Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-industry-feature/expert-perspectives-in-acute-pain-management-strategies-advancements-in-care/13061/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Expert Perspectives in Acute Pain Management Strategies & Advancements in Care

Announcer:
You're listening to ReachMD.

This Medical Industry Feature examining Expert Perspectives in Acute Pain Management Strategies and Advancements in Care is sponsored by Trevena.

Dr. Jones:
Welcome!

Today, we've got a great program discussing acute pain management strategies in perioperative care with two leading experts: Dr. Joseph Answine, an anesthesiologist, and Dr. Timothy Beard, a general surgeon. This program is intended for US healthcare professionals. I'm your host, Dr. Barbara Joy Jones.

Advancing age. Obesity. Renal impairment. Comorbidities such as these are just a few of the more common patient characteristics that can complicate perioperative care and acute postoperative pain management. When opioid-free multimodal analgesia is not sufficient, what clinical gaps exist in the use of conventional IV opioids with these clinically challenging patients? And can OLINVYK®, also known as oliceridine, injection, the first IV opioid advancement in decades,[1] be considered the turning point for the IV opioid class.

Dr. Jones:
Joining me today are Drs. Timothy Beard and Joseph Answine to share their perspectives on this important topic.

Dr. Beard is a general surgeon and certified by the American Board of Surgery and a Fellow of the American College of Surgeons. He works for Summit Medical Group in Bend, Oregon, and holds a faculty position at Oregon Health and Sciences University. Dr. Beard, welcome to the program.

Dr. Beard:
Thank you. Happy to be here.

Dr. Jones:
Dr. Answine is an anesthesiologist in Harrisburg, Pennsylvania, and is part of a large private-practice group. He holds an active teaching appointment at Penn State and is affiliated with multiple hospitals in the area, including UPMC Pinnacle and Penn State Health Milton S. Hershey Medical Center. Dr. Answine, it's great to have you here today.

Dr. Answine:
And it's great to be here. Thank you for giving me the opportunity to speak to you.

Dr. Jones:
Before we begin, let's take a moment to review some important safety information.

Announcer
OLINVYK is an opioid agonist indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. OLINVYK has a boxed warning with risks of addiction, abuse and

misuse; life-threatening respiratory depression; neonatal opioid withdrawal syndrome; and risks from concomitant use with benzodiazepines or other central nervous system depressants.[2]

Dr. Jones:
Dr. Answine, let's start with you. Can you tell us about your anesthesiology practice and how it's informed your current views on acute pain management?

Dr. Answine
Sure. I've been a practicing anesthesiologist at a private practice in Pennsylvania for twenty-nine years, and I also have an active teaching appointment at Penn State. I specialize in treating morbidly obese patients, and as you can imagine, many of them develop additional comorbidities, such as advanced cardiac disease. These are the patients that I consider clinically challenging. Their condition or advanced disease state oftentimes requires surgery or another type of painful intervention[3] such as open abdominal procedures or thoracotomies. Procedures such as these cause deep, visceral pain, and opioid-free multimodal analgesia is simply not enough in these cases. The intense postoperative pain in these types of procedures requires IV-opioid-level pain control.

Clinically challenging patients and the procedures they undergo can cause additional concerns in the operating room and in the PACU.[4] That's because these patients are at greater risk for opioid-related adverse events such as nausea, vomiting, and respiratory depression. These risks can make managing severe acute pain in clinically challenging patients quite difficult.

Dr. Jones:
Thanks, Dr. Answine. That paints a very clear picture of some of the difficulties you face in your practice today. Clearly, if IV opioids are still needed in certain patient types and procedures, an unmet need persists in the IV opioid class.

Dr. Beard, are you seeing similarities in your practice today?

Dr. Beard:
In my practice, I handle a wide variety of cases, and I agree with Dr. Answine that in looking back over the years, the trends show that patients are becoming more high-risk; and what I mean by that is, the patients I'm treating today are more challenging because of their conditions and comorbidities.

The changing demographic of our patient populations has also coincided with an increased overall demand for surgical and postoperative care.[4] We've seen a shift in the setting and number of surgeries performed. And more recently, we've been moving more surgical patients from hospitals to outpatient surgery centers. This is both a testament to advances in surgical care and a logistical necessity based on continuing growth in surgical volume despite limited hospital capacities.[4]

- For example, I may see a patient who is morbidly obese and develops an inflamed gallbladder that requires a laparoscopic cholecystectomy. This otherwise complicated procedure is now being shifted to the outpatient setting. For these clinically challenging patients, a procedure like this would have previously only been performed in the hospital or inpatient setting. And I'm seeing more and more of this in my practice.

