EDUCATION MODULE

PRESCRIBING FENTANYL*

*This module provides information about fentanyl 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. Fentanyl is a synthetic opioid agonist that is at least 50 to 100 times more potent than morphine.[1,2]

2. Fentanyl can be prescribed in multiple non-parenteral dosage forms.

    a. *Transdermal fentanyl* (i.e., patch) is the only **long-acting (ER/LA)** fentanyl dosage form.
        i. Extended-release/long-acting (ER/LA) opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment when alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.[3]
        ii. Adults are considered opioid-tolerant if they are receiving a total daily opioid dosage equivalent to at least 60 mg of oral morphine (60 MME) per day for one week or longer.[3] (See 'Treatment' section 5a in the **"Safe and Responsible Opioid Prescribing in Adults"** 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
        iii. Tolerance to an opioid's respiratory depressant effects (and thus the risk of an overdose) develops more slowly and less completely than to its analgesic and euphoric effects.[4,5]

    b. *Rapid-onset, short-acting fentanyl dosage forms* [i.e., transmucosal immediate-release (IR) fentanyl (TIRF) products] include buccal lozenges, tablets, and film; sublingual tablets and spray; and intranasal spray. These formulations are only indicated for the management of breakthrough pain in patients with cancer who are 18 years of age (16 for lozenges) or older and already receiving and tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.[1,2,6,7]

        These dosage forms are not discussed further in this clinical decision support module that is focused on opioid therapy for pain management in adult outpatients, and excludes treatment of patients with active cancer or receiving palliative or end-of-life care.

Transdermal fentanyl and opioid overdose

1. Even at label-recommended doses, opioid analgesics carry the risk of overdose as well as misuse, abuse, opioid use disorder (OUD), and death.[3]

    a. Fentanyl is associated with an increased risk for serious opioid-induced respiratory depression (overdose) compared with some other opioid analgesics and some other ER/LA opioids.[8-10]

2. Fentanyl is metabolized by the hepatic CYP450 3A4 isoenzyme system to inactive metabolites.[1,2,6,11] Fentanyl plasma levels may be increased leading to respiratory depression and over-sedation in a patient who:

    a. Begins concurrent use of a CYP 3A4 inhibitor (e.g., erythromycin, clarithromycin, ketoconazole, diltiazem, HIV protease inhibitors)
    b. Discontinues concurrent use of a CYP3A4 inducer (e.g., carbamazepine, phenytoin, St. John's Wort)
    c. Has severe hepatic impairment.[6,12,13]

3. Less than 10% of a fentanyl dose is excreted as unchanged fentanyl. In patients with impaired renal function, reduced clearance may lead to increased fentanyl plasma levels, leading to respiratory depression and over-sedation.[1-3]

4. Transdermal fentanyl has complex pharmacokinetic properties.
    a. It has a long duration of action due to its controlled-release dosage form.
    b. After patch removal, drug absorption continues from a depot of fentanyl in the stratum corneum.[1,6.14]
    c. External heat, fever, exertion, and compromised dermal integrity (e.g., eczema, psoriasis) can increase absorption of fentanyl leading to fatal overdose.[1.6]

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

1. Fentanyl should only be used by clinicians who are familiar with the complexity of this dosage form and who are able to monitor patients closely.[15,16]

2. Reserve transdermal fentanyl for patients who are opioid-tolerant to manage pain severe enough to require daily, around the clock, long-term opioid treatment when alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.[6,15-17]
    a. Adults are considered opioid-tolerant if they have been receiving a total daily opioid dose equivalent to at least 60 mg of oral morphine (60 MME/day) for one week or longer.[17] (See 'Treatment' section 5a in the **"Considerations for Safe and Responsible Opioid Prescribing"** module)

3. Before prescribing fentanyl, estimate the glomerular filtration rate using either the eGFR or creatinine clearance (ClCr) method. In patients with mild to moderate renal or hepatic impairment, reduce the starting dose to 50% of the usual starting dose for persons with normal renal or hepatic function. Avoid using fentanyl in patients with severe renal or hepatic impairment.[6,18,19] (See **"Renal Impairment"** module)

