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Clinical Rationale for Immediate-Release Opioid Prescribing: Information for Pharmacists

Based on the evidence, **immediate-release (IR) opioids are preferred over extended-release/long-acting (ER/LA) opioids** in multiple patient populations due to safety considerations established by the CDC, FDA, and VA/DoD guidelines.

The following summarizes the key populations and clinical scenarios:

Patient Populations Requiring Immediate-Release Opioids

- 1. Opioid-naïve patients:** The CDC 2022 guidelines explicitly state that clinicians should not initiate opioid treatment with ER/LA opioids for acute, subacute, or chronic pain. ER/LA opioids are only appropriate for opioid-tolerant patients who have received at least 60 mg daily of oral morphine (or 30 mg daily of oral oxycodone, or equianalgesic doses) for at least one week.[\[1\]](#)
- 2. Patients with intermittent or variable pain patterns:** ER/LA opioids should not be prescribed for intermittent or as-needed use. Patients whose pain fluctuates significantly require the dosing flexibility that only IR opioids provide.[\[1\]](#)
- 3. Patients with renal or hepatic dysfunction:** The CDC recommends additional caution with ER/LA opioids in these patients because decreased clearance can lead to drug accumulation to toxic levels and prolonged duration of effects including respiratory depression. IR opioids allow for more precise dose titration and faster clearance if adverse effects occur.[\[1\]\[2\]](#)
- 4. Patients during dose titration:** The FDA recommends initiating therapy with as-needed IR opioids to establish the effective dose before considering ER/LA formulations. This allows safer determination of opioid requirements.[\[3\]](#)
- 5. Elderly patients:** Due to increased risk of respiratory depression and altered pharmacokinetics, IR opioids allow more careful titration and monitoring.[\[4\]](#)

The following figure from a JAMA study demonstrates the markedly elevated mortality risk during the first 30 days of long-acting opioid therapy (hazard ratio 4.16), which then declines substantially over time—supporting the use of IR opioids during initiation:

	Anticonvulsant or Cyclic Antidepressant			Long-acting Opioid			Risk Difference (95% CI)	Hazard Ratio (95% CI)
	No. of Patients	Person-Years	No. of Deaths	No. of Patients	Person-Years	No. of Deaths		
Time since drug started, d								
≤30	22912	2054	13	22912	2042	53	200 (80 to 420)	4.16 (2.27-7.63)
31-180	11752	3026	40	12194	3534	70	74 (7 to 172)	1.56 (1.05-2.30)
>180	3765	2986	34	5584	5494	62	3 (-37 to 65)	1.03 (0.67-1.57)
Study drug dose during follow-up								
Low	13345	3311	31	19564	5381	75	51 (1 to 125)	1.54 (1.01-2.34)
High	13495	4755	56	9637	5689	110	111 (47 to 200)	1.94 (1.40-2.70)
Short-acting opioid at baseline, mg								
≤30	14590	5275	54	14504	6949	110	63 (16 to 128)	1.62 (1.16-2.25)
>30	8322	2792	33	8408	4121	75	80 (13 to 184)	1.68 (1.11-2.56)
All	22912	8066	87	22912	11070	185	69 (28 to 121)	1.64 (1.26-2.12)

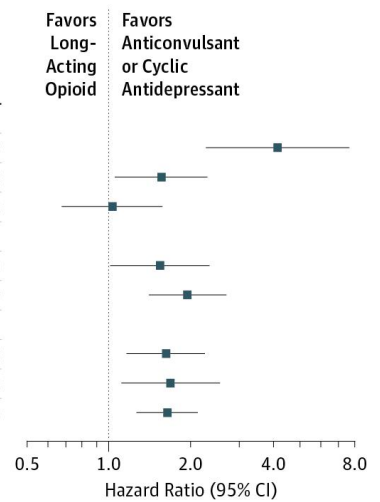


Figure 1 Mortality According to Study Drug Duration, Dose, and Baseline Use of Short-Acting Opioids undefined

Clinical Justification for Immediate-Release Opioid Prescribing

Dear Pharmacy Colleague,

The need for this communication is based on the recent practice of local pharmacies, limiting the number of immediate release, opioids prescribed to them. By limiting this number, especially in patients with long-standing history of stable, morphine equivalent dosing, it places the patient at risk of opioid withdrawal symptoms, as well as definitively reducing the adequacy of their pain control, and thus impairing their ability to maintain their activities of daily living and maintain an acceptable quality of life. A taper such as reducing the number of tablets dispense from 180 per month to 120 per month represents a 33% drop in analgesic benefit, which is highly unlikely to be well tolerated by the patient.

