TITLE: The Use of OxyNEO® and OxyContin® in Adults: A Review of the Evidence on Safety

DATE: 20 September 2011

CONTEXT AND POLICY ISSUES:

One in three Canadians experience chronic pain in their lifetime and opioid analgesics are the most commonly prescribed treatment.1,2 Opioid prescriptions have increased as chronic pain has been recognized as a treatable condition and prescribers have become familiar with opioid analgesics.3 OxyContin® (Purdue Pharma, www.purdue.ca) is indicated for the management of moderate to severe pain when continuous analgesic is needed for an extended period of time.4 OxyContin® contains oxycodone, an opioid agonist with abuse liability similar to that of morphine.4 While extended release (ER) formulations were designed to reduce abuse liability, simply chewing or crushing oxycodone extended release (OER) tablets and either inhaling, injecting or swallowing them, rapidly releases oxycodone producing a heroin-like euphoria with potentially lethal consequences.4-9 OxyContin® is often consumed with alcohol, other opioids, illicit drugs or other central nervous system depressants despite box warnings.4,10,11 In 2002, a risk management program, Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®), was implemented to capture and analyze the prevalence of abuse and diversion of OER by United States 3-digit ZIP code.12,13

A tamper-resistant formulation of OxyContin®, known as OxyNEO® (Purdue Pharma, Stamford, CT, USA), has recently been developed in an effort to prevent individuals seeking OxyContin®’s euphoric properties from unintended overdose.1 OxyNEO® was marketed in the United States in April 201014,15 as a difficult to crush tablet that when hydrated, forms a viscous gel that resists oxycodone extraction for injection purposes.16 Having received a notice of compliance from Health Canada in August 2011,17 OxyNEO® will be replacing OxyContin® on the Canadian market prompting questions regarding its ability to deter abuse, how to integrate the new formulation into clinical practice, and how to identify candidates for therapy.18

The purpose of this report is to review the clinical evidence on the safety and harms of OxyNEO® and OxyContin® in adults with moderate to severe chronic pain.
RESEARCH QUESTIONS:

1. What is the clinical evidence on the safety and harms of OxyNEO® in adults?

2. What is the clinical evidence on the safety and harms of OxyContin® in adults?

KEY MESSAGE:

No evidence was found regarding the safety and harms of OxyNEO® in adults. Oxycodone prescriptions and oxycodone-related deaths increased after OxyContin® ER was added to a provincial drug formulary. While most deaths were accidental polydrug overdoses and deliberate overdoses were more common in older pain patients and women.

METHODS:

Literature search strategy

A limited literature search was conducted on key resources including Medline, EMBASE, PubMed, The Cochrane Library (2010, Issue 8), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and August 26, 2011.

Selection Criteria and Methods

One reviewer screened citations to identify health technology assessments, systematic reviews, meta-analyses, randomized and non-randomized studies regarding the safety and harms of OxyNEO® and OxyContin® in adults. Potentially relevant articles were ordered based on titles and abstracts, where available. Full-text articles were considered for inclusion according to the selection criteria listed in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults on pain medications</th>
</tr>
</thead>
</table>
| Intervention | 1. Reformulation of oxycodone, new oxycodone formulation and OxyNEO®  
               2. Extended release Oxycodone, old oxycodone formulation and OxyContin® |
| Comparator | Not applicable |
| Outcomes | Safety  
           Clinical harms  
           Patient adverse events |
| Study Designs | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies |
Exclusion Criteria

Articles were excluded if they did not satisfy the selection criteria, provided incomplete study methods, or they were narrative reviews or editorials.

Critical Appraisal of Individual Studies

Non-randomized studies were assessed for quality using the Down’s and Black instrument. Instead of calculating numeric scores, the strengths and limitations of each study were described.

