

# Topics in PAIN MANAGEMENT

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## CONTINUING EDUCATION ACTIVITY

### Tapering Opioids for Chronic Pain: Further Evidence of Alarming Risks for Millions of Patients

Mark L. Schoene

**Learning Objectives:** After participating in this continuing professional development activity, the provider should be better able to:

1. Examine the negative impact of long-term opioid therapy for chronic pain management.
2. Evaluate the support care needs of patients who are tapering long-term opioid therapy for chronic pain management.
3. Analyze the findings from a study that investigated adverse effects associated with opioid tapering.

**Key Words:** Chronic pain, Opioids, Tapering

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Long-term opioid therapy for chronic pain carries a broadly unfavorable risk/benefit profile and can lead to complex dependence issues, addiction, overdose, suicide, and a host of other adverse events. High-dose opioid therapy magnifies these risks.

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Given the increasingly negative publicity and inadequate pain relief associated with long-term opioid therapy, many patients have opted to taper their opioid dosage—gradually or rapidly.

However, a recent study appears to confirm the fears of prominent opioid researchers that tapering itself can be a life-threatening experience for a disturbing proportion of patients. And this raises a pivotal question: Is it safe for most patients with chronic pain to embark on long-term opioid therapy at all?

This is one of the critical issues in the treatment of back and other forms of chronic pain in the United States going forward.

Alicia Agnoli, MD, and colleagues took a retrospective look at more than 113,000 chronic pain patients on “higher doses” of medically prescribed opioids. All had stable daily dosages of at least 50 morphine milligram equivalents (MMEs) per day.<sup>1</sup>

## A recent study appears to confirm fears that opioid tapering can be a life-threatening experience.

They compared the results of patients who tapered their dosages by at least 15% over a several-month period with people who did not taper at all.

The results are alarming. “Among patients prescribed stable, long-term, higher-dose opioid therapy, tapering events were significantly associated with increased risk of overdose and

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mental health crisis,” according to the authors. The risk of overdose among the patients who tapered was almost double that of those who didn’t.

“Prescribers are really in a difficult position. There are conflicting desires of ameliorating pain among patients while reducing the risk of adverse outcomes related to prescriptions,” said Agnoli, in a statement from the University of California, Davis. “Our study shows an increased risk of overdose and mental health crisis following dose reduction. It suggests that patients undergoing tapering need significant support to safely reduce or discontinue their opioids.”

Unfortunately, that level of support and care does not exist in most medical systems across the United States.

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**There does not appear to be an easy way to identify patients at high risk of adverse outcomes from tapering. Nor has there been much research to identify safe tapering practices or which patients require special precautions.**

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“Our study results support the recent federal guidelines for clinicians considering opioid dose reduction for patients,”<sup>2</sup> said Joshua Fenton, MD, of the University of California, Davis. “But I fear that most tapering patients aren’t receiving close follow-up and monitoring to make sure they’re coping well on lower doses.”

And there does not appear to be an easy way to identify patients at high risk of adverse outcomes from tapering. There has not been much research to identify safe tapering practices or which patients require special precautions, said Fenton recently via email.

“Both the Department of Health and Human Services and the Centers for Disease Control and Prevention guidelines acknowledge the limited evidence base. Each guideline suggests that patients should be tapered if the risks of opioid therapy outweigh the benefits. This risk-benefit is a clinical determination and would ideally be discussed and agreed upon by the patient and the physician. The rapidity of tapering is another area of uncertainty; our study suggests faster tapers may be more risky, but risks were increased even in patients with slower dose reductions, so caution and close follow-up are needed in all tapering patients,” he added.

Pain researcher Jane Ballantyne, MD, has warned about the dangers of tapering long-term opioid therapy for more than a decade. She and her colleagues have emphasized that many patients on long-term opioid therapy develop what has come to be known variably as opioid dependence, complex persistent opioid dependence, or refractory opioid dependence. (There is no widely agreed-upon terminology in this area.)

“When opioids were first promoted as safe and effective treatment for chronic pain, the argument for safety relied on the [idea] that dependence would reverse within days, and the treatment could be easily stopped after a taper, if necessary. But experience does not bear this out,” Ballantyne and colleagues noted in a 2019 article.<sup>3</sup>

“As the number of patients grows who have difficulty tapering their opioids despite poor pain control, the pain and addiction fields have moved closer to accepting that withdrawal from opioid pain treatment is not simple or easily reversed,” they added.

