

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.^{1,2}
- Research shows that patients receiving > 100 mg MED/day had an 8.9-fold increase in overdose risk: 12% of these overdoses were fatal.³
- Dose escalation to > 120 mg MED/day is associated with a 2.6-fold risk of clinical depression.⁴
- 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,^{5,6} and many patients discontinue opioids because of those adverse events or failure to gain a significant analgesic benefit.⁷⁻⁹

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.^{5,10-16}

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

Other effects include:

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

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

High dose, high mortality risk

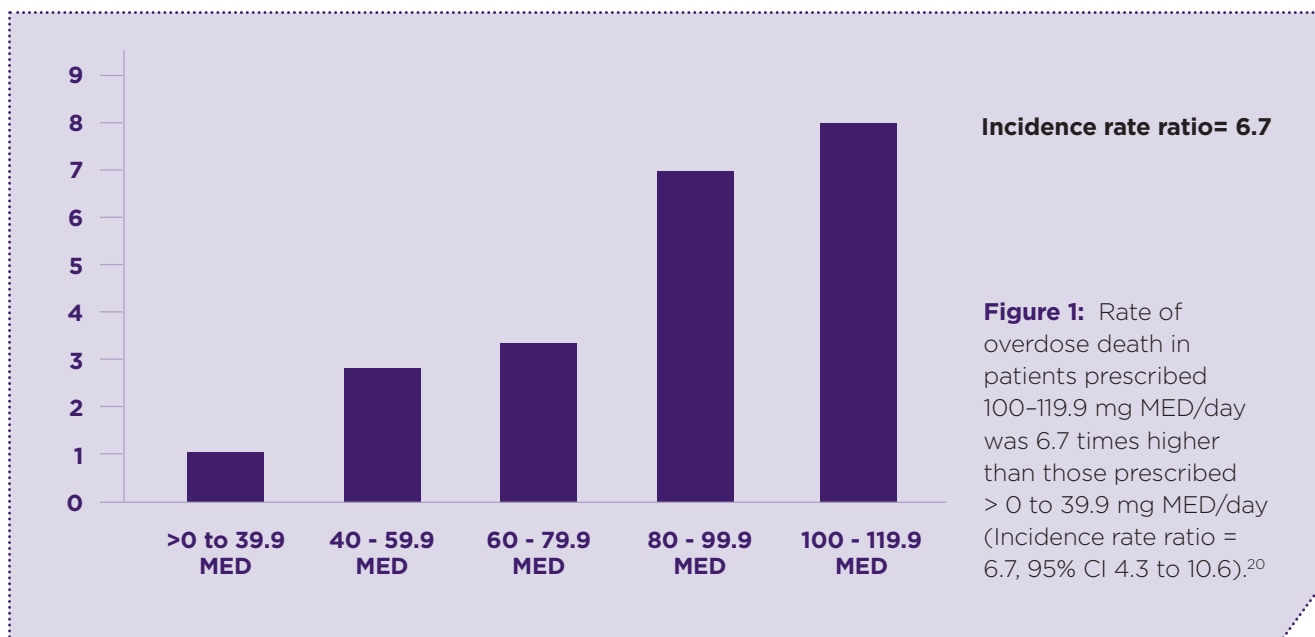
In the last 5 years, studies have identified that higher doses are associated with an increased risk of overdose and death (Table 1). The relative risk of overdose in these studies for patients receiving doses of 100 mg MED/day ranged from a 2-fold to an 8.9-fold risk of overdose (Figure 1).^{3,19-25}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

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.²⁶ 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 ≥ 50 mg MED/day and should generally avoid increasing dosage to ≥ 90 mg MED/day.²⁷

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.²⁶ Short-term randomised trials of opioids for chronic pain have found modest analgesic benefits (a one-third reduction in pain intensity on average).²⁸ 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.⁵

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.^{7, 29, 30}

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.²⁶ 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:²⁶

