

Pain Research & Practice UPDATE

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AN ACHING STOMACH: RESEARCH AIMS TO GET YOUR BOWELS MOVING AGAIN

In a panel discussion at the American Pain Society (APS) 28th Annual Scientific Meeting, researchers presented data on the burden of opioid-induced constipation and possible strategies to help improve bowel function and restore quality of life.

Constipation is a common side effect of opioid medications, which are often prescribed for the management of moderate to severe chronic pain. It is estimated that as many as two out of five people taking opioids for pain relief suffer with constipation that is severe enough to severely limit their quality of life. They often report nagging discomfort, loss of appetite and irritability. Many patients say they are afraid to leave the house due to the unpredictability of their condition—not knowing when they'll need to be near a toilet.

While constipation is generally easily prevented and treated, in patients taking opioids it can be very difficult to manage. According to researchers, patients with opioid-induced constipation report taking up to seven different laxatives to find relief, many of which can take up to 3 days to work. A common concern among clinicians is that some patients may be less willing to try or adhere to treatment regimens with opioids because of the anticipated constipation and bloating.

Presenters urged healthcare providers to talk to their chronic pain patients about the possibility of constipation with opioid use and the need to initiate appropriate drug and non-drug therapies.

Injection may restore predictability of bowel function, helping patients regain control

A Phase III clinical trial showed that methylnaltrexone (Relistor) is effective for the treatment of opioid-induced constipation. Methylnaltrexone appears to counteract the constipating effects of opioids without affecting their ability to relieve pain.

In the study of 460 patients with a variety of chronic, non-cancer pain conditions, 34 percent of those receiving an injection of methylnaltrexone under the skin were able to relieve their bowels within four hours of treatment, compared with just 9 percent who received an inactive placebo. These results are encouraging because the medication seems to give patients the ability to better manage and predict bowel movements, giving them more control over their condition.

"While opioids are often used to treat patients with chronic, non-cancer pain, opioid-induced constipation can complicate their use," said lead study author, E. Richard Blonsky, MD, clinical professor of neurology at Northwestern University's Feinberg School of Medicine. "The results from this double-blind study indicate that subcutaneous Relistor may be a promising treatment option for this patient population. The drug appears to work in a lot of people; it's predictable and worked faster than was expected."

The most common side effects of methylnaltrexone were temporary

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The American Pain Foundation is the nation's leading independent non-profit 501(c)3 organization serving people with pain. Our mission is to improve the quality of life for people with pain by raising public awareness; providing practical information, education and support; advocating to remove barriers and increase access to effective pain management; and, promoting research.

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Welcome to the debut issue of The American Pain Foundation's *Pain Research & Practice Update*. This newsletter, which will be published twice a year, will translate some of the latest pain research and management practices presented at select scientific meetings, as well as those published in reputable medical journals. The *Update* will feature Q&A-style articles on emerging and promising areas of pain research and other hot topics (for example, research into the use of medical marijuana, ethics and pain care, disparities), and showcase the accomplishments of up-and-coming researchers and treatment clinics.

Much of this first issue is devoted to research and practice updates emerging from the 28th Annual Scientific Meeting of the American Pain Society that took place in San Diego, CA in May 2009.

We are excited to bring this new resource to people living with pain, their caregivers and healthcare providers who care for this patient population. Promoting sound research is key to improving pain care in America. We hope this newsletter will spark interest and dialogue about pain research and the need for increased funding.

Highlights of studies and practice guidelines included in this issue are for informational and educational purposes only; inclusion does not mean or imply APF's endorsement.

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AN ACHING STOMACH

abdominal pain, gas, nausea and dizziness. Overall, researchers say the injection was well tolerated, and no adjustments in dosing were needed in elderly patients or those with impaired kidney function. Patients who developed severe diarrhea or in whom doctors believed there was some sort of blockage in the intestines were not permitted to take the medication.

Currently, methylnaltrexone is approved for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care and have not responded well to other treatments.

Rocking in a rocking chair relieves abdominal symptoms following surgery

Robert Massey, PhD, RN director of clinical nursing at the University of Texas MD Anderson Cancer Center tested the use of rocking chairs in individuals experiencing postoperative ileus, a condition where the bowel quits working

for a few days following surgery.

During this time, patients may have difficulty eating and complain of nausea, vomiting and pain due to a buildup of gas and fluid in the bowel.