In a 2019 commentary, Roger Chou, MD, Anna Lembke, MD, and Ballantyne warned that tapering and complex opioid dependence could become staggering problems for both patients and the US health care system.<sup>4</sup>

There are millions of patients on long-term opioid therapy in the United States. Some of these—a common, current estimate is 1.5 million—suffer from opioid use disorder (OUD), including addiction. However, a much larger group falls short of satisfying the criteria for OUD. Instead, they display complex dependence with serious but unpredictable risks.

As addiction specialist Lembke noted in a 2020 article in the *BackLetter*,<sup>5</sup> “It is essential that we build an infrastructure inside the house of medicine to help the millions of patients struggling with opioid dependence. Public policy to date has addressed opioid addiction and prevention, but the large cohort of patients who are opioid dependent but not addicted has been left behind.”

“Many of these patients are struggling with the adverse effects of long-term opioid therapy, including the risks of addiction and overdose death. They will need an infusion of resources to support tapering and provide alternative treatments for pain. This is not just an addiction crisis, it is a pain crisis, and I would add it is an iatrogenic opioid-dependence crisis. This latter group has fallen between the cracks of our public policy measures.”

### **Is the New Study Consistent With Prior Research?**

A *BackLetter* editor asked Chou whether the new study by Agnoli et al<sup>1</sup> documents the scale of risks that he and his colleagues have warned about.

“I think the results of the study are consistent with others we’ve seen on increased risk of adverse events in people undergoing opioid discontinuation/tapering. I do think it’s consistent with what we have noted in terms of the difficulty in tapering patients,” said Chou via email.

## What Proportion of People Who Attempt Opioid Tapering Have a Successful Result?

Tapering opioids appears to result in a significant dose reduction for most long-term opioid users who attempt it.

In a recent study,<sup>2</sup> Joshua Fenton, MD, and colleagues looked at the opioid dose trajectory among 113,618 insured or Medicare Advantage patients who engaged in tapering during the period from 2008 to 2018. These were all patients who were taking “higher doses” of opioids at baseline—at least 50 MMEs per day.

“Tapering was defined as  $\geq 15\%$  relative reduction in average MME/day during any of six overlapping 60-day periods in the initial 7 months of follow-up after the period of stable baseline dosing. Average monthly dose was ascertained during consecutive 60-day periods up to 16 months of follow-up,” according to Fenton et al.<sup>2</sup>

Over two-thirds of the group achieved long-term opioid dose reductions of at least 15% of their initial dose. And the proportion who achieved significant dosage reductions increased over the course of the study.

However, it was not clear from this study what proportion of patients who reduced their dosages also avoided worrisome adverse events.

A *BackLetter* editor asked lead author Fenton how many patients had broadly successful outcomes, in terms of *both*

tapering success and a lack of adverse events such as overdoses or mental health crises.

“This is a good question, and I can’t give a precise estimate,” Fenton responded.

“Overall, it must be the case that most patients can achieve long-term dose reductions without serious adverse events such as emergency or hospital visits for overdose or mental health crisis. The latter events occurred in fewer than 10 persons per 100 person-years in the tapering group of our study,” he explained.

“These serious events therefore affect a minority of patients, but this is a concerning high event rate. Probably most patients who taper have less severe adverse effects, but incident depression that does not result in an emergency or hospital visits may be relatively common.

“Indeed, if one were to account for less serious adverse events with tapering, such as mild withdrawal or milder mood effects, I suspect that most tapering patients will experience some of these effects. Hence, tapering patients need close follow-up and monitoring, especially for withdrawal symptoms or worsening mental health.”

Unfortunately, that type of careful follow-up and monitoring may not be routinely available in many US healthcare settings.

“As the study notes, it’s consistent with the US Department of Health and Human Services guidance on tapering—as well as guidance from the Oregon Pain Guidance group and others,” according to Chou.

“Like other research on this topic, the study does have limitations, in particular not being designed or able to know the indication for tapering—and residual confounding,” he added.

Chou is referring to the fact that this study was not able to determine why the patients decided to taper their opioid use in the first place. This, of course, might have influenced outcomes.

Residual confounding refers to the possibility that unmonitored factors besides the opioid tapering might have contributed to the overdoses and mental health crises.

