

UNIVERSITY WISCONSIN-MADISON SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Diversifying the Pain Management Toolbox: A Review of IV Lidocaine and Oral Mexiletine as Non-opioid Options

by *Stephaney Cheng, 2022 PharmD Candidate, Katie M. Fermanich, 2022 PharmD Candidate, Sommer L. Gay, 2022 PharmD Candidate, Jillian M Kolasinski, 2022 PharmD Candidate*

In 2017, the US Department of Health and Human Services declared the opioid epidemic a public health emergency.¹ The following year, approximately 10.3 million Americans misused prescription opioids, highlighting the need for safe and effective alternative pain management options.

One solution to the growing epidemic is the use of intravenous (IV) lidocaine for the management of both acute and chronic pain.^{2,3} Lidocaine is a class 1B sodium channel blocker and produces analgesia and anti-inflammatory effects at low doses.³ Lidocaine is commonly used as a local injection, and increasingly used via IV to manage perioperative pain.² Intravenous lidocaine has additionally been used in the management of neuropathic pain, fibromyalgia, burns and other pain conditions, and may reduce or even eliminate the need for opioids in both acute and chronic pain management.^{3,4}

Another pain management alternative is mexiletine, the oral analogue of lidocaine. Similar to lidocaine, mexiletine is a class 1B sodium channel blocker with analgesic properties useful in the treatment of neuropathic pain.⁵ Currently, mexiletine usage in chronic pain therapy is limited due to a perceived lack of efficacy and tolerability.⁴ One study demonstrated that a stronger response to IV lidocaine was predictive of patient acceptance of mexiletine.⁵ Additionally, mexiletine provides unique benefits as an oral therapy in comparison to lidocaine, which may not be delivered orally due to high first-pass metabolism.⁴ Although it is not commonly used as a first-line option, mexiletine can be considered as a safe alternative to opioids

for chronic pain management.

The purpose of this article is to raise pharmacists' awareness of the use and benefits of two non-opioid pain management medications, IV lidocaine and oral mexiletine.

Clinical Indications and Administration

Currently, intravenous lidocaine is clinically indicated for local or regional anesthesia as well as treatment of ventricular arrhythmias.⁶ However, its potential off-label uses show promise in the world of refractory pain conditions. Sodium channel blockers, such as lidocaine, are commonly used to interrupt pain signal transmission. Through this mechanism, lidocaine therapy can have an impact on refractory neuropathic pain,⁷ diabetic neuropathy, post-operative pain,⁸ and migraine.⁹ A meta-analysis of IV lidocaine for neuropathic pain by Tremont-Lukats et al. demonstrated modest benefits over placebo, which were more apparent at doses of 5mg/kg and above.

Despite its beneficial effects, IV lidocaine is not an appropriate option for every patient. The analgesic is not advised to be used in patients with underlying heart conditions due to QT prolongation.⁹ Lidocaine is hepatically metabolized primarily by CYP1A2 and partially by CYP3A4, and thus should be used cautiously with other drugs that might induce or inhibit these same enzymes. For this same reason, the healthcare team should take precautions when dosing patients with liver dysfunction. Serum concentrations above 5 mg/ml lower the seizure threshold and should also be

avoided in patients at risk of seizure or with a history of epilepsy.¹⁰ Additionally, patients often must fail other first- or second-line pain relief options, such as antidepressants, gabapentin, tramadol, topical agents, and other anticonvulsants before lidocaine infusion can be considered.⁹

One limiting factor in the availability of IV lidocaine for patients are the complexities associated with its administration. Lidocaine infusions or injections must be administered in a clinic setting to provide appropriate patient monitoring. Prior to therapy, a patient's reaction to lidocaine is measured with a test to rule out any allergic reactions or adverse effects. On the initial visit, a test dose of 5 mg/kg is infused over one hour followed by a 30-minute monitoring period.⁹ While the patient is in clinic, it is appropriate to measure their vitals, conduct an assessment of their current pain, and note any adverse effects they might experience. The cost of lab testing and availability of chairs in the pain clinic are barriers to patients receiving this care. Often, insurance companies will not cover the cost of lidocaine infusion. When making a therapeutic decision, the cost of the procedure should be weighed against the quality-of-life improvements that stand to be gained from this non-opioid option.