And there are even greater issues facing healthcare today as we navigate the COVID-19 pandemic. There are millions of backlogged procedures due to limiting elective cases to prevent the spread of infection.[5]

While an outpatient setting is designed to handle patient and surgical volume, it is crucial that acute pain in these settings is managed effectively to ensure timely recovery for discharge while mitigating risks for adverse events.

Dr. Answine
The science behind OLINVYK, also known as oliceridine, is based on Nobel Prize-winning chemistry in biased ligand technology.[6] This emerging science is a major development for the IV opioid class. Biased ligand technology allows for the preference of the G-protein pathway over β-arrestin at the mu-opioid receptor.[7,8] OLINVYK is a full-opioid agonist that is relatively selective for the mu-opioid receptor, a G-protein-coupled receptor, or GPCR.[2,9] This kind of selectivity has the potential to have a significant impact on opioid therapeutic pharmacology.[8,10]

However, it is important to recognize that the clinical evidence to support this hypothesis isn't yet fully established in humans. Having said that, any advancement to the IV opioid class is exciting given the safety profile and reputation of conventional IV opioids.

Dr. Jones:
Thank you for that, Dr. Answine. It's been a long time since we've seen any major improvements to the class. Dr. Beard, how do you

see OLINVYK advancing IV opioids and impacting acute pain management strategies?

Dr. Beard:
Let me start by sharing my experience. When I do colon resections, I typically use a medication with patients to offset or minimize the side effects of IV opioids. More specifically, I'm using anti-nausea medications prophylactically at the same time I am administering an IV opioid to manage pain. Essentially, it is like administering a treatment for the treatment. So, to me, it is very exciting to see an advancement to the IV opioid class as the science progresses. OLINVYK feels like a step in the right direction.

The most striking feature about OLINVYK is its rapid onset of action—approximately 1 to 3 minutes after the initial dose, with a half-life of 1.3 to 3 hours.[2] I think this is a key feature that we're very excited about. The idea is that we would be able to give patients OLINVYK intraoperatively and then postoperatively. In fact, we're currently exploring this in our outpatient surgery center and the goal is to minimize patient recovery time. Postoperative patients are uncomfortable, and a fast onset of relief could potentially help them reach their next milestone.

Dr. Jones:
Thank you, Dr. Beard. Dr. Answine, can you elaborate on how the safety and tolerability for OLINVYK was studied?

Dr. Answine:
Sure. What we know about OLINVYK is that its safety and tolerability have been well established through a strong clinical development program, which included not only the traditional blinded placebocontrolled trials, but also an open-label safety study called ATHENA.

Dr. Answine:
And what I like about the ATHENA study is that it reflects the real world – what I see in my practice. This study was a phase 3, open-label study that evaluated the safety and tolerability of OLINVYK in over 700 patients.[2,11] Many of these patients had BMIs over 30, were older than 65, and all patients had at least one underlying comorbidity.[2,11]

Dr. Answine:
The data from ATHENA showed that OLINVYK was very well tolerated. Most adverse events reported were mild or moderate in severity, and the most common ones were nausea, constipation, and vomiting. For our patients, by far the most serious complication that we are concerned about is opioid-induced respiratory depression. It is compelling that in this study in over 700 patients, when given as part of a multimodal analgesic regimen, there was not a single use of naloxone in patients taking OLINVYK.[11] That's really interesting data in my estimation.

And it's great to see the data show that OLINVYK was well tolerated, with less than 5% of patients discontinuing from lack of efficacy and only 2% of patients discontinuing use due to adverse events.[11]

Dr. Jones:
Having a large safety study reflective of real-world patients as part of its clinical development program is impressive. Dr. Beard, what has been your clinical experience with OLINVYK? What are you seeing with your patients?

Dr. Beard:
We're starting to use OLINVYK in our high-risk laparoscopic cases at our outpatient surgery center. In the past, we were using a multimodal pain management strategy, and we'd give IV opioids when needed, but you're running a fine line with these clinically challenging patients on how much you can give. A high volume of patients move through our surgery center and managing recovery can be difficult when using conventional IV opioids with these types of patients. We cannot have patients in recovery for hours at a time.

Now with OLINVYK, we're still using the multimodal approach but including OLINVYK in the operating room as well as postoperatively. We're giving a milligram intraoperatively and then another one or two milligram bolus in the recovery room. In our experience using this approach, we are not seeing nausea and respiratory events in our patients the way we've witnessed it in the past. Patients are recovering quickly, and able to be discharged in a reasonable amount of time. This trend suggests that as we gain experience with OLINVYK, we potentially will be able to handle more clinically challenging patients in both outpatient and inpatient settings.