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**Both rapid and slow tapering appeared to increase the risk of adverse events.**

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Chou also pointed to the fact that both rapid and slow tapering appeared to increase the risk of adverse events. “Though

there was some dose-response relationship between the speed of tapering and risk of adverse events, I think the fact that there was increased risk even with ‘slower’ tapers suggests that people undergoing tapering as a whole are in general at higher risk—not necessarily [just] due to the taper,” according to Chou.

“We of course need more data to understand how to safely taper and factors associated with adverse events. And as Anna, Jane, and I (and others) have suggested, many patients with prescription opioid dependence may in fact do better if they are transitioned to buprenorphine,” he asserted.

Buprenorphine can play a key role in “medication-assisted treatment” of opioid dependence and addiction.

In the wake of the pandemic, changes in the licensing and regulation of buprenorphine have made it more widely available. However, access is still uneven in many parts of the United States, particularly for those on the fringes of society.

There are millions of patients in the United States and Canada on long-term opioid therapy—many on high doses. And, despite a recent downturn in opioid prescription rates, US physicians still commonly prescribe opioids for people with back pain—particularly the elderly. This will be an ongoing problem.



## Large Retrospective Study of Tapering Risks

To briefly describe the recent study, Agnoli et al<sup>1</sup> used data from the OptumLabs Data Warehouse covering the period from 2008 to 2019.

**Overall, opioid dose tapering was associated with a statistically significant risk of subsequent overdose and with mental health crisis.**

The researchers included patients with stable, long-term, elevated levels of daily opioid use ( $\geq 50$  MMEs per day prescribed for at least 12 months). The patients in the tapering group had a mean age of 57.7 years (vs 58.3 years in the non-tapering group). A little more than half were women and 38.8% were commercially insured.

They divided the group into 2 cohorts: (1) those engaged in opioid tapering (at least a 15% relative reduction in mean daily dose during 6 overlapping 60-day windows within a 7-month follow-up period); and (2) those who did not taper their doses.

The main study outcomes were: (1) emergency department visits and/or inpatient hospital admissions for drug overdose, alcohol intoxication, or drug withdrawal; and (2) evidence of a mental health crisis (depression, anxiety, and/or suicide attempt).

The results were worrisome. Study subjects in the tapering group had 9.3 opioid overdose events per 100 person-years versus 5.5 events in the nontapering group.

And there was a similar bulge in mental health crises among those tapering off opioids. Men and women in the tapering group had 7.6 mental health crisis events per 100 person-years versus 3.3 events in the nontapering group.

Overall, “undergoing opioid dose tapering was associated with statistically significant risk of subsequent overdose and mental health crisis,” according to Agnoli et al.<sup>1</sup>

“These findings suggest that adverse events associated with tapering may be relatively common and support US Department of Health and Human Services (HHS) recommendations for more gradual dose reductions, when feasible, and careful monitoring for withdrawal, substance use, and psychologic distress,” they explained.

As mentioned earlier, patients on higher baseline opioid dosage had an elevated risk of adverse outcomes than those on lower dosages. However, as an accompanying editorial by Marc Larochelle et al<sup>6</sup> pointed out, a series of sensitivity analyses suggested that the adverse effects were not confined to men and women who engaged in rapid tapering.

Every researcher consulted for this article recommended caution in tapering going forward.

## Steady Increase in the Proportion of Patients Who Attempted Opioid Tapering Over a 9-Year Period

Tapering opioids is clearly on the rise in the United States, according to recent studies. In a 2019 study,<sup>7</sup> Joshua J. Fenton, MD, and colleagues from the University of California, Davis, looked at trends in dose tapering—and the rapidity of tapering—from 2008 to 2017—among more than 100,000 commercial insurance and Medicare Advantage enrollees.

The proportion tapering daily dosages increased from 10.5% in 2008 to 13.7% in 2015 to 16.2% in 2016 to 22.4% in 2017.

However, many of these subjects tapered more aggressively than is currently recommended. “Among patients tapering daily opioid doses, the mean (SD) maximum dose reduction was 27.6% (17.0%) per month, and 18.8% of patients had a maximum tapering rate exceeding 40% per month.”

This type of rapid tapering seems to put people on long-term opioid therapy at risk for significant adverse events such as overdoses and mental health crisis. “The downstream effects of opioid tapering on pain, withdrawal, mental health, and overdose risk warrant careful evaluation,” according to the researchers.

