EDUCATION MODULE

PRESCRIBING OPIOIDS FOR PATIENTS WITH RENAL IMPAIRMENT*

*This module provides additional details and risk-reduction guidance specific for this risk factor for serious prescription opioid overdose. It **supplements** but does not replace the general best practices for opioid prescribing presented in the **"Considerations for Safe and Responsible Opioid Prescribing"** module.*

How renal impairment can increase the risk for opioid overdose

1. Most opioids are metabolized by the liver and excreted by the kidneys. Decreased renal elimination can lead to accumulation and prolonged action of many opioids and their metabolites. The resulting higher opioid plasma levels narrow the therapeutic window between safe dosages and dosages at which central nervous system (CNS) and respiratory depression and other toxicities may occur.[1-4]

    a. **Codeine:** Overall, 90% of a codeine dose is renally excreted. Codeine undergoes hepatic biotransformation into many metabolites; 50% to 70% is transformed to codeine-6-glucuronide, 15% to morphine (via CYP2D6), and 10-15% to norcodeine via CYP3A4. Morphine is glucuronidated and not metabolized via phase I CYP450 enzymes (see 'Morphine' below and **"Morphine"** module).
        i. In patients with renal impairment, codeine and its metabolites may accumulate, leading to respiratory depression, over-sedation, and neuroexcitation, particularly in patients who are ultra-rapid metabolizers (i.e., those with multiple copies of the CYP2D6 gene).[4-6] (see also: FDA Label)

    b. **Hydromorphone** is converted via hepatic glucuronidation to hydromorphone-3-glucuronide (H3G), and to a lesser extent hydromorphone-6-glucuronide (H6G). (Smith 2011, Smith 2000) H3G does not possess analgesic properties, but is neurotoxic, while H6G has analgesic properties.[6]
        i. 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.[4-7] (see also: FDA label; ***"Hydromorphone"*** module)

    c. **Meperidine's** active metabolite normeperidine has about 50% the analgesic potency as meperidine, is twice as neurotoxic, and has a 5 to 10-fold longer elimination half-life as meperidine. Accumulation of normeperidine in patients with renal impairment can lead to seizures, confusion, and mood alterations.[6,8-10]

    d. **Morphine's** 6-glucuronide metabolite (M6G) may be twice as potent as morphine and can accumulate in renal impairment, leading to respiratory depression and over-sedation. Accumulation of morphine's neurotoxic 3-glucuronide metabolite (devoid of analgesic properties) may lead to myoclonus, hyperalgesia, and allodynia.[6,7] (see also: FDA Label; **"Morphine"** module)

    e. **Oxymorphone** is metabolized to oxymorphone-3-glucuronide and 6-OH-oxymorphone, the latter having some analgesic bioactivity. Accumulation of oxymorphone and its 6-OH metabolite in patients with renal impairment may lead to CNS and respiratory depression.[4] (see also: FDA Label)

f. **Tramadol** and its active metabolite o-desmethyltramadol (M1) are renally excreted (30% as unchanged drug and 60% as metabolites). Tramadol binds weakly to the mu-opioid receptor, having an affinity about 1/6000th that of morphine, while M1 binds to the mu-opioid receptor with an affinity 200-300 times that of tramadol.[11] Impaired renal clearance results in increased plasma levels of tramadol and M1, which may lead to respiratory depression and seizures.[4,6] (see also: FDA Label)

Risk-mitigation interventions to consider when prescribing opioids in patients with renal impairment:
(Refer to the full prescribing information, see FDA Label for important product-specific details)

1. Before prescribing opioids, estimate the glomerular filtration rate (GFR) using either the eGFR or ClCr (Cockcroft-Gault) method.[2,12]

2. For pain severe enough to require opioid analgesics, prescribe an immediate-release opioid with a short half-life at the lowest effective dose.[2,13,14] Immediate-release opioids may permit more dosing flexibility than ER/LA opioids in the setting of acute, worsening, or unstable renal impairment and decreased renal excretion.[15]

    a. In selecting an opioid, consider the degree of renal elimination of both the parent opioid and its active metabolites. Review full prescribing information for recommended dosage adjustments based upon the degree of renal impairment. Adjustments include lower dosage, less frequent dosing, and more cautious dose titration (see Table 1). Extensive clinical data supporting specific opioid dosing recommendations are lacking.[4,6,15] (see also: FDA Label)
    b. Regardless of renal function, use caution with long-acting/extended-release opioids such as methadone, buprenorphine, and transdermal fentanyl.[15]
    c. Use additional caution when initiating opioids **in older individuals** (≥65 years of age) due to age-related renal changes.[2]
        i. Start with a 25% to 50% lower dose than would be prescribed for a younger person with normal renal function.[16]

Table 1: General guidance regarding dosage adjustment by opioid in patients with renal impairment.

