analog scale (VAS) scores for pain and side effects, rescue analgesic use, or level of satisfaction with pain management. The authors suggested that sub-therapeutic plasma levels (mean C<sub>max</sub> 10.0 ng/mL) of oxycodone found in the study participants could have contributed to the lack of analgesic efficacy. Ho (25) compared the efficacy and safety of CR oxycodone and intravenous PCA morphine following laparoscopic colorectal surgery. Patients in the oxycodone group received CR oxycodone 10 mg postoperatively upon return to the ward followed by 10 mg twice a day as needed. The morphine group received intravenous PCA morphine bolus one mg, with a lockout time of 5 min and a maximum of 10 mg/h. Results showed that pain control was similar in both treatment groups and all patients experienced a reduction in postsurgical pain intensity from day one to day 2. The incidence of nausea and vomiting was 14.2% and 20% for the oxycodone and PCA morphine groups, respectively.

#### Open abdominal surgery

Santoso and colleagues (26) studied the effectiveness of a multimodal analgesic regimen, including

Table 2. Oral oxycodone for laparoscopic abdominal surgery.

| Author             | Pain scores  | Changes in rescue medication use   | Side-effects/ complications  | Length of hospital stay                  | Patient satisfaction  | Mobilisation |
|--------------------|--|--|--|--|---|--------------|
| Fanelli et al (23) | NRSr and NRSi significantly lower in the oxycodone group than in the placebo group   | Mean tramadol use (mg):<br>Oxycodone = 129.55<br>Placebo = 329<br><i>P</i> < 0.05  | NS   | No data                                  | No data   | No data      |
| Jokela et al (24)  | VAS at rest and in motion during the first 2 h post-op or during 2–24 h post-op:<br>NS (oxycodone vs placebo)                    | Median fentanyl use (µg):<br>Oxycodone = 100<br>Placebo = 125<br>NS<br><br>Time to first dose (min):<br>Oxycodone = 19<br>Placebo = 16<br>NS<br><br>% of patients:<br>Oxycodone = 31<br>Placebo = 31<br>NS | NS   | No data                                  | % satisfied Excellent/good/fair:<br>Oxycodone = 63/30/7<br>Placebo = 71/25/4<br>NS              | No data      |
| Ho (25)            | Mean VAS<br>Post-op day 1:<br>Oxycodone = 2.07<br>PCA = 2.78<br>NS<br><br>Post-op day 2:<br>Oxycodone = 1.14<br>PCA = 1.67<br>NS | No data  | Incidence of PONV:<br>Oxycodone = 14.2%<br>PCA = 20%<br>No <i>P</i> values given | All patients discharged on post-op day 4 | All patients from both groups reported satisfaction with pain control (no numerical data given) | No data      |

NRSr, Numerical rating scale for pain at rest; NRSi, Numerical rating scale for pain at movement; NS, not significant; VAS, visual analog scale; PCA, patient controlled anaesthesia; PONV, postoperative nausea and vomiting

oxycodone, in reducing a hospital stay after open abdominal hysterectomy (Table 3). The study was designed to compare a prospective cohort of patients with a retrospective historical control. Postoperative pain control with the multimodal regimen consisted of gabapentin, acetaminophen, ketorolac, PCA morphine and oxycodone/acetaminophen 10/325 mg by mouth every 6 hours as needed. Patients receiving a multimodal regimen including oxycodone had a 50% shorter hospital stay compared with patients who received PCA morphine alone (2 mg every 10 minutes as needed for the first night postoperatively). Singla and colleagues (27) evaluated the analgesic efficacy of a single dose combination of oxycodone 5 mg/ibuprofen 400 mg with either agent alone or with placebo in women who had undergone abdominal or pelvic surgery. The combination regimen was associated with better pain control and lesser need for rescue analgesia compared with the other treatment arms. The study also reported

significantly greater pain relief with oxycodone alone compared with placebo at 1.5 and 2 hours after dosing. Nausea was the most frequently reported adverse event. The study was underpowered to detect differences in side effects. These studies show that oxycodone administered as part of a multimodal analgesic regimen delivers superior pain relief and shortens the hospital stay in patients undergoing open abdominal or pelvic surgery.

### Orthopaedic Surgery

#### Joint arthroplasty

Kerpsack and Fankhauser (28) compared the level of pain control achieved with postoperative CR oxycodone (20–40 mg as needed) with that of scheduled oxycodone (10 mg) plus acetaminophen every 4 hours given during the first 48 hours following total knee or hip arthroplasty (Table 4). Results from the McGill Short

Table 3. Oral oxycodone for open abdominal surgery.

| Author             | Pain scores  | Changes in rescue medication use   | Side-effects/ complications  | Length of hospital stay  | Patient satisfaction | Mobilisation |
|--------------------|--|--|--|--|----------------------|--------------|
| Santoso et al (26) | No data  | No data  | No data  | Mean days<br>Oxycodone = 1.6<br>PCA = 3.3<br><i>P</i> < 0.0001 | No data              | No data      |
| Singla et al (27)  | Significantly better TOTPAR6 ( <i>P</i> < 0.009) and SPID6 ( <i>P</i> < 0.001) scores with oxycodone/ibuprofen vs oxycodone alone<br><br>Pain relief at 1.5 and 2 h was significantly greater in the oxycodone group vs placebo ( <i>P</i> < 0.05) | Time to first dose (h):<br>Oxycodone/ibuprofen = 5.23<br>Ibuprofen = 3.95*<br>Oxycodone = 2.5*<br>Placebo = 2.28*<br>* <i>P</i> < 0.05 vs Oxycodone/ibuprofen<br><br>% of patients:<br>Oxycodone/ibuprofen = 55.0%<br>Ibuprofen = 70.7%<br>Oxycodone = 84.6% | % of patients with nausea:<br>Oxycodone/ibuprofen = 14.2<br>Ibuprofen = 12.6<br>Oxycodone = 23.1<br>Placebo = 20.0 | No data  | No data              | No data      |

PCA, patient controlled anaesthesia; TOTPAR6, total pain relief 6 hours after dosing; SPID6, sum of pain intensity differences 6 hours after dosing

Form Pain Questionnaire showed no difference in the pain scores except for 2 out of the 20 data points where CR oxycodone was more effective than scheduled oxycodone.

Richards and colleagues (29) compared the efficacy and tolerability of a flexible dose combination morphine/oxycodone (3 mg/2 mg to 24 mg/16 mg) versus oxycodone/acetaminophen (5 mg/325 mg) or fixed dose morphine/oxycodone (3 mg/2 mg) given every 4 to 6 hours and starting at one day after undergoing total knee arthroplasty. During the 48-hour treatment period, the analgesic efficacy of the flexible dose regimen was superior to the fixed dose morphine/oxycodone and comparable to oxycodone/acetaminophen. Nausea was more common with oxycodone/acetaminophen than with morphine/oxycodone. The most common opioid-like adverse events among all patients were nausea (15.9%), constipation (13.6%), and decreased oxygen saturation (13.6%).

