

PAIN[®] LIVE

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Study Provides Novel Insight on OUD Diagnosis Factors in Opioid-Naive Patients

GIULIANA GROSSI

A new retrospective cohort study evaluated opioid-naive patients who were prescribed at least one opioid during an inpatient hospital visit to determine baseline factors associated with a new diagnosis of opioid use disorder (OUD). The ultimate goal was to better understand factors associated with the disorder in order to inform pain management strategies in this setting.

The team of investigators, led by Elizabeth C.S. Swart, BS, UPMC Centers for High-Value Health Care and Value-Based Pharmacy Initiatives, UPMC Health Plan, alluded not only to the 2.5 million individuals living with OUD in the US, but also the economic impact of this epidemic.

In the US, the cumulative societal cost of opioid use disorder is nearly \$80 billion and has been associated with the rise of illicit drug use.

Investigators acknowledged the numerous methods of response to this crisis, including policy and treatment approaches aimed at harm-reduction, medication-assisted treatment (MAT), Good Samaritan laws and increased availability of naloxone.

“Other efforts to curtail the epidemic have mainly focused on reducing inappropriate prescribing,” they wrote, “which have led to decreased opioid

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FDA Extends PDUFA Timeline for MYFEMBREE Endometriosis Application

KEVIN KUNZMANN

The US Food and Drug Administration (FDA) has extended the period to review the supplemental New Drug Application (sNDA) for relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg (MYFEMBREE) for managing moderate-to-severe endometriosis pain.

The delay, announced by applicant companies Myovant Sciences and Pfizer late last week, will grant the

FDA more time to review additionally requested information from the application regarding bone mineral density impact with the combination therapy. As such, the new PDUFA date for the sNDA will be August 6 of this year.

Myovant chief medical officer Juan Camilo Arjona Ferreira stated the company’s intent to continue working with the FDA during the ongoing sNDA review.

“We remain confident in the clinical profile of MYFEMBREE and its poten-

tial to become a therapeutic option for the management of endometriosis-associated pain,” Ferreira said in a statement.

The relugolix/estradiol/norethindrone acetate combination therapy was originally approved by the FDA for the treatment of menstrual bleeding associated with uterine fibroids for up to 24 months in premenopausal women. It is the first once-daily oral

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prescriptions; however, rates of OUD, nonmedical opioid use, and opioid-related overdose deaths remain prevalent.”

Focusing on Factors Associated with OUD

While many studies have evaluated inpatient opioid administration, this study explored baseline characteristics including medication use pre-admission, during hospitalization, and at discharge to identify associations with a new diagnosis of opioid use disorder in the year following hospitalization.

“To our knowledge, this is one of the first studies to evaluate patient- and medication-related risk factors in the development of OUD in opioid-naïve inpatients exposed to opioids during hospitalization,” investigators wrote. “The inpatient setting is a critical setting for opioid exposure and can serve as a conduit to long-term opioid use.”

Investigators developed a dataset of electronic health records (EHR), pharmacy claims, and medical claims that reflected data of patients aged 14 or older who were discharged between 2014-2017 from UPMC Health Plan, a vertically integrated healthcare delivery and finance

system. Patients who were diagnosed with OUD, or prescribed an opioid prior to the study onset were excluded.

Assessing Patient Characteristics

Out of the final sample of 23,033 opioid-naïve patients, 2.1% were diagnosed with the disorder within a year of receiving their first opioid in the hospital. Within that population, investigators discovered that a substantial number of those individuals were young and white, residing in high opioid geo-rank regions and had a history of nonopioid related drug disorder, tobacco use, and gabapentin use.

When examining the 6 months prior to hospital admission among those with a new OUD diagnosis, investigators observed that the average number of prescriptions filled were higher, the number of days’ supply was higher, and prescriptions filled for gabapentin and skeletal muscle relaxants were higher, compared with those without a new diagnosis.

