

# Risks of prescribing high-dose opioids

Information for health professionals



## Risks of high-dose opioids

- GPs are increasingly prescribing high-dose opioids > 100 mg morphine-equivalent dose (MED) per day.<sup>1,2</sup>
- Research shows that patients receiving > 100 mg MED/day had an 8.9-fold increase in overdose risk: 12% of these overdoses were fatal.<sup>3</sup>
- Dose escalation to > 120 mg MED/day is associated with a 2.6-fold risk of clinical depression.<sup>4</sup>
- Patients with persistent pain have a two- to three-fold risk of suicide regardless of dose.
- Those on opioids are particularly at risk due to opioid-specific risks and psychological distress.

Most patients experience adverse events with opioids,<sup>5, 6</sup> and many patients discontinue opioids because of those adverse events or failure to gain a significant analgesic benefit.<sup>7-9</sup>

Opioid-induced hyperalgesia (increased sensitivity to pain) and tolerance (reduced efficacy of opioid analgesia) can develop. These appear related to dose and duration of exposure to opioids, with opioid-induced hyperalgesia seen in patients on high doses and tolerance a consequence of prolonged use.<sup>5, 10-16</sup>

Prolonged opioid treatment also predisposes male patients to opioid-induced androgen deficiency that may require testosterone replacement therapy.<sup>17</sup>

Other effects include:

- sleep-disordered breathing
- risk of falls causing hip and pelvic fractures
- xerostomia with dental decay and tooth loss
- intestinal obstruction.<sup>18</sup>

All these aspects require active management and, if warranted, a reappraisal of the need for opioids and the dose.



### High dose, high mortality risk

In the last 5 years, studies have identified that higher doses are associated with an increased risk of overdose and death (Table 1). The relative risk of overdose in these studies for patients receiving doses of 100 mg MED/day ranged from a 2-fold to an 8.9-fold risk of overdose (Figure 1).<sup>3, 19-25</sup> In one study, one in 32 patients receiving doses of 200 mg MED or more died an opioid-related death,<sup>19</sup> and the concurrent prescription of benzodiazepines increased the rate of overdose mortality as much as 10-fold in another study.<sup>20</sup>

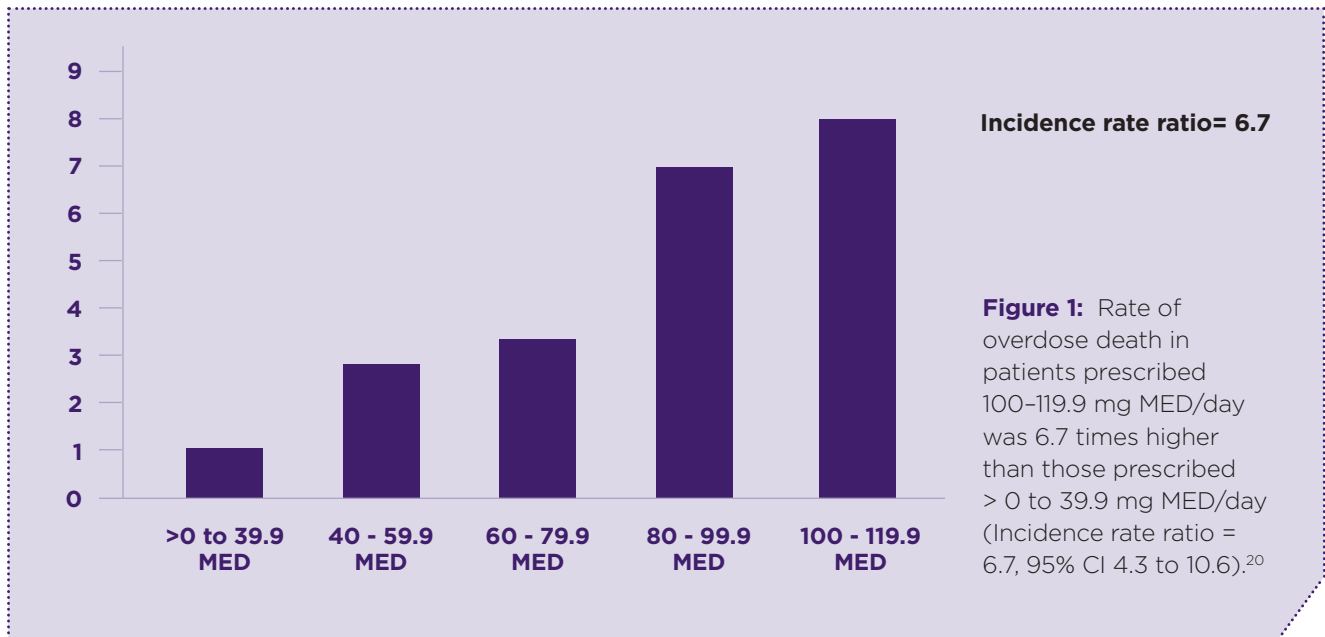


### Ceiling dose recommendations have decreased

In 2015, the RACGP released a clinical governance framework recommending a ceiling opioid dose of not more than 80-100 mg MED/day.<sup>26</sup> The more recent Centers for Disease Control and Prevention guidelines recommend providers use caution when prescribing opioids at any dosage, use additional precautions when increasing the dose to  $\geq 50$  mg MED/day and should generally avoid increasing dosage to  $\geq 90$  mg MED/day.<sup>27</sup>

A [MED calculator](#) is available to work out the MEDs of different opioids.