Mexiletine provides an alternative therapy for refractory pain, especially in patients who benefit from IV lidocaine, although its tolerability limits its use. Studies of neuropathic pain show a median dose of 600mg of mexiletine delivers a marginal improvement in pain intensity visual analog scale over placebo.⁷ One prospective and one retrospective cohort study indicate that response to lidocaine

therapy can predict mexiletine's usefulness in that patient.^{4,11} This correlation can help maximize the benefit of this medication by choosing the patient population for whom it is most likely to work. However, its practicality as an off-label pain reliever is limited by adverse events. Its side-effect profile includes nausea and vomiting with a reported incidence of up to 40% as well as dizziness, drowsiness, and anxiety but at lower rates.¹² Potential candidates for mexiletine include patients whose pain responds well to lidocaine therapy and can tolerate the drug. While this option might not work for all patients, the ability to manage the medication from home lessens the burden on the healthcare system.

Benefits of Opioid Alternatives

The Centers for Disease Control and Prevention (CDC) states that between the years of 1999 and 2017 almost 400,000 people died from an overdose involving opioids. Considering the high-stakes consequences associated with opioids, opioid therapy is an important issue for the healthcare system in the United States.¹³ The use of non-opioid medications has the potential to demonstrate statistically significant pain improvement compared to pain management with opioids, without the consequences associated with opioids, such as addiction, tolerance, and even death. Thus, opioid pain management should be used as a last-line treatment plan for refractory pain.¹⁴ Pharmacists can further support healthcare providers with evidence-based guidelines outlining the benefits of non-opioid therapies including IV lidocaine and oral mexiletine.

Intravenous lidocaine is considered a relatively safe drug that acts as an analgesic and an anti-inflammatory agent that might have a role in pain relief after trauma or surgery by decreasing the need for other opioid medications. Forouzan and colleagues studied the use of IV lidocaine compared to morphine sulfate in pain management in bone fractures.³ The subjects' pain was scored from 1 to 10 using a visual analog scale (VAS). A pain score reduction of at least 3 points was required for the treatment to be considered successful. Success in decreasing

pain severity 12 minutes after injection was 49.28% in the lidocaine group and 33.57% in the morphine sulfate group. Similar results were also found when comparing the level of decreased pain 30 minutes post injection.³ The physiologic risks associated with lidocaine therapy are relatively low, in comparison to morphine sulfate. Lidocaine toxicity can produce bradycardia, hypotension, headache, nausea, and muscle weakness. Mexiletine, as previously stated, is an oral analogue of lidocaine and has been shown to be relatively safe and effective in treatment of pain associated with fibromyalgia, erythromelalgia, postoperative pain, and other chronic disease states.¹⁵ Wu et. al, conducted a study to evaluate the change in pain intensity while using mexiletine compared to both morphine and placebo in patients with post-amputation pain. The study found that patients' self-reported pain relief during treatment was, on average, 53% with morphine, 30% with mexiletine, and 19% with placebo.¹⁶ This shows that mexiletine was more effective in reducing pain scores than placebo, yet not as effective as morphine. While morphine should be reserved for patients with refractory pain, mexiletine would be sufficient for non-refractory pain.

Pharmacist Role

The CDC developed guidelines aimed at primary-care clinicians who are prescribing opioids for chronic pain. The recommendations address appropriate initiation of therapy, decisions about dosing regimens, discontinuing therapy, and proper assessment of the risk-to-benefit ratio of continued opioid use.¹⁷ As front-line healthcare providers, pharmacists have a role in both the inpatient and outpatient setting for assessing and managing pain. Within healthcare teams, pharmacists can recommend other analgesics over opioids to help ensure a decrease in use of opioids. Implementing organizational guidelines targeted to reducing opioid use has been effective in reducing emergency department and discharge opioid use and reducing the length of stay.¹⁸ With access to inpatient records, pharmacists can monitor patients for recommendations to switch to non-opioid therapies, such as IV lidocaine, to decrease the use of opioids.

