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Media reports tend to blame the public health crisis of prescription opioid misuse and overdose on clinicians prescribing opioids in excess of clinical need, even though overprescribing was not the sole cause of the problem.1-3 At the same time, policymakers struggle to develop balanced policies that address the opioid crisis, which also safeguard appropriate patient access and clinicians’ ability to individualize treatment decisions based on patients’ needs.1-3 Caught in the middle are legitimate ability to individualize treatment decisions based on patients’ needs.1-3

During this roundtable discussion, the faculty responded to five questions, several of which focused on the CDC Guideline for Prescribing Opioids for Chronic Pain. “The majority of recommendations in the CDC guideline are really just good practice and good medicine,” began Martin D. Cheatle, PhD, Associate Professor and Director, Pain and Chemical Dependency Program, Center for Studies of Addiction, Perelman School of Medicine, University of Pennsylvania, in Philadelphia, Pennsylvania. “However, there has been some controversy around the CDC guideline. We’re going to try to address this from a policy perspective and from a clinical perspective.”

Question #1: The CDC suggests that opioids are not first-line or routine therapy for chronic pain. How realistic is it in many communities to first try a range of non-drug and non-opioid therapies?

The CDC found that that there is no evidence for the long-term effectiveness of opioids for chronic pain because no study evaluated outcomes for longer than 1 year.4 However, pain experts have noted that lack of evidence does not mean that opioid therapy is not effective for anyone with chronic pain.5,6 Indeed, other common pharmacologic and behavioral therapies for chronic pain recommended in the CDC guideline have not been studied over longer intervals than opioids.6 “I think all of us who practice in the field of pain management realize that opioids are not first-line for the majority of pain conditions,” explained Dr. Cheatle. “However, a subgroup of patients does benefit from opioids.”

Bill H. McCarberg, MD, Adjunct Assistant Clinical Professor, University of California at San Diego School of Medicine, San Diego, California, agreed that opioids should not be the first-line treatment for chronic pain. “We start with a workup, do an NSAID typically, maybe acetaminophen, send them to physical therapy … before we even think about an opioid,” he explained. However, often insurers will not pay for treatments that the CDC recommends as first- or second-line for chronic pain before opioids, such as cognitive behavioral therapy (CBT), biofeedback, relaxation, and interdisciplinary rehabilitation. “Suggesting that we do alternatives that aren’t available or are out-of-pocket isn’t very helpful for us,” said Dr. McCarberg.

However, when other treatments have failed, Dr. McCarberg noted that fewer primary care providers (PCPs), to whom the CDC opioid guideline is targeted, are now willing to prescribe opioids for any patient with chronic pain. Many quote guidelines, flawed systematic reviews, or media stories to claim there is no evidence to support such use.5,7 Dr. McCarberg, who has a unique perspective as a family medicine physician and pain specialist with decades of experience, explained that many PCPs now refer patients who could be appropriately managed in primary care to pain specialists. Although the medical home for a patient who is at high risk for substance abuse or has multiple comorbidities would be better served by a specialist, Dr. McCarberg argued that the majority of low-risk chronic pain patients who are doing well on opioids can be managed by PCPs, with help and guidance from a specialist when needed. PCPs must get the education necessary to follow the best practices that go along with prescribing any controlled medication, but he emphasized that pain specialists should also develop relationships with PCPs to help avoid inappropriate referrals, because there are not enough pain medicine specialists to manage the population of patients with chronic pain. “Just by the sheer numbers, primary care have to be the medical home for most of them,” said Dr. McCarberg. In Washington, after consultation with a pain management specialist before exceeding 120 morphine milligram equivalents (MME)/day became required, many PCPs reported great difficulty accessing pain specialty consultation, and some PCPs stopped prescribing opioids for chronic pain.8 This left some patients without access to the opioids they had taken responsibly for years.9

Michael C. Barnes, Esq, Managing Attorney, DCBA Law & Policy, Washington, DC, emphasized that providers should document in the patient’s medical record the legitimate medical need for opioids, results with nonpharmacologic or lower-risk noncontrolled pharmacologic options that were tried before moving onto controlled substances, and approaches used to manage risk. He suggested that providers document when the patient cannot afford certain therapies, but also include in the medical record that they directed the patient to walk for 30 minutes for exercise or advised the patient to lose weight, for example. “From my perspective dealing with the DEA and medical boards looking at controlled substance prescribers, the best piece of practical advice that I can give is to make a note of the individual’s unique life narrative,” said Mr. Barnes. “Know what is going on in that person’s life and document it … That factual information is probably going to be what will save the day if the time comes when you have to defend your decision.” This is consistent with recommendations in the CDC guideline, such as setting and reassessing realistic goals for pain and function to ensure that the opioid regimen and overall treatment plan is effective for the patient and improving his or her quality of life.

Question #2: The CDC recommends that prescribers carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 MME/d, and avoid increasing dosage to ≥90 MME/d or carefully justify decision. What effect is this recommendation having in practice?