Lamplot and colleagues (30) performed a randomized controlled trial of patients undergoing total knee arthroplasty to compare a multimodal analgesic regimen (consisting of intraoperative periarticular injection [bupivacaine, MSO4 and ketorolac] plus postoperative multimodal analgesics [oral oxycodone 10 mg every 12 hours, tramadol, ketorolac, hydrocodone and hydromorphone as needed]) with intravenous hydromorphone PCA. Compared with those on hydromorphone PCA, patients receiving a multimodal analgesic regimen including oxycodone had significantly lower pain scores;

decreased opioid consumption and opioid-related side effects (nausea, vomiting, constipation, insomnia, pruritus or mood irritability); higher levels of satisfaction; and reached physical therapy milestones sooner.

Stessel and colleagues (31) compared the efficacy and safety of acetaminophen/naproxen 500 mg twice a day for 48 hours postoperatively with either acetaminophen/CR oxycodone 10 mg twice a day for 24 hours or acetaminophen/CR oxycodone 10 mg twice a day for 48 hours after knee arthroscopy or inguinal hernia repair surgery. Acetaminophen 1000mg 4 times a day for 48 hours postoperatively was prescribed to all 3 study groups. No significant differences were found between the acetaminophen/naproxen group and either of the 2 acetaminophen/CR oxycodone groups for pain at movement and at rest. The adverse effects were comparable across the groups except for constipation, which occurred in significantly fewer patients in the acetaminophen/CR oxycodone (24 hours) group compared with the acetaminophen/naproxen group. Adverse effects assessed included fatigue, nausea, vomiting, pyrosis, abdominal complaints, and pruritus. A disadvantage of this study is that it combined patients who underwent 2 types of surgery.

#### Anterior cruciate ligament reconstruction

Woods and colleagues (32) compared a postoperative pain control protocol using a continuous ropivacaine femoral nerve block plus oral hydrocodone 5 mg as needed with another protocol using an

Table 4. Oral oxycodone for joint surgery.

| Author  | Pain scores  | Changes in rescue medication use  | Side-effects/ complications   | Length of hospital stay  | Patient satisfaction   | Mobilisation   |
|---|--|---|---|--|--|--|
| Kerpsack and Fankhauser (28)  | Post-op day 1 total pain score:<br>CR oxycodone = 9.82<br>Oxycodone/acetaminophen = 12.02<br>$P = 0.03$<br><br>Post-op day 2 VAS score:<br>CR oxycodone = 3.95<br>Oxycodone/acetaminophen = 3.52<br>$P = 0.02$   | Rescue medication (mean doses):<br><br>CR oxycodone = 2.58<br>Oxycodone/acetaminophen = 3.23<br>NS                                      | No data   | No data  | No data  | No data  |
| Richards et al (29)   | Median SPID (0–48 h):<br>Flexible dose group = 148.0<br>Fixed dose group = 71.3<br>Oxycodone/acetaminophen = 139.5<br>No significant difference between any two groups<br>BPI-SF score for pain interfering with general activity significantly lower in the flexible dose group than the Oxycodone/acetaminophen group at 48 hours<br>$P = 0.023$ | Supplemental acetaminophen (mean total dose in mg):<br><br>Both morphine/oxycodone arms = 970–990<br><br>Oxycodone/acetaminophen = 1150 | Incidence of nausea:<br>Flexible dose group = 0%<br>Fixed dose group = 20%<br>Oxycodone/acetaminophen = 26.7%<br><br>Incidence of vomiting:<br>Flexible dose group = 0%<br>Fixed dose group = 0%<br>Oxycodone/acetaminophen = 20% | No data  | No data  | BPI-SF score for pain interfering with walking ability lower in the flexible dose group than the Oxycodone/acetaminophen group at 48 hours |
| Lamplot et al (30)  | Multimodal group had significantly lower VAS pain scores compared to PCA at all time points<br>$P < 0.05$  | Total morphine equivalent consumption:<br>Multimodal = 66.2<br>PCA = 150.4<br>$P < 0.0004$  | % of patients with narcotic-related adverse effects:<br>Multimodal = 16<br>PCA = 94<br>$P < 0.01$   | Trend towards decreased length of hospital stay (mean days)<br>Multimodal = 1.9<br>PCA = 2.3 | Satisfaction scores from day 0 to week 3 post-op were higher in the multimodal group<br>$P < 0.05$ | Multimodal group performed better in straight leg raise, stair climbing, walking assisted or unassisted<br>$P < 0.01$                      |
| Stessel et al (31)<br>(Includes patients with inguinal hernia repair) | VAS scores for pain at movement and at rest:<br>Group 1 vs Group 2: NS<br>Group 1 vs Group 3: NS   | Three patients in Group 2 used rescue medication  | % of patient with constipation:<br>Group 1 = 34<br>Group 2 = 11*<br>Group 3 = 31<br>* $P = 0.041$ vs Group 1  | No data  | Mean satisfaction score:<br>Group 1: 8.3<br>Group 2: 8.1<br>Group 3: 8.6                           | No data  |
| Woods et al (32)  | VAS and Category-ratio scale pain ratings:<br>NS   | Total narcotic pain medication (morphine-equivalent doses):<br>Block group = 1.1<br>Injection group = 1.1<br>NS                         | No data   | No data  | % of patients satisfied:<br>Block group = 93<br>Injection group = 91<br>NS                         | % of patients unable to perform supine straight-leg raise:<br>Block group = 40<br>Injection group = 13<br>$P = 0.004$                      |

CR, controlled release; VAS, visual analog scale; NS, not significant; SPID, sum of pain intensity difference; BPI-SF, brief pain inventory-short form; PCA, patient controlled anaesthesia

intraoperative bupivacaine/morphine intraarticular injection plus oral oxycodone 5 mg as needed for pain relief after anterior cruciate ligament reconstruction. In the first 24 hours after surgery, postoperative pain ratings and total opioid use were comparable between the 2 groups. Patients were satisfied with pain control in both groups. The authors concluded that the continuous femoral block with ropivacaine appeared to have no clinical advantage over bupivacaine/morphine intraarticular injection in the immediate postoperative

period. Although oxycodone was used in one of the multimodal treatment protocols, this study was not designed to address the precise role of oxycodone in relieving postoperative pain.

