EDUCATION MODULE

PRESCRIBING MORPHINE*

*This module provides information about morphine as a risk factor for opioid overdose and specific risk-reduction guidance. It **supplements** but does not replace the general best practices for opioid prescribing presented in the "**Considerations for Safe and Responsible Opioid Prescribing**" module.*

Background

1. Morphine, derived from the resin of the opium poppy, is one of the oldest naturally occurring opiates isolated from opium.

2. Morphine is available in both parenteral and non-parenteral dosage forms including oral liquid, immediate release (IR) tablets, extended-release/long acting (ER/LA) tablets, and rectal suppositories.

Morphine and opioid overdose

1. Even at label-recommended doses, morphine carries the risk of overdose as well as misuse, abuse, opioid use disorder (OUD), and death.[1]

    a. Morphine use (ER/LA) is associated with an increased risk for serious opioid-induced respiratory depression (overdose).[2,3]

2. About 90% of an orally administered morphine dose is converted [via hepatic glucuronidation (i.e., phase II metabolism)] to metabolites, mainly morphine-3-glucuronide (M3G which does not possess analgesic properties, but has neuroexcitatory properties) and morphine-6-glucuronide (M6G, which has up to twice the analgesic potency of morphine).[4,5]

3. Morphine is not metabolized through phase I CYP450 enzymes (e.g., CYP2D6, 3A4, etc."). Therefore, it is less likely to be adversely affected by, or adversely affect the metabolism of other drugs.[5]

4. In patients with renal impairment, M6G metabolite accumulation may lead to respiratory depression and over-sedation, and M3G accumulation may cause neuroexcitatory effects such as myoclonus, hyperalgesia, and allodynia.[6,7] (see also: FDA label)

    a. In patients with cirrhosis, the pharmacokinetics of morphine are altered, which may result in accumulation of morphine and its M3G and M6G metabolites.[8] (see also: FDA label)

Risk-mitigation interventions to consider when prescribing morphine
[Refer to the full prescribing information (FDA label) for important product-specific details]

1. Before prescribing morphine, estimate the glomerular filtration rate using either the eGFR or creatinine clearance (ClCr) method. Avoid using morphine in patients with renal insufficiency (ClCr<30ml/min) or hepatic failure/cirrhosis due to the risk of accumulation of morphine and its metabolites that can lead to serious adverse events, including respiratory depression (overdose) and death. (See **"Renal Impairment"** module)

2. When initiating morphine therapy to manage chronic non-cancer pain, prescribe an IR formulation, particularly in individuals who are either opioid-naïve or not opioid-tolerant.[9,10]

    a. Adults are considered opioid-tolerant if they have been receiving a total daily opioid dosage equivalent to at least 60 mg of oral morphine (60 MME/day) for one week or longer.[1] (See 'Treatment' section 5a in the "**Considerations for Safe and Responsible Opioid Prescribing"** module) This dosage is comparable to:
        - 60 mg oral morphine per day
        - 25 mcg transdermal fentanyl per hour
        - 30 mg oral oxycodone per day
        - 60 mg oral hydrocodone per day
        - 8 mg oral hydromorphone per day
        - 25 mg oral oxymorphone per day

3. Reserve ER/LA formulations of morphine for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment when alternative treatment options (e.g., non-opioid analgesics or IR opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.[10] (see also: FDA 2017) (See **"ER/LA"** module)

4. Closely monitor the patient for respiratory depression or over-sedation during morphine initiation and after dosage escalation. The risk for overdose is greatest at this time because tolerance to an opioid's respiratory depressant effects is slower to develop and less complete than tolerance to its analgesic or euphoric effects.[10-13]

