Opioid-induced hyperalgesia (OIH) is a key factor in the clinical management of patients experiencing pain. However, limited knowledge exists regarding the specific mechanisms involved in OIH and its treatment. A thorough assessment is usually required, and clinical diagnosis is mainly determined by exclusion in medical practice. Patients who are taking opioids should receive ongoing, comprehensive assessment by a clinician. Early identification of OIH will lead to improved patient outcomes.

**AT A GLANCE**

- Understanding OIH is essential to the clinical management of patients with cancer experiencing pain.
- Although a comprehensive assessment of pain is usually required, diagnosis of OIH primarily occurs through exclusion, with opioid rotation being the fundamental method of treatment.
- The early recognition and diagnosis of OIH is essential for treatment effectiveness and better patient results.

Because of progressively worsening tumor-related pain, a 48-year-old woman with metastatic spindle cell sarcoma was referred to palliative care services. She was prescribed methadone (Dolophine®) twice daily and hydromorphone (Dilaudid®) as needed for breakthrough pain, but required frequent dose escalations. Gabapentin (Neurontin®), celecoxib (Celebrex®), and dexamethasone (Decadron®) were added, providing temporary relief. Following cancer surgery, the previous pain regimen with hydromorphone administered via epidural delivery system failed to control her pain. She was diagnosed with opioid-induced hyperalgesia (OIH) and transferred to the intensive care unit for a ketamine (Ketalar®) infusion.

**Opioid-Induced Hyperalgesia**

In the clinical management of cancer-related pain, opioids are the most frequently prescribed type of analgesia. Unfortunately, long-term use of opioids, gradual increase of dosages, or rapid dose titrations may lead to a phenomenon called OIH (Tompkins & Campbell, 2011). OIH is a state of nociceptive sensitization caused by exposure to large doses of opioids during a prolonged period of time, or by rapid dose titrations in patients who have been on them for a short period of time (Leal, Clivatti, Garcia, & Sakata, 2010; Raffa & Pergolizzi, 2012; Ramasubbu & Gupta, 2011). OIH is a paradoxical response to opioid agonists, resulting in an increased perception of pain rather than analgesia. Possible mechanisms behind OIH include activation of N-methyl-D-aspartate (NMDA) receptors; activation of prostaglandins, cytokines, and chemokines; changes in descending facilitation and intensifications in dynorphin levels; increases in antiopioid peptides; and activation of the mechanistic target of rapamycin (Leal et al., 2010; Lutz, Nia, Xiong, Tao, & Bekker, 2015; Pasero & McCaffery, 2012; Raffa & Pergolizzi, 2012). Although the mechanisms behind OIH are not completely understood, OIH may be part of an adaptive response, and which patients are at higher risk remains unclear (Treister, Eisenberg, Lawental, & Pud, 2012).

**Assessment**

Hyperalgesia plays an important role in the clinical management of patients with pain. Because limited knowledge exists regarding the specific mechanisms involved, OIH is mainly a diagnosis of exclusion in clinical practice, and assessment is essential for an accurate diagnosis. The first step is a thorough pain assessment. Advanced practice nurses (APNs) must determine whether (a) the patient has increased sensitivity to pain and (b) the nature of the pain extends beyond the preexisting anatomic area. In OIH, increased pain coincides with escalation in opioid titrations or opioid administration. Therefore, a thorough and accurate assessment by the clinician will improve patient outcomes.
because the treatment regimens can be tailored to the patient’s needs (Pasero & McCaffery, 2012).

Clinical symptoms of hyperalgesia include heightened sensitivity to painful stimuli, worsening pain even with increasing opioid doses, pain that becomes more widespread, and pain that extends beyond the distribution of the preexisting pain (Leal et al., 2010; Ramasubbu & Gupta, 2011). A review of the patient’s medication profile, particularly the use of opioid and non-opioid medications, as well as symptoms and diagnostic tests should occur, along with ongoing comprehensive assessment of pain and physical assessment.

**Diagnosis**

Diagnosis of OIH is made by ruling out all other causes for pain unrelieved by opioids, including worsening pain pathology, opioid tolerance, opioid withdrawal, and pseudo-addiction (Pasero & McCaffery, 2012). The presentation of worsening pain in a patient with cancer may suggest disease progression (Pasero & McCaffery, 2012). Imaging scans and other diagnostic tests should be performed to evaluate disease status. OIH should be considered if pain persists, regardless of disease state, and if the use of opioid rotation and/or increases in opioid dosages are required for persistent pain.

Although tolerance is expected with long-term opioid use for cancer-related pain, it is generally handled by increasing the opioid dose, applying opioid rotation, or combining opioids like methadone with morphine to manage pain (Pasero & McCaffery, 2012). In OIH, the APN must ascertain whether the pain is actually made worse with a dosage increase. Opioid withdrawal results in increased pain and appears similar to OIH (Pasero & McCaffery, 2012). This results in pain presenting as more diffuse and extending beyond the existing site of the pain. If increasing the dose provides relief, this rules out OIH.

Opioid-addictive disease is associated with pain that is more widespread and extends beyond the distribution of the preexisting pain (Pasero & McCaffery, 2012). The behaviors of patients with addiction issues are characterized by inability to control opioid use, request of opioids from multiple providers, or repeat unauthorized escalations in dose, despite discussions with the patients about these behaviors. Pseudo-addiction is a mistaken diagnosis of addictive disease in patients with undertreated pain who manifest behaviors similar to those of addictive disease (Pasero & McCaffery, 2012). The behaviors of pseudo-addiction resolve when the pain is better managed.