“I think we would all agree it is probably more risky to have people on higher doses than lower doses in a population,” said Dr. McCarberg. But for an individual
patient whose opioid dose has been gradually increased over time based on clinical response, who is benefiting from a higher dose without onerous adverse effects or significant harm, and who does not take other medications or have comorbidities that increase overdose risk, being on 150 MME/day, for example, may be no more risky than 90 MME/day. Although the CDC guideline provides recommendations rather than requirements that are binding on clinicians, if such a patient has an untoward event, the concern is that a prosecutor or a plaintiff’s attorney will use the CDC dosage threshold as a standard of practice. All three faculty agreed that it is essential for providers to document a clear justification for deviating from the CDC guideline for an individual patient, based on a combination of the available medical scientific literature, best practices in the field, and clinical experience. “This goes back to that initial notion of the individual’s narrative,” said Mr. Barnes, such as the specific functional improvements that result from a higher opioid dosage.

Several state legislators and medical boards have created prescribing policies containing opioid dosage thresholds, that are either statutes/rules (mandatory) or guidelines (recommendations).11 The state thresholds frequently differ from the CDC guideline; for example, Washington requires a documented consultation with a pain management specialist before exceeding 120 MME/day, in Maine clinicians may not exceed 100 MME/day, and the California Medical Board recommends that providers proceed cautiously and consider consultation above 80 MME/day.11,14 Inconsistent dosage thresholds coupled with the absence of MME thresholds from the current product labeling for opioid analogesics and the variability in patient responsiveness to opioids have the potential to create confusion and hinder optimal opioid prescribing.11,15 Mr. Barnes stressed that providers must know what rules apply to them, and be aware of new state legislation in this rapidly changing landscape. Typically, the good laws allow clinicians to use their expertise and clinical judgement and document in the medical record their justification for deviating from the threshold.

There are also anecdotal reports of the CDC recommendations becoming de facto requirements when insurers use the dosage thresholds to deny or impose hurdles to coverage (eg, prior authorization), creating barriers for prescribers to use their clinical judgment when treating their patients.11,15

**Question #3: Is the CDC guideline a burden or benefit to prescribers and patients?**

The CDC checklist outlines what should be done when considering long-term opioid therapy and when reassessing therapy at a return visit (Table 1). “Yes, primary care has to do things that we weren’t doing before,” said Dr. McCarberg. “But most of these steps are not onerous, and specialists perform those things every day.” However, for PCPs who have less time with patients than pain specialists, and also have to address a multitude of other problems during the visit, another checklist to complete may seem overwhelming. “I hear repeatedly from primary care physicians: ‘I don’t feel comfortable doing it in the first place, and now I have to follow all these rules—I’m just going to stop,’” said Dr. Cheatle. However, Dr. McCarberg suggested it shouldn’t be daunting. “Primary care completes checkboxes all the time for other chronic diseases, whether it be diabetes or hypertension,” he said. “Is that onerous? No, we do it and we don’t complain about it—it’s just getting into the routine.” For pain specialists, checking the prescription drug monitoring program (PDMP) when prescribing an opioid or determining whether the risk-benefit ratio favors a higher dose before increasing a patient’s dose have become second nature. “Don’t underestimate your value in teaching the primary care provider, who really should be doing this work because chronic disease management is what primary care are trained to do,” said Dr. McCarberg. “They give up and refer, never seeing that patient again for that chronic pain issue, when they don’t feel competent enough.” Pain specialists can help make them competent by being available for consultation, sending the patient back with useful information on the referral that PCPs can utilize and include in the chart, and being willing to take the patient back again if necessary. “Give the primary care guidance so that they continue to do the appropriate thing, and when they’re not, help them learn what they should be doing,” he said.

The CDC guideline received enormous media attention, and policymakers tend to hold CDC recommendations in high regard, which can influence their own efforts to develop statutes and rules.11 Mr. Barnes noted that when states adopt opioid prescribing legislation based on the CDC guideline recommendations, it can help promote

### Table 1. Checklist for prescribing opioids for chronic pain for PCPs treating adults with chronic pain ≥3 months, excluding cancer, palliative, and end-of-life care\(^1\)

<table>
<thead>
<tr>
<th>When CONSIDERING long-term opioid therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Set realistic goals for pain and function based on diagnosis (eg, walk around the block).</td>
<td></td>
</tr>
<tr>
<td>□ Check that non-opioid therapies tried and optimized.</td>
<td></td>
</tr>
<tr>
<td>□ Discuss benefits and risks (eg, addiction, overdose) with patient.</td>
<td></td>
</tr>
<tr>
<td>□ Evaluate risk of harm or misuse.</td>
<td></td>
</tr>
<tr>
<td>• Discuss risk factors with patient.</td>
<td></td>
</tr>
<tr>
<td>• Check prescription drug monitoring program (PDMP) data.</td>
<td></td>
</tr>
<tr>
<td>• Check urine drug screen.</td>
<td></td>
</tr>
<tr>
<td>□ Set criteria for stopping or continuing opioids.</td>
<td></td>
</tr>
<tr>
<td>□ Assess baseline pain and function (eg, PEG scale).</td>
<td></td>
</tr>
<tr>
<td>□ Schedule initial reassessment within 1–4 weeks.</td>
<td></td>
</tr>
<tr>
<td>□ Prescribe short-acting opioids using lowest dosage on product labeling; match duration to scheduled reassessment.</td>
<td></td>
</tr>
</tbody>
</table>