Dr. Massey studied 66 patients who had undergone abdominal surgery. He asked one group to rock for one hour each day following surgery in addition to walking around, while the other group sat in a non-rocking chair in addition to walking around.

Patients who used rocking chairs passed gas nearly 17 hours earlier than patients in the non-rocking group. The rocking group patients reported less pain and used less pain medication than the non-rocking group, however, the data was not statistically significant, according to Dr. Massey. This was probably the result of the excellent pain control provided to our patients and possible effects of the rocking motion allowing patients to relax.

"We are really connecting the dots that what happens in those first few days



after surgery has an effect on pain later on," said Dr. Massey. "If pain is not managed well, we do see patients transition to chronic pain much more easily than patients who have a better quality recovery."

Dr. Massey believes this non-drug approach in conjunction with comprehensive pain management may have clinical benefits for patients with pain, but further studies are needed.



CANNABINOIDS FOR PAIN MANAGEMENT FROM BENCH TO BEDSIDE AND BEYOND

A conversation with Dr. Mark A. Ware MBBS MRCP MSc

Assistant professor of anesthesia and family medicine, McGill University, Montreal, Quebec, Canada

In your session, you summarized data from several randomized controlled trials of pharmaceutical cannabinoids. What do these research findings reveal in terms of the use of cannabinoids for pain relief?

In the last five years, clinical trials of pharmaceutical cannabinoids have begun to identify the target symptoms that may be most influenced by the use of this novel class of agents. The conditions that have received the most attention in trials of cannabinoids include multiple sclerosis, fibromyalgia, HIV-associated neuropathic pain and cancer pain. Within these diseases, symptoms such as neuropathic pain, muscle spasticity and insomnia have been observed to respond significantly to cannabinoids when compared to placebo or control groups. Previous work with pharmaceutical cannabinoids in HIV and cancer studies suggests they may also be effective for appetite stimulation and easing nausea and anxiety.

So we are learning that cannabinoids have wide ranging therapeutic potential that goes beyond pain relief alone, and extends to multiple symptom management. This means that if an appropriate therapeutic cannabinoid is found to be useful, it may ultimately serve several medicinal purposes at the same time.

Exactly how do cannabinoids work in the body to relieve pain?

We now know that cannabinoids, which are defined as drugs that are either derived from or based on compounds found in cannabis (or marijuana), act by binding to specific receptors in the brain, spinal cord and peripheral nervous system. In doing so, they alter nerve activity. We also know that cannabinoid receptors exist in other tissues of the human body, including the gut, the heart,

the skin, and the immune system. The extent to which all of the therapeutic effects of cannabinoids operate through these different receptor systems remains unclear, and there may be additional receptors that have not yet been identified. These actions have been shown in animal models to protect nerves from damage and may normalize the function of these nerves where they have been disrupted by disease activity.

The cannabinoid receptors that are found in the brain are widely distributed and are involved in the complex behaviors and symptoms associated with chronic pain. While the effects of cannabinoids include analgesia, they may also serve to reduce the unpleasantness associated with chronic pain, to separate pain from unpleasant memories associated with the pain, and to increase a feeling of wellness in spite of persistent pain.

Does medical cannabis appear to be more effective in certain pain conditions or patients?

The pain syndromes that have been most extensively studied with respect to medical cannabis and cannabinoids are predominantly syndromes where the pain is believed to be neuropathic in nature. This includes peripheral neuropathy, such as HIV/AIDS, central neuropathic pain such as multiple sclerosis, or disorders of central pain processing such as fibromyalgia. Cancer pain may be both nociceptive and neuropathic and has also been shown to be responsive to cannabinoids.

Acute pain syndromes, such as postoperative pain, have not responded well to cannabinoid therapy. It may be that chronic pain syndromes are more responsive to cannabinoids because of increases in the number of cannabinoid receptors in chronic pain conditions. There are data from clinical trials

suggesting that cannabinoids have important effects on sleep and this may be useful for patients with chronic pain syndromes in whom sleep disturbance is an important contributing factor.

Some experts are concerned about delivery route, particularly smoking, given the negative impact on the lungs. What other delivery methods are being studied in patients?