Regarding reduction of prescribed immediate release opioid medications

Dosing Frequency Considerations

The alternative to providing adequate pain control when reducing a patient for example from 180 tablets per month to 120 tablets per month (effectively, reducing opioid dosing from every four hours to every six hours per day), would be to raise the dosage of the opioid prescribed four times a day.

For example, if one were to reduce Percocet-10 mg (or oxycodone – 10 mg) prescribed 180 tablets per month (one tablet every four hours for 30 days) and prescribe another equianalgesic alternative and rotate the patient to oxycodone-15 mg every six hours to meet the standard of reducing the number of prescribed tablets from 180 to 120 per month. However, in doing so the quality and safety of the patients care may be compromised.

Immediate-release opioids require administration every 4 hours to maintain stable blood levels and analgesia.^[2] The six-dose regimen (10 mg every 4 hours) aligns more closely with this pharmacokinetic principle, potentially providing more consistent pain control throughout the day. The four-dose regimen (15 mg doses) would require 6-hour intervals, which may result in periods of suboptimal analgesia between doses.

From a safety perspective, lower individual doses (10 mg) may reduce peak opioid concentrations and associated risks of sedation and respiratory depression compared to higher individual doses (15 mg), though both remain within commonly prescribed ranges. The more frequent dosing schedule may also allow for better titration and dose adjustment based on patient response.

Clinical Recommendation regarding frequency of prescribing immediate release medications

While both regimens carry similar overall risks given the equivalent total daily dose of 60 MME, the six-dose regimen of 10 mg every 4 hours offers potential advantages in maintaining more stable blood levels consistent with the pharmacokinetics of immediate-release formulations and may provide more consistent analgesia throughout the day.

Regarding rotation of immediate release medications to extended release formulations

Another alternative to overcome this situation, would requires replacing the deficit of the immediate release medications with extended release medications in an effort to maintain adequacy of pain control. As noted below, this action is contrary to a patient's best interest in many situations and is a detriment to the patient's safety. Additionally, it creates an additional financial burden which is in many cases is impossible for the patient to absorb.

This communication provides evidence-based rationale for prescribing immediate-release (IR) opioids rather than extended-release/long-acting (ER/LA) formulations in specific patient populations. The intent is to clarify that conversion to ER/LA opioids is contraindicated or inappropriate in certain clinical scenarios, and that IR opioid prescribing—even at higher quantities—represents guideline-concordant care.

Regulatory and Guideline Framework

The CDC Clinical Practice Guideline for Prescribing Opioids for Pain (2022) provides a Category A recommendation: "When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release and long-acting (ER/LA) opioids."[\[6\]](#)

The FDA has added the following warning to all ER/LA opioid preparations: "Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve [extended-release opioid preparations] for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain."[\[7\]](#)

The VA/DoD Clinical Practice Guideline (2022) similarly recommends against the use of long-acting opioids for treating acute pain, for as-needed pain, or when initiating long-term opioid therapy.[\[1\]](#)

Patient Populations for Whom ER/LA Opioids Are Contraindicated or Inappropriate

1. Opioid-Naïve Patients

- ER/LA opioids are only appropriate for opioid-tolerant patients who have received ≥ 60 mg daily oral morphine equivalents (or ≥ 30 mg daily oral oxycodone) for at least one week.[\[6\]](#)[\[1\]](#)
- Initiating ER/LA opioids in opioid-naïve patients carries significantly higher overdose risk, particularly in the first 2 weeks of therapy.[\[1\]](#)

2. Patients with Intermittent or Variable Pain

- ER/LA opioids should not be prescribed for intermittent or as-needed use.[\[6\]](#)
- Patients with pain that fluctuates in intensity require the dosing flexibility of IR formulations.
- ER/LA opioids are reserved for "severe, continuous pain" only.[\[6\]](#)

3. Patients with Renal Impairment

- Decreased renal clearance leads to accumulation of ER/LA opioids to toxic levels.[\[6\]](#)
- The prolonged duration of action increases risk of sustained respiratory depression.
- IR opioids allow more precise titration and faster elimination if toxicity occurs.

