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A Painful Medication Reconciliation Mishap

January 1, 2018
Chou R. A Painful Medication Reconciliation Mishap. PSNet [internet]. 2018.
https://psnet.ahrq.gov/web-mm/painful-medication-reconciliation-mishap

Case Objectives

- Recognize that substance use disorders are common in patients with acute pain.
- Understand that substance use impacts the presentation of pain and pain management.
- Recognize naltrexone as a first-line pharmacologic treatment option for alcohol use disorder.
- Discuss the management of naltrexone in patients undergoing surgery.
- Recognize that naltrexone is contraindicated in patients on opioids.

The Case

A 56-year-old woman with a history of alcohol dependence was admitted to the hospital after falling while intoxicated. Prior to this episode, she had been taking naltrexone to treat her alcohol use disorder and had been sober for 3 months. After the fall, a CT scan revealed a fracture of the cervical spine, which required spinal fusion surgery.

Postoperatively, the patient's pain was severe and opioids were initiated for pain control. She was discharged to a skilled nursing facility (SNF) on a long-acting opioid twice a day with a short-acting opioid for breakthrough pain every 6 hours. On admission to the hospital, her naltrexone had been held in anticipation of the fact that she would require opioid therapy for pain control. However, the provider performing medication reconciliation at the SNF restarted her on her home dose of naltrexone (a powerful opioid antagonist), along with the newly prescribed opioid medications. The provider overrode the drug–drug interaction alert regarding the risk of simultaneously prescribing naltrexone and opioids.

While at the SNF, the patient continued to receive naltrexone daily in addition to high-dose opioids. Her pain worsened and remained uncontrolled for most of her time there. The providers at the SNF did not realize that, as a ?-opioid receptor antagonist, the naltrexone was blocking the effect of the opioids, thus explaining why her pain was uncontrolled. The patient was seen in the general medicine clinic for follow-up 3 weeks after being discharged from the SNF, and the medication error was quickly recognized. Her primary care physician instructed her to stop the naltrexone, to halve the total opioid dose to prevent an

overdose, and to return to clinic for close follow-up in 2 days.

The Commentary

by Roger Chou, MD

Pain is one of the most common reasons that patients seek medical care. Almost everyone experiences moderate to severe acute pain at some point, often related to an injury, surgical procedure, or medical condition. Nearly 100 million surgeries take place annually in the United States; more than 80% of surgical patients report postoperative pain.(1) Over 60% of emergency department visits are related to pain.(2) Adequate treatment of acute pain is necessary to reduce suffering and health care utilization, and to reduce the risk of progression to chronic pain.(3) However, studies have shown that fewer than half of postoperative pain patients receive adequate pain relief.(1)

Substance use disorders are also common. In 2015, the prevalence of alcohol use disorder in the US was estimated at 6.2%.(4) About 10.1% of Americans age 12 years and older report use of an illicit substance within the last month.(5) Substance use disorders are even more common among hospitalized patients (19%–26%) and those with major trauma (40%–60%).(6) The presence of a substance use disorder impacts the presentation and management of pain. Patients with substance use disorders may have lower tolerance to painful stimuli, slower resolution of pain after surgery, and a high prevalence of psychiatric comorbidities such as depression, anxiety, and sleep disturbance that can affect the severity of pain, coping behaviors, and response to treatments.(6-8) Patients with a substance use disorder and chronic pain may self-medicate with alcohol, opioids, or other drugs and substances.(6,9) This use can provide analgesia or be perceived as helping with coping, which can reinforce substance use behaviors.

Treatment is critical for reducing the adverse health, social, and other consequences of alcohol use disorders. However, it is estimated that fewer than 10% of patients who meet criteria for alcohol use disorder receive formal treatment.(10) Treatments for alcohol use disorder include psychosocial as well as pharmacologic approaches. Naltrexone is a first-line pharmacologic option for treatment of both alcohol and opioid use disorders. It is recommended in persons with moderate or severe alcohol use disorder as an alternative or adjunct to psychosocial treatments.(10) Naltrexone principally exerts its effects through blockade of the ?-opioid receptor (which modulates the reinforcing effects of alcohol) and therefore blocks the euphoric and sedating effects of opioids.(10) Naltrexone does not precipitate alcohol withdrawal; therefore, it can be initiated while a patient is still drinking.

Naltrexone is usually administered as an oral medication, though monthly injectable formulations are also available. Its use is associated with a reduction in the risk of heavy drinking (relative risk 0.83 compared with placebo, 95% confidence interval 0.76–0.90) and with a reduction in the number of drinking days (~4% decrease), number of heavy drinking days (~3% decrease), and amount of alcohol consumed (~11% decrease).(11) Naltrexone is considered relatively safe, though its adverse effects include nausea, headache, and dizziness (all of which often resolve with ongoing use), as well as a risk of liver enzyme elevations.(10,11) The optimal duration of naltrexone therapy is not known, though therapy is usually recommended for at least 6 months.(10) Because naltrexone blocks opioid effects, it cannot be used in persons with alcohol use disorder who are on long-term opioid therapy, as it will precipitate opioid

withdrawal and cause reversal of analgesic effects. In persons being treated with naltrexone for opioid use disorder, opioids must be tapered before initiation of naltrexone.