Several novel approaches to the administration of cannabinoids are currently under investigation. Delivery of cannabinoids using a mouth spray has been evaluated and is currently the delivery system for a cannabinoid drug called Sativex. This spray delivers precise quantities of two cannabinoids (THC and CBD) into the oral cavity, some of which is absorbed into the bloodstream directly and some is swallowed.

Other approaches, such as delivery through skin patches, rectal suppositories, inhalers, and vaporizers, are all under investigation at various stages by companies and individuals around the world. Currently, the available pharmaceutical cannabinoids are administered orally as tablets, capsules or spray.

The use of medical marijuana remains controversial in the United States. What lessons can we learn from Canada and the UK?

Medical marijuana remains a controversial topic in many countries around the globe, with a range of legislative approaches that vary widely from country to country. In Canada, we have a federally approved program for medical marijuana access that has been in place for 10 years. This program has had its share of controversy

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and difficulties, but it continues to function with more than 3,500 patients currently authorized to possess cannabis for medical purposes, and the participation of 2,000 Canadian physicians. Authorized patients in Canada may obtain cannabis either directly from a federally authorized cannabis cultivation and distribution program, or they may grow their own, or they may obtain it from an authorized grower. This program was established following extensive stakeholder consultations with law enforcement agencies, addiction specialists, medical associations (including medical protection programs), patients and federal officials. The cannabis provided is tested for impurities, contaminants (including mold) and cannabinoid content, and strict quality control measures are in place.

There are important potential improvements to Canada's regulatory system, however. The program was initially put in place in response to legal challenges to Canada's constitution and continues to undergo legal challenges since only one strain of cannabis is currently available. Medical cannabis users have repeatedly claimed that different cannabis strains are used to treat different symptoms, a claim which has never been validated in clinical studies, and so this needs to be investigated. There is little education for physicians participating in this program and no active research program in place to follow the patients who are receiving cannabis legally from Health Canada.

In Canada, we have formed a non-profit physician and scientist-led consortium called the Canadian Consortium for the Investigation of Cannabinoids (www.ccic.net), which is mandated with educating physicians about cannabinoids as well as promoting and stimulating research on novel delivery systems and mechanisms of action. We believe that ongoing research and education are vital to continuing to inform us all of the potential risks and benefits of cannabis and cannabinoids in medical practice.



From your perspective, what are some of the major misconceptions about the use of medical marijuana that might be challenging access?

I think the main misconceptions around cannabis stem from almost half a century of cultural and social perspectives of cannabis. It is very hard to conceive of cannabis as a source of medicine when it is so powerfully associated in our society as a recreational drug. However, in the past 20 years, our knowledge of the mechanism of action of cannabinoids and our increasing awareness of the potential medical utility of cannabinoids is forcing us to rethink the way that we conceptualize cannabis. This is not always an easy proposition, as the drug has its enemies who propose absolute prohibition, as well as its fervent supporters who propose complete legalization. These polarized positions only serve to make the debate more flammable.

For medical use, it is important that we clearly separate medical use from recreational use, and consider cannabis and cannabinoids as we consider other medications. There must be a supply of quality-controlled product, with known consistency and purity, adequate studies of safety and efficacy, and ongoing monitoring at the population level of patients who choose or are prescribed this form of therapy.

The politics of marijuana have played an

important role in shaping our opinion of these drugs and, unfortunately, continue to provide barriers to a more open discussion of their potential role. I trust that science and the clinical evidence around cannabinoids will encourage us to rationally reconsider and re-evaluate the potential of cannabinoids in medical practice in this century.

Do you think cannabinoids will soon find their place in modern medicine?

I think cannabinoids have already begun to find a place in modern medicine. The evidence of the safety and efficacy of a small number of cannabinoids in clinical trials is evidence of the potential utility of cannabinoids. The major limitation now is the side effect profile of existing cannabinoid preparations, and a major focus of current pharmaceutical research is the development of cannabinoids that have no psychoactive effects. This is not to say that the existing cannabinoids are without merit, but there is an art to prescribing cannabinoids (using a “start low—go slow” approach is very useful) to minimize side effects and improve compliance.

One can only speculate as to how far the use of cannabinoids may go, and judging from the reports that are emerging worldwide of the potential therapeutic applications of cannabinoids, the limit for the potential market for cannabinoid therapeutics may be economic, as small drug companies struggle to find funding to pursue their research programs in tough economic times. It is impossible to anticipate the possible role of herbal cannabis in medical practice until steps are taken to provide quality controlled cannabis products for clinical trials, and until large-scale trials with herbal cannabis are conducted.