- 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) ¹⁹	<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) ²⁰	<p>Overdose mortality rates increased steadily with dose, even at lower doses, and increased significantly at doses > 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 ²¹	<p>Life-threatening opioid-related respiratory/CNS depression or overdose were strongly associated with MED \geq 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) ³¹	<p>The risk of opioid-related overdose death increased with > 100 mg MED/day (OR 11.2, 95% CI 8.3 to 15.1).</p>
Paulozzi, et al (2012) ²³	<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 > 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) ²⁴	<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 \geq 200 mg MED/day had a much higher risk of mortality compared with patients receiving < 20 mg MED/day (OR 2.88, 95% CI 1.79 to 4.63).</p>
Bohnert, et al (2011) ²⁵	<p>The risk of opioid overdose at doses \geq 50 mg MED/day is increased.</p> <p>The death rate of cases (per 1000) receiving \geq 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) ³	<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

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

References

1. Kobus AM, Smith DH, Morasco BJ, et al. Correlates of higher dose opioid medication use for low back pain in primary care. J Pain 2012;13:1131-8. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3641146/>.
2. Gomes T, Mamdani MM, Paterson JM, et al. Trends in high-dose opioid prescribing in Canada. Canadian Family Physician 2014;60:826-32.
3. Dunn KM, Saunders KW, Rutter CM, et al. Overdose and prescribed opioids: Associations among chronic non-cancer pain patients. Ann Intern Med 2010;152:85-92. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3000551/>.
4. Merrill JO, Von Korff M, Banta-Green CJ, et al. Prescribed opioid difficulties, depression and opioid dose among chronic opioid therapy patients. Gen Hosp Psychiatry 2012;34:581-7. <http://www.sciencedirect.com/science/article/pii/S0163834312002101>.
5. eTherapeutic Guidelines. Analgesic: Chronic pain. 2012. <http://www.tg.org.au/> (accessed 9 March 2016).
6. Kalso E, Edwards JE, Moore RA, et al. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain 2004;112:372-80. <http://www.ncbi.nlm.nih.gov/pubmed/15561393>.
7. Graziottin A, Gardner-Nix J, Stumpf M, et al. Opioids: How to Improve Compliance and Adherence. Pain Practice 2011;11:574-81. <http://dx.doi.org/10.1111/j.1533-2500.2011.00449.x>.
8. Reid MC, Henderson CR, Papaleontiou M, et al. Characteristics of Older Adults Receiving Opioids in Primary Care: Treatment Duration and Outcomes. Pain Medicine 2010;11:1063-71. <http://painmedicine.oxfordjournals.org/content/painmedicine/11/7/1063.full.pdf>.
9. Moore RA and McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. Arthritis Research & Therapy 2005;7:1-6. <http://dx.doi.org/10.1186/ar1782>.
10. Lee M, Silverman SM, Hansen H, et al. A comprehensive review of opioid-induced hyperalgesia. Pain Physician 2011;14:145-61. <http://www.ncbi.nlm.nih.gov/pubmed/21412369>.
11. Manchikanti L, Vallejo R, Manchikanti KN, et al. Effectiveness of long-term opioid therapy for chronic non-cancer pain. Pain Physician 2011;14:E133-56. <http://www.ncbi.nlm.nih.gov/pubmed/21412378>.
12. Chou R, Turner JA, Devine EB, et al. The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med 2015. <http://www.ncbi.nlm.nih.gov/pubmed/25581257>.
13. Wachholtz A, Foster S and Cheatle M. Psychophysiology of pain and opioid use: implications for managing pain in patients with an opioid use disorder. Drug Alcohol Depend 2015;146:1-6. <http://www.ncbi.nlm.nih.gov/pubmed/25468815>.
14. Koob GF, Sanna PP and Bloom FE. Neuroscience of addiction. Neuron 1998;21:467-76. <http://www.ncbi.nlm.nih.gov/pubmed/9768834>.