Acamprosate, which acts on glutamate receptors, is another pharmacologic option for treatment of alcohol use disorder. It has long been used in Europe and was approved by the US Food and Drug Administration for this indication in 2004. Its effectiveness appears to be similar to that of naltrexone (12), although some more recent trials have not found beneficial effects on alcohol use outcomes.(13-15) Another pharmacologic option is disulfiram, which inhibits the metabolism of alcohol's primary metabolite, resulting in unpleasant symptoms after drinking.(10) Evidence supporting effectiveness of disulfiram is limited and compliance can be a challenge due to its mechanism of action. Therefore, it is not considered a first-line option and may be most effective when used in motivated patients under supervised circumstances.(10,16) Other medication options supported by limited evidence and not approved for treatment of alcohol use disorder include the antiseizure medications topiramate and gabapentin, baclofen, selective serotonin reuptake inhibitors, and ondansetron.

The patient described in this case experienced trauma resulting in a neck fracture requiring surgery. She was being treated successfully with naltrexone for alcohol use disorder at the time of her injury. Appropriately, naltrexone was held at the time of hospital admission to facilitate pain management with opioids. The blocking effects of oral naltrexone are reduced by about 50% at 72 hours.(9,17) Therefore, under ideal circumstances, oral naltrexone should be discontinued at least 72 hours prior to elective or nonurgent surgery. However, such discontinuation is not possible in urgent or emergent cases such as this one. In patients on injectable naltrexone, discontinuation a month prior to surgery is optimal. In cases in which naltrexone cannot be discontinued according to the above parameters, much higher doses of opioid agonists are required to achieve analgesia. Although human data are lacking, animal studies suggest that opioid doses necessary to overcome naltrexone blocking effects to control pain may be 6 to 20 times higher than doses required without naltrexone.(18) Even when oral naltrexone is discontinued 72 hours prior to surgery, required opioid doses are often higher due to residual opioid blocking effects.(17) Multimodal approaches for postoperative pain management that include nonopioid medications, regional anesthetic techniques, and nonpharmacologic therapies may help improve pain control and reduce opioid requirements.(3) Close monitoring and rapid tapering of opioids may be required to avoid respiratory depressant effects as ?-blockade effects of naltrexone dissipate, and consultation with a pain service is suggested if available.

Following discharge to the skilled nursing facility (SNF), this patient was restarted on naltrexone while simultaneously on opioids for post-operative analgesia, a medication error. Predictably, the naltrexone blocked the opioid analgesic effects, resulting in inadequate pain control for 3 weeks. The primary care clinician in this case recognized the error and appropriately discontinued the naltrexone and restarted an opioid at a lower dose. Evidence is lacking on optimal strategies for tapering opioids, which should be based on the severity and duration of pain expected for the injury and procedure, as well as on the pain status of the patient. A recent study found that for common surgical procedures, the average duration of opioid prescriptions ranged from 4 to 15 days, though surgery for neck fracture was not addressed.(19) Another study found that the number of opioid pills prescribed on the day before discharge was the strongest predictor of the amount of opioids required following discharge.(20) Given the nature of her injury and surgical procedure, and her complicated course (with a period of abrupt uncontrolled pain), it would be

reasonable to taper this patient off of opioids starting in 1 to 2 weeks. As no tolerance is likely given the short duration of opioid exposure, opioids could be rapidly tapered (e.g., reduction by 20%–25% of the starting dose every 1–2 days) without risk of withdrawal. The patient should be restarted on naltrexone following the discontinuation of opioids.

The providers at the SNF attempted to satisfy medication reconciliation issues while ignoring a warning on the interaction between naltrexone and opioids, likely a classic example of alert fatigue. This error could have been avoided if the providers had heeded the warning. A potential method to prevent an unwarranted simultaneous prescribing of naltrexone and an opioid is to automatically trigger a consultation with a pharmacist or specialist in pain or addiction medicine when both medications are prescribed.

Take-Home Points

- Substance use disorders are common in persons with acute pain and impact the presentation and management of pain.
- Naltrexone is a first-line pharmacologic treatment for alcohol use disorder and works by blocking the effects of opioid ?-receptors.
- In patients undergoing elective surgery who are likely to require postoperative opioid therapy, oral naltrexone should be discontinued at least 72 hours prior to surgery.
- Patients on naltrexone at the time of surgery or in whom naltrexone was recently discontinued require higher doses of opioids for analgesia. Multimodal techniques to control pain, close monitoring, and pain service consultation are suggested.
- To avoid withdrawal symptoms, do not restart naltrexone for management of alcohol use disorder until opioids have been discontinued.
- Avoid coprescribing of naltrexone in a patient on opioids can be avoided by heeding drug–drug interaction alerts in the electronic health record. Such situations can create complex management decisions, and consultation with a pharmacist or pain management specialist can be helpful.

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Faculty Disclosure: Dr. Chou has declared that neither he, nor any immediate member of his family, has a financial arrangement or other relationship with the manufacturers of any commercial products discussed in this continuing medical education activity. In addition, the commentary does not include information regarding investigational or off-label use of pharmaceutical products or medical devices.

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This project was funded under contract number 75Q80119C00004 from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services. The authors are solely responsible for this report's contents, findings, and conclusions, which do not necessarily represent the views of AHRQ. Readers should not interpret any statement in this report as an official position of AHRQ or of the U.S. Department of Health and Human Services. None of the authors has any affiliation or financial involvement that conflicts with the material presented in this report. View AHRQ Disclaimers