However, there is excitement in this field, there is enormous potential, and there is an enormous unmet clinical need for safe molecules and medicines to treat pain and relieve suffering. It is in this capacity that I think cannabis and cannabinoids are likely to find their true future.

THIS WILL HURT ME MORE THAN IT HURTS YOU (OR VICE VERSA): CONSIDERING INDIVIDUAL DIFFERENCES IN PAIN RESPONSES

General session explored why some people feel more pain, respond more readily to treatment

Why would two people undergoing the same surgery report vastly different levels of post-operative pain? Are genetic factors involved? What about gender? Do cultural expectations of pain and whether to report it play a role?

Roger B. Fillingim, PhD, professor, University of Florida College of Dentistry, addressed the issue during a crowded session at APS. He told the audience that while individual differences in pain responses have long been a research concern, scientists and clinicians alike have sometimes dismissed pain variability as a nuisance. He says many researchers will instead opt to study homogeneous groups of patients (for example, males only) or exclude or give less credence to “outliers”—those whose pain responses differ from the norm. Clinicians may respond to these same “outliers” by using words like “atypical” or “unexplained.”

As one would expect, this can add to patients’ frustration when trying to find the root cause of their pain.

But, understanding the obvious and even subtle variations in pain responses and why they exist is critical, especially as pain medicine evolves. In particular, such information will allow clinicians to more readily identify individuals at risk for persistent pain early on and tailor pain

treatment plans to maximize the therapeutic benefits for each patient.

In his opening remarks, Dr. Fillingim asked the audience of professionals to consider Norma, a 57-year-old, white female about to undergo a modified radical mastectomy (removal of the breast) for breast cancer. We don’t know how much pain she will experience after surgery, how well she will respond to pain medication like morphine or whether she will be at risk for chronic pain months after healing. But, by understanding individual differences in the pain experience, clinicians may be able to better answer these questions in the future.

Although there has been renewed interest in individual variability thanks to the genetic revolution, Dr. Fillingim cautions that a person’s genes won’t solve the whole pain riddle.

“Though genetic influences are significant in determining someone’s response to pain, both genetic and nongenetic variables interact to influence the pain experience,” said Dr. Fillingim. “Characteristics such as age, sex, race and ethnicity and personality all have been associated with pain responses, as well as other variables like mood, stress and cognitive processes that can amplify pain.”

Dr. Fillingim is a strong supporter of a biopsychosocial model of pain response. That is, individual differences are shaped by a complex interaction of biological, psychological and sociocultural factors and not only by linking pain to its clinical or diseases processes.

“Abundant evidence shows that pain and tissue damage are poorly related and there are significant differences among individual patients in their perception of pain that extend beyond pathology,” he said.

For example, in evaluating arthritis patients, Dr. Fillingim said tender and swollen joints and X-ray findings are relatively poor predictors of pain and function. However, psychosocial factors consistently account for significant variance in pain reports in these patients.

Dr. Fillingim urges clinicians to dig deeper to uncover the social and psychological circumstances of their patients to help gauge responses to pain and pain treatments. “It’s true that one size does not fit all, so we can’t assume everyone is average when it comes to managing pain,” he said. “The best course for clinicians is to get to know your patients better from a holistic perspective.”