Upon initiation, pharmacists can play an important role in the monitoring of patients in clinic for their first dose and addressing adverse events immediately. Another area to be further studied involves the transition of lidocaine infusions to home administration, expanding the use of non-opioid therapies for pain management. With expanding roles in home healthcare, this could be a new service for pharmacists to help with pain management.

Therapeutic interchange from IV lidocaine to oral mexiletine further involves pharmacists in the monitoring of patients upon initiation and with continued use for adverse events. As an oral analgesic alternative, mexiletine can offer benefits patients perceive as valuable, such as ease of administration and reduced costs associated with returning to the clinic for lidocaine infusions. Although not a first-line therapy, its safety profile and ease of use should prompt its clinical use before opioid therapy.

Use of non-opioid therapies over opioid counterparts is an important shift that healthcare providers need to take advantage of to combat the opioid crisis and associated consequences. There needs to be a balance between reasonable pain management and the risks of opioid abuse when evaluating patients for alternative therapies.¹⁹ There is a significant deficiency in services for community pharmacists in chronic pain management, but with increasing demand for non-opioid therapy, it creates an opportunity for pharmacists to take advantage of and help optimize patient quality of life.

Stephaney Cheng, Katie Fermanich, Sommer Gay, and Jillian Kolasinski are Third Year Doctor of Pharmacy Candidates at the University of Wisconsin-Madison School of Pharmacy in Madison, WI.

PR This article has been peer-reviewed.
The contribution in reviewing is greatly appreciated!

Disclosure: The authors declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

References

1. "What is the U.S. opioid epidemic?" U.S. Department of Health and Human Services. Published online September 4, 2019. Accessed January 24, 2019. <https://www.hhs.gov/opioids/about-the-epidemic/index.html>
2. Mayhew A, Argaez C. Intravenous lidocaine for chronic pain: a review of the clinical effectiveness and guidelines. Canadian Agency for Drugs and Technologies in Health. 2018;1-22.
3. Forouzan A, Barzegari H, Motamed H, Khavanin A, Shiri H. Intravenous lidocaine versus morphine sulfate in pain management for extremity fractures; a clinical trial. *Emergency (Tehran, Iran)*. 2017;5(1):e68.
4. Romman A, Salama-Hanna J, Dwivedi S. Mexiletine usage in a chronic pain clinic: indications, tolerability, and side effects. *Pain physician*. 2018;21(5):E573-579.
5. Carroll IR, Kaplan KM, Mackey SC. Mexiletine therapy for chronic pain: survival analysis identifies factors predicting clinical success. *J Pain Symptom Manag*. 2008;35(3):321-326. doi: 10.1016/j.jpainsymman.2007.04.022
6. Lexicomp. Lidocaine (Systemic). Accessed October 10 2020.
7. Tremont-Lukats IW, Challapalli V, McNicol ED, Lau J, Carr DB. Systemic administration of local anesthetics to relieve neuropathic pain: a systematic review and meta-analysis. *Anesth Analg*. 2005;101(6):1738-1749. doi:10.1213/01.ANE.0000186348.86792.38
8. Kranke P, Jokinen J, Pace NL, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. *Cochrane Database Syst Rev*. 2015(7):CD009642. doi: 10.1002/14651858.CD009642.pub2.
9. UW-Health. Systemic lidocaine for the treatment of pain - adult/pediatric - inpatient/ambulatory/emergency department clinical practice guideline. October 2019. Accessed October 10 2020.
10. Detoleto JC, Minagar A, Lowe MR. Lidocaine-induced seizures in patients with history of epilepsy: effect of antiepileptic drugs. *Anesthesiology*. 2002;97(3):737-739. doi:10.1097/00000542-200209000-00031
11. Galer BS, Harle J, Rowbotham MC. Response to intravenous lidocaine infusion predicts subsequent response to oral mexiletine: a prospective study. *J Pain Symptom Manage*. 1996;12(3):161-167. doi: 10.1016/0885-3924(96)00126-1
12. Lexicomp. Mexiletine. Accessed November 20 2020.
13. Opioid overdose. Centers for Disease Control and Prevention. Published March 19, 2020. Accessed April 1, 2020. <https://www.cdc.gov/drugoverdose/epidemic/index.html>
14. Tucker HR, Scaff K, McCloud T, et al. Harms and benefits of opioids for management of non-surgical acute and chronic low back pain: a systematic review. *Br J Sports Med*. 2020;54(11):664. doi:10.1136/bjsports-2018-099805
15. Marmura MJ. Intravenous lidocaine and mexiletine in the management of trigeminal autonomic cephalalgias. *Curr Pain Headache Rep*. 2010;14(2):145-150. doi:<https://doi.org/10.1007/s11916-010-0098-6>
16. Wu CL, Agarwal S, Tella PK, et al. Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial. *Anesthesiology*. 2008;109(2):289-296. doi:10.1097/ALN.0b013e31817f4523
17. 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. doi: 10.15585/mmwr.rr6501e1
18. Minhaj FS, Hoang-Nguyen M, Tenney A, et al. Evaluation of opioid requirements in the management of renal colic after guideline implementation in the emergency department. *Am J Emerg Med*. 2019;38(12):2564-2569. doi: 10.1016/j.ajem.2019.12.042
19. Kang I, Urick B, Vohra R, Ives TJ. Physician-pharmacist collaboration on chronic non-cancer pain management during the opioid crisis: a qualitative interview study. *Res Social Adm Pharm*. 2019;15(8):1027-1031. doi: 10.1016/j.sapharm.2019.04.052