SUMMARY OF EVIDENCE:

Quantity of Research Available

The literature search yielded 214 citations. Upon screening titles and abstracts, eight potentially relevant articles were retrieved for full-text review. No additional potentially relevant reports were retrieved from grey literature or hand searching. Of the eight potentially relevant reports, one did not contain the intervention of interest, one was an editorial, and two were narrative reviews. No articles were identified regarding the safety and patient adverse events of OxyNEO® in adults with moderate to severe pain. Three articles reported on the safety of OxyContin® in adults and one article reported on patient adverse events related to OxyContin® treatment. The process of study selection is outlined in the PRISMA flowchart (Appendix 1). Additional articles of potential interest are provided in Appendix 2.

Summary of Study Characteristics

Study design
Two retrospective database case series, one retrospective observational database cohort, and a post-market surveillance study involving two clinical trials were selected for review. The articles originated from Australia, Canada, the United States and China and ranged in date from 2007 to 2011.

Population
An Australian retrospective database case series reported on 70 cases autopsied at the Department of Forensic Medicine, New South Wales, between 1999 and 2008 in which the cause of death was oxycodone toxicity. A Canadian retrospective database case series reported on 234 opioid-related deaths recorded in the Office of the Chief Coroner of Ontario between 1991 and 2004. The retrospective observational database cohort reported adverse events in 5,684 Oregon fee-for service Medicaid recipients newly prescribed ER opioids between 2000 and 2004. The two-study, multicentre open-label post-market surveillance study reported the clinical efficacy and safety of OER in 386 moderate to severe non-cancer pain patients.

Interventions
In New South Wales, all unnatural deaths are reported to the coroner and fatal oxycodone toxicity cases were identified based on standard autopsy. While twelve of 70 cases involved oxycodone toxicity and 58 cases involved multiple drug toxicity, oxycodone was not prescribed to the decedent in 30% of cases. The Ontario database study analyzed trends in prescribing patterns between 1991 and 2007 and reviewed all opioid-related deaths between 1991 and
2004 following the introduction of oxycodone extended release (OER).² Four-hundred of 464 oxycodone-related deaths involved at least one non-opioid central nervous system depressant; most commonly benzodiazepines, alcohol and cyclic antidepressants.² The Oregon Medicaid retrospective study examined claims for ER opioids including methadone, OER, morphine extended release (MER), and transdermal fentanyl.³ The post-marketing surveillance evaluated the efficacy and safety of OER, 5 mg, 10 mg, 20 mg and 40 mg dosages, for relieving non-cancer pain.²¹

**Outcomes**

The Australian retrospective database cohort evaluated the demographic characteristics, toxicity and autopsy findings of oxycodone toxicity cases presented to the New South Wales Department of Forensic Medicine between 1999 and 2008.²⁰ The Ontario retrospective database case series evaluated trends in opioid prescribing patterns and opioid-related mortality following the addition of OER to the Ontario drug formulary in 2000.² The United States study evaluated the risk of opioid-related adverse events (AEs) among Oregon fee-for-service Medicaid recipients prescribed ER opioids, including emergency department (ED) visits, hospitalizations, and deaths.³ The study characteristics are summarized in Appendix 3.

**Summary of Critical Appraisal**

The three retrospective database studies had clearly described research questions, inclusion criteria, patient characteristics, outcome measures and findings.²,³,²⁰ However, retrospective studies may suffer from bias as subjects were not randomized to treatment and assessors were not blinded. In a third of cases in the Australian study, oxycodone was not prescribed to the decedent and 25% of cases were known injecting drug users (IDUs), so the population may not be representative of the population prescribed oxycodone for moderate to severe pain.²⁰ While oxycodone tablets were the intervention of interest the time from prescription to death and the dosage were not provided in this study.²⁰ The reviewers for the Ontario retrospective database study pilot tested the data-collection forms to ensure agreement on major data fields, including opioid-related death; however, some deaths may not have been captured as coroners do not investigate all deaths and details were not available after 2004.² In the Oregon retrospective cohort study, claims from administrative databases may lead to misclassification errors as the accuracy of diagnostic codes was not validated.³ As with most retrospective database studies, there may be immortal time bias as dispensed prescriptions may not have been consumed or there may be a time lag between prescription filling and consumption.³ Emergency department visits and hospitalization are nonvalidated surrogates for potential AEs.³

The post-marketing surveillance study had a clearly described research question, inclusion and exclusion criteria, intervention, outcomes, and findings.²¹ this was an open label prospective study where subjects and were not randomized to treatment and assessors were not blinded.²¹ The critical appraisal is summarized in Appendix 4.