And I just want to echo what Dr. Answine said about how none of the patients receiving OLINVYK required naloxone in the ATHENA trial – that's quite remarkable.[11] Because currently in our hospital, which is average-sized, we still probably have one to two near-codes a month where people have to get naloxone.

Dr. Jones:
Thank you, Dr. Beard. Dr. Answine, let me turn to you for the final word as we close out our program. What is your personal perspective on the clinical value that OLINVYK brings and its role in the ERAS protocols?

Right now, our postoperative recovery guidelines are shaped by ERAS protocols that focus on opioid-sparing analgesia, and we're going to continue to do that. But many of our clinically challenging patients will likely need IV opioids to address their severe acute postoperative pain.

As with all opioids and other boxed warning products, we have to remain vigilant against known risks associated with use, such as respiratory depression, neonatal withdrawal syndrome, and the risk of misuse, abuse, and addiction.

But considering how promising OLINVYK is, particularly for our clinically challenging patients, both in terms of the safety and tolerability and rapid efficacy in pain relief,[2,11] I think there's a strong case to be made for adding it to our ERAS protocols to give healthcare professionals another option to do what is best for our patients.

Dr. Jones:
Those are meaningful insights to consider as we come to the end of today's program. With that, I want to thank my guests, Drs. Timothy Beard and Joseph Answine, for sharing their perspectives on the acute pain management landscape with respect to clinically challenging patients, and the role of OLINVYK within the IV opioid class given its clinical profile. Dr. Beard and Dr. Answine, it was great speaking with you both.

Dr. Beard:
Thank you. Thanks for having me.

Dr. Answine:
Well thank you. It was great speaking with you as well.

Dr. Jones:
I'm Dr. Barbara Joy Jones. And before we close, let's take a moment to review some important safety information.

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CENTRAL NERVOUS SYSTEM (CNS) DEPRESSANTS

ADDICTION, ABUSE, AND MISUSE
OLINVYK exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing OLINVYK, and monitor all patients regularly for the development of behaviors or conditions.

LIFE-THREATENING RESPIRATORY DEPRESSION
Serious, life-threatening, or fatal respiratory depression may occur with use of OLINVYK. Monitor for respiratory depression, especially during initiation of OLINVYK or following a dose increase.

NEONATAL OPIOID WITHDRAWAL SYNDROME
Prolonged use of OLINVYK during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

RISK FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

INDICATIONS AND USAGE
OLINVYK is an opioid agonist indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate.

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve OLINVYK for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

The cumulative total daily dose should not exceed 27 mg, as total daily doses greater than 27 mg may increase the risk for QTc interval prolongation.

CONTRAINDICATIONS
OLINVYK is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Known hypersensitivity to oliceridine (e.g., anaphylaxis)

WARNINGS AND PRECAUTIONS

- OLINVYK contains oliceridine, a Schedule II controlled substance, that exposes users to the risks of addiction, abuse, and misuse. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OLINVYK. Assess risk, counsel, and monitor all patients receiving opioids.
- Serious, life-threatening respiratory depression has been reported with the use of opioids, even when used as recommended, especially in patients with chronic pulmonary disease, or in elderly, cachectic and debilitated patients. The risk is greatest during initiation of OLINVYK therapy, following a dose increase, or when used with other drugs that depress respiration. Proper dosing of OLINVYK is essential, especially when converting patients from another opioid product to avoid overdose. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status.
- Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia with risk increasing in a dose-dependent fashion. In patients who present with CSA, consider decreasing the dose of opioid using best practices for opioid taper.
- Prolonged use of opioids during pregnancy can result in withdrawal in the neonate that may be life-threatening. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using OLINVYK for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of OLINVYK with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, or alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate, prescribe the lowest effective dose, and minimize the duration.
- OLINVYK was shown to have mild QTc interval prolongation in thorough QT studies where patients were dosed up to 27 mg. Total cumulative daily doses exceeding 27 mg per day were not studied and may increase the risk for QTc interval prolongation. Therefore, the cumulative total daily dose of OLINVYK should not exceed 27 mg.
- Increased plasma concentrations of OLINVYK may occur in patients with decreased Cytochrome P450 (CYP) 2D6 function or normal metabolizers taking moderate or strong CYP2D6 inhibitors; also in patients taking a moderate or strong CYP3A4 inhibitor, in patients with decreased CYP2D6 function who are also receiving a moderate or strong CYP3A4 inhibitor, or with discontinuation of a CYP3A4 inducer. These patients may require less frequent dosing and should be closely monitored for respiratory depression and sedation at frequent intervals. Concomitant use of OLINVYK with CYP3A4 inducers or discontinuation of a moderate or strong CYP3A4 inhibitor can lower the expected concentration, which may decrease efficacy, and may require supplemental doses.
- Cases of adrenal insufficiency have been reported with opioid use (usually greater than one month). Presentation and symptoms may be nonspecific and include nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If confirmed, treat with physiologic replacement doses of corticosteroids and wean patient from the opioid.
- OLINVYK may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is

increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics). Monitor these patients for signs of hypotension. In patients with circulatory shock, avoid the use of OLINVYK as it may cause vasodilation that can further reduce cardiac output and blood pressure.

