

Opioid therapy and sleep apnea

(JUNE 2016)

TO THE EDITOR: I enjoyed Dr. Galicia-Castillo's article about long-term opioid therapy in older adults,¹ which reaffirmed the imperative to "start low and go slow" to minimize the risk of addiction. However, the article missed an opportunity to raise awareness regarding another extremely important side effect of chronic prescription opioid consumption, that of ingestion prior to sleep, with consequent cessation of breathing leading to death.

According to the Drug Enforcement Administration,² most narcotic deaths are a result of respiratory depression. And the American Pain Society has stated, "No patient has succumbed to [opioid] respiratory depression while awake."³

Dr. Galicia-Castillo noted that the prevalence of central sleep apnea in chronic opioid users is 24%, based on a review by Correa et al.⁴ As alarming as this number is, other investigators have estimated it to be even higher—as high as 50% to 90%.⁵

Walker et al,⁶ in a study of 60 patients, found that the higher the opioid dose the patients were on, the more episodes of obstructive sleep apnea and central sleep apnea per hour they had. Yet prescribing a low dose does not adequately protect the chronic opioid user. Farney et al⁷ reported that oxygen saturation dropped precipitously—from 98% to 70%—15 minutes after a patient took just 7.5 mg of hydrocodone in the middle of the night. Mogri et al⁸ reported that a patient had 91 apnea events within 1 hour of taking 15 mg of oxycodone at 2 AM.

Opioids, benzodiazepines, barbiturates, and ethanol individually and additively suppress medullary reflex ventilatory drive during sleep, especially during non-rapid-eye-movement (non-REM) sleep.⁶ During waking hours, in contrast, there is redundant backup of cerebral cortical drive, ensuring that we keep breathing. Therefore, people are most vulnerable to dying of opioid ingestion during sleep.

Moreover, oxygen desaturation during episodes of sleep apnea may precipitate seizures (which may be lethal) or coronary vasospasm with consequent malignant arrhythmias and myocardial ischemia.

Continuous positive airway pressure protects against obstructive sleep apnea, but not against central sleep apnea.⁹

Patients need to be aware of the danger, and physicians need to consider the pharmacokinetic profiles

of the opioid preparations they prescribe. If patients are taking an opioid that has a short half-life, such as immediate-release oxycodone, they should not take it within 5 hours of sleep. Longer-lasting preparations need a longer interval, and some, such as extended-release tramadol, may need to be taken only on awakening.

Safe sleep can be facilitated by medications that are sedating but do not compromise ventilation. Optimal agents also enhance restorative REM and stage III and IV deep-sleep duration, and some may have the additional benefit of reducing the risk of cancer.^{10,11} Such agents may include baclofen, cypheptadine, gabapentin, mirtazepine, and melatonin. Nonpharmacologic measures include sleep hygiene, aerobic exercise, and cognitive behavioral therapy.

A retrospective study¹² found that 301 (60.4%) of 498 patients who died while on opioid therapy and whose death was judged to be related to the opioid were also taking benzodiazepines. Patients who take opioids should avoid taking benzodiazepines, barbiturates, or alcohol before going to sleep, and physicians should be extremely cautious about prescribing benzodiazepines and barbiturates to patients who are on opioids.

AARON S. GELLER, MD
Tufts University School of Medicine
Boston, MA

REFERENCES

1. Galicia-Castillo M. Opioids for persistent pain in older adults. *Cleve Clin J Med* 2016; 83:443–451.
2. Drug Enforcement Administration. *Drugs of Abuse*. 2005 Edition. Washington, DC: US Government Printing Office, 2005:19.
3. American Pain Society, *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain*, 4th ed. Glenview, IL: American Pain Society, 1999:30.
4. Correa D, Farney RJ, Chung F, Prasad A, Lam D, Wong J. Chronic opioid use and central sleep apnea: a review of the prevalence, mechanisms, and perioperative considerations. *Anesth Analg* 2015; 120:1273–1285.
5. Panagiotou I, Mystakidou K. Non-analgesic effects of opioids: opioids' effects on sleep (including sleep apnea). *Curr Pharm Des* 2012; 18:6025–6033.
6. Walker JM, Farney RJ, Rhondeau SM, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. *J Clin Sleep Med* 2007; 3:455–461. Erratum in *J Clin Sleep Med* 2007; 3:table of contents.
7. Farney RJ, Walker JM, Cloward TV, Rhondeau S. Sleep-disordered breathing associated with long-term opioid therapy. *Chest* 2003; 123:632–639.
8. Mogri M, Khan MI, Grant BJ, Mador MJ. Central sleep apnea induced by acute ingestion of opioids. *Chest* 2008; 133:1484–1488.
9. Guilleminault C, Cao M, Yue HJ, Chawla P. Obstructive sleep apnea and chronic opioid use. *Lung* 2010; 188:459–468.
10. Kao CH, Sun LM, Liang JA, Chang SN, Sung FC, Muo CH. Relationship of zolpidem and cancer risk: a Taiwanese population-based cohort study. *Mayo Clin Proc* 2012; 87:430–436.