**Summary of Findings**

No evidence was identified regarding the safety and harms of OxyNEO® for moderate to severe pain in adults.

Three retrospective database studies²,³,²⁰ and a post-marketing surveillance study²¹ provided evidence on the safety, harms and patient AEs associated with OxyContin® in adults with moderate to severe pain (Table 2).
An Australian retrospective database case series of 70 oxycodone-related deaths reported that 58% of cases were men aged 49 years, 21.4% were suicides and oxycodone had not been prescribed to 30% of decedents. Twenty-seven percent of cases occurred in IDU and 21% had injected oxycodone tablets prior to death. Women were significantly older than men ($t_{88}=4.3$, $p<0.001$), more likely to be married [odds ratio (OR): 3.36, 95% confidence interval (CI) 1.16 to 9.71] and less likely to be an IDU (OR: 0.10, 95% CI 0.03 to 0.50) or to have injected oxycodone prior to death (OR: 0.16, 95% CI 0.03 to 0.76). Cases of suicide were more likely to be older women (OR: 3.78, 95% CI 1.13 to 12.66). Thirty-two percent of non-IDU cases were suicides compared with 6.7% of IDU (p=0.007). Of the 14 non-IDU suicides, 12 were chronic pain patients. The mean blood oxycodone concentration in decedents was 9.40 mg/L (range 0.06 mg/L to 53.00 mg/L). Other psychoactive substances were detected in all cases; most commonly hypnosedatives (68%), other opioids (54%), antidepressants (41%), and alcohol (32%). Cardiovascular, pulmonary, hepatic, and renal disease was reported in 64%, 49%, 67% and 44% of cases, respectively.

An Ontario-based database study used time-series analyses to evaluate opioid-related mortality after the introduction of OER. The number of oxycodone prescriptions increased from 23 per 1,000 to 197 per 1,000 between 1991 and 2007. Twenty-eight percent of the oxycodone prescriptions dispensed in 2006 were for the OER. Between 2001 and 2007, the average amount of OER dispensed per prescription increased from 1830 mg to 2280 mg. Similarly, between 1999 and 2994, the annual number of oxycodone-related deaths increased by 416% (p<0.01) from 1.39 per million to 7.17 per million. Oxycodone was present post-mortem in 50 of 75 (67%) patients who were dispensed oxycodone after their last physician visit. Benzodiazepines, alcohol and cyclic antidepressants were reported in 60%, 44%, and 26% of oxycodone-related deaths, respectively.

The risk of serious AEs among Medicaid recipients recently prescribed ER opioids was evaluated using a retrospective observational cohort. Patients prescribed OER were 35% less likely [adjusted hazard ratio (AHR): 0.45; 95% CI 0.26 to 0.77] to experience an emergency department (ED) visit or hospitalization due to opioid-related AE, 23% lower risk of hospitalization (AHR: 0.77; 95% CI 0.66 to 0.91), 41% lower risk of constipation (AHR: 0.59; 95% CI 0.35 to 1.00), and a 29% lower risk of death (AHR: 0.71; 95% CI 0.54 to 0.94) compared with morphine extended release (MER) recipients.

A post-marketing surveillance study evaluated the efficacy and safety of OER tablets for relieving moderate to severe non-cancer pain. While constipation was the most common patient AE reported during the first week of treatment this decreased with use. The study findings are summarized in Appendix 5.
Table 2. Summary of the Clinical Evidence on the Safety, Harms and AE of OxyContin®