| If RENEWING without patient visit |  |
| □ Check that return visit is scheduled ≤3 months from last visit. |  |

| When REASSESSING at return visit |  |
| Continue opioids only after confirming clinically meaningful improvements in pain and function without significant risks or harm. |  |
| □ Assess pain and function (eg, PEG); compare results to baseline. |  |
| □ Evaluate risk of harm or misuse: |  |
| • Observe patient for signs of oversedation or overdose risk. |  |
| – If yes: Taper dose. |  |
| • Check PDMP. |  |
| • Check for opioid use disorder if indicated (eg, difficulty controlling use). |  |
| – If yes: Refer for treatment. |  |
| □ Check that non-opoid therapies optimized. |  |
| □ Determine whether to continue, adjust, taper, or stop opioids. |  |
| □ Calculate opioid dosage morphine milligram equivalent (MME). |  |
| • If ≥50 MME/day total (≥50 mg hydrocodone; ≥33 mg oxycodone), increase frequency of follow-up; consider offering naloxone. |  |
| • Avoid ≥90 MME/day total (≥90 mg hydrocodone; ≥60 mg oxycodone), or carefully justify; consider specialist referral. |  |
| □ Schedule reassessment at regular intervals (≤3 months). |  |
safer care of patients, particularly by PCPs who are not experts in pain management. But he cautioned that when state legislation does not allow providers to document in a patient’s medical record their rationale for deviating from a regulation, it may be harmful to patients. “All patients are not better off—many probably are, but we also know anecdotes about patients who have committed suicide and people who are turning to the streets,” said Mr. Barnes.

**Question #4: Should prescribers be required to check their state PDMP?**

Some, but not all, states require prescribers to check their state PDMP when prescribing opioids. However, Mr. Barnes stressed that prescribers should take this extra step of risk mitigation before prescribing any controlled medication, and then periodically thereafter. Dr. McCarberg, who performs medical-legal defense work for PCPs and pain specialists, agreed. “That’s one of the things that they look at every single time: ‘Was the PDMP checked? What did you do with that information? Did you follow up appropriately?’” he said. “In this climate, where it’s available in all states except Missouri, not checking it is not defensible.”

However, Dr. Cheatle has encountered PCPs in Pennsylvania who are concerned that new legislation requires them to check their PDMP every time they prescribe an opioid. “I’m hearing: ‘This is the final straw, I can’t do this anymore, so I’m not going to write opioids,’” he said. But Dr. McCarberg compared it to looking up the Hba1c for a patient with diabetes during an office visit. “Does the doctor say ‘Oh no, that’s way too much, I can’t look it up?’” he asked. “No, looking it up become part of the culture of seeing that particular patient.” Specialists can help PCPs to integrate checking the PDMP into their practice. “When I come into my office, I have PDMP reports on my desk for all my patients that day on chronic opioid therapy,” said Dr. McCarberg. “If I have to look one up when I’m in the office, I can do it in 90 seconds.”

**Question #5: What can we do to shift the focus from politics to patients?**

Pain advocates hoped that the 2011 Institute of Medicine (IOM) report—Relieving Pain in America—would bring much needed attention to chronic pain.3,5 “It pointed out where we’ve been failing patients in terms of pain management,” said Dr. Cheatle. The National Pain Strategy, published in March 2016, advanced the IOM recommendations.6 However, the CDC guideline was published just days before, focusing the attention of the media, the public, clinicians, and policymakers on the opioid epidemic rather than chronic pain.7 “With all the news around the CDC guideline and the opioid epidemic, everybody is talking about people dying and nobody about people improving on opioids,” said Dr. McCarberg. He encouraged providers to stand up for the rights of patients that do better on an opioid.

Clinicians are being urged to consider nonopioid treatments to manage chronic pain, but insurers that pay for drugs, but not physical therapy, psychotherapy, acupuncture, or massage, drive then to use treatments that may be less effective.8 “What you can do as providers to shift the focus back to the patients is help with insurance appeals and help empower patients—or at the very least connect patients with a patient advocacy group that can serve as insurance watchdogs or ombudsmen—to appeal unjust coverage denials for what you know is the best treatment,” said Mr. Barnes. “Push back against a lot of the patient-unfriendly policies and practices that are in place and complicating your practices and more importantly, patients’ lives.” Clinicians should consider advocating for policy changes that facilitate access to comprehensive pain management encompassing both pharmacologic and nonpharmacologic modalities, and encourage patients confronted with access barriers to do the same.9,10 Clinicians who educate policymakers about the impact of overly restrictive policies to prevent opioid misuse on their ability to individualize clinical judgment for each patient and the voices of patients with pain who can describe barriers to their ability to access essential treatment are compelling.9

