Abstract
The medical use of opioids to treat pain and illness predates historic record. Opioids have a well-defined role in the treatment of acute and cancer pain, and most clinicians are comfortable prescribing opioids in these contexts. However, in persistent non-cancer pain (PNCP) there remains considerable controversy. While there is evidence of short-to-medium-term benefit, concerns exist over long-term efficacy, side effects, safety, and the potential for opioid misuse. Guidelines published to date emphasize the importance of patient selection, opioid preparation, monitoring of therapy, and a multimodal treatment package including other disciplines and non-pharmacological therapies. Worldwide, the use of opioids for PNCP has increased significantly over the past decade and with it, concerns of increases in opioid-related harm.

Keywords
Adverse effects of opioids; chronic pain; modified-release opioids; opioids; oral opioids; transdermal opioids

Evidence for the efficacy of strong opiates in persistent non-cancer pain (PNCP)
There is good evidence for opioids providing effective pain relief in a range of PNCP conditions. A meta-analysis of 41 randomized controlled trials (RCTs) showed that while weak opioids do not out-perform non-steroidal anti-inflammatory drugs (NSAIDs) or tricyclic antidepressants, strong opioids are superior to naproxen and nortriptyline with a clinical difference of greater than 10%. Most RCTs have only analysed short-to-medium-term outcomes. Long-term benefit remains less well-defined with only weak evidence of clinically beneficial analgesia. In addition, in studies where functional outcome is measured rather than just pain relief, the efficacy of strong opioids becomes less clear suggesting that an improvement in pain scores may be offset by a reduction in other quality of life indicators, such as mental state, relationships, sleep quality and level of activity.

Current recommendations for the use of opioids in PNCP
The British Pain Society (BPS) published the guideline ‘Opioids for Persistent Pain: Good Practice’ in 2010 which outlines specific cautions, prescribing advice and information on adverse effects, with an overall emphasis on careful patient selection and monitoring. It suggests that while opioids do have a role in the management of PNCP, they should not be used as first-line therapy. If opioids are being considered then long-acting oral or transdermal preparations (Table 1) are recommended over short-acting preparations that have more potential for abuse and adverse effects. Injectable opioids should never be prescribed for PNCP. A comprehensive assessment should identify patients with depression, anxiety, or a history of drug dependence. These patients may require additional support from specialist psychiatric or addiction services. Goals of therapy, such as improved sleep and mobility, should be agreed before a trial of opioid therapy and achievement of these goals can then be used to assess outcome (Table 2).

An opioid trial should commence at a low dose and be titrated carefully in response to analgesia, function and adverse effects. Therapy should be reviewed at least monthly and if analgesia is not achieved with doses in the range of 120–180 mg morphine (or equivalent) then it is unlikely that the pain is opioid sensitive. In such cases an alternative strategy should be sought with referral to a pain management clinic. It is also recommended that patients requiring doses greater than 180 mg morphine daily (or equivalent) should be referred to specialist pain services for advice.

The BPS guidelines are due to be updated in 2013. Given the recent concern over the increased use of prescription opioids, particularly from the USA, the updated guidance may include a greater degree of prescribing restrictions for strong opioids.

Adverse effects of opioids in PNCP
Around 80% of patients taking opioid therapy will experience an adverse effect. In the short term these include sedation, nausea, and pruritus. Other short-term effects include respiratory depression and euphoria. These are more frequently encountered with immediate-release preparations but can also occur with long-acting therapy. Advancing age, co-prescribed drugs, and alcohol or illicit drug use can also predispose to sedation and respiratory depression. Constipation is a significant adverse effect that is difficult to manage and laxatives should be co-prescribed. Opioids also have effects on the endocrine system,
for example hypogonadism, and there is evidence that opioids mediate suppression of the innate and acquired immune system. Commonly, pharmacological tolerance will develop over time, where an increase in dose is required to achieve the same analgesic effect. Opioid rotation to a different preparation is sometimes advocated in such circumstances. Physical dependence may also develop where severe symptoms of sweating, agitation, and abdominal cramps are experienced if the drug is discontinued or the dose reduced sharply. If opioids are to be stopped, then a gradual reduction of the dose over several weeks or months is advised. All of the potential adverse effects should be fully discussed with the patient prior to initiation of therapy. It should be stressed that many of the short-term effects will lessen with time. Patients will need regular support during the initial phase of therapy. Driving should be avoided initially and there is an obligation for the patient to inform the DVLA (Driver and Vehicle Licensing Agency). However, once stabilized on a regular dose of opioid, without impairment, driving can resume without DVLA restriction.

A common concern for both patients and caregivers is the possibility of developing problem drug use or addiction. It is difficult to estimate the likelihood in an individual, but patients with a history of substance misuse have generally been considered at greatest risk and although opioids are not absolutely contraindicated in these patients, such patients should have a full and careful assessment including referral to specialist pain and addiction services before opioids are considered. Patients without prior history of substance misuse can also develop problem drug-taking behaviour. A recent trial showed evidence of drug craving, independent of pain symptoms, in patients deemed at low risk of opioid misuse. Such craving had a strong correlation with urge to take more medication and mood fluctuations.

In the USA, concerns over the safety of opioids has resulted in the US Food and Drug Administration (FDA) developing a Risk Evaluation and Mitigation Strategy (REMS) that aims to increase safety and reduce risks associated with opioid use. The number of prescription opioid-related deaths in the USA increased from 4000 in 1999, to 13,800 in 2006, with opioids accounting for 40% of all deaths attributable to poisoning. Efforts to avoid the under-treatment of pain may have resulted in a growing public health problem of opioid misuse; it is likely that future public health measures both in the USA and in Europe will reinforce more cautious use.

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### Table 1

<table>
<thead>
<tr>
<th>Route</th>
<th>Approved name</th>
<th>Proprietary names</th>
<th>MEP&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Dosing interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral formulations</td>
<td>Morphine sulphate</td>
<td>MST Continus, Morphgesic SR, MXL, Zomorph</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Oxycodeone MR</td>
<td>Oxycontin</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
<td>Non-linear</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dihydricodine (DHC)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DHC Continus</td>
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<td>12</td>
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<tr>
<td></td>
<td>Tapentadol</td>
<td>Palexia</td>
<td>0.25</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Tramadol MR*</td>
<td>Zamadol SR</td>
<td>0.2</td>
<td>12</td>
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<tr>
<td>Transdermal</td>
<td>Fentanyl</td>
<td>Durogesic DTrans</td>
<td>see table</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine</td>
<td>Transtec</td>
<td>2</td>
<td>96</td>
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<tr>
<td></td>
<td></td>
<td>BuTrans</td>
<td>1 week</td>
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</tbody>
</table>

<sup>a</sup> Although commonly classified as ‘weak’ opioids, when given in doses exceeding the British National Formulary recommended doses, these drugs should be considered as strong opioids.

<sup>b</sup> Morphine equivalent dose: potency compared to morphine.

### Table 2

<table>
<thead>
<tr>
<th>Oral morphine equivalent (mg/24 hours)</th>
<th>10</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>180</th>
<th>270</th>
<th>360</th>
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<tbody>
<tr>
<td>Transdermal buprenorphine (µg/hour)</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td>35</td>
<td>52.5</td>
<td>70</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Transdermal fentanyl (µg/hour)</td>
<td>12</td>
<td>25</td>
<td>50</td>
<td>75</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

REFERENCES


FURTHER READING


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