**Foot surgery**

Daniels and colleagues (33) compared the efficacy and safety of 2 strengths of oxycodone HCl/niacin tablets (2x5/30 mg and 2x7.5/30 mg) and placebo taken every 6 hours for 48 hours following bunionectomy sur-

Table 5. Oral oxycodone for foot surgery.

| Author              | Pain scores  | Changes in rescue medication use   | Side-effects/ complications  | Length of hospital stay | Patient satisfaction | Mobilisation |
|---------------------|--|--|--|-------------------------|----------------------|--------------|
| Daniels et al (33)  | SPID48:<br>Oxycodone HCl/niacin<br>2x5/30 mg = 998.46*<br>2x7.5/30 mg = 1224.97*<br>Placebo = 604.48<br><br>*P < 0.0001 vs placebo   | Total ketorolac tromethamine (mean exposures):<br>Oxycodone HCl/niacin<br>2x5/30 mg = 2.3*<br>2x7.5/30 mg = 2*<br>Placebo = 3.6<br>*P < 0.0001 vs placebo<br>% of patients:<br>Oxycodone HCl/niacin<br>2x5/30 mg = 88.1†<br>2x7.5/30 mg = 82.8‡<br>Placebo = 97.1<br>†P = 0.0038 vs placebo<br>‡P < 0.0001 vs placebo<br>Time to first dose (h):<br>Oxycodone HCl/niacin<br>2x5/30 mg = 2.4§<br>2x7.5/30 mg = 2.9§<br>Placebo = 1.4<br>§ P < 0.0001 vs placebo | % of patients with any adverse event:<br>Oxycodone HCl/niacin:<br>2x5/30 mg = 77<br>2x7.5/30 mg = 87.3<br>Placebo = 38.2<br>No P value given         | No data                 | No data              | No data      |
| Daniels et al (34)  | SPID48 LS mean difference from placebo:<br>Oxycodone = 81.5*<br>Tapentadol (50 mg) = 62.4*<br>Tapentadol (75 mg) = 84.6*<br>*P < 0.001 versus placebo  | % of patients:<br>Oxycodone = 3.2<br>Tapentadol (50 mg) = 6.2<br>Tapentadol (75 mg) = 1.4<br>Placebo = 23.2<br>No P-value given  | % of nausea and/or vomiting<br>Oxycodone HCl IR = 59<br>Tapentadol IR (50 mg) = 35<br>P < 0.001  | No data                 | No data              | No data      |
| Stegmann et al (35) | Mean SPI-24 VRS score on day 3:<br>Oxycodone = 35.7*<br>Tapentadol (50 mg) = 33.6†<br>Tapentadol (100 mg) = 29.2‡§<br>Placebo = 41.9<br>*P = 0.0365 vs placebo<br>†P = 0.0133 vs placebo<br>‡P = 0.0001 vs placebo<br>§P = 0.0455 vs oxycodone | % of patients:<br>Oxycodone = 80.6<br>Tapentadol (50 mg) = 80.6<br>Tapentadol (100 mg) = 76.5<br>Placebo = 98.5<br><br>No P-values given   | % adverse events<br>Oxycodone vs placebo:<br>Nausea = 71.6 vs 17.9<br>Dizziness = 56.7 vs 14.9<br>Somnolence = 26.9 vs 7.5<br>Vomiting = 38.8 vs 1.5 | No data                 | No data              | No data      |

SPID48, sum of pain intensity difference over the first 48 h of treatment; LS, least squares; SPI-24, summed pain intensity over 24 h; VRS, verbal rating scale

ger (Table 5). Both doses of active drug demonstrated superior analgesic efficacy and lesser need for rescue medication compared with placebo. Both active groups also experienced more mild to moderate adverse events (nausea, vomiting, dizziness, flushing, and pruritus), typical of those associated with opioid and/or niacin exposure.

In another trial, Daniels and colleagues (34) compared tapentadol immediate release (50 or 75 mg) with oxycodone IR (10 mg) for pain management after bunionectomy. Patients received study medication or placebo every 4–6 hours over a 72 hour period following surgery. Both oxycodone IR and tapentadol IR treatments were associated with significant reductions in pain intensity compared with placebo. Furthermore, oxycodone provided analgesic efficacy that was comparable to that of both doses of tapentadol. More patients in the placebo group received rescue analgesics compared with the active treatment groups. A significantly higher percentage of patients reported nausea and/or vomiting in the oxycodone group compared with the tapentadol 50 mg group. Other adverse effects, including dizziness, headache, somnolence, pruritus, and constipation also occurred more frequently in the oxycodone group.

Stegmann and colleagues (35) assessed the effectiveness of multiple-dose (50 and 100 mg) tapentadol,

oxycodone (10 mg) or placebo in managing pain after bunionectomy surgery. The study drug was taken every 4–6 hours over a 72 hour period starting one day after surgery. Oral oxycodone demonstrated comparable efficacy to tapentadol 50 mg but was inferior to tapentadol 100 mg. Compared with placebo, oxycodone treatment was associated with a significant decrease in pain intensity, less likelihood of rescue medication use, but a higher incidence of adverse events, including nausea, dizziness, somnolence, vomiting, headache, and constipation.

The above 2 studies demonstrate that oxycodone 10 mg is equally effective as tapentadol 50 mg and 75 mg but is inferior to tapentadol 100 mg in controlling pain after bunionectomy.

### Spine surgery

Blumenthal and colleagues (21) evaluated the perioperative administration of oral CR oxycodone in patients undergoing lumbar discectomy (Table 6). Every 12 hours patients received either 20 mg CR oxycodone or placebo, starting from the evening before surgery until the second postoperative morning. All patients received intravenous morphine for postoperative PCA. Compared with placebo, oxycodone treatment resulted in decreased morphine consumption, better

Table 6. Oral oxycodone for spine surgery.

| Author                | Pain scores  | Changes in rescue medication use  | Side-effects/ complications   | Length of hospital stay | Patient satisfaction                                     | Mobilisation  |
|-----------------------|--|---|---|-------------------------|--|---|
| Blumenthal et al (21) | Postop IV morphine consumption vs placebo<br>T0–24: 26 mg vs 52 mg<br>T24–48: 13 mg vs 33 mg<br>$P < 0.001$<br><br>VAS scores for pain at rest, during coughing and with motion during 0–48 h postop were significantly lower with oxycodone vs placebo<br>$P < 0.005$ | No data   | Lower incidence of side effects for oxycodone vs placebo<br>PONV (0–24 h):<br>$P < 0.05$<br><br>Pruritus:<br>NS<br><br>Mild sedation:<br>NS                 | No data                 | Score:<br>Oxycodone = 9.1<br>Placebo = 7.5<br>$P < 0.05$ | No data   |
| Rajpal et al (36)     | Mean least pain ratings:<br>Multimodal = 2.36<br>IV PCA = 3.18<br>$P < 0.01$<br>Mean worst pain ratings:<br>NS   | Mean parenteral morphine equivalent (0–24 h):<br>Multimodal = 31.2<br>IV PCA = 49.97<br>$P < 0.001$ | Severity of nausea:<br>Multimodal = 1.72<br>IV PCA = 3.61<br>$P < 0.001$<br><br>Severity of drowsiness:<br>Multimodal = 4.51<br>IV PCA = 5.55<br>$P < 0.05$ | No data                 | Improved scores vs IV PCA                                | Mean score for interference from pain with walking:<br>Multimodal = 4.39<br>IV PCA = 5.62<br>$P < 0.05$ |

VAS, visual analog scale; PONV, postoperative nausea and vomiting; NS, not significant; PCA, patient controlled anaesthesia

pain control and fewer side effects. Furthermore, the oxycodone-treated patients experienced a faster return of bowel function and expressed higher satisfaction with pain therapy 72 hours postoperative.