The 2016 Centers for Disease Control and Prevention prescribing guideline cautioned against higher-dose long-term opioid therapy and recommended tapering daily opioid doses by approximately 10% per week or less if the risks outweigh the benefits.<sup>8</sup>

As Larochelle et al<sup>6</sup> noted in their editorial in *JAMA*, “It is increasingly clear that opioid tapering needs to be approached with caution. In almost all cases, rapid or abrupt discontinuation should be avoided. Achieving the goals of minimizing risk yet also improving pain and function will require individualizing care and evidence-based approaches with more nuanced strategies that embrace the clinical complexity of the population of patients with chronic pain.” ■

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## Patient to Physician: “I Smoke Pot. I Need Surgery. Is That a Problem?”

*Editor's note: This composite article was adapted by Elizabeth A.M. Frost, MD, from a report by Michael Vlessides that was published originally in Anesthesiology News, online November 2021, with permission.*

In several parts of the United States over the last 10 years, cannabis has been legalized for medical and even recreational use. Decades before that, medical uses for cannabis were recognized, such as for easing cancer symptoms and chemotherapy side effects. As state and local governments with legal cannabis regulated its sale and prescribing within their borders, action groups arose to dissent and argue that the herb would have major adverse effects on all age groups, and especially on children.

What pain specialists, anesthesiologists, certified registered nurse anesthetists, and other medical professionals most want to know is this: How do cannabinoids affect a patient who ingests or smokes them regularly, when that patient is in the operating room and postanesthesia care unit, and how do they interact with anesthetic agents and postsurgery analgesia?

Anecdotal accounts and studies (some poorly designed) have been published pointing to the dangers. Other studies have suggested that exposure to the substance may not affect surgical outcomes.

A Canadian study concluded that routine cannabis use does not affect a composite outcome of respiratory/cardiac arrest, intensive care unit (ICU) admission, stroke, myocardial infarction, and mortality during hospital stays.<sup>1</sup>

However, a more recent study from Ohio reviewed the pharmacologic aspects and pathophysiologic effects that should be considered during perioperative management of chronic cannabis/cannabinoids users.<sup>2</sup> These researchers noted that the synthetic analogues provide higher potency with increased risk for complications. Cannabinoid liposolubility allows rapid accumulation in fatty tissue, thus prolonging elimination up to several days after exposure.

The research team further suggests that the multisystemic effects of cannabinoids and pharmacologic interactions with anesthetic agents may have serious consequences.

For example, low doses of cannabinoids increase sympathetic response (tachycardia, hypertension, and increased contractility), with high levels of norepinephrine detected 30 minutes after use.<sup>2</sup>

High doses enhance parasympathetic tone, leading to dose-dependent bradycardia and hypotension.<sup>2</sup>

Cannabinoids can interact with neurotransmitters, thereby creating potential drug interactions in the perioperative period.<sup>2</sup>

Preclinical studies indicate the potential for cardiovascular complications such as arrhythmias and blood pressure changes. Other vascular complications associated with cannabis exposure, which may include coronary spasm, sudden death, cerebral hypoperfusion and stroke, hyperreactivity, and upper airway obstruction, are commonly reported.<sup>3-7</sup>

### Effect on Pediatric Patients

Children may suffer adverse events. Smaller retrospective studies have suggested that cannabis may be associated with increased propofol requirements for induction and sedation. Hypothermia, shivering, and increased platelet aggregation have been documented.<sup>2</sup>

Aside from the systemic effects of the cannabinoids themselves, the smoking of cannabis—a common way that children and teens use it—can cause airway hypersensitivity, and upper airway obstruction.

**The multisystemic effects of cannabinoids and pharmacologic interactions with anesthetic agents may have serious consequences.**

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**Most studies include patients with cannabis use disorder, which may not reflect those who consume average daily doses.**

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## Cannabis and Perioperative Analgesia

Other research has demonstrated a potential link between cannabis use and perioperative analgesia both for and against good outcomes.<sup>8</sup> Results were mixed with respect to postoperative pain control. However, most studies include patients with cannabis use disorder, which may not reflect those who consume average daily doses.

## Research Addresses the Big Questions

It would thus seem that the question as to whether cannabis use may have adverse or beneficial effects during anesthesia remains unanswered.

Are there significant cardiovascular perturbations, drug interactions, or postoperative respiratory difficulties?

Should the anesthesiologist or the pain specialist advise stopping cannabis use 2 weeks preoperatively and risk withdrawal?