“Notably, although a baseline history of skeletal muscle relaxant use was more common in those who were diagnosed with OUD, in our multivariable model it was not associated with subsequent OUD” they wrote. “This is contrary to similar studies which looked at factors influencing long-term opioid use among

opioid-naïve patients.”

Discoveries within the Data

Adjusted multilevel mixed-effects logistic regression models were used to indicate the factors associated with a new opioid use disorder diagnosis within 12 months of discharge.

“Overall, presence of chronic liver disease and being discharged to a long-term hospital, rehabilitation center, or special needs facility were significant factors for patients in the surgery cohort who developed OUD ($P < .0001$). For patients who did not receive surgery, opioid geo-rank was significant at $P < .0001$ for those diagnosed with OUD compared to those who were not.”

General characteristics that were associated with higher odds of a diagnosis included being between the ages of 25–34, compared to those 65 years of age and older. When looking at race, White patients were associated with higher odds of a diagnosis.

Medical history and comorbidities played a significant role. Previous history of chronic liver disease was associated with higher odds of an OUD diagnosis in the surgery cohort. Those with nonopioid-related drug disorder (excluding

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therapy to receive such an indication from the FDA.

The agent additionally carries a Boxed Warning regarding risk of thromboembolic disorders and vascular events among treated patients, as well as a contraindication in women with current or history of thrombotic or thromboembolic disorders, as well as women at risk of such issues.

As previously explained to HCPLive by Maria Sophocles, MD, medical director of Women’s Healthcare of Princeton,

endometriosis is capable of “wreaking havoc on the daily lives of reproductive-age women.”

“Like fibroids, endometriosis is a large burden of pathology for American women, in terms of days of lost work and school pain, undiagnosed pain, infertility,” Sophocles said at the time. “And so, it’s important that we try to treat it. It’s been treated medically, it’s still treated medically and surgically, but the focus is now on medical treatment, on non-invasive treatment suppressing the endometrial implants.”

Relugolix is among the GnRH receptor agonist drug class that is among the

leading agents for treating endometriosis and uterine fibroid pain. As explained to HCPLive by Erica Marsh, MD, MSCI, professor of Obstetrics and Gynecology at University of Michigan Medical School last year, the steadily rolled-out agonist drug class may have a specific, but beneficial, role in complementing the armament of endometriosis and fibroid pain management.

“I think it’s been nice as somebody who focuses on helping someone with fibroids by offering them something new that’s on the market, but also make sure they’re counseled on our other options that we would maybe start with,” Marsh said. ■

Nasal Nalmefene Produces Positive Results Reversing Respiratory Depression

GIULIANA GROSSI

Opiant Pharmaceuticals announced positive topline results from a head-to-head pharmacodynamic (PD) study that compared nasal nalmefene (OPNToo3), to nasal naloxone. Nasal nalmefene met the primary endpoint of non-inferiority and produced a greater reversal in remifentanyl-induced respiratory depression than nasal naloxone.

Nasal nalmefene is an investigational treatment for opioid overdose. In this crossover

study, a 3 mg dose of nasal nalmefene hydrochloride was compared with a 4 mg dose of nasal naloxone hydrochloride to assess its capability of reversing the effects of an opioid overdose.

Investigators measured changes in minute ventilation after 1 of the 2 trial drugs was administered to the 50 healthy volunteers. The primary endpoint was at 5 minutes. The nalmefene increases in minute ventilation were 5.745 L/min and the naloxone increases were 3.011 L/min.

According to a preliminary analysis of the participants, nasal

nalmefene produced a reversal of respiratory depression that was almost twice that produced by nasal naloxone at the 5 minute endpoint. The completion of this study concluded the planned clinical development program for nasal nalmefene and the company expects to file a New Drug Application (NDA) in the second half of 2022.