Rajpal and colleagues (36) compared spine surgery patients who were treated with a multimodal oral regimen that included pre- and postoperative CR oxycodone with a historical control cohort who received intravenous PCA with either morphine or hydromorphone (1–2 mg or 0.2–0.4 mg, respectively, with a 6–10 minute lockout interval between doses). The multimodal regimen included CR oxycodone 10–20 mg, gabapentin, acetaminophen, dolasetron, and as-needed postoperative short-acting oral oxycodone. Compared with the PCA group, the multimodal group had significantly lower least-pain ratings, less opioid consumption in the first 24 hours after surgery, and spent less time in moderate to severe pain. Furthermore, patients receiving the multimodal regimen including oxycodone experienced less severe nausea and drowsiness, and less interference from pain with walking and coughing and deep breathing.

**Breast surgery**

Kampe and colleagues (22) assessed the clinical efficacy of CR oxycodone for the management of pain after breast surgery for cancer (Table 7). A CR oxycodone 20 mg tablet or placebo was administered one hour before surgery and another tablet 12 hours later. The primary efficacy variable, the area under the curve (AUC) for opioid (pirtamide) consumption over 24 hours postoperatively, was significantly lower in the CR oxycodone group than in the placebo group ( $P = 0.01$ ). The CR oxycodone group required a lower intravenous opioid loading dose and consumed less opioid rescue medication at the 4 hour, 16 hour, and 24 hour time points. The cumulative pain experienced over the 24 hours as represented by the AUC for VAS pain scores was significantly lower for the CR oxycodone group while at rest, but not with movement. The incidence of nausea was comparable between the 2 groups and there were no differences in patients' assessment of the quality of pain management.

Kampe and colleagues (37) conducted another study to assess the clinical equivalence of 20 mg CR oxy-

Table 7. Oral oxycodone for breast surgery.

| Author           | Pain scores   | Changes in rescue medication use   | Side-effects/ complications  | Length of hospital stay | Patient satisfaction  | Mobilisation |
|------------------|---|--|--|-------------------------|---|--------------|
| Kampe et al (22) | AUC for VAS pain scores at rest:<br>CR oxycodone = 92 x time<br>Placebo = 188 x time<br>$P = 0.05$<br><br>AUC for VAS pain scores at movement:<br>CR oxycodone = 324 x time<br>Placebo = 504 x time<br>NS | Cumulative pirtamide consumption over 24 h (mg):<br>CR oxycodone = 28<br>Placebo = 53<br>$P = 0.002$ | Incidence of nausea:<br>CR oxycodone = 55%<br>Placebo = 35%<br>NS  | No data                 | VAS quality of analgesia score:<br>Oxycodone = 89<br>Placebo = 83<br>NS | No data      |
| Kampe et al (37) | 90% CI of mean differences in VAS pain scores (8–24 h post-op):<br>VAS at rest [-4.5 to +1.7]<br>VAS on coughing [-6.2 to +1.7]   | Cumulative IV acetaminophen use over 24 h (g):<br>Oxycodone = 1.32<br>Tramadol = 1.61<br>NS          | No significant differences in side effects:<br>Nausea ( $P = 0.13$ )<br>Vomiting ( $P = 0.24$ )<br>Itching ( $P = 0.77$ )<br>Sedation ( $P = 0.97$ )<br>Dizziness ( $P = 0.35$ ) | No data                 | Scores:<br>Oxycodone = 3.56<br>Tramadol = 3.53<br>NS                    | No data      |

AUC, area under the curve; VAS, visual analog scale; CR, controlled release; NS, not significant

codone and 200 mg CR tramadol on a 12-hour dosing schedule (30 minutes preoperative and 12 hours later) in patients undergoing surgery for breast cancer. The 90% confidence intervals of the mean differences between the treatment groups for VAS pain scores at rest and on coughing were found to be within the predefined equivalence margin (-10.0 to +10.0), suggesting clinical equivalence regarding these pain scores. Furthermore, the 2 treatments were comparable in terms of adverse events, use of rescue analgesia, patient satisfaction, and patients' general perception of postoperative pain management.

### Caesarean section

Davis and colleagues (38) compared oral oxycodone/acetaminophen with intravenous morphine PCA for postcaesarean pain relief (Table 8). Women in the oral analgesia group received 2 oxycodone/acetaminophen (5/325 mg) tablets immediately after surgery and every 3 hours for the first 12 hours, and thereafter, one to 2 tablets every 4 hours as needed. Patients assigned to the intravenous morphine PCA group received one mg/h + one mg on demand for the first 12 hours, and thereafter, PCA was discontinued and the patients were allowed to take one to 2 oxycodone/acetaminophen (5/325 mg) tablets every 4 hours as needed. Patients who received oral analgesia had less pain at 6 and 24 hours after caesarean delivery compared with those who received PCA. They also experienced less nausea and drowsiness at 6 hours, but nausea was more severe at the 24-hour assessment. There were no differences between the 2 groups with regard to length of hospital stay, rescue medication use, incidence of pruritus and vomiting, or ambulation.

Dieterich and colleagues (39) compared oral oxycodone with intravenous piritramide (not available in the US) PCA for postcaesarean pain control. Patients were randomized to receive CR oxycodone 20 mg (administered at 2 hours and 12 hours after caesarean surgery) or intravenous piritramide PCA (2 mg/mL, 0.9% saline, discontinued at 24 hours). Both treatments resulted in comparable pain relief and need for rescue medication. There was a statistically nonsignificant increase in the demand for rescue analgesia in the PCA group at 48 hours after caesarean section. No significant differences were found in side effects, time to first mobility, or overall satisfaction with pain management. The study also reported that the oxycodone regimen was less expensive than PCA.