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Evidence</th>
<th>Results</th>
</tr>
</thead>
</table>
| Oxycodone    | Retrospective database case series<sup>20</sup> | • Oxycodone was not prescribed to the decedent in 84% of IDU and 32% of other oxycodone-related deaths.  
• Suicides were more likely to occur in older women who were not IDU.  
• Oxycodone-related deaths were often associated with use of hypnosedatives, other opioids, antidepressants and alcohol and were more common in individuals with pre-existing disease. |
| OER          | Retrospective database case series<sup>4</sup>  | • Oxycodone prescriptions increased from 23/100 to 197/1000 between 1991 and 2007. Average OER prescribed increased from 1830 mg to 2280 mg between 2001 and 2007.  
• Oxycodone related deaths increased from 1.39 to 7.17 per million annually between 1991 and 1994. Benzodiazepines, alcohol and cyclic antidepressants were commonly associated with use. |
| OER          | Retrospective observational database cohort<sup>3</sup> | • Patients prescribed OER were less likely to experience an ED visit or hospitalization for an opioid-related AE, or constipation compared to patients who were prescribed MER. |
| OER          | Post-marketing surveillance study<sup>21</sup>  | • OxyContin®-related constipation decreases with use. |

AE: adverse event; ED: emergency department; IDU: injecting drug users; MER: morphine extended release; OER: oxycodone extended release

Limitations

No evidence was identified regarding the safety and harms of OxyNEO® in adults with moderate to severe chronic pain. The quantity of evidence on the safety, harms and patient adverse events related to using OxyContin® in adults with chronic pain is limited to three retrospective database studies and a post-marketing surveillance study.<sup>2,3,20,21</sup> For instance, patients in retrospective database studies are not randomized to treatment, and assessors are not blinded. Database studies also suffer from misclassification errors when the accuracy of diagnostic codes are not validated, and immortal time bias as drugs may not be consumed as soon as they are dispensed.<sup>2,3,20</sup> Only the post-marketing surveillance study reported the formulation and dosages of oxycodone studied and hospitalization and ED visits are nonspecific surrogates for potential AEs.
CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Oxycodone prescriptions and oxycodone-related deaths have increased since 1991 following the addition of OER to the Ontario drug formulary.² Most patients who received a prescription for oxycodone at their last physician visit had oxycodone in their system post-mortem. Benzodiazepines, alcohol and cyclic antidepressants were commonly associated with oxycodone-related deaths. While most deaths were accidental, polydrug overdoses and deliberate overdoses were more likely among older pain patients and women. OER offered a modest safety advantage over MER. OER users experienced a significantly lower risk of ED visits or hospitalization for opioid-related AE, all-cause death, hospitalization, and constipation compared to MER users. Constipation was the most common adverse drug reaction but the incidence decreased with use.

People take more of a drug to experience the euphoria of an opioid whether it is tamper-resistant or not. For this reason, the benefits of tamper-resistant products need to be determined in large, randomized controlled trials or epidemiological studies designed to track abuse over time in a wide range of relevant populations. A risk management program based on the OxyContin® experience could be prepared to universally capture and analyze the prevalence of abuse and diversion of OxyNEO® as it replaces OxyContin® on the Canadian market.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca
REFERENCES:


15. FDA approves new formulation for OxyContin [Internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2010 Apr 5. [cited 2011 Sep 16]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm207480.htm


APPENDIX 1: Selection of Included Studies

214 citations identified from electronic literature search and screened

→ 206 citations excluded

8 potentially relevant articles retrieved for scrutiny (full text, if available)

→ 0 potentially relevant reports retrieved from other sources (grey literature, hand search)

4 potentially relevant reports

→ 4 reports excluded:
- irrelevant intervention (1)
- other (review articles, editorials)(3)

4 reports included in review
APPENDIX 2: Additional Articles of Potential Interest


3. FDA approves new formulation for OxyContin [Internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2010 Apr 5. [cited 2011 Sep 16]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm207480.htm


12. Weeks C. High doses of opioids tied to risk of death [Internet]. Toronto: Globe and Mail; 2011 Apr 11. [cited 2011 Sep 16]. Available from:
### APPENDIX 3: Summary of Study Characteristics

