The search results from the literature review are outlined in Figure 1. A grey literature search of internet-based resources related to acute pain was also conducted to identify additional evidence. Grey literature review

Three days Pain intensity; sourced from a single Athanasakis 20136

Ten days

et al.

et al.

VAS, visual analogue scale

et al.

et al.

Figure 1. PRISMA diagram of the search results for evidence review of acute pain

Methods

Electronic databases literature searches

Three targeted literature searches were conducted in the following databases:

- EMBASE
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Cited MEDLINE(R)
- EMBASE
- Cochrane Database of Systematic Reviews
- EMBASE Reviews - Database of Abstracts of Reviews of Effects
- EMBASE
- EBM Reviews - Health Technology Assessment
- EMBASE Reviews - NHS Economic Evaluation Database

The searches were limited to English language and articles published up until April 2016. All retrieved publications were screened to identify:

- Cost-effectiveness models for the management of acute pain (search (i))
- Systematic reviews and meta-analyses reporting relative efficacy and tolerability of Step 2 analgesics such as tramadol, transcutaneous or co-codamol (search (ii))
- Health utility values for different pain states (search (iii))

Grey literature search

A search of internet-based resources related to acute pain was also conducted to identify additional evidence relating to cost-effectiveness studies of acute pain. Grey literature reviews and meta-analyses of Step 2 analgesics or health utilities of pain states and epidemiology data on the incidence of acute pain.

Results

The search results from the literature review are outlined in Figure 1. Four publications reporting on health economic models of acute pain were identified as part of the literature review (Table 1).

The time horizons reported ranged from two days to ten days. Efficiency was assessed using well-described pain intensity scales, visual analogue scales and measuring time with pain.

Three models included nausea and vomiting as inputs in the analysis, while two also considered central nervous system adverse events such as drowsiness, confusion and congestion problems.

The key way resource use was measured varied substantially.

Table 1. Data inputs and characteristics of models reported in the publications identified by the literature review

<table>
<thead>
<tr>
<th>Publication</th>
<th>Time horizon</th>
<th>Measure of effectiveness</th>
<th>Aliases included</th>
<th>Distribution/technology</th>
<th>Resource use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klitz et al. 2017</td>
<td>Three days</td>
<td>Pain intensity, sourced from a single RCT</td>
<td>Neuraxone/Complementary opioid; Digital withdrawal function</td>
<td>Not included</td>
<td>Cost of drug (in the UK) and time spent on pain-related visits and supplements</td>
</tr>
<tr>
<td>Biallas et al. 2016</td>
<td>Five days</td>
<td>Number of days with pain, sourced from a single RCT</td>
<td>Not included</td>
<td>Not included</td>
<td>Cost of drug (in the UK) and time spent on pain-related visits and supplements</td>
</tr>
<tr>
<td>Hong et al. 2015</td>
<td>Three days</td>
<td>Days with uncontrolled pain (measured as pain on a 0-10 scale)</td>
<td>Not included</td>
<td>Neuraxone/Complementary opioid; Digital withdrawal function</td>
<td>Not included</td>
</tr>
<tr>
<td>Timol et al. 2016</td>
<td>Ten days</td>
<td>Concluded pain (defined as mild pain reduction on the VAS 80% and 100% scale)</td>
<td>Neuraxone/Complementary opioid; Digital withdrawal function</td>
<td>Not included</td>
<td>Not included</td>
</tr>
</tbody>
</table>

Relative efficacy and safety of Step 2 analgesics (Search (iii))

- Five publications reporting on the relative safety and efficacy of Step 2 analgesics were identified as part of the literature review: two from the electronic database search and three from the grey literature review.

- One publication reported solely on the adverse events associated with Step 2 analgesics. Two reported only on efficacy, while the rest reported on both relative efficacy and safety.

- The most common metric for relative efficacy was the proportion of patients achieving at least 50% pain relief, which was used to calculate relative risk, relative benefit and number-needed-to-treat (Table 2).