Niklasson and colleagues (40) conducted a ran-

domized parallel group study to evaluate if oral oxycodone offers equivalent or better postcaesarean analgesic efficacy compared with nurse-administered intravenous morphine followed by oral codeine. The oxycodone group received a 20 mg dose immediately after surgery, and thereafter, 10 mg every 12 hours for a minimum of 48 hours. The other group received 10 mg/mL morphine for 24 hours, and thereafter, 2x30 mg codeine every 6 hours for up to at least 48 hours. All patients received postoperative multimodal analgesic therapy, including ibuprofen and acetaminophen. There were no differences between the 2 treatments in mean pain intensity at rest during the first 24 hours; however, during the 25–48 hour period, the oxycodone-treated patients experienced significantly lower pain intensity at rest and had lower opioid intake than those on morphine/codeine. Furthermore, in the first 24 hours, side effects (including dizziness, nausea, and itching) and the need for rescue medication were less frequent in the oxycodone group. Time to first bowel movement was also significantly shorter in the oxycodone group ( $P = 0.038$ ).

McDonnell and colleagues (41) compared the quality of postoperative analgesia provided by intrathecal morphine versus oral oxycodone in women undergoing caesarean section under spinal anesthesia. Patients were randomized to receive either sustained release (SR) oxycodone 20 mg in the recovery room followed by IR oxycodone 10 mg every 6 hours for 24 hours or intrathecal morphine 100 µg at the time of spinal anesthesia. In general, oral oxycodone produced comparable postoperative pain relief compared to intrathecal morphine; however, patients in the oxycodone group had higher pain scores at rest at 12 hours, reported high worst pain scores more frequently ( $P = 0.007$ ), and were more likely to require additional analgesia. The severity and incidence of pruritus were higher in the intrathecal morphine group, but the incidences of nausea and epigastric pain were similar. Maternal satisfaction with analgesia was lower in the oxycodone group at 24 hours, but this difference was not evident at 48 hours.

### Elective cardiac surgery

Following elective cardiac surgery, Ruetzler and colleagues (20) randomly assigned patients to receive either oral opioid (oxycodone/naloxone) or intravenous morphine PCA and compared the total opioid use and postoperative analgesic efficacy of the 2 groups (Table 9). After postoperative respiratory weaning, patients

## Oral Oxycodone for Postoperative Pain

Table 8. Oral oxycodone for caesarian section.

| Author               | Pain scores  | Changes in rescue medication use  | Side-effects/ complications   | Length of hospital stay   | Patient satisfaction  | Mobilisation  |
|----------------------|--|---|---|---|---|---|
| Davis et al (38)     | Mean VAS pain score<br>At 6 h postop:<br>Oral analgesic = 3.2<br>Morphine = 4.1<br>$P = 0.04$<br><br>At 24 h post-op:<br>Oral analgesic = 2.9<br>Morphine = 4.1<br>$P = 0.004$   | No. of patients:<br>Oral analgesic = 4<br>Morphine = 3<br>NS  | Oral analgesic vs morphine<br>At 6 h postop:<br>less nausea ( $P = 0.001$ )<br>less drowsiness ( $P < 0.001$ )<br><br>At 24 h post-op:<br>More nausea ( $P = 0.04$ )  | Mean days,<br>Oral analgesic = 4.6<br><br>Morphine = 4.6<br>NS    | No data   | % of patients ambulating<br>At 6 h post-op:<br>Oral analgesic = 11<br>Morphine = 15<br>NS<br><br>At 24 h post-op:<br>Oral analgesic = 2<br>Morphine = 4<br>NS |
| Dieterich et al (39) | Mean VAS pain scores comparable at all time points of evaluation (12, 24, 32, 40, 48, 72 h post-caesarean)   | % of patients<br>After 24 h:<br>Oxycodone = 45<br>Piritramide = 51<br>NS<br><br>After 48 h:<br>Oxycodone = 21<br>Piritramide = 23<br>NS<br><br>After 72 h:<br>Oxycodone = 7<br>Piritramide = 11<br>NS | Side effects equally distributed between groups:<br>Nausea<br>Vomiting<br>Headache  | NS  | Scores:<br>Oxycodone = 8.75<br>Piritramide = 8.4<br>NS  | Mean time to mobilisation (h)<br><br>Oxycodone = 4.9 (1.3)<br>PCA = 5.2 (1.6)<br>NS   |
| Niklasson et al (40) | Mean NRS pain scores at rest<br>0–24 h:<br>Oxycodone = 3.43<br>Morphine/codeine = 3.93<br>NS<br><br>25–48 h:<br>Oxycodone = 2.89<br>Morphine/codeine = 3.80<br>$P = 0.039$   | Mean number of rescue medications during 0–24h:<br>Oxycodone = 4.3<br>Morphine/codeine = 8.4<br>$P = 0.047$   | % of patients with opioid-related side effects:<br>Oxycodone = 3<br>Morphine/codeine = 15<br>$P = 0.007$  | Mean days:<br><br>Oxycodone = 2.4<br>Morphine/codeine = 2.4<br>NS | Number of women unsatisfied with pain relief:<br>Oxycodone = 4<br>Morphine/codeine = 6  | NS  |
| McDonnell et al (41) | AUC for pain scores to 24 h between groups NS at rest ( $P = 0.465$ ) and on movement ( $P = 0.533$ )<br><br>Numerical pain scores were similar except at rest at 12 h:<br>Oxycodone = 2<br>Morphine = 1<br>$P = 0.03$ | Time to first analgesic request (min):<br>Oxycodone = 144<br>Morphine = 160<br>NS<br><br>Request for additional analgesia:<br>Oxycodone = 82%<br>Morphine = 63%<br>$P = 0.034$                        | Incidence of pruritus:<br>Oxycodone = 56%<br>Morphine = 87%<br>$P = 0.001$<br><br>Global severity score for pruritus:<br>Oxycodone = 1<br>Morphine = 4<br>$P = 0.001$ | No data   | Maternal NRS score<br>At 24 h:<br>Oxycodone = 8<br>Morphine = 10<br>$P = 0.01$<br><br>At 48 h:<br>Oxycodone = 9<br>Morphine = 9<br>NS | No data   |

VAS, visual analog scale; NS, not significant; PCA, patient controlled anaesthesia; NRS, Numerical rating scale; AUC, area under the curve

Table 9. Oral oxycodone for cardiac surgery, radical prostatectomy, and retinal surgery.