In an attempt to answer these questions, especially with regard to recreational users, Zhang and colleagues evaluated the effect of routine cannabis use on perioperative outcomes in a large patient cohort. They presented their results (as yet unpublished) at the annual meeting of the Regional Anesthesiology and Acute Pain Medicine Meeting of the American Society of Regional Anesthesia and Pain Medicine (abstract 1875) in October 2021. The researchers reviewed data from 1818 surgical patients presenting to the institution between January 2018 and March 2019. Cannabis users were identified by self-disclosure at their preoperative visit.

Multiple logistic regression with propensity score matching was used to adjust for potentially confounding baseline variables, including age, sex, body mass index, smoking status, other recreational drug use, surgical setting (inpatient vs ambulatory), type of surgery, and type of anesthesia.

The researchers reported that 606 patients preoperatively reported cannabis use, whereas the remaining 1212 served as the control group.

The total prevalence of reported cannabis use was 4% (606/15,048).

For the propensity score–matched analyses, there was a final cohort of 524 cannabis users with complete information, and 1152 patients in the control group.

The researchers found no difference between groups with respect to the primary end point: 7 cannabis users (1.2%) experienced the composite outcome of respiratory/cardiac arrest, ICU admission, stroke, myocardial infarction, or mortality

during their hospital stay, compared with 11 control patients (0.9%) (odds ratio of 1.06; 95% confidence interval, 0.23–3.98).

However, cannabis users experienced a greater incidence of arrhythmias than patients in the control group (2.7% vs 1.6%;  $P = 0.15$ ), and a decreased incidence of postoperative nausea and vomiting requiring treatment (9.6% vs 12.6%;  $P = 0.08$ ), but these differences were not statistically significant.

The incidence of severe pain during recovery was also comparable between groups, affecting 30.9% of cannabis users and 33.5% of the control group ( $P = 0.31$ ).

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**The investigators were confident that there is no convincing association between self-reported cannabis use and either major surgical outcomes or pain management.**

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Although this study answers the question as to whether recreational cannabis users can safely undergo anesthesia without stopping ingestion, more investigation is indicated.

For example, the variables that were not identified—such as alcohol or smoking, or the underlying pathology for which cannabis was being taken, among others—should be teased out.

Also, how much ingestion should be considered recreational, and what exactly defines the borders of abuse and disorder? Self-reporting, by definition, is subject to interpretation.

However, the study represents the largest single-center effort examining regular cannabis use in average doses, and the investigators were confident with the findings that there is no convincing association between self-reported cannabis use and either major surgical outcomes or pain management.

Nevertheless, perioperative decisions should be made based on appropriate considerations of dose, duration, and indication of use as suggested by recent guidelines.<sup>9</sup>

Other experts have noted that primary challenge in studies such as this is how to accurately estimate the percentage of cannabis users in a population of surgical patients. Although cannabis use is more common, there are still many patients who will be reluctant to volunteer the information or even admit to it. This may be especially true in states that have resisted any legislation to legalize it. Furthermore, under federal law, there is no such thing as medical marijuana. There is only marijuana, and it remains illegal for any use except research, although enforcement grows more sporadic.

The percentage of patients that can be identified preoperatively as recreational or medical cannabis users by self-disclosure is still very low (4.0%–4.2%), as we can observe in other studies that have included larger sample sizes.<sup>10</sup>



This continues to be an important limiting factor of studies that seek to accurately estimate the real impact of cannabis use on perioperative outcomes.

## Perioperative decisions should be made based on appropriate considerations of dose, duration, and indication of use as suggested by recent guidelines.

Other researcher teams might look at retrospective observational studies using secondary data repositories that may identify a higher percentage of cannabis users who undergo major or minor surgical procedures and may show different results from those revealed in this study or a study to examine perioperative outputs comparing cohorts of cannabis users and cohorts of patients with cannabis abuse disorders, using secondary data repositories that integrate large clinical data from multiple data sources, including the Veterans Affairs System and health insurance companies.

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## Matalafi: Study Indicates This Samoan Traditional Medicine Could Be as Effective as Ibuprofen, With Wider Application

Elizabeth A.M. Frost, MD

Matalafi is a small, inconspicuous tree about 2 meters high, with glossy red berries and small white flowers (Figure 1). Also known as *Psychotria insularum*, matalafi grows along the coasts and in cloud forests of Samoa. Traditional healers have used its leaves for centuries by grinding them into a paste or extracting the juice to alleviate inflammation associated with fevers, swelling such as elephantiasis, and skin infections, and to treat ailments from supernatural forces (ie, ghost diseases).

