Why Opioids Belong in Chronic Pain Care

On Monday, November 9, 2015, at the American College of Rheumatology (ACR) annual meeting, a neurologist and a rheumatologist took the stage to debate whether or not opioid analgesic medications belong in the management of chronic, noncancer pain.[1] John Markman, MD, a neurologist at the University of Rochester Medical Center, took the pro position; Daniel Clauw, MD, a professor of anesthesiology, rheumatology, and psychiatry at the University of Michigan, argued against opioid use in certain patients. Speakers were each given 15 minutes to argue their side, as well as a 5-minute rebuttal each.

Dr. Markman started things off: "Opioids," he began, "are tools, like a car. Or like an Uber here in California. Or a gun. As such, they can be used well, or they can be used in ways that are dangerous. When used properly, they can be incredibly helpful."

Despite the session’s title—"Opioids for the Treatment of Chronic Non-cancer Pain... Use or Abuse?"—Markman feels it doesn't make any sense to be either "for" or "against" opioids, given that the issue of whether or not their benefits outweigh their harms—or vice versa—simply isn't that black and white. From his perspective, the bigger question is: "Which patients will benefit from this class of therapy, and which won't?"

Markman commented that pain management is a major priority for patients with rheumatoid arthritis and reviewed the evidence supporting opioid therapies, citing the fact that there have been over 60 randomized controlled trials for the drug class in chronic noncancer pain over the last 20 years or so. About one half of these, according to Markman, included follow-up of 1 year or longer; and overall they suggest that opioids demonstrate broad-spectrum efficacy across neuropathic pain, acute pain, and chronic musculoskeletal pain.

"One area of debate that is raging in my field, and yours as well," he continued, "is whether or not there is a dose-dependent risk with opioids." He then presented findings from a 2003 paper[2] by Rowbotham and colleagues published in the New England Journal of Medicine showing that in 81 patients with central or peripheral chronic neuropathic pain, there was an analgesic dose-dependent benefit. "This is a very important point because, as you know, in the US there are legislators, insurers, and other institutions that are looking to cap the maximum dose of opioids per day," he said.

The current standard of pain care is multimodal analgesia, and Markman feels that if clinicians aren't including opioids as one option, they're doing at least some of their patients a disservice.

Next Markman revealed that one of the points that he and Dr. Clauw were tasked with discussing was the role of opioids for chronic central pain syndrome. "I have fished in these waters for 20 years, and I have no idea what chronic central pain syndrome is," he admitted, "It's sort of like coming to the ACR meeting and saying joints that are red, hot, and swollen are all red, hot, and swollen in the same way." Markman feels that the notion that there is a single chronic central pain condition is far too reductionist and an oversimplification.

Though a supporter of opioid analgesics in certain patients, Markman is well aware of the risk associated with these agents. "Opioid abuse is a colossal problem in the US at the moment," he commented, flashing a graph showing a sharp rise in opioid use starting in 1997. It was around this time, he recalled, that a marketing plan for long-acting opioids was launched, one that portrayed the agents as safe.

"Ultimately this was a settled case with the government because that wasn't true, and it led us down a 20 year slippery slope to what has turned into a devastating issue for our country," said Markman. "Forty people will die today due to opioid-related complications, and 40 will die tomorrow. It's a small plane crash every day. But it doesn't negate the value of
these drugs for people who have chronic pain."

Markman concluded by emphasizing how important it is to risk-stratify patients; to inquire about risk factors for abuse, misuse, and diversion, including a history of abuse or a history of abuse in a family member, and what their other habits are.

### Why Opioids Don't Belong in Chronic Pain Care

Dr Clauw then took the stage to respond.

"I'm a friend of John's, so this won't become personal between the two of us," he joked, before reviewing what he sees as some of the major problems with the use of opioid analgesics to manage chronic pain. "A lot of people are trained to take care of pain patients in the inpatient setting. And for acute pain, opioids work extremely well," he admitted. "[Plus in the hospital] you can look for side effects like respiratory depression...but people have had a tendency to think that this class of drug would likewise translate into being effective for chronic pain. Opioids are considerably less effective for chronic pain."