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8. Ingold J. Chronic pain patients say they are hurt by Colorado’s opioid prescription guidelines. Some Colorado doctors are refusing to prescribe opioids to chronic pain sufferers. The Denver Post. October 6, 2016.
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A Framework for Successful Intrathecal Pain Management: New Insights from the 2017 Polyanalgesic Consensus Conference (PACC) Guidelines

Introduction

Once perceived to be a management approach reserved for salvage therapy—the final straw—after failure of oral high dose opioids, intrathecal drug delivery (IDD) has been established as a cost-effective and efficacious pain management strategy for patients with refractory chronic pain. As the use of IDD expands, there is a need to reduce variability among health care providers in medications that are used, patient selection, trialing, and dosing in order to improve safety and patient outcomes.

To standardize care, the Polyanalgesic Consensus Conference (PACC) was formed to provide guidance and recommendations to physicians utilizing IDD to promote safe and effective therapy for patients with refractory chronic pain. As new devices were introduced, new evidence emerged, and experience with IDD expanded—identifying both deficiencies and opportunities—the PACC guidelines were updated. The consensus panel determined that evidence and practice for IDD has improved since the last guidelines were published in 2012 requiring an update in the guidance and practice algorithms to meet current gaps in practice. On January 2, 2017, the updated PACC: Recommendations on Intrathecal Drug Infusion Systems Best Practices and Guideline were released.

Authors of the 2017 PACC Guidelines poignantly stated, “Evidence assessment, regardless of the strength, needs interpretation for clinical application whenever used.” A symposium at the American Academy of Pain Medicine annual conference presented a prime opportunity for dissemination and expert translation of the new guidelines, so that pain physicians and their interprofessional teams have the knowledge, confidence, and skills to apply patient-centric strategies to their clinical decision-making in patients with refractory chronic pain.

Faculty and Learning Objectives

The symposium was led by two experts in the field of intrathecal pain management and authors of the PACC Guidelines. Gladstone C. McDowell, II, MD chaired the presentation. Dr. McDowell is the Medical Director of Integrated Pain Solutions in Columbus, Ohio. Dr. McDowell was joined by Jason E. Pope, MD, DABPM, FIPP, President of Summit Pain Alliance in Santa Rosa, California.

The symposium content was designed to address three learning objectives:

1. Translate updates and recommendations in the 2017 PACC Guidelines to clinical decision-making for patients with refractory chronic pain who are candidates for intrathecal therapy.
2. Apply PACC recommendations for trialing of appropriate patients who are candidates for intrathecal therapy.
3. Implement dosing and titration strategies in patients utilizing IDD to maximize results while mitigating risks.

Patient Safety as the Foundation of Care

“Everything that we do should be based upon quality and safety”, stated Dr. McDowell. Pain medicine has learned from the aviation industry the importance of standardizing processes and looking at things differently to ensure that practices mitigate risk. These actions undertaken to protect patients and health care providers are important to prevent harm from health care services. The Institute of Medicine report To Err is Human: Building a Safer Health System revealed that errors cause between 44,000 and 98,000 deaths each year in American hospitals and over one million injuries. Dr. McDowell quoted patient safety pioneer and thoracic surgeon Lucian Leape, MD, “Incompetent people are, at most, 1% of the problem. The other 99% are good people trying to do a good job who make very simple mistakes and it’s the process that set them up to make these mistakes.” Instituting a schema for care promotes patient safety to ensure that clinicians are ordering the right tests, for the right diagnosis, and providing the right treatment followed by close monitoring to ensure it is efficacious or to adjust treatment if there is disease progression, followed by preventive measures to keep people safe and optimize their quality of life.

Evaluating our processes, in light of medical errors, is ongoing. At times, health care providers must hit the reset button and engage in process re-engineering to eliminate opportunities for error and implement safeguards to catch and correct errors before they affect the patient. Structured plans help people recognize an event and take action. In this vein, guidelines provide best practice, evidence-based recommendations for what should be done and algorithms are the structured processes that help guide care. The 2017 PACC Guidelines have been created with both guideline recommendations and algorithms to help guide patient care.

Translating the 2017 PACC Guidelines to Clinical Decision-Making

Many physicians do not follow clinical practice guidelines. Reviewing 76 published articles on barriers to adherence to guidelines, Cabana and colleagues identified awareness, familiarity, agreement, and self-efficacy as barriers to adherence. Other experts propose that it could be because physicians are getting mixed messages about what those best practices really are. These barriers and perceptions indicate a need for education that translates the 2017 PACC Guidelines as clinical decision support tools that include decision making algorithms to meet current gaps in practice.
algorithms and clear direction for patient-centric IT care strategies.

Despite proved durability of IDD, Dr. Pope noted that during his training, there was not clear pathway to give people the tools to succeed and everyone found their own way of doing things. The first PACC Guidelines, and following iterations helped to standardize care. The purpose of the 2017 PACC Guidelines is to create a living document that is continually updated to give people the tools in their armamentarium to succeed.