<table>
<thead>
<tr>
<th>First Author, Publication Year Country</th>
<th>Study Design</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Clinical Outcomes Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darke(^2), 2011 Australia</td>
<td>Retrospective database case series</td>
<td>Autopsy cases from DOFM (1999 to 2008) (n=70; 41% M)</td>
<td>Oxycodone</td>
<td>NA</td>
<td>Toxicology, pathology, prescription status, suicide</td>
</tr>
<tr>
<td>Dhalla(^2). 2009 Canada</td>
<td>Retrospective database case series</td>
<td>Opioid-related deaths from OCCO (1991 to 2004) (n=234; 67% M)</td>
<td>OER</td>
<td>NA</td>
<td>Prescribing, death, healthcare use prior to death</td>
</tr>
<tr>
<td>Hartung(^3) 2007 United States</td>
<td>Retrospective observational database cohort</td>
<td>Opioid-related AE from Medicaid (200 to 2004) (n=5684; M: 35)</td>
<td>OER</td>
<td>Methadone, MER, fentanyl</td>
<td>ED visits, hospitalization, death, opioid-related AE</td>
</tr>
<tr>
<td>Yuguang(^2) 2007 China</td>
<td>2-study multicentre, open-label, prospective, post-market surveillance</td>
<td>Moderate to severe non-cancer pain patients (n(_1)=196; M: 51%; n(_2)=190; M: 52%)</td>
<td>OER (OxyContin(^\circ), Mundipharma International, Cambridge, UK) (5mg, 10 mg, 20 mg, 40 mg)</td>
<td>NA</td>
<td>Clinical efficacy and safety</td>
</tr>
</tbody>
</table>

AE: adverse events; DOFM: Department of Forensic Medicine; ED: emergency department; M: male; MER: morphine extended release; NA: not applicable; n\(_1\): number of subjects in study 1; n\(_2\): number of subjects in study 2; OCCO: Office of the Chief Coroner of Ontario; OER: oxycodone extended release
### APPENDIX 4: Summary of Critical Appraisal

<table>
<thead>
<tr>
<th>First Author, Publication Year Country</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| **Darke**<sup>20</sup> 2011 Australia | - Research question and inclusion criteria were established before conducting the study.  
- Main outcome measures and findings, mostly patient characteristics, are clearly described. | - While all unnatural death cases are reported, some suicide cases may be missed if they occur without the presence of notes or statements.  
- While oxycodone tablets are the intervention, formulation and dosage were not provided.  
- In a third of cases, oxycodone was not prescribed to the decedent so they may not be representative of the population prescribed oxycodone for moderate to severe chronic pain.  
- This is a retrospective case series and assessors are not blinded. Time from prescription to death was not reported.  
- Approximately 25% of cases were known IDU and oxycodone tablets were injected immediately prior to death by a fifth. |
| **Dhalla**<sup>2</sup> 2009 Canada | - The objective, patient characteristic, main outcomes and findings were clearly described.  
- Data abstraction forms were pilot tested before data-collection to ensure agreement on major data fields including whether death was opioid-related. | - This is a retrospective case series; patients were not randomized and assessors were not blinded.  
- Some opioid-related deaths may not have been captured as coroners do not investigate all deaths and detailed opioid-related death data were not available after 2004.  
- Most deaths involved a single opioid but most opioids-related deaths involved at least one non-opioid central nervous system depressant that could impact outcomes. |
<table>
<thead>
<tr>
<th>First Author, Publication Year Country</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Hartung\(^3\) 2007 United States     | - The objective, patient characteristics, interventions, outcomes, and main findings are well described. | - This is a retrospective observational database cohort study and assessors are not blinded and patients were not randomized to treatment.  
- Claims from administrative databases may lead to misclassification errors as the accuracy of diagnostic codes was not validated.  
- Outcomes (any ED or hospitalization) were often a nonspecific surrogate for potential AE.  
- Dispensed prescriptions may not have been consumed. |
| Yuguang\(^2\) 2007 China              | - The objective, patient characteristics, interventions, outcomes, and main findings are well described. | - This is an open label, prospective, post-market surveillance study; assessors are not blinded and patients were not randomized to treatment. |

AE: adverse event; ED: emergency department; IDU: injecting drug users
# APPENDIX 5: Summary of Findings