| Author              | Pain scores   | Changes in rescue medication use   | Side-effects/ complications   | Length of hospital stay                                | Patient satisfaction   | Mobilisation  |
|---------------------|---|--|---|--|--|---|
| Ruetzler et al (20) | Adjusted difference in mean VAS pain scores [95% CI]:<br>3.44 [-4.29–11.17]<br>NS   | Adjusted morphine equivalent dose:<br>Oral opioid = 34<br>Morphine = 69<br>Ratio [95% CI] = 0.49 [0.41–0.58]<br>$P < 0.001$  | % for oral opioid vs morphine:<br>Nausea = 12 vs 31<br>Vomiting = 21 vs 12<br>Anorexia = 17 vs 31<br>Dizziness = 25 vs 42<br>Headache = 4 vs 19<br>Itching 4 vs 4 | Median (days):<br>Oral opioid = 8.5<br>Morphine = 9    | No data  | No data   |
| Hohwu et al (42)    | Median VAS pain score<br>During operation day:<br>Oxycodone = 1.8<br>Ropivacaine = 0.7<br>NS<br><br>During hospital stay:<br>Oxycodone = 1.7<br>Ropivacaine = 1.7<br>NS | Total injected morphine (mg):<br>Oxycodone = 16.2<br>Ropivacaine = 19.0<br>NS<br><br>Total oral morphine (mg):<br>Oxycodone = 261<br>Ropivacaine = 111.4<br>No $P$ value given | Side effects observed with ropivacaine only:<br>Loss of sensor function in legs = 40%<br>Hypotension = 30%<br>Orthostatic hypotension = 10%                       | Median (nights)<br>Oxycodone = 3<br>Epidural = 3<br>NS | No data  | % of patients achieving free mobilization at the end of first post-op day:<br><br>Oxycodone = 60<br>Epidural = 30<br>NS |
| Kaufmann et al (43) | AUC for pain scores at rest: NS<br><br>VAS pain scores at rest for oxycodone vs TM<br><br>At 16 h:<br>$P = 0.03$<br><br>At 24 h:<br>$P = 0.029$                         | One patient in the oxycodone group required 3 mg IV piritramide  | Incidence of nausea:<br>Oxycodone = 6% TM = 53%<br>$P = 0.012$<br><br>Incidence of vomiting:<br>Oxycodone = 6% TM = 26%<br>NS                                     | No data  | Higher quality of analgesia with oxycodone vs TM<br><br>At 8 h:<br>$P = 0.048$<br><br>At 16 h:<br>$P = 0.009$<br><br>At 24 h:<br>$P = 0.001$ | No data   |

VAS, visual analog scale; NS, not significant; AUC, area under the curve; TM, tramadol/metamizol

in the oral opioid group received 18 mg of oxycodone at 12-hour intervals and an additional 5 mg oxycodone every 30 minutes if needed. The PCA group received 0.3 mg morphine per hour. Oral opioid administration provided comparable analgesia to intravenous morphine with reduced overall opioid consumption. Furthermore, oral opioid was associated with fewer side effects except vomiting.

### Radical retropubic prostatectomy

Hohwu and colleagues (42) evaluated whether a combined oral acetaminophen/oxycodone regimen provides adequate postsurgical analgesia that is equivalent to epidural analgesia (EDA) in patients undergoing radical retropubic prostatectomy. The oxycodone group received a 10 mg oxycodone tablet

on the morning of the operation and thereafter every 12 hours until postoperative day 2 or 3. Patients in this group also received bupivacaine (perioperative wound infiltration), acetaminophen, and morphine on demand. The EDA group was given ropivacaine (2 mg/mL, 4–12 mL/h until the second or third postoperative day), acetaminophen, and morphine on demand. Both treatments produced comparable and satisfactory analgesia. Treatment complications (including hypotension, and loss of sensory function in the legs) were observed in 80% of patients in the EDA group compared with only 5% in the oxycodone group. No significant differences were observed between the groups with regard to postoperative vomiting, constipation, mobility, or length of hospital stay, but the cost of the oxycodone regimen was much lower.

**Retinal surgery**

Kaufmann and colleagues (43) compared the analgesic efficacy and safety of CR oxycodone versus intravenous tramadol/metamizol (TM) (metamizol not available in the US) combination in patients undergoing retinal surgery. Patients were randomized to receive CR oxycodone 10 mg at 0 hours and 12 hours postsurgery or intravenous tramadol 100mg/ metamizol 1g every 4 hours up to 24 hours postoperatively. The AUC for quality of analgesia was significantly higher with oxycodone than TM but the AUC for pain at rest was comparable between groups. Furthermore, the VAS pain scores at rest were significantly lower in the oxycodone group at 16 hours and 24 hours postoperatively. Patients in the oxycodone group also experienced less nausea.

**Dental surgery**

Korn and colleagues (44) carried out a randomized, double-blind, placebo- and active comparator-controlled trial to compare a postoperatively administered single oral dose of rofecoxib (not available in the US)

50 mg with oxycodone/acetaminophen 5/325 mg and placebo for pain relief after dental surgery (Table 10). Rofecoxib provided superior analgesia compared with oxycodone/acetaminophen in terms of overall analgesic effect (as assessed by the total pain relief score over 6 hours (TOPAR6) ( $P < 0.001$ ), peak effect ( $P < 0.01$ ), and duration of effect ( $P < 0.001$ ). Oxycodone/acetaminophen was also associated with significantly higher TOPAR6 compared with placebo. Both active treatments achieved significantly higher pain relief versus placebo as early as 30 minutes after dosing ( $P < 0.001$  for rofecoxib and  $P < 0.005$  for oxycodone/acetaminophen). Rofecoxib was superior to oxycodone/acetaminophen in terms of rescue medication use within 24 hours. The incidence of drug-related adverse effects (nausea and vomiting) was significantly lower in the rofecoxib group than in the oxycodone/acetaminophen group ( $P < 0.001$ ). Post-extraction alveolitis, headache and dizziness were comparable between the 2 groups. Overall, more patients were satisfied with rofecoxib than the oxycodone/acetaminophen treatment.

Table 10. Oral oxycodone for dental surgery.