The 2012 PACC Guidelines had some deficiencies that authors sought to remedy in the 2017 version. Previously, there was no clear method for qualifying the evidence behind the recommendations—was it consensus or graded evidence? Prior PACC guidelines did not tailor algorithmic approaches to patient specific characteristics that factor into patient outcomes such as diagnoses, expected survival time, age, risk stratification, previous exposure to opioids, locating of pain, type of pain (nociceptive, neuropathic, or mixed), IT catheter location, psychological status of the patient, and implementation and maintenance of the therapy. To accomplish these goals, authors made sure that they married the disease with patient selection and the implementation of therapy.

To classify the evidence, authors used the U.S. Preventive Services Task Force (USPSTF/Task Force) criteria on evidence level assessment. Level I is at least one controlled and randomized clinical trial, properly designed. Level II-1 reflects a well-designed, controlled, nonrandomized trial. Level II-2 represents cohort or case studies and well-designed controls, preferably multicenter and Level II-3 evidence is multiple series compared over time, with or without intervention, and surprising results in noncontrolled experiences. Finally, Level 3 evidence is defined as clinical experience-based opinions, descriptive studies, clinical observations or reports of expert committees. Based on those level of recommendations, one can levy the degree of recommendation from A (extremely recommendable), B (recommendable), C (neither recommendable nor advisable), D (inadvisable) or I (insufficient, low quality or contradictory evidence). Although not typically done, the authors also classified consensus as strong (greater than 80% consensus), moderate (50%-79% consensus), and weak (less than 49% consensus).

Based on these criteria, the 2017 PACC Guidelines identified Level I evidence, recommendation grade A, and strong consensus to support that IDD be utilized for cancer-related pain with the use of opioids and ziconotide and for noncancer-related pain with ziconotide. Dr. Pope noted key takeaways from the 2017 PACC Guidelines should be that 1) IDD should not be used as salvage therapy for patients failing systemic opioids; and 2) spinal cord stimulation should not be placed before or after IDD, but the choice should be made based on the disease and patient selection criteria.

When looking at medication selection, a differentiating feature between the 2012 and 2017 PACC Guidelines recommendations in localized nociceptive or neuropathic pain, is the use of Line 1-A and 1-B. Line 1-A reflects agents that are FDA-approved, ziconotide and morphine, and have Level 1 evidence, recommendation class A, and strong consensus. Additional recommendations based on evidence and consensus follow Line 1-A, including combination therapy and can be referenced in the publication. The 2017 PACC went one step further than in 2012 by separating pain states as diffuse versus localized and cancer versus noncancer. Similar to localized pain, Line 1-A recommendations are consistent across pain disorders and support the use of FDA-approved agents ziconotide and morphine.

Dr. Pope concluded this section by emphasizing that the purpose of the 2017 PACC was to provide guidance based on established evidence and literature to give people a pathway to offer IDD in a way that is safe and effective.

### Application of PACC Recommendations for Trialing

A screening trial of IDD offers a glimpse into how a patient will respond. The preimplantation trial is considered standard of care and is often required for insurance reimbursement. The PACC recognized that there is no evidence to support the predictive value of trialing with opioids or nonopioids. There are several different trialing methods—single shot trialing, bolus trialing, and continuous infusion—all with equal levels of evidence. PACC recommends a psychological assessment prior to implantation to understand if the patient is a reasonable candidate with reasonable expectations. Patients with an appropriate profile have better outcomes than those deemed inappropriate. Several studies state that depression, hysteria, and hypochondriasis may be present, but that does not constitute a contraindication to implants. Prior to implantation with ziconotide, a behavioral specialist should evaluate patients for exclusion criteria including active psychosis, suicidal or homicidal, uncontrolled depression or other mood disorders, somatization or other somatoform disorders, alcohol or illicit drug dependency, lack of appropriate social support, or neurobehavioral or cognitive deficits that preclude sound decision-making.

Dr. McDowell stated, “One of the most important things we can do is to define the goals of the trial because our goal is achieving success. We want to treat the patients, but we want to be sure we have a happy patient. Together, it is important to establish a few easily achievable goals that we can benchmark. Goals should be shared goals of both the physician and patient.