Clauw then pointed out that almost all opioid industry trials use a randomized withdrawal design, which doesn't demonstrate efficacy in an entire population of people but rather in a subset who initially respond to a drug. "I think this violates the entire principle of intent to treat when you're only randomizing people who respond to the drug in advance," he said. "There are very few trials that I'm aware of that have used the classic parallel group design for opioids that showed efficacy in a classic parallel group design."

Clauw's other primary gripe with opioids is the fact that often when an agent is shown to be effective in one chronic pain condition, its labeling will sometimes imply that it's also effective for other types of chronic pain. "This is quite different from drugs like pregabalin or duloxetine that had to [be tested in] chronic pain condition after chronic pain condition—and which only get labels for the conditions that they worked in. If opioids had labels like that, I would be entirely okay with opioids," he said.

Generally speaking—as Clauw pointed out—practice guidelines for the centralized pain conditions like fibromyalgia, headache, and irritable bowel have for decades shied away from opioids. Guidelines for other pain conditions like low back pain and osteoarthritis typically have included opioids but not as first-line options. However, recent findings show that opioids are the first drug prescribed for pain in the United States 40% of the time and, further, that 40% of patients with conditions like fibromyalgia are on opioids.

"This is a study[3] that was published by Jenna Goesling, who is in the audience here, looking in our pain clinic in Michigan at who is taking opioids," Clauw continued. "It shows that the exact people that we're concerned about opioid use in are the people who are using them the most, people with high levels of comorbid depression." Past research[4] has shown that depressed patients with pain often don't respond adequately to opioids. "They still have very high pain scores.... These people probably are taking these drugs as bad, unsafe antidepressants rather than taking them because they're truly having a strong analgesic effect," said Clauw.

Next Clauw tackled the opioid misuse and abuse epidemic in the United States: "If you don't live in the United States, you don't have this problem. We consume so much of the world's opioid supply that you couldn't possibly have the problem that we have." The United States comprises just 5% of the world's population, yet we consume about 80% of the world's opioids. The latest data, from 2013, show that 16,000 people in the United States died of prescription opioid overdoses that year. Furthermore, Clauw pointed out this is likely an underestimation given that in many states, death certificates don't specify which agents contributed to the cause of death.

An unfortunate byproduct of the increased abuse of opioids is that it appears to be a frequent gateway to heroin use. In past decades, most people who became addicted to heroin started out using heroin. However, a 2014 report by the National Institute on Drug Abuse found that 54% of heroin addicts in the United States started out on opioid analgesics,
primarily obtained from friends or family members. Also contributing to the problem is that often heroin is cheaper than prescription opioids.

Though opioid abuse and misuse is most prevalent in the United States, Clauw warned that the problem could soon spread to other countries: "The pharmaceutical companies are doing what the tobacco companies did 10-15 years ago. Now that they see that the huge sales in the US are in danger because of us having talks like this, they are going to developing countries."

Why REMS Could Fall Flat

Moving on, Clauw observed that conditions like fibromyalgia, tension headache, and irritable bowel syndrome all seem to involve centralized pain—and further that the data suggest that the most effective treatments for these conditions include serotonin and norepinephrine reuptake inhibitors, gabapentinoids, and tricyclic drugs.

"I don't know that in any of these conditions, quite frankly, opioids have been tested in a parallel group and shown to be efficacious and broadly recommended for use," said Clauw, who then reviewed a study[5] by his colleague Chad Brummett that he feels confirms that opioid efficacy is lacking in patients with centralized pain.

The study looked at perioperative opioid use in patients undergoing knee and hip arthroplasty and found that patients with centralized pain or fibromyalgia-type symptoms didn't respond as well to opioids and had worse surgical outcomes. Clauw believes that this is due to their pain being at least partially centralized—or coming from the brain—hence, operating on their knees won't make their knees feel better. These patients were found to consume significantly more opioids following surgery, suggesting that they are suffering from more pain or that opioids fail to provide them with desired relief.

"One of the scariest things about these perioperative studies that Chad has led is that 7% of patients who were not taking an opioid prior to their knee replacement surgery were taking an opioid chronically 6 months after the surgery," said Clauw. "REMS programs don't work when the overwhelming majority of people who are staying on opioids were not intentionally prescribed to opioid for chronic pain. They get it after a surgical procedure, they get it after an emergency room, they get it from a medicine cabinet." Clauw then pointed out that the healthcare system doesn't evaluate patients after surgical procedures with a REMS program to determine if a patient might be at high risk of developing an opioid problem.