“The findings from this PD study are compelling and add to a body of non-clinical and clinical evidence demonstrating the potential of OPNToo3, nasal

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Non-Opioid Painkiller ACP-044 Fails to Meet Endpoint in Phase 2 Acute Pain Trial

GIULIANA GROSSI

Top-line results from a phase 2 clinical trial revealed that Acadia Pharmaceuticals' acute pain treatment for bunionectomy surgery did not meet its primary endpoint. ACP-044, a non-opioid painkiller, failed to display a significant difference in pain intensity scores when compared with placebo.

The data from the Acadia trial followed the announcement of Vertex's results from its own non-opioid painkiller clinical trial which fared superior results by meeting the endpoint. Vertex plans to initiate

the next step for its Nav1.8 inhibitor by launching a pivotal trial in the second half of this year.

This may cause Acadia to shift its target to from acute to chronic pain in order to keep up with Vertex and proceed into phase 3. ACP-044 is also being examined for its role in treating pain associated with osteoarthritis of the knee in a phase 2 trial that's expected to conclude in the first half of 2023.

Those results will largely indicate how much Acadia's molecule is worth to the company after it was obtained for \$52.5 million in 2020 during the acquisition of CerSci

Therapeutics. If the acquired assets are successful, shareholders are expected to receive \$887 million in development, commercialization and sales milestones.

Acadia's Phase 2 Trial for Acute Pain

The effects of the medication were observed over 24 hours at 1600 mg once daily, 400 mg 4 times daily, and then placebo treatment. While the group receiving the 400 mg dose trended better than placebo at 48 and 72 hours, the trend was not statistically significant.

The randomized, double-blind,

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nalmefene, to offer an important treatment option for opioid overdose,” Richard C. Dart, MD, PhD, Director, Rocky Mountain Poison & Drug Center, Denver Health and Hospital Authority, and member of Opiant’s Scientific Advisory Board, said in a statement.

“Synthetic opioids, such as fentanyl, are responsible for the great majority of overdoses today, are far more potent, have a more rapid onset, and can have a long duration of action,” he continued. “They can quickly depress respiration and can continue to deprive the brain of oxygen even after administra-



tion of naloxone, the only current FDA-approved treatment for opioid overdose. Unless quickly reversed,

this can cause severe hypoxic injury to the victim’s organs and brain, and potentially death.” ■

» “NON-OPIOID PAINKILLER”
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placebo-controlled trial included 239 patients undergoing bunion removal. The first dose was administered prior to the surgery with treatment continuing for 4 days before patients reported their final pain intensity scores with a Numeric Rating Scale (NRS).

As a non-opioid, novel, first-

in-class, redox modulator investigational drug, ACP-044 has the potential to fill a gap in pain management care. The mechanism of the drug is believed to function as a redox modulator of reactive oxygen species such as peroxytrite, which may intensify pain as the species are a response to tissue injury and inflammation.

“We are disappointed that the

ACP-044 bunionectomy study did not meet its primary endpoint, especially given the significant need for novel, non-opioid treatment options for postsurgical pain,” Steve Davis, Chief Executive Officer, Acadia, said in a statement. “We will continue to analyze the totality of the data to best determine whether further development in acute pain is appropriate.” ■

» “STUDY PROVIDES NOVEL INSIGHT” CONTINUED FROM PAGE 2

cannabis and cocaine), tobacco use disorder, and mental health conditions also demonstrated higher odds of diagnosis.

Investigators noted that the use of benzodiazepines or skeletal muscle relaxants in the 12 months prior to index hospitalization event was not associated

with an OUD diagnosis; however, use of gabapentin 12 months prior to index date was.

Additionally, patients discharged to long-term hospitals, rehabilitation centers, or special needs facilities instead of going home were more likely to receive a diagnosis.

“Future research is needed to evaluate if identification of high-risk patients

can mitigate risk of subsequent OUD through proactive effective pain management strategies that include reducing opioid exposure when feasible,” investigators concluded.