There is not good Level I data on trialing. Moderate consensus supports trialing in noncancer pain, but it may not be necessary in cancer pain. If a trial is performed, there is strong consensus that delivery of the medication within the intrathecal space is an acceptable method. All trials should be monitored in a safe setting, with due diligence. Recommended doses for trialing are outlined in the publication and should be as low as reasonably expected to provide analgesia.
A successful trial is defined as pain relief without side effects. If there is relief with side effects, a reduction in the medication for retrial or medication switch should be considered. If no pain relief and side effects are noted, a medication switch is recommended for retrial. Finally, consider retrial with higher dose or medication switch if no pain relief is achieved and no side effects are experienced.18

New in the 2017 PACC Guidelines, authors addressed site of service for trialing and dosing of IDD. The recommendation is that you can trial with opioids in an outpatient setting with modified dose. The previous recommendation of 12-hour observation in the outpatient setting with ziconotide has been revised, by consensus, to six hours, as long as there is no neurologic dysfunction prior to initiation. An overnight admission is advised for morphine.1

Strategies To Maximize Results While Mitigating Risks

Economic data demonstrate that costs associated with IDD and safety are markedly better compared with systemic opioids.9,10 One of the key safety consensus points of the 2017 PACC Guidelines states that the risk to benefit ratio of IDD makes it a relatively safe therapy for both cancer- and noncancer related pain and compared to chronic, long-lasting opioid therapy, it is markedly more safe and has less associated morbidity and mortality.10

Dr. Pope reviewed the safety profiles of the two FDA-approved agents, morphine and ziconotide. Morphine has demonstrated considerable side effects, but morbidity and mortality of IDD is markedly less compared to long-acting systemic delivery. He cautioned about risk of intrathecal catheter tip granuloma with morphine. Ziconotide should be considered in the first choice in the treatment of cancer or noncancer-related pain in the absence of psychiatric comorbidities or significant baseline renal disease. Studies suggest that ziconotide’s long-term efficacy is greater if it is first in pump, rather than introduced later in IDD. A narrow therapeutic window requires careful and strategic dosing for efficacy and reduction in side effects. Rapid titration has been associated with cognitive and neuropsychiatric adverse events. Finally, ziconotide has not been associated with the formations of granulomas to date.10

Dr. Pope emphasized that the use of IDD is truly a team approach and as such, it is important the there is an awareness of the differences between pumps. This includes among first responders who should be trained to distinguish between pacemakers, spinal cord stimulation devices and implantable pumps so that the patient can be appropriately cared for during a crisis.

Conclusion

Dr. McDowell concluded the presentation by encouraging participants to think of intrathecal therapy earlier rather than either a salvage therapy or consideration of high dose opioids. This is a paradigm shift from using high dose opioids long-term without good data to support it, so providers should think about pumps earlier. “And what we’d really love you to do is please, please, please review, carry with you and integrate the key concepts from these PACC Guidelines.”

References


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The Nuts and Bolts of Coprescribing Naloxone and Implementing an Opioid Emergency Plan in Your Practice

Introduction

Prescription opioid-related fatalities more than quadrupled between 1999 and 2015 in the United States.1 Due to the potentially life-saving nature of the opioid antagonist naloxone, state and federal agencies, professional organizations, and advocacy groups are calling for improved access to naloxone for individuals at risk of experiencing an opioid emergency and life-threatening opioid-induced respiratory depression (OIRD).2-7

The Need to Coprescribe Take-Home Naloxone

“If you’re prescribing opioids, I would argue that you need to be thinking about risk mitigation,” began Mark A. Kallgren, MD, Medical Director of Pain Medicine, at Oregon Anesthesiology Group, PC, Portland, Oregon. Most prescription opioid overdose deaths occur in the decedent’s home, and the vast majority are unintentional.12 OIRD can result in hypoxia, which can lead to severe and permanent brain damage after approximately 4 minutes.2,8 If not treated quickly, prolonged hypoxia may lead to death.2,8 “With an average response time for emergency medical services [EMS] in the US of 9.4 minutes,9 that presents a problem,” said Dr. Kallgren. “If these things start to become irreversible and problematic at 4 minutes, we need to intervene sooner.” Most opioid emergencies in the home are witnessed by a close friend, partner, or family member, who may be in the best position to intervene quickly prior to the arrival of EMS.2

Naloxone

Naloxone has been used in opioid overdose management since it was approved by the Food and Drug Administration (FDA) in 1971, with minimal adverse effects beyond the induction of opioid withdrawal symptoms in patients who are physically dependent on opioids.2,3 This competitive opioid antagonist has a high affinity for mu opioid receptors, rapidly displacing most opioids.2 Timely administration of naloxone can reverse clinical signs of OIRD and reduce associated morbidity and mortality.2,3 Traditionally, it has been administered in medical settings, by trained EMS personnel, and more recently in the harm reduction community.2,3 There have been concerns that prescribing naloxone will promote intentional misuse among opioid users.10,11 However, pilot programs that distribute naloxone to opioid users indicate that this is not the case.10,11 More recently, coprescribing naloxone to patients receiving long-term opioids for chronic pain has been shown to significantly reduce opioid-related emergency department (ED) visits.12

Risk Factors for an Opioid Emergency

There are many risk factors for life-threatening OIRD, beyond just opioid dose (Table 1).2,3,13-22 “We’d love to have a number that we can all hang our hat on and say at X point on the graph everyone needs take-home naloxone,” said Dr. Kallgren. “The simple answer is there is no number.” Comorbidities, opioid-related factors, and concomitant medications (sometimes prescribed by other clinicians) can all increase patient risk, despite good intentions and good medical care.2,3,13-22 The CDC Guideline for Prescribing Opioids for Chronic Pain suggests offering naloxone when opioid doses exceed 50 morphine milligram equivalents (MME)/day.4 However, Dr. Kallgren has treated patients on less than 50 MME/day who are worrisome because of comorbidities or an unstable social environment. “Any patient in my practice who is going to be on long-term opioids is counselled as to why I’m insistent they should have take-home naloxone along with an opioid emergency plan,” he stressed. An opioid emergency may occur in a patient thought to be at low risk if his or her underlying medical condition changes or a medication that depresses the central nervous system (CNS) is added.