- The most commonly reported adverse events included nausea, vomiting, somnolence, dizziness and headaches.

Table 2. Efficacy and safety metrics reported by publications identified in the literature review

<table>
<thead>
<tr>
<th>Publication</th>
<th>Drug</th>
<th>Efficacy metrics</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biallas et al. 2016</td>
<td>Tramadol</td>
<td>Proportion of patients with 50% pain relief (NNT)</td>
<td>NA</td>
</tr>
<tr>
<td>Athanasakis et al. 2016</td>
<td>Tramadol</td>
<td>Proportion of patients with 50% pain relief (NNT)</td>
<td>NA</td>
</tr>
<tr>
<td>Moise et al. 1997</td>
<td>Tramadol</td>
<td>Proportion of patients with 50% pain relief (NNT)</td>
<td>NA</td>
</tr>
<tr>
<td>Moise et al. 2010</td>
<td>Tramadol</td>
<td>Proportion of patients with 50% pain relief (NNT)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Utility values for acute pain (Search (iii))

While the search for utility values directly for acute pain did not yield any results, one publication reporting on health utility values for chronic pain was identified in the literature. The utilities and disutilities derived from this study were based on opioid-related adverse events for chronic pain in oncology and elderly (65 years old) patients populations in the US and Germany.

Discussion and conclusions

Existing HE models identified in the literature

Despite the high prevalence of acute pain, there is a lack of evidence available to inform the economic impact of this condition as demonstrated by the results of our literature review. Figure 2 depicts a graphical representation of ideal model inputs and highlights substantial data gaps in the following factors: adverse event reporting, utility values, pain control measures, discounting rates and resource utilisation.

Table 2 Key inputs for an ideal health economic model of acute pain

- In the models identified, the main driver of cost-effectiveness was factors associated with additional contact with health care professionals, particularly given the low cost nature of many of the treatments that are widely used in acute pain treatment. Examples of these drivers include lack of pain control achieved with the treatment, treatment emergent adverse events, and the need to discontinue or swap to another treatment. Where these costs were present, they consistently and significantly outweighed the acquisition cost of the treatment under consideration.

- There was substantial variation in the assessment of clinical effectiveness, treatment-associated adverse events and time horizon in the models. Additionally only one model incorporated the results of a meta-analysis as a data input and healthcare resource use was reported in markedly different ways depending on the healthcare system.

Key data gaps identified

- The most commonly reported efficiency measurement in the literature for acute pain was the proportion of patients achieving at least 50% pain relief, which was used to calculate the number-needed-to-treat. While number-needed-to-treat is a useful measure for determining a treatment effect and relative efficacy of analgesics, the usefulness of this metric is limited by the pooling of data from different patient populations as the number-needed-to-treat for each analgesic is obtained by pooling studies of patients with acute pain in comparative dental, gynaecological, orthopaedic and general surgery settings. Such variability would be challenging to integrate into an economic model.

- There is therefore a need for accurate data on adverse events from trials of analgesics from patients in specific settings (e.g. specific surgical procedures, disorders with intermittent episodes of pain) and an agreement on the most appropriate efficacy measure for use in economic models.

- Other relevant and required inputs for a robust health economic model, such as medication discontinuation or use of rescue medication were not readily available in the literature. This highlights the need for robust data on why and how often patients switch or discontinue pain medication. There is also a need for literature detailing algorithms health care professionals typically follow when prescribed pain killers for acute pain.

- The generalisability of the results identified may be limited to the populations sampled as these scores are influenced by sociodemographic-specific cultural differences and clinical factors. Furthermore, the only publication identified reporting health utility values for acute pain assessed their chronic pain values per unit of time were equivalent to acute pain values.

- Overall, there are limited robust data available to inform HE models, including efficiency data available across different therapeutic options, adverse event data, utilities and disutilities and resource utilisation. There is therefore a need for research in this area to support future HE modeling and value-based treatment decision-making.