Dr. Fillingim’s Top 10 List: What We Know About Variability in Pain Experience

1. There are major individual differences for both clinical and experimental pain (created by applying heat, cold, pressure or electrical stimulation).
2. There are major individual differences in responses to pain treatment. For example, patients vary widely in terms of the number of doses they need to get pain relief after surgery or tooth extraction.
3. Individual differences reflect the complexity of pain processing. Those highly sensitive to thermal pain show more pain-related activation on functional MRI brain imaging than those with low sensitivity.
4. Individual differences explain the poor correspondence between tissue damage and pain. Patients undergoing an identical surgical procedure can experience widely differing levels of post-operative pain. Differences in gender, pre-operative anxiety, and genetic factors can help us understand why the pain is so different even with similar levels of tissue damage from the surgery.
5. Multiple non-genetic factors contribute to individual differences. For example, studies show ethnic minorities report more pain related to AIDS, arthritis and after surgery than whites; compared to men, women are more likely to have migraine, irritable bowel syndrome, rheumatoid arthritis and osteoarthritis, among other pain conditions.
6. Genetic factors are important, too. In studies of twins, migraine, neck and low back pain and other types of pain may be hereditary and changes in certain genes appear to be linked with increased feelings of pain.
7. Our genes and other social and emotional factors interact. There is a need to understand how genetics combine with other characteristics to affect pain. For example, there is evidence that people who have both a genetic risk for higher pain and a psychological risk for higher pain report more pain than people who have either risk alone.
8. Understanding individual differences will inform treatment tailoring. In doing so, we can identify the best treatments for people in advance, rather than going through a trial and error process.
9. Individual differences may help identify risk for chronic pain. After certain exposures, such as surgeries, accidents or injuries, a small percentage of individuals go on to develop chronic pain, and once it is established, chronic pain is very difficult to treat. A better understanding of the risk factors for chronic pain in these situations would allow providers to start treatment early in hopes of preventing chronic pain from ever developing.
10. Understanding individual differences will help patients facing a variety of pain conditions.

MORE HIGHLIGHTS FROM AMERICAN PAIN SOCIETY ANNUAL MEETING

More than 100 leading researchers and clinicians in pain management attended the 28th Annual Scientific Meeting of the American Pain Society. Current research about the diagnosis, treatment and management of acute pain, chronic cancer and noncancer pain, and recurrent pain was presented. Workshops and sessions spanned basic science to advanced clinical guidelines and evolving drug and non-drug approaches to treating various pain conditions. Here are just a few highlights:

SKIN GEL EFFECTIVE IN TREATING OSTEOARTHRITIS OF THE KNEE AND HAND

Topical medicines applied directly to the skin have been shown in clinical trials to be safe and effective for treating osteoarthritis pain in superficial joints—those of the knee, wrist or hand that are surrounded by very little tissue and fat.

According to research, a topical nonsteroidal anti-inflammatory drug (NSAID) called diclofenac sodium 1 percent gel (DSG), could be an effective alternative treatment option for osteoarthritis patients who have experienced adverse side effects after using oral anti-inflammatory medications. DSG is applied to the skin over arthritic joints in the knee or hand.

Overall, study participants using DSG showed improvement in physical function over a 12-week course of treatment, with some improvement in pain also reported in participants over the age of 65.

According to study author Roy Altman, MD, of the University of California Los Angeles, topical NSAIDs have long been used to successfully treat osteoarthritis symptoms in Europe, but have not been assessed or made available in the United States until recently.

“Now we have the first well done set of studies in the U.S. showing that DSG is not only effective, but also quite safe, in improving pain and function in patients with osteoarthritis of the knee and hand,” said Dr. Altman. “The adverse effects of DSG are minimal and are usually skin reactions associated with the application of the gel itself.” The Food and Drug Administration (FDA) has approved the use of DSG under the trade name Voltaren Gel, as the first prescription skin gel to treat osteoarthritis joint pain.

NEW DRUG MAY RELIEVE PAIN ASSOCIATED WITH RESTLESS LEGS SYNDROME

Gabapentin encarbil (GEN), a new drug currently in development, appears to improve restless legs syndrome (RLS) and reduce the associated pain and discomfort.

RLS is a neurological disorder characterized by an irresistible and uncomfortable urge to move the legs, especially while resting or sleeping.

In a 12-week study, patients with moderate to severe RLS were randomized into two study groups and were either asked to take a GEN extended release tablet (1,200 mg) or an inactive placebo pill once daily with food.

Participants taking GEN experienced improvements in overall sleep quality, with fewer sleep disturbances and a decrease in nights with RLS symptoms. They also reported less daytime sleepiness and a greater ability to function during the day.

Researchers found that GEN significantly improved mood, and pain was reduced roughly twice as much in patients taking GEN versus those taking a placebo.

GEN has been proven safe and effective in treating RLS symptoms in several clinical trials, according to researchers. The trials have also demonstrated that GEN is well tolerated overall with mild to moderate adverse side effects. Drowsiness and dizziness were the most commonly reported adverse effects in study participants taking GEN.