“There is also an issue beyond just the intended prescribing consequences paradigm that we are responsible for,” noted Dr. Kallgren, citing the death of a 2-year-old Oregon boy who ingested morphine prescribed for his grandmother.24 Indeed, ED admissions involving accidental ingestion of prescription opioids by children aged 5 years or younger increased by 225% from 2004 to 2011.25

Dr. Kallgren compared coprescribing naloxone when treating chronic pain with opioids as being analogous to defibrillators located in public places, patients at risk of anaphylaxis carrying an epinephrine auto-injector, keeping a fire extinguisher at home, or equipping cars with airbags and seat belts. “Someday we may well look back and say, why would we have ever prescribed an opioid without naloxone at least being available,” he said. “It works, it’s a simple intervention, and I’m going to let Chris [Dr. Gharibo] talk to you about how to make that work in your practice.”

Table 1. Factors increasing risk for life-threatening opioid-induced respiratory depression2,3,13-22

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Opioid-related factors</th>
<th>Concomitant medication/substance</th>
<th>Certain populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute or chronic respiratory disease</td>
<td>Initiation, titration, and rotation</td>
<td>CNS depressants, eg. benzo diazepines</td>
<td>Young children in the household</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>Higher doses</td>
<td>Antidepressants</td>
<td>Elderly, cachectic, or debilitated individuals</td>
</tr>
<tr>
<td>Hepatic/renal impairment</td>
<td>ER/LA opioids</td>
<td>Drugs affecting CYP metabolism</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>Illicit fentanyl</td>
<td>Alcohol: dose dumping</td>
<td></td>
</tr>
<tr>
<td>Substance use disorder</td>
<td>Intrathecal pumps</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Polyopioid use</td>
<td></td>
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</tbody>
</table>

CNS=central nervous system; CYP=cytochrome P450; ER/LA=extended-release/long-acting

CSS SYNOPSIS 12
Initiating an Opioid Emergency Plan

Creating an opioid emergency plan starts with conducting a comprehensive assessment of patients' risk for an opioid emergency, which includes checking the state prescription drug monitoring program to determine if potentially dangerous medication combinations are being prescribed by other clinicians, explained Christopher G. Gharibo, MD, Associate Professor of Anesthesiology, Pain Medicine, and Orthopedics, at NYU School of Medicine, New York, New York. It is also important to assess the home environment, for example, to determine if children live in the home who might intentionally or unintentionally access the patient’s medications, or if any family members have a substance use disorder. This is followed by patient and family education on the need to have an opioid emergency plan in place, as well as coprescribing an FDA-approved naloxone product to reverse opioid effects.

Elements of the opioid emergency plan, which should be shared with friends, partners, and caregivers, include a description of the signs and symptoms of an opioid emergency, where the person's naloxone is kept in case of an emergency, and the patient's known risk factors for an opioid emergency, including the patient's current opioid therapy and other medications that increase the risk. Patients educated on risk factors for OIRD may recognize changes in their medical conditions that could transiently increase their risk for OIRD, and take steps to mitigate that risk. “Let's not minimize the value of education,” stressed Dr. Gharibo. “It does require a comprehensive approach, like opioid prescribing does in general.” The emergency action steps in the plan outline how to respond to an opioid emergency, including administering naloxone, calling 911, and repeating the naloxone dose as needed if signs and symptoms recur.

Take-Home Naloxone Products

Naloxone has been used for decades in the United States, predominantly in medical settings. “But most patients on chronic opioid therapy are not in those facilities,” noted Dr. Gharibo, and opioid emergencies often occur at home. Two FDA-approved take-home naloxone products are now available:

- **EVZIO®** (naloxone HCl) 2 mg Auto-Injector, for intramuscular (IM) or subcutaneous (SC) use only.
- **NARCAN®** (naloxone hydrochloride) 2 mg or 4 mg Nasal Spray, for intranasal (IN) use only.

Improvised IN naloxone kits, which are not FDA approved, consist of injectable naloxone adapted for IN administration by attaching a mucosal atomization device. These kits require the user to be trained on how to assemble all of the materials and administer the naloxone.

**EVZIO Auto-Injector**

EVZIO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or CNS depression in adults and pediatric patients. EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present, but is not a substitute for emergency medical care. EVZIO is supplied as a carton containing one Trainer for EVZIO to practice with and two EVZIO 2 mg auto-injectors, to allow for another dose if needed.

