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The Case for IV Opioid Use in Acute Postoperative Pain

### ReachMD Announcer:

Welcome to ReachMD. This Medical Industry Feature, The case for IV Opioid Use in Acute Postoperative Pain is sponsored by Trevena. This program is intended for US Physicians.

Here's your host Dr. Jennifer Caudle.

### Dr. Caudle:

Pressure to reduce opioid use perioperatively has led to gaps in acute postoperative pain control<sup>1,2</sup>. While IV opioids are still a critical component of recovery for some postoperative patients, there's a clear need to balance pain control with minimizing the risk of adverse events<sup>1-4</sup>. So how do surgeons and anesthesiologists maintain this balance, especially in clinically challenging patients? Today, we'll be discussing evolving clinical strategies in acute postoperative pain management, with a focus on a new treatment option, OLINVYK, the first IV opioid advancement in decades<sup>5</sup>.

This is ReachMD, and I'm your host Dr. Jennifer Caudle. And joining me is Dr. Sabry Ayad, Professor of Anesthesiology at the Cleveland Clinic Lerner College of Medicine at Case Western Reserve University in Cleveland, Ohio.

Dr. Ayad, welcome to the program.

### Dr. Ayad:

Great to be with you!

### Dr. Caudle:

Before we begin, let's take a moment to review some important safety information about OLINVYK.

### ReachMD 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<sup>6</sup>. OLINVYK has a black box 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<sup>6</sup>.

### Dr. Caudle:

Dr. Ayad, to start, can you put the current landscape of acute postoperative pain management into perspective for us and the challenges that you and your colleagues face on your patients' behalf?

### Dr. Ayad:

Thanks, Dr. Caudle. I think we first need to consider the current societal opioid crisis in context, since this crisis is both large

and pervasive<sup>1</sup>. But while it emanated largely from inappropriate prescribing, marketing, and misuse of oral prescription opioids<sup>2</sup>, it's become common in the current environment to lose sight of a key factor giving rise to this crisis, which is poorly controlled pain<sup>1</sup>. And this is very much an ongoing issue in surgery and anesthesiology since acute postoperative pain remains poorly treated<sup>1</sup>. In a US survey of 300 adults who had undergone surgery within 5 years of the survey date, 75% reported experiencing moderate-to-severe postoperative pain<sup>4</sup>. But unfortunately, despite this takeaway, we also know that more than 80% of postoperative patients report inadequate pain relief, and that metric has remained largely unchanged over the past 20 years<sup>7</sup>. So this underscores an important role that opioids still play for postoperative analgesia, especially for moderate to severe pain<sup>3</sup>.

**Dr. Caudle:**

But I take it, despite those takeaways, procedural practice is still complicated when it comes to the use of opioid analgesics, is that correct?

**Dr. Ayad:**

That's right. The opioid crisis has put an important emphasis on thoughtfully scrutinizing perioperative opioid use and prescribing, but what we've also seen is a trend toward precipitously reducing or eliminating opioid use in these settings altogether<sup>1</sup>. And this has gone on despite there being no clear evidence that opioid-free strategies benefit patients above and beyond opioid-sparing strategies<sup>8</sup>. Those aren't synonymous terms or approaches, and it's important to distinguish them in practice. Consider non-opioid analgesic agents such as acetaminophen, NSAIDs, local/regional analgesic techniques, and adjuncts such as steroids, gabapentinoids, and ketamine<sup>8</sup>. In the setting of opioid-free analgesia, there is a ceiling effect with these agents and a small therapeutic index for safety<sup>8</sup>; and other than the local/regional analgesic options, we can't titrate these agents to individual patient requirements, which is a necessity during the intraoperative period<sup>8</sup>. These limitations can render non-opioid agents insufficient against moderate to severe pain<sup>2</sup>. So I think there's a lot at stake here in the intraoperative and postoperative settings because, in my experience, if acute surgical pain isn't managed promptly, it can be even more difficult to address later or when this acute pain turns into chronic pain<sup>1</sup>. Some of the patients develop chronic pain following invasive procedures such as laminectomy, hernia repair, thoracotomy, and breast surgery, and these patients are very hard to manage. That's why tackling acute surgical pain in a controlled surgical setting is extremely important<sup>1</sup>.