Clauw feels that opioids should be reserved as the last option for some types of chronic noncancer pain but points out that this is not how they're being used. "I don't think John and I actually inherently disagree a great deal, and I think there are people in whom opioids can be effective," he acknowledged. "But the problem is that's not who is using them. That's not who is becoming addicted to them. That's not who is dying from their use. The purposeful use of opioids in chronic pain patients now is actually quite rare."

To conclude, Clauw reaffirmed that REMS programs and other types of abuse monitoring programs are not likely to solve the opioid problem. "People have no idea what the danger is of writing these prescriptions for 60 or 90 days of oxycodone or hydrocodone after a surgical procedure. This is where the problem is."

The Debate Concludes

During his 5-minute rebuttal, Dr Markman began by agreeing that REMS strategies—at least at the moment—have significant shortcomings. But he also pointed out that implementing a monitoring strategy is the job of all clinicians involved in the multidisciplinary pain management team. "This is the culture we have to create," he said, "but I don't think [the shortcomings] are a set of professional liabilities and flaws...not a property of opioids."

Markman then returned to the idea that the concept of "centralized pain syndromes" is still in many senses vague: "I don't really even know what's meant by centralized pain or centralized sensitization. All of these terms...are used to describe patients we can't explain. I feel like it lacks a certain rigor to just paint these patients as all the same. It's just not that simple."
Regarding Clauw's criticism of opioid clinical trial design, Markman acknowledged that these types of trials have their flaws but pointed out that many patients can't tolerate opioids. "I run clinical trials," he explained, "and if someone can't be on an opioid because they're throwing up six times a week, I don't want them in a trial!" That said, Markman reported that there are actually numerous randomized, controlled opioids trials without an enrichment design.

Markman does agree that changes to opioid labeling should be considered and also that more efforts should be made to monitor short-acting opioids. He feels that clinicians should be extra cautious when combining opioids with benzodiazepines and cautions not to use the agents as sleep medications.

"I don't think a lot of effort has gone into developing abuse-deterrent opioids," he said, approaching the end of his allotted time. "I think in the next 20 years, the opioid companies who are going to distinguish themselves are the ones who make the safer opioids. There are many companies in that race, and I'm glad the race is going on."

Markman concluded by returning to his car metaphor: "75 years ago, there was a company that decided to focus on a safety adaptation to their car. Which company was that? Volvo. They developed the seatbelt...and become synonymous with safety. Where are the innovations that we can bring to [opioid therapy]—which is clearly useful and which has been around for 2000 years—to make it safer, so fewer people get hurt, and more people get better?"

Alternatives to REMS

"I didn't know this was a debate about whether we understand the neurobiology of centralized pain," Clauw joked as he begin his rebuttal. "Next year, if you want to invite John and me to debate that, please do; and John, bring it on!"

Continuing, Clauw commented that "abuse-deterrence is silly. As soon as a company develops an abuse-deterrent formulation, the addicts go to find something else," he said. "This is is what's happening with heroin." His argument is that by developing abuse-deterrent formulations, drugs companies feel and appear more ethical. "But it's not going to help this problem whatsoever," he said.

He then returned to REMS: "I live in the real world, not the make-believe world." There is never going to be a time when ERs and surgeons are using REMS before giving out prescription opioids for acute pain; and therein lies the problem."

Clauw rehashed his point that very few of these opioids are now being used for what they were initially prescribed for but cited the new Centers for Disease Control and Prevention guidelines, which limit people undergoing certain procedures to 3 days of opioids, as a major step in the right direction.

"You know the number one, two, three and four reasons that surgeons prescribe 90 days of oxycodone or hydrocodone?" he asked the audience. "Because they don't want to get called back. The opioids end up in a medicine cabinet."

References

1. Clauw DJ, Markman J. Opioids for the treatment of chronic non cancer pain... use or abuse? Program and abstracts of the American College of Rheumatology 2015 Annual Meeting; November 7-11, 2015; San Francisco, California. ARHP Debate.

