



EDUCATION MODULE

PRESCRIBING HYDROMORPHONE*

*This module provides information about hydromorphone 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. Hydromorphone is a semi-synthetic opioid agonist whose oral formulation is approximately 5 times more potent than oral morphine. Parenteral analgesic equivalence ratios may vary from oral.¹
2. Hydromorphone is available in multiple non-parenteral dosage forms including oral liquid, immediate-release (IR) tablets, extended release/long acting (ER/LA) tablets, and rectal suppositories.

Hydromorphone and opioid overdose

1. Even at label-recommended doses, hydromorphone carries the risk of overdose as well as misuse, abuse, OUD, and death.² Hydromorphone use (IR or ER/LA) is associated with a greater risk for serious opioid-induced respiratory depression (overdose) compared with some other opioid analgesics.³⁻⁵
2. Similar to morphine, hydromorphone is converted [via hepatic glucuronidation (i.e., phase II metabolism)] to hydromorphone-3-glucuronide (H3G), and to a lesser extent hydromorphone-6-glucuronide (H6G). H3G does not possess analgesic properties, but is neurotoxic, while H6G has analgesic properties.⁶
 - a. In patients with renal impairment, clearance of hydromorphone, H3G, and H6G are reduced, and their accumulation may lead to somnolence, delirium, respiratory depression and neuroexcitatory effects such as myoclonus, hyperalgesia, and allodynia.⁷⁻⁹
 - b. Hydromorphone is not metabolized through phase I CYP450 enzymes (e.g., CYP2D6, 3A4, etc.). It is therefore unlikely to be adversely affected by, or adversely affect the metabolism of other drugs.⁶

Risk-mitigation interventions to consider when prescribing hydromorphone

[Refer to the full prescribing information (FDA label) for important product-specific details]

1. Before prescribing hydromorphone, assess renal function based on calculation of the estimated GFR or creatinine clearance (ClCr).
 - a. In patients with moderate renal impairment, initiate hydromorphone therapy with 50% of the dose that would be prescribed for patients with normal renal function.^{7,9}

- b. Use 25% of the usual dose in patients with severe renal impairment. (FDA label, See **“Renal Impairment module”**)
2. In patients with moderate hepatic impairment start with 25% of the hydromorphone dose that would be used in patients with normal hepatic function. Avoid using hydromorphone in patients with severe hepatic impairment.^{7,10}
3. When initiating hydromorphone therapy to manage chronic non-cancer pain, prescribe an IR formulation, particularly in individuals who are either opioid-naïve or not opioid-tolerant.^{11,12}
 - 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.² (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
4. Reserve ER/LA formulations of hydromorphone 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.^{7,12} (See **“ER/LA”** module)
5. Closely monitor the patient for respiratory depression or over-sedation during hydromorphone 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.¹²⁻¹⁵
6. 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.¹¹⁻¹³ (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 hydromorphone-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.^{7, 11-13}
7. Consider prescribing take-home naloxone to patients treated with hydromorphone 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.^{12, 16} (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](#).

References

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