Drug Class Review

Long-Acting Opioid Analgesics

Preliminary Scan Report #3

December 2017

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OBJECTIVE

The purpose of this preliminary update literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist Participating Organizations’ consideration of allocating resources toward updating this report. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow if the Participating Organizations commission a full update. The literature search for this report focuses on new evidence that would be included in an update of this report.

Date of Last Update Report

Update #7: September 2015 (searches through March 2015)

Date of Last Preliminary Update Scan Report

Scan #2: December 2016

Scope and Key Questions

The Participating Organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of different long-acting opioids in reducing pain and improving functional outcomes in adult patients being treated for chronic non-cancer pain?

2. What is the comparative effectiveness of long-acting opioids versus short-acting opioids in reducing pain and improving functional outcomes when used for treatment of adults with chronic non-cancer pain?

3. What are the comparative harms (including addiction and abuse) of different long-acting opioids in adult patients being treated for chronic non-cancer pain? Do harms differ between drugs with and without abuse-deterrent mechanisms or between drugs with different abuse-deterrent mechanisms?

4. What are the comparative harms (including addiction and abuse) of long-acting opioids versus short-acting opioids in adult patients being treated for chronic non-cancer pain?

5. Are there subpopulations of patients (specifically by race, age, sex, socio-economic status, type of pain, or comorbidities) with chronic non-cancer pain for which one long-acting opioid is more effective or associated with fewer harms?

6. Are there subpopulations of patients (specifically by race, age, sex, socio-economic status, type of pain, or comorbidities) with chronic non-cancer pain for which long-acting opioids are more effective or associated with fewer harms than short-acting opioids?
Inclusion Criteria

**Populations**
- Adult (18 years old or greater) patients with chronic noncancer pain (continuous or recurring pain for at least 6 months)

*Excluded: cancer patients and patients with HIV*

**Interventions**
We included oral, sublingual, or transdermal long-acting opioids. Although dosing frequency varies for an individual formulation of morphine, we refer to dosing twice daily in a trial as “sustained-release” and once daily as “extended-release”. “Long-acting” was defined as opioids administered 3 times daily or less frequently. Included drugs are shown below in Table 1.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade name</th>
<th>Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>Butrans</td>
<td>ER transdermal film</td>
</tr>
<tr>
<td>Buprenorphine HCL</td>
<td>Belbuca</td>
<td>Buccal film</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Duragesic</td>
<td>ER transdermal film</td>
</tr>
<tr>
<td>Hydrocodone bitartrate</td>
<td>Hysingla ER</td>
<td>ER oral tablet</td>
</tr>
<tr>
<td></td>
<td>Zohydro ER</td>
<td>ER oral capsule</td>
</tr>
<tr>
<td></td>
<td>Vantrela ER</td>
<td>ER oral tablet</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Exalgo</td>
<td>ER oral tablet</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>Generic only</td>
<td>Oral tablet</td>
</tr>
<tr>
<td>Methadone</td>
<td>Dolophine</td>
<td>Oral tablet</td>
</tr>
<tr>
<td></td>
<td>Methadose</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>Kadian</td>
<td>ER oral capsule</td>
</tr>
<tr>
<td></td>
<td>MS-Contin</td>
<td>ER oral tablet</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>Morphabond</td>
<td>ER oral tablet</td>
</tr>
<tr>
<td></td>
<td>Arymo ER</td>
<td>ER oral tablet</td>
</tr>
<tr>
<td>Morphine sulfate and naltrexone HCL</td>
<td>Embeda</td>
<td>ER oral capsule</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oxycontin</td>
<td>ER oral tablet</td>
</tr>
<tr>
<td></td>
<td>Xtampza ER</td>
<td>ER oral capsule</td>
</tr>
<tr>
<td>Oxycodone HCL and naloxone HCL</td>
<td>Targiniq ER</td>
<td>ER oral tablet</td>
</tr>
<tr>
<td>Oxycodone HCL and naltrexone HCL</td>
<td>Troxyca ER</td>
<td>ER oral capsule</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>Opana</td>
<td>ER oral tablet</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>Nucynta ER</td>
<td>ER oral tablet</td>
</tr>
</tbody>
</table>

ER, extended release. HCL, hydrochloride. Shaded = drugs approved since the last scan.