EVZIO is the first and only intelligent take-home 2 mg naloxone auto-injection system with voice and visual guidance designed to help caregivers take fast, confident action administering naloxone in an opioid emergency, including reminding the user to seek emergency medical care. If the electronic voice instruction system does not operate properly, EVZIO will still deliver the intended dose of naloxone when used according to the printed instructions on its label. It is a self-contained system (the auto-injector is prefilled), durable, and portable (small enough to fit in most pockets). EVZIO has an auto-retractable needle so the user does not see the needle before, during, or after injection. It is administered IM or SC by pressing into the outer thigh, through clothing if necessary. It is important to emphasize to patients that EVZIO is not a substitute for emergency medical care.

The usability of EVZIO by laypersons was evaluated before training and approximately one week after training in two randomized, open-label usability studies using a simulated opioid overdose emergency. The studies included three stages:

- **Stage 1**: untrained participants presented with a simulated overdose victim (a mannequin) were instructed to administer a simulated dose of naloxone into the...
mannequin with EVZIO. Participants could rely only on the instructions-for-use found on the product itself.

- **Stage 2**: participants received one-on-one training from a nurse on the correct use of EVZIO.
- **Stage 3**: approximately one week following training, participants’ ability to correctly use EVZIO was evaluated again in an identical opioid emergency scenario simulation.

During Stage 1, 94% of untrained participants correctly administered EVZIO, with an average time to successful administration of 56 seconds.29 “That speaks to the ease of use of the product,” stressed Dr. Gharibo. All participants successfully completed the training on EVZIO.29 During stage 3, approximately one week after training, 100% of participants correctly administered EVZIO, and the average time to successful administration decreased to 35 seconds.29

Because most opioid emergencies occur in the home and are witnessed by friends or family,2 patients should inform those around them about the presence of EVZIO.27 Patients and caregivers or family members should prepare for an opioid emergency by practicing with the Trainer for EVZIO, which contains no needle or medicine, and is black and white to differentiate it from the blue and purple EVZIO.27,32 However, untrained individuals should still attempt to use EVZIO during a suspected opioid emergency while awaiting definitive emergency medical care.27

**Starting the Conversation**

Some clinicians have expressed fear that offering to coprescribe naloxone might offend patients on stable, long-term opioid therapy.33 “In my experience, there hasn’t been pushback,” said Dr. Kallgren, who explains to his patients that it was not mentioned previously because take-home naloxone was not readily available in the past. While nonopioid interventions for chronic pain are preferred, the risk-to-benefit ratio of opioids may make them appropriate.28,29 Nonopioid interventions for chronic pain are preferred, but this requires clinicians to educate patients on the risks associated with opioids, the most serious of which are OIRD and death, and what the plan is to address them. “It’s usually well received because it shows that you care about the patient and that you’re looking out for their best interests,” he said.

Dr. Gharibo stressed that take-home naloxone and an opioid emergency plan should be part of the conversation with family members, so that they are ready to respond to an opioid emergency.

**Conclusion**

Opioid emergencies are a growing public health epidemic, with a spectrum of factors increasing the risk.1-3,13-23 “Like a car accident, you don’t know when it [an opioid emergency] is going to happen, but you want to be ready when it happens,” emphasized Dr. Gharibo. “That’s where the value of take-home naloxone comes into play—there’s no absolute safety in anything that we do, but this is one way to make it [opioid prescribing] safer.” Helping chronic pain patients understand their risk for an opioid emergency and coprescribing an FDA-approved take-home naloxone product may help save a life in an opioid emergency.

**References**


**IMPORTANT SAFETY INFORMATION (continued)**

The following warnings and precautions should be taken when administering EVZIO:

- **Risk of Recurrent Respiratory and CNS Depression**: Due to the duration of action of naloxone relative to the opioid, keep the patient under continued surveillance and administer repeated doses of naloxone using a new EVZIO, as necessary, while awaiting emergency medical assistance.

- **Risk of Limited Efficacy With Partial Agonists or Mixed Agonists/Antagonists**: Reversal of respiratory depression caused by partial agonists or mixed agonists/antagonists, such as buprenorphine and pentazocine, may be incomplete. Larger or repeat doses may be required.

- **Precipitation of Severe Opioid Withdrawal**: Use in patients who are opioid dependent may precipitate opioid withdrawal. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated. Monitor for the development of opioid withdrawal.

- **Risk of Cardiovascular (CV) Effects**: Abrupt postoperative reversal of opioid depression may result in adverse CV effects. These events have primarily occurred in patients who had pre-existing CV disorders or received other drugs that may have similar CV effects. Monitor these patients closely in an appropriate healthcare setting after use of naloxone hydrochloride.

Please see Important Safety Information on pages 13 and 15, and full Prescribing Information at [EVZIO.com](http://www.evzio.com/patient/evzio-savings/) or call 1-855-77-EVZIO (1-855-773-8946).
Please see Important Safety Information on pages 13 and 14, and full Prescribing Information at EVZIO.com.
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