| Author                | Pain scores  | Changes in rescue medication use   | Side-effects/ complications  | Patient satisfaction   |
|-----------------------|--|--|--|--|
| Korn et al (44)       | Mean TOPAR6 score:<br>Oxycodone/acetaminophen = 5.9*<br>Rofecoxib = 11.7†<br>Placebo = 1.9<br>† $P < 0.001$ vs oxycodone/acetaminophen or placebo<br>* $P < 0.005$ vs placebo  | % of patients:<br>Oxycodone/acetaminophen = 94.5<br>Rofecoxib = 72.2†<br>Placebo = 96.8<br><br>Time to first dose (h):<br>Oxycodone/acetaminophen = 3.3<br>Rofecoxib = 8.3†<br>Placebo = 1.7<br>† $P < 0.001$ vs oxycodone/acetaminophen | Incidence of nausea:<br>Oxycodone/acetaminophen = 39.6%<br>Rofecoxib = 18.9%<br>$P < 0.001$<br><br>Incidence of vomiting:<br>Oxycodone/acetaminophen = 23.1%<br>Rofecoxib = 6.7%<br>$P < 0.001$                | % of patients rating study medication as good, /very good/ excellent:<br>Oxycodone/acetaminophen = 39.6<br>Rofecoxib = 62.2†<br>Placebo = 3.3<br>† $P < 0.001$ vs oxycodone/acetaminophen or placebo |
| Gammaitoni et al (45) | Mean PPAR score:<br>Oxycodone/acetaminophen = 2.4*<br>CR oxycodone = 1.6<br>Placebo = 0.8<br>* $P < 0.05$ vs CR oxycodone and placebo<br><br>Mean PPID score:<br>Oxycodone/acetaminophen = 1.1†<br>CR oxycodone = 0.8†<br>Placebo = 0.2†<br>† $P < 0.05$ vs CR oxycodone and placebo | % of patients:<br>Oxycodone/acetaminophen = 47.5<br>CR oxycodone = 50.8<br>Placebo = 83.3<br><br>Median time to remedication (h:min):<br>Oxycodone/acetaminophen = 4:31<br>CR oxycodone = 2:45<br>Placebo = 1:19                         | Incidence of nausea (%):<br>Oxycodone/acetaminophen = 30.5<br>CR oxycodone = 37.7<br>Placebo = 6.7<br><br>Incidence of vomiting (%):<br>Oxycodone/acetaminophen = 30.5<br>CR oxycodone = 41.0<br>Placebo = 6.7 | % of patients rating pain relief as good to excellent:<br>Oxycodone/acetaminophen = 50.9<br>CR oxycodone = 35.7<br>Placebo = 6.7   |

TOPAR6, total pain relief score over 6 hours; PPAR, peak pain relief; CR, controlled release; PPID, peak pain intensity difference

Gammaitoni and colleagues (45) compared the efficacy and safety of a single dose of oxycodone/acetaminophen 10/325 mg with that of CR oxycodone 20 mg and placebo for the management of acute pain following dental surgery. In addition to providing a faster onset of pain relief, the combination was superior to CR oxycodone in 4 of 5 outcome measures of pain intensity and pain relief. Furthermore, there was a 24% reduction in the number of patients reporting treatment-related adverse events in the combination group compared with the CR oxycodone group. A higher proportion of patients rated pain relief with oxycodone/acetaminophen as good to excellent versus CR oxycodone.

## Summary of Efficacy and Safety Outcomes

### Postsurgical Analgesic Efficacy

Compared with placebo, oral oxycodone demonstrated superior efficacy in relieving acute postoperative pain in 9 of the 10 placebo-controlled clinical trials. These trials involved laparoscopic cholecystectomy (23), open abdominal or pelvic surgery (27), foot surgery (33-35), spine surgery (21), dental surgery (44,45) and breast surgery (22).

Oral oxycodone plus acetaminophen provided better pain control than intravenous morphine (38), and oral oxycodone provided pain relief comparable to that of intrathecal morphine (41), following caesarean delivery. Given that intrathecally administered morphine is more effective than intravenous morphine for post-caesarean pain relief (46), oral oxycodone appears to offer satisfactory analgesia in this pain setting. In postsurgical situations involving colorectal (25) and cardiac surgeries (20), the analgesic quality of oral oxycodone was comparable to intravenous morphine.

When administered as part of a multimodal regimen, oral oxycodone demonstrated superior analgesic efficacy over unimodal intravenous hydromorphone or morphine following open abdominal hysterectomy (26), total knee arthroplasty (30) and spine surgery (36).

Among studies that included other active comparators, oral oxycodone demonstrated a degree of analgesia comparable to that provided by 6 agents: oral tramadol (breast cancer surgery) (37), acetaminophen/naproxen (ambulatory knee arthroscopy or inguinal hernia repair surgery) (31), intravenous piritramide (caesarean) (39), epidural ropivacaine (radical retropubic prostatectomy) (42) and oral tapentadol (bunionectomy) (34,35). However, in the study by Korn and

colleagues (44), oral oxycodone/acetaminophen combination was inferior to rofecoxib in alleviating pain after dental surgery.

### Rescue analgesic use

Oral oxycodone was associated with a reduced demand for rescue analgesia compared with placebo (laparoscopic cholecystectomy [23], foot surgery [33-35], breast surgery [22]), intravenous morphine (caesarean section [40], cardiac surgery [20]) and intravenous hydromorphone (knee arthroplasty [30]); this was also true for scenarios when oral oxycodone was part of a multimodal analgesic regimen (spine surgery [36]). The study endpoints reported were lower amounts of rescue medication/total opioid use (20,23,30,33,36,40), fewer patients requiring rescue medications (33-35), and/or a reduction in time to first rescue analgesic dose (33) in the oxycodone treatment group versus the comparator group. Few studies reported comparable rescue analgesic use between treatment groups (24,28,37,39). Demand for rescue analgesia was greater with oral oxycodone treatment compared with intrathecal morphine (caesarean section [41]) and rofecoxib (dental surgery [44]).

### Postoperative Side Effects

The occurrence of PONV associated with oral oxycodone was comparable to that of placebo (laparoscopic cholecystectomy [23], gynecological laparoscopic surgery [24], and breast surgery [22]), intravenous piritramide (caesarean section [39]), oral tramadol (breast surgery [37]) and naproxen (knee arthroscopy or inguinal hernia repair surgery [31]).

In one placebo-controlled trial (spine surgery), PONV was significantly reduced in the oxycodone group (21). All studies that compared oral oxycodone with intravenous morphine (caesarean section [38,40], cardiac surgery [20]), intrathecal morphine (caesarean section [41]), or intravenous tramadol/metamizol (retinal surgery [43]) reported a decrease in one or more opioid-related side effects in the oxycodone treatment group; this was also true for scenarios when oral oxycodone was part of a multimodal analgesic regimen (knee arthroplasty [30], spine surgery [36]). One study (radical retropubic prostatectomy) reported significantly less treatment-related complications in oxycodone-treated patients compared with those treated with epidural ropivacaine (42).

### Postoperative Recovery and Patient

### Satisfaction

Among studies that evaluated patient recovery following surgery, Lamplot and colleagues (knee arthroplasty) (30) and Rajpal and colleagues (spine surgery) (36) reported improvements in physical functioning associated with a multimodal regimen including oral oxycodone, versus intravenous morphine or hydromorphone. Hohwu and colleagues (radical retropubic prostatectomy) (42) found that oxycodone-treated patients became mobile faster than patients receiving epidural ropivacaine. Furthermore, 2 studies (spine surgery [20], caesarean section [40]) documented an earlier return of bowel function in oral oxycodone-treated patients (versus intravenous morphine and intravenous morphine/oral codeine, respectively). Three trials of postcaesarean surgery patients found no difference in mobility between oral oxycodone and intravenous morphine (38,40) or piritramide (39).