## Overdose mortality rate per 10,000 person-years



### Avoid prescribing high-risk opioid doses

Before the opioid ceiling is reached, assess the effectiveness of opioid therapy by tracking and documenting both functional improvement and pain relief.<sup>26</sup> Short-term randomised trials of opioids for chronic pain have found modest analgesic benefits (a one-third reduction in pain intensity on average).<sup>28</sup> Avoid sole reliance on opioids, and maximise the use of non-drug therapies, including self-management strategies beyond medicines, as opioids have a limited role in chronic pain management.<sup>5</sup>

Patient requests for rapid dose escalations in the first few days or weeks require careful assessment. Such requests may suggest the need for adequate assessment and management of pain, and the clarification of patient perceptions of pain management. Review for the presence of undiagnosed psychological disorders and anxiety disorder which are common comorbidities with high-dose opioid prescribing. Requests may result from unrealistic expectations that the opioid will stop pain rather than reduce it by a limited margin. They may also be warning signs of drug misuse.<sup>7, 29, 30</sup>

If a patient is approaching the ceiling, or currently taking high-dose opioids that expose them to risk, discuss the idea of tapering to a safer dose level. GPs can safely carry out tapering in the community.<sup>26</sup> See the fact sheet '[Recommendations for deprescribing or tapering opioids](#)' for further information.

Seek assistance from a senior GP or pain management consultant to address:<sup>26</sup>

- evidence of undiagnosed conditions
- presence of significant psychological condition affecting treatment
- potential alternative treatments to reduce or discontinue opioids
- risks and benefits of a possible trial with opioid dose > 100 mg MED/day
- the most appropriate way to document improvement in function and pain
- a possible need for consultation with other specialists.

## Studies linking higher-dose opioids with higher risk of overdose and death (Table 1)

STUDY AUTHOR	RESULTS
Kaplovitch, et al (2015) <sup>19</sup>	<p>589 (1.8%) patients receiving chronic opioid therapy escalated to high-dose therapy and 59 (0.2%) died of opioid-related causes.</p> <p>Men prescribed opioids for chronic non-cancer pain were more likely than women to escalate to a daily dose of 200 mg MED or more, and twice as likely to experience an opioid-related death.</p> <p>Those who escalated to high-dose opioid therapy were nearly 24 times as likely to die from an opioid-related cause as those who did not escalate (3.1% and 0.1% respectively), equal to 1 in 32.</p>
Dasgupta, et al (2015) <sup>20</sup>	<p>Overdose mortality rates increased steadily with dose, even at lower doses, and increased significantly at doses &gt; 200 mg MED/day.</p> <p>These rates were 10 times higher among those codispensed benzodiazepines (7.0 per 10,000 person-years, 95% CI 6.3 to 7.8) than opioid analgesics alone (0.7 per 10,000 person-years, 95% CI 0.6 to 0.9).</p> <p>Overdose mortality risk increases with dose, with no clearly defined threshold for mortality.</p>
Zedler, et al 2014 <sup>21</sup>	<p>Life-threatening opioid-related respiratory/CNS depression or overdose were strongly associated with MED <math>\geq</math> 100 mg/day (OR 4.1, 95% CI 2.6 to 6.5). A daily MED of 20 mg or more was also significantly associated.</p>
Gwira Baumblatt, et al (2014) <sup>31</sup>	<p>The risk of opioid-related overdose death increased with &gt; 100 mg MED/day (OR 11.2, 95% CI 8.3 to 15.1).</p>
Paulozzi, et al (2012) <sup>23</sup>	<p>There is an increased risk of overdose for persons receiving opioid doses from as low as 20 mg MED at any one time, with an increased risk in men.</p> <p>A single prescription for &gt; 120 mg MED/day corresponded to a high overdose risk. Patients with fatal overdoses had been prescribed a mean daily dose of 180 mg MED/day.</p>
Gomes, et al (2011) <sup>24</sup>	<p>There is a significant association between prescribed daily dose of opioids and opioid mortality. A significant response was found for 50–99 mg MED/day (OR 1.92, 95% CI 1.30 to 2.85) and 100 to 199 mg MED/day (OR 2.04, 95% CI 1.28 to 3.24)</p> <p>Patients receiving <math>\geq</math> 200 mg MED/day had a much higher risk of mortality compared with patients receiving &lt; 20 mg MED/day (OR 2.88, 95% CI 1.79 to 4.63).</p>
Bohnert, et al (2011) <sup>25</sup>	<p>The risk of opioid overdose at doses <math>\geq</math> 50 mg MED/day is increased.</p> <p>The death rate of cases (per 1000) receiving <math>\geq</math> 100 mg MED/day was 1.24 per 1000 person-months for chronic non-cancer patients, which was higher than the rate for those receiving lower daily MEDs.</p>
Dunn, et al (2010) <sup>3</sup>	<p>The risk of overdose increased with increasing opioid dosage level, with an 8.9-fold increase in persons receiving 100 mg MED or more per day (95% CI 3.99 to 19.72).</p>



## Resources

**Australian Pain Society – Facility Directory:** [www.apsoc.org.au/facility-directory](http://www.apsoc.org.au/facility-directory)

### Faculty of Pain Medicine ANZCA

- **Recommendations Regarding the Use of Opioid Analgesics in Patients with Chronic Non-Cancer Pain**  
<http://fpm.anzca.edu.au/Documents/PM1-2010.pdf>
- **Quick Reference Recommendations for Conduct of an Opioid Trial in Chronic Non-Cancer Pain**  
[http://fpm.anzca.edu.au/Documents/4462\\_001.pdf](http://fpm.anzca.edu.au/Documents/4462_001.pdf)

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