<table>
<thead>
<tr>
<th>First Author, Publication Year Country</th>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darke 2011 Australia</td>
<td>Oxycodone deaths (1999-2008): 70 IDU were significantly younger than other cases (36.5 vs. 56.6, t_{68}&lt;0.001) Oxycodone was not prescribed to decedent in 84.3% of IDU and 31.6% of other cases (OR: 11.65, 95% CI 3.42 to 39.72) Women were older than men (t_{68}=4.3, p&lt;0.001), more likely to be married (OR: 3.36, 95% CI 1.16 to 9.71), and less likely to be an IDU (OR: 0.10, 95% CI 0.03 to 0.50) or to inject oxycodone before death (OR: 0.16, 95% CI 0.03 to 0.76). Suicides were more likely to be women (OR: 3.78, 95% CI 1.13-12.66), and significantly older (58.7 vs 46.3 years, t_{68}&lt;2.7, p&lt;0.01); 6.7% were IDU (p=0.07), 32.7% were non-IDU. Of the non-IDU suicides, 12 were chronic pain patients. Mean blood oxycodone: 0.40 mg/L Other psychoactive substances: 68% hypnotedatives, 54% other opioids, 41% antidepressants, 32% alcohol. Pre-existing disease: 64% CV, 49% pulmonary, 67% hepatic, 43% renal. IDU were more likely to have hepatic disease (88.9% vs 58.3%, OR: 5.71, 95% CI 1.18 to 27.68) and non-IDU to have CVD (71.4% vs 44.4%, OR: 3.13, 95% CI 1.02 to 9.52).</td>
<td>“While most cases were accidental, polydrug overdoses, and deliberate overdose was prominent among older pain patients and women.”</td>
</tr>
<tr>
<td>First Author, Publication Year</td>
<td>Country</td>
<td>Main Study Findings</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Dhalla 2009&lt;sup&gt;2&lt;/sup&gt; Canada</td>
<td>Oxycodone prescriptions rose from 23/1000 (1991) to 197/1000 (2007). Of 2.3 million oxycodone prescriptions dispensed (2006), 28% were for OER. Average OER prescribed increased 1830 mg (2001) to 2280 mg (2007)</td>
<td>Opioid-related deaths increased from 13.7/million (1991) to 27.2/million (1994). Median age: 40 years; M: 67%; 1847 (52%) unintentional, 803 (24%) suicide, 725 (22%) undetermined. Between 1999 and 2004, oxycodone-related deaths increased from 1.39 to 7.17 per million annually. Fifty (66.7%) of 75 individuals who were dispensed oxycodone following their last physician visit had oxycodone present on post-mortem toxicological analysis.&lt;sup&gt;2&lt;/sup&gt; Benzodiazepines (60%), alcohol (44%) and cyclic antidepressants (26%) were commonly related to oxycodone use.&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hartung 2007&lt;sup&gt;3&lt;/sup&gt; United States</td>
<td>Patients prescribed OER were 35% less likely (AHR: 0.45; 95% CI 0.26 to 0.77) to experience and ED or hospitalization involving an opioid-related AE, 23% lower risk of hospitalization (AHR: 77; 95% CI 0.66 to 0.91), 41% lower risk of constipation (AHR: 0.59; 95% CI 0.35 to 1.00), and 29% lower risk of death (AHR: 0.71; 95% CI 0.54 to 0.94) compared to those prescribed MER.</td>
<td>OER has a modest safety advantage over MER. OER users experienced significantly lower risk of combined ED or hospitalization for opioid-related AE, as well as for the individual outcomes all-cause death hospitalization, and constipation compared to MER users.</td>
</tr>
<tr>
<td>Yuguang 2007&lt;sup&gt;21&lt;/sup&gt; China</td>
<td>Constipation was the most common adverse drug reaction in the first week, which decreased to 10% of patients from the second week of treatment.</td>
<td>OER tablets demonstrate superior efficacy for relieving moderate and severe non-cancer pain, as well as a reduction in concomitant medications, and a good safety profile.</td>
</tr>
</tbody>
</table>

AHR: adjusted hazard ratio; CI: confidence interval; CVD: cardiovascular disease; ED: emergency department; IDU: Injecting drug users; MER: morphine extended release; OER: oxycodone extended release; OR: odds ratio