15. Trescot AM, Datta S, Lee M, et al. Opioid pharmacology. Pain Physician 2008;11:S133-53. <http://www.ncbi.nlm.nih.gov/pubmed/18443637>.
16. Smith HS and Peppin JF. Toward a systematic approach to opioid rotation. J Pain Res 2014;7:589-608.
17. Gudin JA, Laitman A and Nalamachu S. Opioid Related Endocrinopathy. Pain Medicine 2015;16:S9-S15. http://painmedicine.oxfordjournals.org/content/painmedicine/16/suppl_1/S9.full.pdf.
18. Baldini A, Von Korff M and Lin EHB. A Review of Potential Adverse Effects of Long-Term Opioid Therapy: A Practitioner's Guide. The Primary Care Companion to CNS Disorders 2012;14:PCC.11m01326. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3466038/>.
19. Kaplovitch E, Gomes T, Camacho X, et al. Sex Differences in Dose Escalation and Overdose Death during Chronic Opioid Therapy: A Population-Based Cohort Study. PLoS One 2015;10:e0134550. <http://dx.doi.org/10.1371/journal.pone.0134550>.
20. Dasgupta N, Funk MJ, Proescholdbell S, et al. Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality. Pain Medicine 2016;17:85-98. <http://painmedicine.oxfordjournals.org/content/painmedicine/17/1/85.full.pdf>.
21. Zedler B, Xie L, Wang L, et al. Risk Factors for Serious Prescription Opioid-Related Toxicity or Overdose among Veterans Health Administration Patients. Pain Medicine 2014;15:1911-29. <http://painmedicine.oxfordjournals.org/content/painmedicine/15/11/1911.full.pdf>.
22. Atluri SL and Sudarshan G. Development of a screening tool to detect the risk of inappropriate prescription opioid use in patients with chronic pain. Pain Physician 2004;7:333-8. <http://www.ncbi.nlm.nih.gov/pubmed/16858471>.
23. Paulozzi LJ, Kilbourne EM, Shah NG, et al. A History of Being Prescribed Controlled Substances and Risk of Drug Overdose Death. Pain Medicine 2012;13:87-95. <http://painmedicine.oxfordjournals.org/content/painmedicine/13/1/87.full.pdf>.
24. Gomes T, Mamdani MM, Dhalla IA, et al. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med 2011;171:686-91. <http://dx.doi.org/10.1001/archinternmed.2011.117>.
25. Bohnert AB, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA 2011;305:1315-21. <http://dx.doi.org/10.1001/jama.2011.370>.
26. The Royal Australian College of General Practitioners. Prescribing drugs of dependence in general practice. Part A. Melbourne VIC: The Royal Australian College of General Practitioners, 2015. <http://www.racgp.org.au/download/Documents/Guidelines/Addictive-drugs/Addictive-drugs-guide-A.pdf> (accessed 9 March 2016).
27. Centers for Disease Control and Prevention. CDC guideline for prescribing opioids for chronic pain—United States. Morbidity and Mortality Weekly Report 2016;65. <http://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6501e1.pdf>.
28. Von Korff MR. Long-term Use of Opioids for Complex Chronic Pain. Best practice & research Clinical rheumatology 2013;27:663-72. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4036624/>.
29. Larance B, Bruno R, Lintzeris N, et al. Development of a brief tool for monitoring aberrant behaviours among patients receiving long-term opioid therapy: The Opioid-Related Behaviours In Treatment (ORBIT) scale. Drug Alcohol Depend 2016;159:42-52. <http://www.sciencedirect.com/science/article/pii/S0376871615017792>.
30. Holliday S, Hayes C and Dunlop A. Opioid use in chronic non-cancer pain Part 2 Prescribing issues and alternatives. Aust Fam Physician 2013;42:104-11. <http://www.racgp.org.au/afp/2013/march/opioid-use-part-2/>.
31. Baumblatt J, Wiedeman C, Dunn JR, et al. High-risk use by patients prescribed opioids for pain and its role in overdose deaths. JAMA Internal Medicine 2014;174:796-801. <http://dx.doi.org/10.1001/jamainternmed.2013.12711>.

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