**Dr. Caudle:**

Can you give us a better sense of the patient populations and factors that influence your postoperative pain management decisions?

**Dr. Ayad:**

Sure. In any assessment of acute postoperative pain management of our patients, we need to balance expected benefits with potential risks. And with IV opioids, that balance centers on delivering effective analgesia alongside acceptable tolerability<sup>9</sup>. So we focus on risks of opioid-related adverse events, or ORAEs, such as nausea, vomiting, ileus, confusion or delirium, and the most serious side effect, respiratory depression<sup>3</sup>.

And we've found that certain patient types may be at higher risk for these ORAEs, which can make for much more challenging clinical management<sup>10</sup>. A large, retrospective database analysis of patients who underwent inpatient surgical procedures and received conventional opioids found several factors that put patients at higher risk of opioid-induced respiratory depression, including comorbid obesity, respiratory conditions, sleep apnea, and older age<sup>10</sup>.

Patients who are older, obese, and/or have multiple comorbidities are particularly challenging for us since they're more likely to experience respiratory depression<sup>10</sup>, so good providers need to keep these factors in mind when evaluating patients ahead of surgery.

**Dr. Caudle:**

And do these postoperative adverse events with conventional opioids impact healthcare systems as well?

**Dr. Ayad:**

Absolutely. The care complications and close management required after patients experience ORAEs can also be associated with substantial increases in healthcare utilization<sup>3</sup>.

A large, retrospective study that assessed clinical and administrative data of patients who underwent inpatient surgery and received opioids found a 25% increase in 30-day readmissions, a 30% increase in length of hospital stay, and a 47% greater total cost of hospitalization in patients who experienced an opioid-related adverse event<sup>3</sup>.

So clearly, from both patient care and healthcare system standpoints, there's an ongoing need to monitor patients carefully to reduce the risk of ORAEs<sup>3</sup>.

**Dr. Caudle:**

Well given this foundation you've provided on the clinical priorities and challenges concerning opioid use in surgical settings, I want to focus now on the emerging role of OLINVYK, which as we talked about earlier represents the first IV opioid advancement in decades<sup>5</sup>. Dr. Ayad, what makes this a novel treatment option among opioids, mechanistically?

**Dr. Ayad:**

OLINVYK, or oliceridine, is a full opioid agonist that features what's called a biased ligand technology which preferentially targets not just specific opioid receptors such as the  $\mu$ -opioid receptor, but the specific signaling pathways *downstream* of those receptors<sup>11,12</sup>. And this is a novel level of selectivity that may lead to a differentiated pharmacology<sup>13,14</sup>.

**Dr. Caudle:**

So let's dive into that pharmacological profile for a moment. What are some key clinical characteristics that stand out for you regarding this treatment option?

**Dr. Ayad:**

OLINVYK has been very well-studied from a strong clinical program consisting of more than 1900 patients<sup>6,15-17</sup>. Early phase trials have shown that OLINVYK has a rapid onset of analgesia with the median onset of pain relief at one to three minutes after the first dose<sup>6,18</sup>. We talked about clinically challenging patients earlier, including the elderly, obese, and those with comorbidities. And based on the results of a phase 3 open label study called the ATHENA Trial<sup>17</sup>, OLINVYK's safety profile was established in these patient populations<sup>6,17</sup>. It also has no active metabolites, which provides a predictable level of analgesia and reduced dose stacking concerns<sup>6,19</sup>. Plus, with simple flexible dosing, there are no dose adjustments needed in patients with renal impairment<sup>6,19</sup>, which is different from the conventional opioids that we use. So features like these are actually very exciting when seen in clinical practice.