Patient satisfaction with postsurgical analgesia was generally high and comparable between treatments in most of the trials (22,24,25,31,37,39). However, the quality of pain management for oxycodone treatment was rated higher by patients undergoing spine surgery (versus placebo) (21) and retinal surgery (versus tramadol) (43), as was the quality of pain management for a multimodal regimen involving oxycodone in the setting of knee arthroplasty (versus intravenous hydromorphone) (30) and spine surgery (versus intravenous morphine or hydromorphone) (36). In the postcaesarean study by McDonnell and colleagues (41), maternal satisfaction with intrathecal morphine was higher than with oral oxycodone at 24 hours postop despite the presence of more pruritus in this group; the authors suggested that a more consistent delivery of analgesia in the intrathecal morphine group might have influenced the patients' level of satisfaction more than side effects. Korn and colleagues (44) also reported a higher degree of patient satisfaction with rofecoxib compared with oral oxycodone in patients who underwent dental surgery.

### Drug/Hospital Costs

Santoso and colleagues (26) and Lamplot and colleagues (30) demonstrated that oral oxycodone as part of a multimodal pain control regimen versus intravenous opioid significantly reduced the length of hospital stay after open abdominal hysterectomy and knee arthroplasty, respectively. Several other studies found no difference in the duration of hospitalization with oral oxycodone compared to intravenous morphine (20,25,38,40), intravenous piritramide (39), or epidural ropivacaine (42).

Rajpal and colleagues (36) calculated the average drug cost for postoperative analgesia in the first 24 hours and concluded that the cost difference between treatments was negligible (\$2.52–\$4.50 for intravenous PCA versus \$5.36–\$10.48 for oral multimodal). However, these calculations did not include costs related to PCA pump, tubing, or nursing time. Dieterich and colleagues (39) and Hohwu and colleagues (42) also assessed the relative costs of oral oxycodone versus piritramide PCA or ropivacaine EDA, while taking into account material and personnel costs, and showed an increase of 12- and 13-fold, respectively.

### DISCUSSION

Oral oxycodone provided superior analgesia and reduced rescue analgesic demand compared with placebo. Compared with intravenous opioids, oral oxycodone provided comparable or better pain control and reduced the demand for rescue analgesia in some surgeries. A reduction in rescue analgesic use signifies adequate pain control, which could facilitate early discharge from hospital. Oral oxycodone was inferior to rofecoxib in alleviating pain after dental surgery. This is in line with similar studies of postsurgical dental pain management using other cyclooxygenase-2 (COX-2) selective nonsteroidal anti-inflammatory drugs (NSAIDs) where the analgesic efficacy of oxycodone has been reported to be inferior to etoricoxib (not approved for use in the US) (47) and comparable to valdecoxib (withdrawn from the US market) (48). Since postoperative dental pain includes an inflammatory component, NSAIDs may be a better choice than opioids (4).

Oral oxycodone has several advantages over PCA with intravenous opioids, such as morphine, for postoperative pain control. Higher oral bioavailability, ease of oral administration, more efficient penetration of the BBB, and potentially fewer side effects make oxycodone a good alternative to morphine. Several studies demonstrated oxycodone's rapid onset of analgesia, even as soon as 30 minutes after oral administration (22,29,35,44), further supporting its value in postoperative pain management. In studies included in this review, the dosage of oxycodone ranged between 5 mg/d and 120 mg/d.

The adverse events commonly reported with oxycodone (nausea, vomiting, headache, pruritus, dizziness, somnolence, and constipation) are typical of centrally acting  $\mu$ -opioid analgesics (49). These side effects were less common with oral oxycodone compared with placebo or parenteral opioids in some studies,

while others did not show significant differences. Most of these studies additionally documented a lower overall opioid consumption in the oxycodone treatment arms (19-21,30,36,40) that may have mitigated these adverse effects. Interestingly, studies that documented fewer side effects with oxycodone treatment also reported greater patient satisfaction with the therapy, indicating better patient acceptance of oral oxycodone (21,30,36,43). Although respiratory depression is a known pharmacological action of oxycodone (49), there were no reported instances of respiratory depression related to oxycodone use in the studies examined (20,22,23,25,29,31,33,41,43).

A multimodal analgesic approach combining opioid and nonopioid drugs with different mechanisms of action can produce synergistic effects resulting in maximum pain relief with minimal opioid consumption. This opioid-sparing effect has been shown to reduce opioid-related adverse effects and hasten recovery following various surgical procedures (50-53). Several studies in our review also showed that oral oxycodone, given as part of a multimodal analgesic regimen, provides effective pain relief comparable to intravenous PCA opioid, while at the same time reducing side effects, lowering overall opioid consumption, allowing earlier analgesic discontinuation, shortening the hospital stay, and reducing cost (26,27,30,36,38,45).

The Enhanced Recovery After Surgery (ERAS) protocol is a multimodal evidence-based approach to patient care which is implemented with the aim of reducing morbidity and enhancing recovery, thereby allowing earlier discharge from the hospital (54). Achieving optimal postoperative pain control is one of the key elements of ERAS and opioid-sparing regimens are recommended to reduce unwanted side effects (5). In this regard, multimodal analgesia involving oral oxycodone can be a potential alternative to intravenous opioids for effective postoperative pain control. Some studies in this review reported enhanced physical functioning (30,36) or reduced hospital stay (26) associated with a multimodal regimen using oral oxycodone versus intravenous opioid alone.

This narrative review has several limitations. The limited number of randomized double-blind studies in

each surgical discipline makes it difficult to form firm conclusions. Furthermore, unlike systematic reviews, which provide the best research evidence by following explicit, unbiased methods to evaluate scientific literature, narrative reviews can have considerable bias because of the subjective nature by which the studies are selected and analyzed. Nevertheless, this qualitative exploratory analysis provides a broad overview of the clinical utility of oral oxycodone in different acute postsurgical pain situations.

The purpose of this review was to evaluate oral oxycodone in the acute postoperative period. With the current emphasis on ERAS, surgical patients are now able to take oral medications earlier. However, there are still postsurgical patients who are put on a strict fast for a significant period of time after surgery, during which oral oxycodone would not be a feasible analgesic option.

## **CONCLUSION**

Oral oxycodone was more effective than placebo in reducing acute postoperative pain and was associated with comparable levels of PONV. Compared with intravenous morphine or hydromorphone, oral oxycodone may provide superior analgesia, and reduce overall opioid consumption and need for rescue medication; in some studies, oral oxycodone was associated with fewer side effects, such as PONV. More randomized, double-blind, controlled trials comparing oral oxycodone with other standard analgesics in different postsurgical pain models are needed to determine the most effective approach in each scenario.

## **Disclosure:**

None of the authors have any competing interest to report. There are no conflicts of interest to report. The authors certify that they or members of their family have no commercial relationship that causes a conflict of interest with regards to the submitted manuscript.

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