4. Initiate transdermal fentanyl therapy in a patient already receiving the equivalent of at least 60 mg of oral morphine (60 MME/day) for one week or longer. (See **"MME"** module) Use conservative dosing to avoid unintentional overdose due to incomplete cross-tolerance and individual variability in pharmacokinetics between the current opioid regimen and transdermal fentanyl.[6,20,21]

    a. Discontinue or taper all other around-the-clock (ER/LA or IR) opioid analgesics when initiating transdermal fentanyl therapy.[6]
    b. To determine the recommended initial fentanyl dose, calculate dose conversions based on the equianalgesic dose ratios included in the full prescribing information.[6.16]
    c. Use particular caution with dose conversions involving fentanyl because it is dosed in mcg/hr instead of mg/day, and its absorption is affected by heat and other factors.[1,6,14]

5. Closely monitor the patient for respiratory depression or over-sedation during fentanyl 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.[4,5,16,22]

    a. Plasma concentrations of fentanyl will peak 24 to 72 hours after application of the initial patch or after subsequent dose increases.[6,14,23]
    b. Significant amounts of fentanyl continue to be absorbed from the skin for ≥24 hours after patch removal. Rotate the application site and only apply to intact skin.[6,14,23]

6. Frequently assess the clinical response (analgesia) as well as adverse events (opioid specific and localized rash). Slowly titrate to the lowest effective dose with tolerable adverse events. Some patients may require patch changes at 48 hours rather than at 72 hours, only if adequate pain control cannot be achieved using a 72-hour regimen.[6,14,23]

    a. After beginning therapy (applying the initial patch), wait at least 3 days before the first patch change. Steady state levels will not be achieved until 72 hours after application of the third patch. At that time, increasing the dose may be considered based on pain intensity.[6,14,23]
    b. For patients on a stable dosage of transdermal fentanyl, wait at least 6 days before further dose increases.[6,24]
    c. If a dose increase is necessary, increase by the smallest dose increment available.[6,23] (i.e., 12 mcg/h)

7. Consider reducing the fentanyl dosage in patients who concurrently use medications that are CYP3A4 inhibitors, or who discontinue concurrent use of a CYP3A4 inducer, which may increase plasma fentanyl levels. Closely monitor for respiratory depression or over-sedation until stable drug effects are achieved.[1,2,6]

a. Conversely, for patients on a stable fentanyl regimen, the addition of a CYP3A4 inducer or discontinuation of a CYP3A4 inhibitor may decrease plasma fentanyl levels and lead to loss of analgesic efficacy and/or signs of withdrawal in persons who are physically dependent on fentanyl.[1,2,6,11]

8. Apply and handle fentanyl products properly to avoid the risk of unintentional overdose.
    a. External heat, strenuous exertion, local erythema and fever can increase absorption of transdermal fentanyl and lead to fatal overdose. Warn patients to avoid exposing the transdermal application site and surrounding area to direct external heat sources. Closely advise patients to monitor for respiratory depression and over-sedation during fever.[1,6,14,17]
    b. Prescribers and pharmacists must specifically question patients or their caregivers about the presence of children (and pets) in the home (on a full-time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure. Warn patients to keep any fentanyl products and other controlled substances secured, and out of reach of children or others who may enter their home.[17]

9. Avoid concurrent use of other medications or substances that are central nervous system depressants, such as benzodiazepines, sedatives/hypnotics, and alcohol in fentanyl-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.[6.15.16]

10. Consider prescribing take-home naloxone to patients treated with fentanyl 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.[16,18] (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, inpatient). 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. **Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics** (FDA ER/LA REMS) (2017)
3. **CDC Guideline Resources**: Clinical Tools for Prescribing Opioids. https://www.cdc.gov/drugoverdose/prescribing/clinical-tools.html
4. **Flockhart Table of Drug-Drug Interactions: Cytochrome P450 Drug Interactions** (2016)
5. **Opioid Milligram Morphine Equivalent (MME) Calculators**
   a. New York City Department of Health and Mental Health (online interactive and mobile app)
   b. Washington State Agency Medical Directors' Group (online interactive and mobile app)
   c. CDC Factsheet: Calculating total daily dose of opioids for safer dosage (manual calculator and mobile app)