11. **Kripke DF.** Hypnotic drug risks of mortality, infection, depression, and cancer: but lack of benefit. *F1000Res* 2016; 5:918.
12. **Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN.** Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med* 2011; 171:686–691.

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IN REPLY: Dr. Geller makes some excellent points about sleep and opioid use.

Opioids pose risks,¹ just like any other type of medication. In particular, opioids have been linked to sleep-disordered breathing, which affects 70% to 85% of patients taking opioids.²⁻⁴

Other options can be used in some older adults, but they are not always successful. Ideally, nonpharmacologic strategies and nonopioid medications such as acetaminophen, nonsteroidal anti-inflammatory agents, antidepressants, and anticonvulsants should be used, although these medications have their own side effects. Optimum pain control may offer the potential for significant improvement in function, and opioids are but one tool in the clinician's kit.

Ongoing discussions of the risks and benefits are necessary, along with continuous re-evaluation of the need for and effect of opioids.

MARISSA C. GALICIA-CASTILLO, MD
Eastern Virginia Medical School
Norfolk, VA

■ REFERENCES

1. **Davis MP, Mehta Z.** Opioids and chronic pain: where is the balance? *Curr Oncol Rep* 2016; 18:71.
2. **Jungquist CR, Flannery M, Perlis ML, Grace JT.** Relationship of chronic pain and opioid use with respiratory disturbance during sleep. *Pain Manag Nurs* 2012; 13:70–79.
3. **Webster LR, Choi Y, Desai H, Webster L, Grant BJ.** Sleep-disordered breathing and chronic opioid therapy. *Pain Med* 2008; 9:425–432.
4. **Mogri M, Khan MI, Grant BJ, Mador MJ.** Central sleep apnea induced by acute ingestion of opioid. *Chest* 2008; 133:1484–1488.

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Submassive pulmonary embolism

(DECEMBER 2016)

TO THE EDITOR: I read with interest the review on submassive pulmonary embolism by Ataya et al¹ in the December 2016 issue. I had 3 questions or observations for the authors

First, systemic thrombolytic therapy for massive or hemodynamically unstable pulmonary embolism is given a grade 2C recommendation, similar to the

level for select patients with submassive pulmonary embolism with low bleeding risk but at high risk of developing hypotension. The reference for this is the 2012 American College of Chest Physicians guidelines.² I would like to point out that these guidelines were updated and published in February 2016,³ and systemic thrombolytic therapy for massive pulmonary embolism now carries a grade 2B recommendation. Thrombolytic therapy still has a grade 2C recommendation for select patients with submassive pulmonary embolism.

Second, the Moderate Pulmonary Embolism Treated With Thrombolysis (MOPETT) trial is described as a randomized trial in patients with moderate pulmonary hypertension and right ventricular dysfunction. I would like to point out that right ventricular dysfunction was not a criterion for enrollment in the trial.⁴

Finally, catheter-directed thrombolytic therapy is mentioned as an option for select patients with submassive and massive pulmonary embolism. The advantage is believed to be due to local action of the drug with fewer systemic effects. Since the protocol involves alteplase for 12 or 24 hours with a maximum dose of 24 mg, and since in most cases pulmonary embolism originates in the lower extremity, are we not exposing these patients to further clot propagation for 12 or 24 hours without the benefit of concomitant systemic anticoagulation or an inferior vena cava filter?