Samoa, officially the Independent State of Samoa, is a Polynesian island country consisting of 2 main islands (Savai'i and Upolu), 2 smaller, inhabited islands (Manono and Apolima), and several, uninhabited islands. The Lapita people discovered and settled the Samoan Islands around 3500 years ago. The country has been variously under the control of Germany, Britain, and New Zealand. It has been famous for its production of coconut derivatives and cocoa. Although Samoa

is mainly a Christian country, superstition and mythological beliefs have been widely held by much of the population.

Clearly, the matalafi plant was surrounded by a lot of superstition, even in traditional medicine, but recent research has focused on attempting to discover any scientific merit to the traditional medicines of the Samoan people. After all, many plants over the years that indigenous peoples have used for millennia have been shown to provide medicinal properties.

For example, over the past 40 years, the FDA has approved approximately 1560 new drugs, 64% of which were extracted,



**Matalafi plant.** (Photo by National Park Service of American Samoa, National Tropical Botanical Gardens.)



derived from, or based on chemicals found in plants and other natural products. And over the centuries, aspirin was derived from the willow tree. The malaria drug artemisinin was derived from sweet wormwood (*Artemisia annua*).

Digitalis comes from the foxglove. Metformin, a first-choice diabetes drug, originated with the French lilac, also known as goat's rue (*Galega officinalis*), a plant used in folk medicine for several centuries.

And, of course, opiates come from the poppy. There are myriad other historical examples, and sure to be more in the future.

Samoa, this small Polynesian archipelago in the Pacific Ocean, actually has a long history in regard to traditional medicines. Indeed, a devastating outbreak some 100 years ago emphasized the need for more reliance on traditional medicines. In 1918, during the final stages of World War I, the Spanish flu had taken its toll, spreading rapidly from country to country. On Samoa, there had been no epidemic of pneumonic influenza in Western Samoa before the arrival of the SS *Talune* from Auckland on November 7, 1918.

The New Zealand administration allowed the ship to berth in breach of quarantine; within 7 days of this ship's arrival, influenza became epidemic in Upolu and then spread rapidly throughout the rest of the territory.

Samoa suffered the most of all among the Pacific islands, with 90% of the population infected. The death rate was devastating: 30% of adult men, 22% of adult women, and 10% of children died. The cause of the epidemic was confirmed in 1919 by a Royal Commission of Inquiry into the Epidemic, which concluded that there had been no epidemic of pneumonic influenza in Western Samoa before the arrival of the *Talune* from Auckland.<sup>1,2</sup>

There was little that could be done at that time. The epidemic was blamed on the Papalagi-Jehovah, a Samoan term for foreigners and distrust of their God, further turning the people to use of traditional remedies.

But in 1989, a landmark agreement in Samoa—between traditional healers and researchers who had identified a potential retroviral agent against HIV, prostratin, in the bark of mamala plant—paved the way for access and benefit-sharing agreements that are now enforced under international law and designed to protect against biopiracy.

A new study was conducted recently by Seesei Molimau-Samasoni, PhD, a native Samoan, as part of her doctoral studies at Te Herenga Waka, Victoria University of Wellington, New Zealand.<sup>3</sup> She combined traditional knowledge with chemical and genetic analyses to investigate how matalafi works to reduce inflammation.

Molimau-Samasoni worked with traditional healers to harvest matalafi (and other plants native to Samoa, such as fue fuel

**The researchers found that matalafi interacts with iron inside cells. *P. insularum* juice and one of its bioactive components, rutin, both reduced fever-inducing pathways while increasing anti-inflammatory responses.**

sina), then mashed the leaves up in a blender, and shipped the juice to Aotearoa (the Maori name for New Zealand) for testing.

Using the model organism *Saccharomyces cerevisiae* (brewer's yeast), which shares some genes with humans, the researchers found that matalafi interacts with iron inside cells.

They identified and characterized an iron homeostasis mechanism of action in the traditional medicine as an unfractionated entity to emulate its traditional use. Matalafi interacted with the iron within cells of the body. The research team identified bioactive compounds—namely rutin and nicotiflorin—which both act to bind iron in a process called iron chelation.

The matalafi and its anti-inflammatory properties were compared against ibuprofen in laboratory-grown immune cells. The *P. insularum* juice and one of its bioactive components, rutin, both reduced fever-inducing pathways while increasing anti-inflammatory responses in freshly collected immune cells. In these cell experiments, matalafi was found to be as potent as the anti-inflammatory drug ibuprofen.