PAIN-RELIEVING POWER OF ROMANTIC LOVE

Researchers interested in studying the pain-relieving power of romantic love had participants complete tasks known to produce feelings of love, as well as a separate distraction technique while exposed to periods of moderate and high acute pain (through the application of heat in the lab). They then looked at the activation of areas of the brain using functional magnetic resonance imaging. The love task was associated with a 46 percent reduction of low-intensity pain and a 13 percent reduction in high-intensity pain. Although the love and distraction tasks significantly reduced self-reported pain, only the love task was linked with the body's natural reward system. Feelings of love were also better at easing neural processing of pain, including sensory, affective and cognitive pain regions.

FIBROMYALGIA DRUG REDUCES DIABETES PAIN REGARDLESS OF PATIENT MOOD

New data shows that pregabalin, an anticonvulsant drug currently approved for the treatment of fibromyalgia, is associated with significant reductions in painful diabetic peripheral neuropathy (DPN) independent of anxiety and depression levels.

Anxiety and depression commonly occur with DPN which is characterized by pain and discomfort in the extremities resulting from the nerve damage caused by diabetes.

To investigate whether or not baseline anxiety and depression scores affected patients' response to treatment with pregabalin, researchers analyzed data from three randomized controlled clinical trials on the use of pregabalin to treat DPN. According to researchers, treatment with pregabalin was associated with significant improvement in pain among patients with anxiety and depression levels ranging from mild to severe.

The researchers concluded that mood symptoms do not affect the response to pregabalin for pain relief in patients with DPN.

POSTTRAUMATIC STRESS AMONG CHILDHOOD CANCER SURVIVORS UPS RISK OF ONGOING PAIN

Untreated posttraumatic stress symptoms (PTSS) may lead to ongoing distress in long-term cancer survivors. PTSS not only appears to contribute to ongoing depression and anxiety, but also pain. PTSS was also associated with a worsening of these symptoms over time.

Researchers at the University of California Los Angeles assessed cancer-related PTSS, pain symptoms and related disability in nearly 7,600 childhood cancer survivors participating in the Childhood Cancer Survivor Study.

Authors say the findings warrant the development of strategies to screen for and treat PTSS as part of routine follow-up care for childhood cancer survivors, especially for populations at risk (for example, women, minorities, people with certain types of cancer, those with low incomes or higher levels of depression and anxiety at baseline—when first surveyed).

ONE-TIME INJECTION OF AN ANTI-NERVE GROWTH FACTOR RELIEVES PAIN MORE EFFECTIVELY THAN NAPROXEN

Nerve growth factors play an important role in the development of the nervous system and also stimulate new nerve growth after injury. However, high levels of these proteins may be associated with more pain in several animal models and human pain conditions.

As a result, researchers suspect that drugs that interfere with nerve growth factor activity may help ease pain in certain patients. In this study, tanezumab, a monoclonal antibody that targets nerve growth factor was given to patients with chronic low back pain intravenously and appeared to effectively relieve symptoms.

The 220 participants in the study were required to have had chronic low back pain for at least three months that was regularly treated with analgesic pain medication. Patients were assigned to one of three groups and either received tanezumab, naproxen or an inactive placebo.

According to researchers, a one-time infusion of intravenous tanezumab reduced pain intensity and improved physical function in patients with persistent low back pain more effectively than either naproxen or placebo taken over a 12-week period. Authors found tanezumab was associated with significant improvements in treatment response (57 percent) versus naproxen (34 percent) and placebo (20 percent).

According to researchers, tanezumab was well tolerated with few adverse side effects reported. Pain, numbness and tingling in the hands and feet were reported as being mild to moderate by some patients.

Tanezumab is currently being investigated to treat a number of other conditions including pain associated with endometriosis, osteoarthritis, and bone metastases in people with cancer.

DIFFERING CONSIDERATIONS WHEN IT COMES TO PAIN TREATMENT DECISIONS

Understanding differences in racial/ethnic concerns about pain management therapies may help clinicians better understand some of the reasons for disparities in treatment. Focus groups including African Americans and Caucasians with cancer-related pain were conducted to identify the factors that are most important to patients when making decisions to use analgesic treatment for cancer pain.

Researchers found the most important consideration among African Americans is the "severity of side effects," whereas Caucasians reported it to be the "degree of pain relief." Caucasians were also most concerned that "pain medications stop working," while African Americans reported "fear of addiction." Both groups admitted worrying about out-of-pocket expenses.