**Management**

Multiple strategies exist for managing suspected OIH. Opioid rotation is a common intervention that introduces a different opioid while the original opioid is gradually withdrawn through dose reduction. This strategy allows the APN to lower the analgesic requirement by using incomplete cross-tolerance between opioids (Pasero & McCaffery, 2012; Ramasubbu & Gupta, 2011). Incomplete cross-tolerance between opioids suggests that the new opioid may result in more pain relief at a lower dose, but may also cause more adverse effects. Therefore, decreasing the dose of the new opioid is reasonable.

Another suggested management strategy is cessation of the opioid. Discontinuing the opioid needs to be done in a logical stepwise process, which also incorporates opioid rotation, the use of other pharmacologic agents, and the use of interventional pain management, like local or regional anesthesia. This strategy, along with other pharmacologic agents, may reduce OIH (Pasero & McCaffery, 2012).

Ketamine is an NMDA receptor antagonist that may reduce development of OIH (Leal et al., 2010; Raffa & Pergolizzi, 2012; Ramasubbu & Gupta, 2011; Treister et al., 2012; Winegarden, Carr, & Bradshaw, 2016). When NMDA receptors are activated, glutamate is released, which results in the inward flow of calcium, increasing the activity of protein kinase C; phosphorylation; and the inactivation of the opioid receptors (Leal et al., 2010). Ketamine prevents the NMDA receptor from releasing glutamate, which activates the calcium channel and is a major contributor to central sensitization and OIH (Leal et al., 2010). It has been used at subtherapeutic anesthetic doses for reversal of OIH (Ramasubbu & Gupta, 2011; Winegarden et al., 2016).

Methadone is a weak NMDA antagonist that can also be useful in the treatment of OIH (Carullo, Fitz-James, & Delphin, 2015). In addition, methadone also acts as a mu- and delta-opioid receptor agonist. Like ketamine, methadone helps to reduce neuronal excitability (Carullo et al., 2015; Pasero & McCaffery, 2012; Ramasubbu & Gupta, 2011). Methadone is also used as a second-line agent in palliative care for opioid rotation in opioid tolerance (Pasero & McCaffery, 2012). High doses of methadone actually overcome the NMDA effect and result in increased pain (Ramasubbu & Gupta, 2011).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the postoperative period as an adjunct to opioids in pain management. NSAIDs induce analgesia by inhibiting cyclooxygenase, which plays an important role in prostaglandin synthesis (Pasero & McCaffery, 2012; Leal et al., 2010; Ramasubbu & Gupta, 2011). A review of the patient’s medication profile, particularly the use of opioid and non-opioid medications, as well as symptoms and diagnostic tests should occur, along with ongoing comprehensive assessment of pain and physical assessment.
Opioid rotation should be the first intervention to address OIH (Pasero & McCaffery, 2012; Ramasubbu & Gupta, 2011). In addition, NSAIDs block prostaglandin synthesis and raise the threshold for transduction at the peripheral afferent fibers. When NSAIDs are used as an adjunct, lower opioid dosages may be implemented to achieve pain control and prevent the onset of OIH. In addition to NSAIDs, the use of other adjuvant pharmacologic agents (e.g., alpha agonists, amantadine [Symmetrel®], anticonvulsants, antidepressants, buprenorphine [Buprenex®], skeletal muscle relaxants) may also help to lower opioid dosages and decrease OIH.

Implications for Practice and Conclusion
The treatment of OIH can be challenging, intense, and time consuming. The balance between optimally managing pain and avoiding the complication of OIH is pivotal. Every patient who is receiving opioid and other analgesics should have an ongoing comprehensive assessment and evaluation of pain management. Early identification of OIH will lead to timely, more efficient management. As more is learned about the mechanisms of OIH, assessment and diagnostic parameters promote earlier recognition and better treatment.

The risk of OIH increases in patients with chronic pain receiving opioids that must be dose-adjusted. The patient should be advised that OIH is a side effect of opioid therapy that can occur when initiating opioid for the management of cancer pain. Clinicians need to be informed of what symptoms and behaviors might suggest OIH and the avenues for pharmacologic management. Interdisciplinary approaches are also helpful; these may include psychological and psychiatric methods to address issues of addiction and coping, interventional pain management for assistance with regional or local anesthesia, and integrative medicine to provide nonpharmacologic enhancements to pain management.

Ann Guastella, MS, ARNP, AOCNP®, and Jessica Latchman, MSN, ARNP, AOCNP®, are advanced RN practitioners in the Supportive Care Medicine Department at H. Lee Moffitt Cancer and Research Institute, and Cindy S. Toft Hansen, PhD, ARNP, AOCNP®, FAANP, is an associate professor and director of oncology in the College of Nursing at the University of South Florida, all in Tampa. Guastella can be reached at ann.guastella@moffitt.org, with copy to CJONEditor@ons.org.

The authors take full responsibility for this content and did not receive honoraria or disclose any relevant financial relationships. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Oncology Nursing Society.

REFERENCES

Note. Based on information from Pasero & McCaffery, 2012; Winegarden et al., 2016.