In addition, iron chelators like matalafi also have the potential to treat iron overload associated with transfusions, and have also been identified as prospective agents against common diseases including cancer, neurodegenerative diseases, cardiovascular diseases, and diabetes.

In addition to the anti-inflammatory and fever-reducing properties, scientists discovered another potential use. The findings highlighted the sensitivity of the *RIM101* gene deletion to the *P. insularum* homogenate, according to Andrew Munkacsi, PhD, also from the Victoria University of Wellington. Munkacsi noted that the gene is a major regulator of lipotoxicity, which underlies obesity.

Moreover, other molecular studies last year predicted rutin as a strong contender in inhibiting the viral replication of the SARS-CoV-2 virus that causes COVID-19, among many other applications.<sup>4</sup>

Molimau-Samasoni concluded that the project was unique in integrating traditional knowledge with different types of biological and chemical methodologies.

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## Coming Soon:

- Acute and Chronic Pain Related to COVID-19 Infection: A Narrative Review

# Game On: FDA Authorizes First Immersive Virtual Reality System to Alleviate Back Pain in Adults

The FDA has authorized marketing of the first immersive virtual reality (VR) system for adults with chronic lower back pain.<sup>1</sup>

EaseVRx (Applied VR, Los Angeles) is a prescription-use immersive VR system that uses cognitive behavioral therapy (CBT) and other methods to reduce pain in patients 18 years or older who have diagnosed chronic lower back pain. The VR system is also intended to provide pain interference. It should be used only after nonpharmacologic therapies (including CBT) have been tried.

EaseVRx was granted “breakthrough device” designation by the FDA. To qualify for this designation, a device must be intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition and meet at least one of the following criteria:

- Must represent a breakthrough technology;
- There must be no approved or cleared alternatives;
- Must offer significant advantages over existing approved or cleared alternatives; and/or
- Availability of the device is in the best interest of patients.

“Millions of adults in the United States are living with chronic lower back pain that can affect multiple aspects of their daily life,” said Christopher M. Loftus, MD, acting director of the Office of Neurological and Physical Medicine Devices in the FDA’s Center for Devices and Radiological Health. Loftus is quoted in the FDA’s press release<sup>1</sup> dated November 16, 2021.

He further was quoted as saying, “Pain reduction is a crucial component of living with chronic lower back pain. Today’s authorization offers a treatment option for pain reduction that does not include opioid pain medications when used alongside other treatment methods for chronic lower back pain.”

EaseVRx is available by prescription for home use and is indicated for moderate to severe back pain of at least 3 months’ duration. The system uses principles of cognitive behavioral therapy (CBT) and other techniques. It is intended for at-home self-use.

The system includes a VR headset and a controller, along with a “breathing amplifier,” which directs the patient’s breath to the headset for use in deep breathing exercises.

Authorization was granted after a randomized, double-blind trial involving 179 patients. The trial compared the device’s immersive three-dimensional program (treatment group) with two-dimensional program that did not use CBT treatment methods (control group).

The system’s treatment protocol consists of 56 VR sessions lasting 2 to 16 minutes as part of an 8-week program. The sessions use elements of behavioral therapy, including deep relaxation, distraction, healthy movement, acceptance and knowledge of pain and rehabilitation. Follow up was for 8.5 months at 1, 2, 3, and 6 months after completion of the program.

Patients using the device had higher satisfaction and greater symptom reduction than those in the control group. At the end of treatment, 66% of the VR participants reported greater than 30% reduction in pain and 46% of EaseVRx participants reported greater than 50% reduction, compared with 41% of control participants who reported greater than 30% reduction in pain and 26% reported greater than 50% reduction.

At 1-month follow-up, all participants in the EaseVRx group continued to report a 30% reduction in pain. After 2 and 3 months of follow-up, 30% reduction in pain remained for all treatment group outcomes, with the exception of pain intensity. In contrast, the control group reported a reduction in pain below 30% at 1-, 2-, and 3-month follow-up for all outcomes.

Current treatment for chronic lower back pain includes prescription and over-the-counter pain medications, exercise, corticosteroid injections, surgery, spinal cord stimulation and transcutaneous electrical nerve stimulation. CBT may be used to reduce the burden of chronic pain and increase function by helping patients shift from negative beliefs about the relationship between their pain and movement.