The study, “Patient and medication-related factors associated with opioid use disorder after inpatient opioid administration” was published in the *Journal of Hospital Medicine*. ■

Ankle Pain Still Tops for Patients With Hemophilia in Germany

KENNY WALTERGERICH

Despite new therapies, patients with hemophilia continue to suffer from joint pain, particularly in the ankles, knees, and elbows.

A team, led by Jamil Hmida, Department of Sports Medicine, University of Wuppertal, detected the most affected joint for patients with hemophilia and evaluated the significance of the source of pain and determined the point prevalence of back pain in Germany.

Joint Pain

Patients with hemophilia often have accompanying joint pain in the ankles, knees, and elbows. However, there have been improvements in factor therapies.

“Hemorrhages in the joints and mus-

cles in the lower extremities (e.g. ankle joint, knee joint or musculus iliopsoas) can alter posture in the entire musculoskeletal chain,” the authors wrote. “The additional reduction in physical activity and the change in muscular load distribution due to bleeding and pain leads to muscular imbalances and a decreased range of motion in the joint.”

Patients

In the retrospective study, the investigators examined 300 patients with severe (n = 217), moderate (n = 47), and mild (n = 36) hemophilia for joint pain, the most common source of pain, and the point prevalence of back pain.

The investigators included data from 5 prospective studies collected between 2018-2021.

Each patient was given an anamnesis questionnaire and the German Pain Questionnaire.

The investigators used the results of the questionnaires to determine the most affected joint, the most frequent source of pain, point prevalence, and pain duration.

Ankle Pain

The investigators found the most affected joint in German patients with hemophilia was the ankle (41%). This was followed by the knee (27%) and the elbow (11%). In addition, the most common source of pain was the ankle joint (32%), while back pain was also identified as 1 of the most common

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Non-Opioid Painkiller Enhances Vertex Drug Pipeline with Latest Phase 2 Results

GIULIANA GROSSIGERICH

Vertex shared promising data from its VX-548 drug trial after years of development. VX-548 works through a cellular pathway associated with pain signaling, making it a potential alternative to managing acute pain with opioids. These results have boosted Vertex's drug pipeline.

While opioid medications are effective, the risk of addiction and opioid misuse has been an escalating public health concern. The research collected regarding VX-548 met the biotech company's “high expecta-

tions of achieving therapeutic pain control,” according to Carmen Bozac, MD, Chief Medical Officer, Vertex.

“The remarkable consistency in the safety, tolerability and efficacy results in these two studies demonstrate the potential of VX-548 to be a first-in-class non-opioid treatment for acute pain,” Bozac said in a statement. “We are working with urgency to advance the program into Phase 3 with the goal of bringing forward the first novel pain treatment in decades to address the unmet needs of patients suffering from acute pain.”

The Newest Data

For each of the trials, patients

were randomized to a placebo group, 1 of 3 groups with varying doses of VX-548, or the group that received an opioid painkiller and Tylenol regimen. Neither study displayed success with the moderate or low doses of the drug, but there was an impact when VX-548 was taken at the highest dose.

The latest trial focused on patients who were undergoing abdominoplasty by enrolling 303 patients, which was structured similarly to the first trial. In this phase 2 trial, patients on the

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» “ANKLE PAIN STILL TOPS”
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sources of pain. This was also comparable to the elbow (elbow:15%; back:13%). There was also no significant correlation between the most affected joint and the severity of hemophilia ($P > .05$).

The study also shows that patients with hemophilia have higher prevalence of back pain compared to the general German population (43% vs 37%).

However, patients with mild hemophilia had a higher prevalence of back pain as well, but the investigators said it could be because of a small sample size compared to other groups.

The point prevalence in patients with hemophilia for back pain was also substantially higher compared to the general German population ($P = .031$).

Ultimately, the results show not much has changed in this regard in the last 20 years.



“Our data showed that the ankle is still the most affected joint and the most common source of pain in Germany,” the authors wrote. “These results also showed the relevance of back pain as a pain source. The evaluations also demonstrated the high point prevalence of back pain in [patients with hemophilia].”