Opioid	General guidance about dosage adjustment in renal impairment[a]
Buprenorphine	No dose reduction needed
Hydrocodone	Start patients with moderate to severe renal impairment on 50% of the dose that would be prescribed for patients with normal renal function.
Hydromorphone	Start patients with moderate renal impairment on 50%, and patients with severe renal impairment on 25% of the dose that would be prescribed for patients with normal renal function.
Tapentadol	No dose reduction needed if ClCr ≥30 mL/min.
Fentanyl	Start patients with mild to moderate renal impairment on 50% of the usual dose for patients with normal renal function; avoid in severe renal impairment.
Methadone	The use of methadone has not been extensively evaluated in patients with renal insufficiency. Start patients with severe renal impairment (ClCr <10 mL/min) on 25% to 50% of the dose that would be prescribed for patients

	with normal renal function.
Oxycodone	In patients with renal impairment initiate therapy with a lower dose than usual.[b]
Oxymorphone	In patients with ClCr <50 mL/min, start with the 5mg tablet if the patient is opioid-naiive; if not opioid-naive, start with 50% of the dose that would be prescribed for patients with normal renal function.
Tramadol	In patients with ClCr <30mL/min, increase dosing interval to 12 hrs and limit to a maximum daily dose of 200 mg.
Avoid in renal impairment	
Codeine	Avoid (Koncicki 2016, Pham 2017)
Meperidine	Avoid (Koncicki 2016, Pham 2017)
Morphine	Start at a lower dose than usual. Avoid if CLCr <30 mL/min.
Tapentadol	Avoid if ClCr <30 mL/min (Pham 2017)

ClCr: creatinine clearance

[a]*From the FDA-approved full prescribing information for each opioid, with additional sources as noted.*

[b]*Alternatively, in patients with ClCr <10ml/min, prescribe 50% of the oxycodone dose that would be prescribed for patients with normal renal function. For patients with ClCr 10-50ml/min, prescribe 75% of the dose that would be prescribed for patients with normal renal function. No dose adjustment is necessary for patients with ClCr >50ml/min. (British Columbia Renal Agency, 2011)*

3. **Frequently assess** the initial clinical response. If necessary, slowly titrate the dose of opioid to optimize outcomes (adequate analgesia and tolerability and minimal adverse effects).[2,13]

4. Closely monitor renal function, and watch for signs of respiratory depression, over-sedation, or hypotension, particularly during opioid initiation and dose 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.[2,17-19]

5. Optimize non-pharmacologic, non-opioid pharmacologic analgesic therapies to reduce the amount of opioid needed.[4,15] In patients with renal impairment:

    a. Acetaminophen is the preferred analgesic for mild to moderate pain.
    b. Adjuvant analgesics that are useful for neuropathic pain include certain anticonvulsants (gabapentin, pregabalin, carbamazepine) and tricyclic antidepressants (amitriptyline, nortriptyline).
    c. Reserve non-steroidal anti-inflammatory drugs (NSAIDs) for only short-term use (3 to 7 days) for specific indications (e.g., acute pain such as an acute gout flare). Prescribe short-acting products (e.g., sulindac, salsalate) at reduced dosing frequency.

6. Avoid concurrent use of other medications or substances that are central nervous system depressants, such as benzodiazepines, sedatives/hypnotics, and alcohol in opioid-treated patients with renal impairment. 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.[2,13,17] (See also: FDA Label)

7. Consider prescribing take-home naloxone for opioid-treated patients with renal impairment to reverse life-threatening respiratory depression if an overdose occurs. 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.[2,20]

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. Chronic kidney disease and Drug Dosing: Information for Providers. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
3. VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain. February 2017 (pp 81-98)

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