4. Patients with Hepatic Impairment

- Impaired hepatic metabolism prolongs ER/LA opioid effects unpredictably.[\[6\]](#)
- Some ER/LA formulations (e.g., oxymorphone ER) are contraindicated in moderate-to-severe hepatic impairment.[\[1\]](#)
- IR opioids provide safer, more controllable analgesia in this population.

5. Patients During Active Dose Titration

- The FDA recommends establishing effective opioid dose with IR formulations before considering ER/LA conversion.[\[1\]](#)
- IR opioids allow rapid dose adjustments based on pain response and tolerability.

6. Elderly Patients (≥ 65 years)

- Respiratory depression risk is elevated in elderly patients on opioids.[\[8\]](#)
- Age-related changes in renal and hepatic function affect ER/LA opioid clearance unpredictably.
- IR opioids allow careful, incremental titration with closer monitoring.

7. Patients with Sleep-Disordered Breathing

- ER/LA opioids pose greater risk of sustained respiratory depression during sleep.
- IR opioids with shorter duration of action may be safer when opioids are necessary.

Evidence: ER/LA Opioids Carry Greater Risk Than IR Opioids

- A fair-quality study demonstrated higher overdose risk among patients treated with ER/LA opioids compared to IR opioids, especially within the first 2 weeks of therapy.[\[1\]](#)
- Patients receiving long-acting and Schedule II short-acting opioid formulations simultaneously were 4.7 times more likely to die of an overdose than those receiving non-Schedule II opioids alone.[\[1\]](#)
- Long-acting opioids increased the risk of being treated for opioid use disorder compared to short-acting opioids.[\[1\]](#)
- Clinical evidence reviews did not find evidence that continuous, time-scheduled use of ER/LA opioids is more effective or safer than intermittent use of IR opioids, or that ER/LA opioids reduce risk for opioid use disorder.[\[1\]](#)

Clinical Implications for Dispensing

When a prescriber has determined that IR opioids are clinically appropriate for a patient, conversion to ER/LA formulations may:

- Increase overdose risk
- Violate FDA labeling requirements
- Contradict CDC and VA/DoD guideline recommendations
- Be medically inappropriate for the patient's specific clinical situation
- The quantity of IR opioids prescribed reflects the patient's pain pattern, dosing interval requirements, and clinical circumstances—not an indication that ER/LA conversion is warranted.

Summary

Immediate release opioid prescribing should be evidence-based, guideline-concordant care for the patient populations described above. The decisions that need to be made regarding the safest and most effective means of controlling a patient's chronic pain should be left to an experienced physician with proper training in opioid management who is familiar with the patients history and medical conditions. It should not be driven by policies that do not take these circumstances into account.

Recommendations to convert patients to different opioid management regimens should be made only after direct communication with the prescribing clinician to confirm that the patient's needs and safety of their opioid use (including assessment of a patient's opioid-tolerance, severity of pain, prescribing contraindications, other medical conditions etc.).

Please contact me directly if you have questions about a specific patient's opioid regimen.

Sincerely,

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- CDC Clinical Practice Guideline for Prescribing Opioids for Pain, 2022[\[6\]](#)
- FDA ER/LA Opioid Labeling Requirements, 2014[\[7\]](#)
- VA/DoD Clinical Practice Guideline: Use of Opioids in the Management of Chronic Pain, 2022[\[1\]](#)
- FDA Guidance on Opioid Initiation[\[1\]](#)
- CDC 2022 Guideline Supporting Rationale[\[1\]](#)
- Oxymorphone ER Prescribing Information[\[1\]](#)
- Hydrocodone Bitartrate ER Prescribing Information[\[8\]](#)

This communication synthesizes the key regulatory and guideline evidence supporting IR opioid prescribing in appropriate patient populations. The CDC 2022 guidelines explicitly recommend initiating opioid therapy with IR rather than ER/LA formulations (Category A recommendation), and the FDA requires that ER/LA opioids be reserved only for patients who have failed or cannot tolerate IR. opioids.[1][8] Evidence demonstrates that ER/LA opioids carry higher overdose risk, particularly in the first 2 weeks of therapy, and do not provide superior efficacy or safety compared to IR opioids.[1][9]

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