The investigators also suggested future medications and therapies should focus on the spine because joint changes can impact posture.

The study, “Most subjectively affected joints in patients with haemophilia – what has changed after 20 years in Germany?,” was published online in *Haemophilia*. ■

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highest dose of VX-548 showed significantly higher improvement rates compared to placebo and were numerically higher than patients taking opioid medications.

The First VX-548 Study

In the first trial, 274 patients undergoing bunionectomy were randomized to the placebo group, to 1 of 3 groups with varying doses of VX-548, or the group that received an opioid painkiller and Tylenol.

Results showed significant improvement in pain relief among the patients taking the highest dose of VX-548 compared to placebo. This

group reported better scores than the patients who received opioid therapy did, however, no direct comparisons were made between these 2 arms.

Adverse events were classified as mild or moderate with patients most commonly reporting nausea, headache and constipation. In 1 of the trials, 2 patients withdrew because of adverse events, which were not related to the treatment, according to Vertex.

In the Works at Vertex

These data accompany multiple recent research achievements by Vertex, increasing its share price by

40% in the last 6 months. The company successfully gained approval for 4 cystic fibrosis treatments and provided positive results for a kidney disease drug.

Phase 3 testing is planned for the second half of 2022. Vertex will be discussing the current data with regulators prior to launching VX-548 into further testing.

A gene editing treatment that Vertex and CRISPR Therapeutics have been collaborating on for sickle cell disease (SCD) and beta thalassemia is expected to be submitted to the US Food and Drug Administration (FDA) for approval soon. ■

Upadacitinib Improves Pain Associated with Ankylosing Spondylitis, PsA

GIULIANA GROSSIGERICH

Upadacitinib has already been found to be safe and effective in the phase 3 SELECT-PsA 1 and 2 studies on patients with active psoriatic arthritis (PsA), as well as among patients with active ankylosing spondylitis (AS) in the phase 2/3 SELECT-AXIS 1 study.

However, a new investigation compiled the data from all 3 randomized trials which brought more insight on upadacitinib's effect. Patients with active psoriatic arthritis or ankylosing spondylitis displayed rapid and sustained improvements

in pain outcomes with upadacitinib for over a year.

The population included patients who have experienced either inadequate responses to non-biologic or biologic disease-modifying antirheumatic drugs (DMARDs), or were biologic-naïve with inadequate response to non-steroidal anti-inflammatory drugs. Improvements were consistent and observed across several endpoints.

The Study

In all 3 studies, patients were randomized to receive either upadacitinib 15 mg once daily, or placebo. In SELECT-PsA 1, an additional group

was administered adalimumab 40 mg every other week. Investigators, led by Iain B McInnes, MD, PhD, University of Glasgow, College of Medical, Veterinary and Life Sciences, evaluated pain outcomes based on increments.

In post hoc analyses, when compared with baseline, outcomes were measured by the proportion of patients who achieved $\geq 30\%$, $\geq 50\%$ and $\geq 70\%$ reduction using a patient global assessment of pain.

Also, changes from baseline were assessed at specific time points, as were particular ques-

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Deanna Baker Frost, MD, Addresses the Difficulties of Treating Autoimmune Disease

GIULIANA GROSSIGERICH

Deanna Baker Frost, MD, PhD is an Assistant Professor at the College of Medicine, Medical University of South Carolina (MUSC). Her clinical interest focuses on autoimmune disease and fibrosis. In an email interview with HCPLive®, she addressed important aspects of treating autoimmune diseases, as they are often accompanied by unique challenges for both the patient and the provider.

The month of March is dedicated to autoimmune disease in order to spread awareness of the various conditions, the patients who live with

them, and the clinicians who treat them. Most importantly, the need for patient and provider education regarding such conditions is emphasized during this month.