**Effectiveness outcomes**
- Pain intensity, Pain relief and Function

**Harms outcomes**
- Specific adverse events, Discontinuation due to adverse events, Serious adverse events

**Study Designs**
- Head-to-head randomized controlled trials
In addition, for Harms:
  - Observational cohort studies

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations from November 16, 2016 to November 20, 2017 using terms for specific included drugs and limits for English language and humans. Literature searches included any new drugs identified in the present scan in addition to those included in Table 1. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, new populations, and new serious harms (e.g., boxed warnings). To identify new drugs, we also searched CenterWatch (http://www.centerwatch.com), a privately-owned database of clinical trial information, and conducted a limited internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrdrResearch.va.gov/Publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm). All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

Study Selection

We included only potentially relevant randomized controlled trials and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

Identified in this Preliminary Update Scan
New Drug Combinations or Formulations

Vantrela ER (Hydrocodone Bitartrate ER tablet; January 2017)

Arymo ER (Morphine sulfate ER tablet; January 2017)

Phase 3: NKTR-181 (Nektar Therapeutics) long-acting opioid intended to provide pain relief without euphoria.

Identified in previous Preliminary Update Scans

Oxycodone hydrochloride/naltrexone hydrochloride (Troxyca® ER; August 2016).
Oxycodone (Xtampza® ER; April 2016)

Buprenorphine hydrochloride (Belbuca™; October 2015)

Morphine sulfate extended release oral tablet (Morphabond; October 2015)

**New Serious Harms (e.g., Boxed Warnings)**

**Identified in this Preliminary Update Scan**

**December 2016:**

New boxed warnings that concomitant use with benzodiazepines or other CNS depressants may result in profound sedation, respiratory depression, coma, and death were added to:

- Buprenorphine (Butrans)
- Buprenorphine Hydrochloride (Belbuca)
- Fentanyl (Duragesic )
- Hydrocodone Bitartrate (Zohydro ER)
- Hydrocodone Bitartrate (Hysingla ER)
- Hydromorphone (Exalgo)
- Morphine (Kadian, MS-Contin)
- Morphine Sulfate (Morphabond)
- Morphine sulfate and naltrexone hydrochloride (Embeda)
- Oxycodone (Oxycontin, Xtampza ER)
- Oxycodone hydrochloride and naltrexone hydrochloride (Targiniq ER)
- Oxycodone hydrochloride and naltrexone hydrochloride (Troxyca ER)
- Oxymorphone (Opana)
- Tapentadol (Nucynta ER)

**Other additions in December 2016:**

- Buprenorphine (Butrans): New boxed warning on risk of neonatal opioid withdrawal syndrome
- Fentanyl (Duragesic ): New boxed warning on risk of increased fentanyl absorption with application of external heat to patch site.
- Hydrocodone Bitartrate (Zohydro ER): New boxed warning on interaction with alcohol.
- Oxymorphone (Opana): New boxed warning on the risk of addiction, abuse, and misuse, life-threatening respiratory depression, accidental ingestion, neonatal opioid withdrawal syndrome, interaction with alcohol

**Identified in previous Preliminary Update Scans**

None.
Comparative Effectiveness Reviews

Identified in this Preliminary Update Scan


Abstracts available upon request.

Identified in previous Preliminary Update Scans


Randomized Controlled Trials

Trials identified since the most recent Scan

No trials eligible for this report were found out of 78 citations screened for this scan.

Trials identified since the most recent Full Report

Cumulatively, out of a total of 321 citations screened, we have identified 2 potentially relevant new trials since the last update report: 1 head-to-head trial and 1 active-controlled trial (i.e. long-acting versus short-acting opioids). Characteristics of these trials are shown in Table 2.

Table 2. New potentially relevant trials of long-acting opioids

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Population</th>
<th>Comparison</th>
<th>Focus</th>
</tr>
</thead>
</table>


### Head-to-head trials

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Condition</th>
<th>Comparator</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ueberall, 2015</td>
<td>453</td>
<td>12 weeks</td>
<td>Chronic low back pain</td>
<td>Oxycodone/naloxone vs. oxycodone vs. morphine</td>
<td>Discontinuations, pain intensity, disability, quality of life, bowel function</td>
</tr>
</tbody>
</table>

### Long-acting versus Short-acting Opioids

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Condition</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pedersen, 2014</td>
<td>60</td>
<td>8 weeks</td>
<td>Chronic non-cancer pain</td>
<td>Long-acting dihydrocodeine vs. short-acting dihydrocodeine</td>
<td>Pain intensity, quality of life, sleep, and depression</td>
</tr>
</tbody>
</table>

## SUMMARY

Cumulatively, since the most recent report, we identified 6 newly approved drugs, combinations, or formulations (2 this scan). We have identified 4 potentially relevant comparative effectiveness reviews that could answer specific pieces of an update report (2 new this scan). We have also identified 2 potentially relevant trials (none new this scan): 1 head-to-head trial and 1 long-acting versus short-acting opioid trial. Neither of the trials included the new drugs approved since the last report.