- Avoid the use of OLINVYK in patients with impaired consciousness or coma. OLINVYK should be used with caution in patients who may be susceptible to the intracranial effects of CO_2 retention, such as those with evidence of increased intracranial pressure or brain tumors, as a reduction in respiratory drive and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy.
- As with all opioids, OLINVYK may cause spasm of the sphincter of Oddi, and may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.
- OLINVYK may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in vulnerable patients. Monitor patients with a history of seizure disorders for worsened seizure control.
- Do not abruptly discontinue OLINVYK in a patient physically dependent on opioids. Gradually taper the dosage to avoid a withdrawal syndrome and return of pain. Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving OLINVYK, as they may reduce the analgesic effect and/or precipitate withdrawal symptoms.
- OLINVYK may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.
- Although self-administration of opioids by patient-controlled analgesia (PCA) may allow each patient to individually titrate to an acceptable level of analgesia, PCA administration has resulted in adverse outcomes and episodes of respiratory depression. Health care providers and family members monitoring patients receiving PCA analgesia should be instructed in the need for appropriate monitoring for excessive sedation, respiratory depression, or other adverse effects of opioid medications.

ADVERSE REACTIONS
Adverse reactions are described in greater detail in the Prescribing Information.

The most common (incidence ≥10%) adverse reactions in Phase 3 controlled clinical trials were nausea, vomiting, dizziness, headache, constipation, pruritus, and hypoxia.

MEDICAL INFORMATION
For medical inquiries or to report an adverse event, other safety-related information or product complaints for a company product, please contact the Trevena Medical Information Contact Center at 1-844-465-4686 or email MedInfo@Trevena.com.

To report SUSPECTED ADVERSE REACTIONS, contact Trevena, Inc. at 1-844-465-4686 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Full Prescribing Information, including Boxed Warning.

Announcer:
This program was brought to you by Trevena. If you missed any part of this discussion or to find others in this series, visit ReachMD.com/IndustryFeature. This is ReachMD. Be Part of the Knowledge.

References
1. Data on file. Trevena, Inc; 2020.
2. OLINVYK. Prescribing information. Trevena, Inc; 2021.
3. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. *Curr Med Res Opin.* 2014;30(1):149-160.
4. American Hospital Association. Trendwatch Chartbook 2020: Supplementary Tables and Data: Utilization and Volume. https://www.aha.org/system/files/media/file/2020/10/Trendwatch Chartbook-2020-Appendix.pdf. Accessed October 7, 2021.
5. Berlin G, Bueno D, Gibler K, Schulz J. Cutting through the COVID-19 surgical backlog. McKinsey & Company. October 2, 2020. https://www.mckinsey.com/industries/healthcare-systems-andservices/our-insights/cutting-through-the-covid-19-surgicalbacklog. Accessed October 7, 2021.
6. Benovic JL. G-protein-couple receptors signal victory. *Cell.* 2012;151(6):1148-1150.
7. Violin JD, Crombie AL, Soergel DG, Lark MW. Biased ligands at Gprotein-coupled receptors: promise and progress. *Trends Pharmacol Sci.* 2014;35(7):308-316.
8. Schmid CL, Kennedy NM, Ross NC, et al. Bias factor and therapeutic window correlate to predict safer opioid analgesics. *Cell.* 2017;171(5):1165-1175.e13.

9. DeWire SM, Yamashita DS, Rominger DH, et al. A G protein-biased ligand at the μ-opioid receptor is potently analgesic with reduced gastrointestinal and respiratory dysfunction compared with morphine. *J Pharmacol Exp Ther.* 2013;344(3):708-717.
10. Siuda ER, Carr R, Rominger DH, Violin JD. Biased mu-opioid receptor ligands: a promising new generation of pain therapeutics. *Curr Opin Pharmacol.* 2017;32:77-84.
11. Bergese SD, Brzezinski M, Hammer GB, et al. ATHENA: a phase 3, open-label study of the safety and effectiveness of oliceridine (TRV130), a G-protein selective agonist at the μ-opioid receptor, in patients with moderate to severe acute pain requiring parenteral opioid therapy. *J Pain Res.* 2019;12:3113-3126.

COM-OLI-2512-v1 12/21