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# Topics in Pain Management CME/NCPD Quiz

To earn CME credit using the enclosed form, you must read the CME article and complete the quiz and evaluation assessment survey on the enclosed form, answering at least 70% of the quiz questions correctly. **Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form.** Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and mail the original answer form in the enclosed postage-paid business reply envelope. Your answer form must be received by Lippincott CME Institute by **February 28, 2024**. Only two entries will be considered for credit.

**Online CME quiz instructions:** Go to <http://cme.lww.com> and click on "Newsletters," then select *Topics in Pain Management*. Enter your *username* and *password*. First-time users must register. After log-in, follow the instructions on the quiz site. You may print your official certificate **immediately**. **Please note:** Lippincott CME Institute, Inc., **will not** mail certificates to online participants. **Online quizzes expire on the due date.**

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- The risk/benefit profile of long-term opioid therapy for chronic pain can be generally described as**
  - unfavorable with a host of adverse events.
  - related to a high quality of life and physical functioning.
  - without any known risks.
  - having positive effects on health and social functioning.
- In the study by Agnoli et al, high-dose opioids were defined as stable daily dosages of**
  - ≤10 MME.
  - 20–30 MME.
  - 40–45 MME.
  - ≥50 MME.
- The 2 patient groups compared in the study by Agnoli et al were (1) patients who did not taper long-term, high-dose opioids; and (2) patients who tapered their dosage by**
  - 5% over several weeks.
  - at least 15% over several months.
  - 10% over several months.
  - at least 10% over several weeks.
- Agnoli et al demonstrated that tapering events in patients on stable, long-term, higher-dose opioid therapy were associated with**
  - decreased risk of using other substances.
  - increased risk of social isolation.
  - decreased risk of self-harm behaviors.
  - increased risk of overdose.
- In addition to difficulty identifying patients at high risk of adverse outcomes from tapering, another area of uncertainty due to lack of evidence is**
  - protocols for managing symptoms of opioid withdrawal.
  - measuring the risk-benefit ratio of continuing long-term opioids.
  - rapidity of tapering long-term opioids.
  - calculating the risk-benefit ratio of opioid tapering.
- Promotion of opioids as safe and effective for chronic pain management relied on the assumption that dependence would**
  - reverse within days and treatment could be easily stopped.
  - not occur with long-term therapy.
  - not cause any withdrawal symptoms.
  - reverse immediately without symptoms.
- Of patients in the United States on long-term opioid therapy, a large number do not fit the criteria for opioid use disorder and instead display**
  - minimal dependence with no risks.
  - complex dependence with unpredictable risks.
  - moderate dependence with minimal risks.
  - minimal dependence with moderate risks.
- The possibility that unmonitored factors in the study may have contributed to overdose and mental health crises is a limitation termed**
  - Hawthorne effect.
  - diffusion.
  - residual confounding.
  - maturation.

9. The findings of the study suggest that adverse events associated with tapering
- are relatively rare.
  - only involve mental health crises.
  - primarily involve opioid overdose.
  - are relatively common.
10. When comparing adverse effects of tapering among patients on higher baseline opioid dosages compared with those on lower dosages, a series of sensitivity analyses suggested that
- only patients with rapid tapering experienced adverse effects.
  - adverse effects were not confined to only those on rapid tapering.
  - dosage and rapidity of tapering do not affect adverse effects.
  - few patients are at risk of adverse effects when tapering.

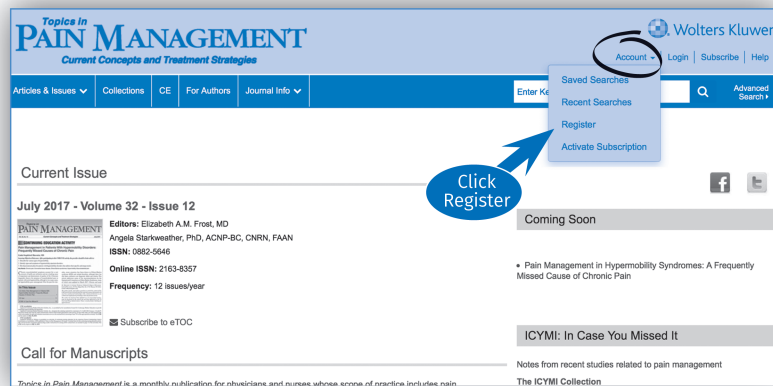
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