**Dr. Caudle:**

You spoke to the ATHENA trial just now. Can you give us some more details on that study and what was uncovered there?

**Dr. Ayad:**

Sure. ATHENA was a phase 3, multicenter, open-label clinical study that evaluated the safety and tolerability of OLINVYK<sup>®</sup> in 768 patients with moderate to severe acute pain warranting the use of a parenteral opioid<sup>6,17</sup>.

Treatment duration for each patient was determined by the clinical need for parenteral opioid therapy, but the maximum duration of treatment was limited to 14 days<sup>17</sup>.

The “End of treatment” period was within 24 hours after the last dose of OLINVYK, while the posttreatment follow-up period was limited to 3 days unless any serious adverse events occurred, at which point that patient would be followed until it was resolved<sup>17</sup>.

I mentioned an important differentiator in this study compared to what’s usually seen in controlled clinical trials, in that the ATHENA study population included a good representation of clinically challenging patients<sup>6,17</sup>.

Many of these patients had a BMI greater than 30 and were older than 65, and all patients included in ATHENA had at least one underlying comorbidity, providing a good representation of what happens in the real world<sup>6,17</sup>.

Many patients also received prophylactic antiemetics and multimodal analgesics such as acetaminophen, NSAIDs, or gabapentinoids along with OLINVYK<sup>17</sup>. But those receiving OLINVYK didn’t receive other opioids during their treatment period<sup>17</sup>.

The data from ATHENA showed that OLINVYK was very well tolerated<sup>17</sup>. Most adverse events reported were mild or moderate in severity, and the most common ones were nausea, constipation, and vomiting<sup>6</sup>.

Interestingly, the incidence of adverse events in the obese and elderly population was similar to that of the overall population<sup>17</sup>, which was something that differentiated OLINVYK from what is seen in the literature with conventional opioids<sup>20</sup>.

Only 2 percent of patients had adverse events leading to early discontinuation<sup>17</sup>, and none of the patients receiving OLINVYK needed to use naloxone during treatment<sup>17</sup>, which further highlights this treatment’s safety profile.

**Dr. Caudle:**

Great insights on that clinical trial, Dr. Ayad, thank you. Now, my last question to you: looking ahead, how do you see OLINVYK changing the practice of acute pain management where an IV opioid is needed, especially for patients with complex clinical needs?

**Dr. Ayad:**

Well, from my vantage point, OLINVYK, with its unique pharmacology<sup>13,14</sup> and established safety profile, is a new option to treat moderate to severe acute intraoperative or postoperative pain for the clinically challenging adult patients that I see in practice every day. So I think that adding OLINVYK to our ERAS protocols will be a very good way of enhancing our acute post-surgical pain management, and I’m looking forward to seeing the impacts of this treatment across all types of surgeries. But as a reminder, as with all opioids and other Black Box warning products, there are certain risks associated with use, including respiratory depression, neonatal withdrawal syndrome, and the risk of misuse and addiction.

**Dr. Caudle:**

Well, with those forward-looking insights in mind, I very much want to thank my guest, Dr. Sabry Ayad, for helping us better understand the role of IV opioids in acute postoperative pain management, and the emergence of OLINVYK as a treatment option for clinically challenging patients. Dr. Ayad, it was great speaking with you today.

**Dr. Ayad:**

It’s been a pleasure. Thank you so much.

**Dr. Caudle:**

I’m Dr. Jennifer Caudle. And before we close, let’s take a moment to review some important safety information.

**ReachMD Announcer:**

**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.

**RISKS 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<sub>2</sub> retention, such as those with evidence of increased intracranial pressure or brain tumors, as a reduction in respiratory drive and the resultant CO<sub>2</sub> 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  $\geq 10\%$ ) 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](mailto: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](http://www.fda.gov/medwatch).

Please see [Full Prescribing Information](#), including Boxed Warning.

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