In addition to the resources that Baker Frost mentioned, the US Pain Foundation published an Autoimmune Diseases Edition of their Invisible Project magazine. It's a free resource designed for patients and healthcare professionals. The print publication can be ordered and access is also available online.

Many individuals who live with an autoimmune disease also live with chronic pain and other complications brought on by their condition.

Symptoms related to these diseases can take some time to properly diagnose and because of how they can progress time is critical.

HCPLive: As a rheumatologist and autoimmune disease expert, are there any conditions that are especially in need of greater awareness?

Baker Frost: In rheumatology, most diseases begin with similar symptoms which then can involve other organs. Thus, expedient evaluation and diagnosis is important so that treatment can begin. Systemic

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tions from Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Additional end points that were unique to each study were looked at.

The Results

The research showed that a higher proportion of patients who received upadacitinib achieved $\geq 30\%$, $\geq 50\%$ and $\geq 70\%$ reduction in pain end points compared with placebo. The improvements were observed as early as week 2 and were sustained or further increased through the

first year (PsA 1/2 studies: 64%/48%, 58%/42% and 38%/22%, respectively; SELECT-AXIS 1 study: 76%, 72% and 54%). The data regarding adalimumab from the SELECT-PsA 1 study produced similar results (59%, 49% and 32%).

Patients who switched from placebo to upadacitinib 15 mg were able to improve to similar levels of the continuous upadacitinib group by the end of year 1 (PsA 1/2 studies: 46%–60%, 35%–49% and 15%–34%; AS study: 83%, 72% and 46%).

Investigators pointed to the importance of pain management in

these populations a key component to the treatment of psoriatic arthritis and ankylosing spondylitis. Pain has an incredible impact on an individual's quality of life, fatigue, and functional work impairment.

The study “Effect of upadacitinib on reducing pain in patients with active psoriatic arthritis or ankylosing spondylitis: post hoc analysis of three randomised clinical trials” was published in RMD Open Rheumatic & Musculoskeletal Diseases. ■

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Sclerosis (scleroderma) is a disease with scarring in the skin, leading to tight skin. But, this tightening can also occur in the lungs leading to inability to breath. Because lung disease can occur in other autoimmune diseases, I urge patients to notify their physicians if they notice an inability to breathe.

HCPLive: What are the most impactful obstacles that patients with autoimmune diseases encounter?

Baker Frost: Because most autoimmune diseases are rare, most patients have a delay in obtaining the proper diagnosis and starting effective treatment. The shortage of rheumatologists nationwide also causes a delay in disease diagnosis for our patients. Often, once the patient is evaluated by a rheumatologist, the patient has developed several medical complications due

to the delay. This delay negatively impacts patients physically and emotionally.

HCPLive: How can healthcare professionals best educate themselves and their patients when it comes to diagnosing, managing, or finding resources for patients with autoimmune disease?

Baker Frost: The American College of Rheumatology (ACR) is a professional organization which has resources available specifically for healthcare providers and patients for most autoimmune diseases. These resources are available through their website and provides in depth information about diagnosing autoimmune diseases and the current treatment options. Additionally, there are foundations centered on most autoimmune diseases which provides patient support resources and information to clinicians.

HCPLive: Where are the biggest gaps in care and what should be

focused on in the future?

Baker Frost: Often we find difficulty obtaining insurance approval for a number of our therapies on behalf of our patients. While this is an exciting time for rheumatology due to a greater number of FDA approved treatments, we still use some medications that are considered off-labeled. Because these therapies are not FDA approved, rheumatology providers will spend several hours appealing to insurance companies, which delays care. Therefore, our patients need better financial support so that they are able to receive important treatments timely. Also, we need more research funding so that scientists can continue to study autoimmune diseases and develop better treatment options to improve patient care. Finally, there is a shortage of rheumatologists nationwide which will make it more difficult for patients to be diagnosed and treated in a timely fashion. There is a need to train more clinicians to help meet the demand. ■