References

1. Schug SA, Ting S. Fentanyl formulations in the management of acute pain: An update. Drugs 2017;77:747-763. PMID: 28337672
2. Stanley TH. The fentanyl story. J Pain. 2014;15:1215–26. PMID: 25441689
3. 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
4. Dumas EO, Pollack GM. Opioid tolerance development: a pharmacokinetic/pharmacodynamic perspective. AAPS J. 2008;10:537-51. PMID: 18989788
5. White JM, Irvine RJ. Mechanisms of fatal opioid overdose. Addiction 1999;94:961-72. PMID: 10707430
6. FDA label: Fentanyl. https://labels.fda.gov
7. FDA TRF REMS. Available at: https://www.tirfremsaccess.com/TirfUI/rems/home.action
8. Zedler B, Xie L, Wang L, et al. Risk factors for serious prescription opioid-related toxicity or overdose among veterans health administration patients. *Pain Med*. 2014;15:1911-1929. PMID: 24931395
9. Nadpara PA, Joyce AR, Murelle EL, et al. Risk factors for serious prescription opioid induced respiratory depression or overdose: Comparison of commercially insured and veterans health affairs populations. Pain Medicine 2018;19:79-86. PMID: 28419384
10. Paulozzi LJ, Kilbourne EM, Shah NG, et al. A history of being prescribed controlled substances and risk of overdose drug death. Pain Medicine 2012;13:87-95. PMID: 22026451
11. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2016). http://medicine.iupui.edu/clinpharm/ddis/clinical-table/
12. Kokubun H, Ebinuma K, Matoba M, Takayanagi R, Yamada Y,Yago K. Population pharmacokinetics of transdermal fentanyl in patients with cancer-related pain. J Pain Palliat Care Pharmacother 2012; 26: 98–104. PMID: 22764844
13. Van Nimmen NFJ, Poels KLC, Menten JJ, Godderis L, Veulemans HAF. Fentanyl transdermal absorption linked to pharmacokinetic characteristics in patients undergoing palliative care. J Clin Pharmacol 2010; 50: 667–78. PMID: 20097932.
14. Grond S, Radbruch S, Lehmann KA. Clinical Pharmacokinetics of Transdermal Opioids: Focus on Transdermal Fentanyl. Clin Pharmacokinet 2000;38:59–89. PMID: 10668859
15. Busse J, Craigie S, Juurlink D, et al. Guideline for opioid therapy and chronic noncancer pain: Appendix. CMAJ 2017. Link: National Pain Centre

16. 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
17. FDA. Risk evaluation and mitigation strategy (REMS) for opioid analgesics. 2017. Available at: https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm
18. 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.
19. Smith H, Bruckenthal P. Implications of opioid analgesia for medically complicated patients. *Drugs Aging*. 2010;27(5):417-433. PMID: 20450239
20. Fine PG, Portenoy RK. Establishing "best practices" for Opioid Rotation: Conclusions of an Expert Panel. Journal of Pain and Symptom Management. 2009 Sep;38(3):418-25. PMID: PMID: 19735902
21. Knotkova H, Fine PG, Portenoy RK. Opioid Rotation: The Science and the Limitations of the Equianalgesic Dose Table. J Pain Symptom Manage. 2009 Sep;38(3):426-39. PMID:19735903
22. 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. Washington State Agency Medical Director's Group
23. Nelson L, Schwaner R. Transdermal fentanyl: Pharmacology and Toxicology. J Med Tox 2009;5:230-241. PMID: 19876859
24. Jeal W, Benfield P. Transdermal fentanyl: A review of its pharmacological properties and therapeutic efficacy in pain control. Drugs 1997;53:109-138. PMID: 9010652