5. Carefully reassess the evidence of benefits and risks if considering total opioid dosage escalation to 50 MME/day or more. Avoid escalating the total opioid dosage to manage chronic non-cancer pain to 90 MME/day or more, or carefully document the rationale for increasing beyond this level based upon individualized clinical assessment of benefits (pain and function) and risks.[6,9,10] (See 'Treatment' section, 6 in the "**Considerations for Safe and Responsible Opioid Prescribing**" module)

    a. Avoid concurrent use of other medications or substances that are central nervous system depressants, such as benzodiazepines, sedatives/hypnotics, and alcohol in morphine-treated patients. The combination can result in profound sedation, respiratory depression, coma, and death and should be restricted to the minimum required dosage and duration in patients for whom alternative treatment options are inadequate or contraindicated. [9-11] (see also: FDA label)

6. Consider prescribing take-home naloxone to patients treated with morphine to reverse life-threatening respiratory depression if an overdose occurs. The long duration of action of ER/LA opioids compared with the short duration of naloxone increases the risk of recurrent respiratory and CNS depression that may require repeated doses of naloxone and prolonged surveillance. Educate the patient, family/household members, and caregivers about signs and symptoms of opioid overdose and train them to properly use naloxone if an opioid-related overdose is suspected.[6,10] (See 'Follow Up' section in the "**Considerations for Safe and Responsible Opioid Prescribing**" module)

Additional Resources

**The information presented in this module highlights some fundamental concepts of opioid prescribing for adult outpatients. It excludes certain populations (pediatrics, pregnancy, patients with active cancer or receiving palliative or end-of-life care) and settings (perioperative, emergency, in-patient). The information provided is intended to support safe and effective opioid therapy and minimize serious adverse outcomes, particularly overdose. It is not intended to be exhaustive nor substitute for consulting a medication's full prescribing information for complete details and warnings. Links and references to selected, more comprehensive clinical and prescribing resources are provided to facilitate safe and effective opioid prescribing.*

1. **FDA-approved drug label information:** FDA Online Label Repository or Daily Med (NIH/National Library of Medicine)
2. **CDC Guideline Resources**: Clinical Tools for Prescribing Opioids. https://www.cdc.gov/drugoverdose/prescribing/clinical-tools.html

References

1. FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. May 2017. https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM515636.pdf
2. Miller M, Barber CW, Leatherman S, Fonda J, Hermos JA, Cho K, Gagnon D. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. JAMA Intern Med 2015;175:608-615. PMID: 25686208
3. Ray WA, Chung CP, Murray KT, Hall K, Stein M. Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. JAMA 2016;315:2415-2423. PMID: 27299617
4. King S, Forbes K, Hanks GW, Ferro CJ, Chambers EJ. A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment. A European palliative care research collaborative opioid guidelines project. Palliative Medicine 2011;25:525-52. PMID: 21708859
5. Smith HS. The metabolism of opioid agents and the clinical impact of their active metabolites. Clin J Pain 2011;27:824-838. PMID: 21677572
6. U.S. Department of Veterans Affairs. VA/DoD clinical practice guideline for opioid therapy for chronic pain. Washington, DC: US Department of Veterans Affairs; 2017. https://www.healthquality.va.gov/guidelines/pain/cot/
7. Smith MT. Neuroexcitatory effects of morphine and hydromorphone: evidence implicating the 3-glucuronide metabolites. Clin Exp Pharmacol Physiol. 2000;27(7):524-8. PMID: 10874511

8. Smith H, Bruckenthal P. Implications of opioid analgesia for medically complicated patients. *Drugs Aging*. 2010;27(5):417-433. PMID: 20450239
9. Busse J, Craigie S, Juurlink D, et al. Guideline for opioid therapy and chronic noncancer pain: Appendix. CMAJ 2017. Link: National Pain Centre
10. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. MMWR Recomm Rep. 2016;65(1):1-49. PMID: 26987082
11. Washington State Agency Medical Directors' Group (WSAMDG). Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain: An Educational Aid to Improve Care and Safety With Opioid Treatment. Corvallis, WA: Washington Department of Health, 2015. www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf
12. Dumas EO, Pollack GM. Opioid tolerance development: a pharmacokinetic/pharmacodynamic perspective. AAPS J. 2008;10:537-51. PMID: 18989788
13. White JM, Irvine RJ. Mechanisms of fatal opioid overdose. Addiction 1999;94:961-72. PMID: 10707430