

EDUCATION MODULE

PRESCRIBING OPIOIDS IN PATIENTS WITH CEREBROVASCULAR DISEASE*

*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.*

Background

The prevalence of cerebrovascular disease, cognitive impairment and chronic medical conditions increase with aging, particularly after age 65 years.¹⁻³

Cerebrovascular disease and opioid overdose

- Opioids are central nervous (CNS) depressants and may exacerbate cognitive impairment, confusion, or cause hallucinations in persons with underlying cerebrovascular disease.⁴⁻⁶
- Psychotherapeutic medications are commonly used by patients with cerebrovascular disease for neuropsychiatric sequelae from stroke such as depression, anxiety, and sleep disorders.⁷
 - a. Benzodiazepines, sedatives/hypnotics, and certain antipsychotics, antidepressants, or anticonvulsants are CNS depressants. Their concomitant use with opioids can increase the risk of over-sedation and respiratory depression (overdose).^{4,6,7}
- Cognitive impairment associated with cerebrovascular disease can increase the risk for medication administration errors and make opioid-related confusion more dangerous.⁴
 - a. Persons with stroke related frontal lobe damage and those with behavioral variant frontotemporal dementia may exhibit symptoms of disinhibition.⁸
 - i. Disinhibition may manifest as impulsivity, alcohol or illicit substance use, or other reckless behaviors, thus increasing risk for drug overdose.^{9,10}
- Certain age-related changes increase the risk of excessive sedation, respiratory depression, coma, and death in opioid treated persons.¹¹⁻¹³
 - a. Age-related decrements in cholinergic neurons predispose to iatrogenic cognitive impairment.¹⁴
 - b. Impaired hepatic metabolism and/or renal elimination of drugs may lead to increased plasma levels and prolonged action of most opioids and their metabolites.¹⁵
 - i. Alterations in hepatic blood flow may decrease the elimination clearance of drugs with flow-limited hepatic clearance.
 - ii. The CYP3A4, CYP2D6, and UGT drug metabolizing enzyme systems are only nominally decreased with advancing age.

- c. Changes in the respiratory system that reduce the ability to tolerate opioid-induced respiratory depression include decreased sensitivity of central and peripheral chemoreceptors to hypercapnia and diminished compensatory respiratory drive.¹⁶
- d. The prevalence of sleep-disordered breathing increases with age and is high in persons with ischemic cerebrovascular disease/accidents.¹⁶⁻¹⁹
- e. Polypharmacy to treat multiple comorbidities is common and increases the risk of dangerous drug-drug interactions, overdose and death.¹¹⁻¹³

Risk-mitigation interventions to consider when prescribing opioids for patients with cerebrovascular disease

- When initiating opioid therapy, start with a short acting, immediate-release opioid at 25% to 50% below the usual adult dose, particularly in older adults. Slowly and cautiously escalate dosage by 25% increments.^{4,20} (See the "**Considerations for Safe and Responsible Opioid Prescribing**" module).
 - Avoid meperidine in patients with cerebrovascular disease, particularly in older people and in those with renal impairment due to the risk of seizures, confusion, and mood alterations from its CNS-toxic metabolite normeperidine.^{4,16,20}
 - Avoid using more than one opioid at the same time to make it is easier to identify the cause of adverse CNS effects should they occur.^{4,21,22}
- Slowly and cautiously titrate dosage by 25% increments to achieve effective analgesia with acceptable tolerability and minimal adverse effects. Monitor closely for cognitive impairment, over-sedation, and respiratory depression during opioid initiation and dose escalation.^{4,6,20}
 - The risk for overdose is greatest during the first 3 to 7 days after starting an opioid or increasing its dose. This occurs because tolerance to an opioid's respiratory depressant effects is slower to develop and less complete than tolerance to its analgesic or euphoric effects.^{4,20,23,24}
 - i. 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.²⁵ (See 'Treatment' section of the "**Considerations for Safe and Responsible Opioid Prescribing**" module). This dosage is comparable to:
 - 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
- 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, thus the combination should be restricted to the minimum required dosage and duration in patients for whom alternative treatment options are inadequate.^{4,6,20} (see also: **FDA Label**)

- For insomnia, avoid benzodiazepines and hypnotic medications.
 - i. If the patient requires pharmacologic treatment consider low-dose doxepin (3 to 6mg) or trazodone, melatonin, ramelteon, suvorexant, or other non-controlled medications.²⁶
- Determine whether a caregiver is needed to responsibly co-manage medication therapy.⁴ Collaborate closely with the patient, patient’s caregiver (if applicable), and pharmacist to ensure safe use of opioids and other medications.^{4,20}
- Confirm that the patient is not receiving controlled medications from multiple prescribers (or pharmacies), is securely storing and safely disposing of unused controlled medications, and that no one else (including the caretaker) is using the patient’s controlled medications.⁴
- 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 extended release/long-acting 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.^{4,27}

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. [UCSF Memory and Aging Centre](#) Weill Institute for Neurosciences.

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