Thermo HeartBeat™

Receive an email alert up to 30 days in advance of a refrigeration unit's failure to maintain proper temperature and take action before an issue occurs.

Reduce stress and strain and prevent inventory loss and expensive after-hours repairs with OneEvent.



FREE Guide
or
Learn More

OneEventTech.com
sales@oneeventtech.com or call (855) 528-8324

2020 Recipients of the “Bowl of Hygeia” Award



Barry Rich
Alabama



Robert Kronenberg
Arizona



Mike Smets
Arkansas



Robert Scheidtman
California



Debra Devereaux
Colorado



Mark Petrucci
Connecticut



Hooshang Shanehsaz
Delaware



Humberto Martinez
Florida



Drew Miller
Georgia



Wendy Iwasaki
Hawaii



David Mikus
Illinois



Tom DeVille
Indiana



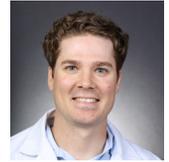
Peter Fay
Iowa



Mike Bellesine
Kansas



Bob Oakley
Kentucky



Stephen Hill
Louisiana



Kevin Holland
Maine



Carol Stevenson
Maryland



Todd Brown
Massachusetts



Carrie Germain
Michigan



Kendra Metz
Minnesota



Ann Franklin
Mississippi



Marty Michel
Missouri



Howard Beall
Montana



Christopher Shaffer
Nebraska



Daniel Heller
Nevada



Thomas Algozzine
New Hampshire



Ed Rucki
New Jersey



Chris Woodul
New Mexico



Amina Abubakar
North Carolina



David Sandberg
North Dakota



Troy Gahm
Ohio



Linda Howrey
Oregon



Gerard O'Hare
Pennsylvania



Tracey Taveira
Rhode Island



Tenny Moss
South Carolina



Doug Johnson
South Dakota



Roger Davis
Tennessee



Takova Wallace-Gay
Texas



Paige Patterick
Utah



Rob Carpenter
Vermont



Mark Vaughan
Virginia



Don Downing
Washington



Jose Diaz-Luna
Washington DC



Ron Mabie
Wisconsin



Antoinette Brown
Wyoming

Photo Not Available
Roger Paganelli
New York



The Bowl of Hygeia award program was originally developed by the A. H. Robins Company to recognize pharmacists across the nation for outstanding service to their communities. Selected through their respective professional pharmacy associations, each of these dedicated individuals has made uniquely personal contributions to a strong, healthy community. We offer our congratulations and thanks for their high example. The American Pharmacists Association Foundation, the National Alliance of State Pharmacy Associations and the state pharmacy associations have assumed responsibility for continuing this prestigious recognition program. All former recipients are encouraged to maintain their linkage to the Bowl of Hygeia by emailing current contact information to awards@naspa.us. The Bowl of Hygeia is on display in the APhA History Hall located in Washington, DC.