ANUP KATYAL, MD
Mercy Hospital
St. Louis, MO

■ REFERENCES

1. **Ataya A, Cope J, Shahmohammadi A, Alnuaimat H.** Do patients with submassive pulmonary embolism benefit from thrombolytic therapy? *Cleve Clin J Med* 2016; 83:923–932.
2. **Kearon C, Akl EA, Comerota AJ, et al; American College of Chest Physicians.** Antithrombotic therapy for VTE disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(suppl 2):e419S–e494S.
3. **Kearon C, Akl EA, Ornelas J, et al.** Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016; 149:315–352.
4. **Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdiour M; "MOPETT" Investigators.** Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). *Am J Cardiol* 2013; 111:273–277.

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IN REPLY: We thank Dr. Katyal for his thoughtful comments.

Dr. Katyal points out that the grade of recommendation for thrombolysis in patients with massive pulmonary embolism was upgraded from 2C to 2B in the 2016 American College of Chest Physicians (ACCP) guidelines¹ compared with the 2012 guidelines² that we cited. The upgrade in this recommendation was owing to 2 small trials and 1 large randomized controlled trial that included patients with submassive pulmonary embolism.^{3–5} Interestingly, these 3 studies led to an upgrade in the level of recommendation for thrombolysis in the treatment of massive pulmonary embolism, perhaps more from a safety aspect (in view of the incidence of major bleeding vs mortality). Regardless, Dr. Katyal is correct in highlighting that the new 2016 ACCP guidelines now give a grade of 2B for thrombolytic therapy in the treatment of massive pulmonary embolism. These guidelines had not been published at the time of submission of our manuscript.

Dr. Katyal is also correct that patients were not required to have right ventricular dysfunction to be enrolled in the MOPETT trial.³ As we pointed out, “Only 20% of the participants were enrolled on the basis of right ventricular dysfunction on echocardiography, whereas almost 60% had elevated cardiac biomarkers.”⁶

Regarding catheter-directed therapy, patients who received low-dose catheter-directed alteplase were also concurrently anticoagulated with systemic unfractionated heparin in the Ultrasound-Assisted, Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism (ULTIMA) trial.⁷ The ULTIMA trial authors commented that unfractionated heparin was started with an 80-U/kg bolus followed by an 18-U/kg/hour infusion to target an anti-factor Xa level of 0.3 to 0.7 $\mu\text{g/mL}$, which is considered therapeutic anticoagulation. The investigators in the SEATTLE II trial⁸ continued systemic unfractionated heparin but targeted a lower “intermediate” anticoagulation target (an augmented partial thromboplastin time of 40–60 seconds), so these patients weren’t completely without systemic anticoagulation either. At our institution,

the current practice is to target an anti-Xa level of 0.3 to 0.7 $\mu\text{g/mL}$ in patients receiving catheter-directed therapy for large-volume pulmonary embolism.

ALI ATAYA, MD
University of Florida, Gainesville

JESSICA COPE, PharmD
University of Florida, Gainesville

ABBAS SHAHMOHAMMADI, MD
University of Florida, Gainesville

HASSAN ALNUAIMAT, MD
University of Florida, Gainesville

REFERENCES

1. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016; 149:315–352.
2. Kearon C, Akl EA, Comerota AJ, et al; American College of Chest Physicians. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(suppl 2):e419S–e494S.
3. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M; “MOPETT” Investigators. Moderate pulmonary embolism treated with thrombolysis (from the “MOPETT” Trial). *Am J Cardiol* 2013; 111:273–277.
4. Meyer G, Vicaut E, Danays T, et al; PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014; 370:1402–1411.
5. Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. *J Thromb Haemost* 2014; 12:459–468.
6. Ataya A, Cope J, Shahmohammadi A, Alnuaimat H. Do patients with submassive pulmonary embolism benefit from thrombolytic therapy? *Cleve Clin J Med* 2016; 83:923–932.
7. Kucher N, Boekstegers P, Muller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation* 2014; 129:479–486.
8. Piazza G, Hohlfelder B, Jaff MR, et al; SEATTLE II Investigators. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism (The SEATTLE II Study). *JACC Cardiovasc Interv* 2015; 8:1382–1392.

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