RETHINKING PAIN MEDICATIONS IN OLDER ADULTS

The American Geriatrics Society (AGS) has issued new guidelines on the use of medications for the management of persistent pain in older adults.

The new guidelines eliminate the use of non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin, ibuprofen and naproxen, which had previously been recommended for the treatment of pain in older adults. The guidelines state that the risks of over-the-counter and prescription NSAIDs often outweigh the benefits when it comes to treating patients over the age of 75. Experts now recommend that NSAIDs be “considered rarely” and with “extreme caution.”

“NSAIDs are wrought with problems. They increase the risk of cardiovascular disease, kidney problems, intestinal bleeding and hypertension, and can be even more problematic among seniors,” said F. Michael Gloth, III, MD, FACP, AGSF, associate professor of medicine, Division of Geriatric Medicine & Gerontology, Johns Hopkins University School of Medicine, who spoke as part of a luncheon symposium at the American Pain Society annual meeting.

If NSAIDs must be used, Dr. Gloth says that topical agents, such as a gel to ease joint pain, are preferred.

The guidelines were created by a panel made up of experts in a variety of specialties including geriatric pain management, pharmacology, neurology and palliative care.

“We reviewed thousands of articles to give clinicians guidance in terms of interventions that can safely be used in this population,” Dr. Gloth said.

The guidelines emphasize that all patients with moderate-severe pain or diminished quality of life due to pain should be considered for opioid therapy, which may be safer for many patients than long term use of NSAIDs. The use of adjuvant and other drugs

for older persons with unmanageable pain problems are also discussed.

AGS currently recommends acetaminophen as the first choice medication for older adults experiencing mild-to-moderate muscle and bone pain, combined with physical therapy, exercise and other non-drug treatment options when appropriate.

While older people frequently experience persistent pain resulting from a variety of chronic health problems including degenerative bone disease, arthritis, and cancer, Dr. Gloth says it’s important to remember that pain is not a normal part of the aging process and shouldn’t be ignored.

“If pain isn’t being relieved, patients may need to request additional consultations or try other interventions. We can almost always be successful in reducing pain if the appropriate steps are taken,” he said.

Ongoing and untreated pain can result in additional harm including falls, sleep problems, depression and anxiety, and diminished quality of life.



OLDER ADULTS SEEK PERSONALIZED CARE PLANS TO MANAGE MULTIPLE HEALTH PROBLEMS

Older adults who already have one medical condition no longer just have one. According to estimates, nearly half (45 percent) of Americans ages 65 to 79 report living with three or more health problems. These often include diabetes, arthritis, high blood pressure, high cholesterol levels, cancer, and heart failure—many of which include pain as a major symptom.

Juggling treatment plans and medication schedules and staying on top of different doctor appointments can be difficult. Unfortunately, many care models often only

focus on one condition (for example, diabetes or blood pressure lowering). And because of the fragmented state of the U.S. health system, patients often feel as though there is no one provider coordinating care. Instead, they report spending much of their time educating new providers about their health histories.

Researchers recently interviewed older patients—most of whom had four to nine chronic conditions—to try to identify what should be included in care models designed to address multiple chronic conditions.

APS ISSUES NEW GUIDELINES FOR LOW BACK PAIN

The American Pain Society has issued new guidelines for the treatment of low-back pain, which recommend the use of noninvasive therapies including physical therapy over surgery or other interventional therapies (for example, injections or spinal cord stimulation).

"We reviewed the best available evidence and, in many cases, we couldn't find strong evidence that these interventional therapies and surgeries were all that helpful for most people with low-back pain," said Roger Chou, MD, lead study author and an associate professor of medicine at the Oregon Health and Science University.

The researchers developed the guidelines after reviewing 161 clinical trials evaluating the effectiveness of both invasive and noninvasive treatments for low-back pain.

According to Dr. Chou, even where surgical interventions appeared to be supported by some evidence, the effects were not large for the average patient and don't necessarily outweigh the risks or the expense of such procedures.

"Most patients should try to stick with noninvasive therapies like exercise, physical therapy, medications, and self-care, which have been proven to work, before considering more invasive interventions," said Dr. Chou.

The guidelines also underline the importance of shared decision making between healthcare providers and patients.

Dr. Chou says that if patients decide to undergo interventional procedures or surgery, it's important that they are well informed about the risks and benefits so they can make decisions that align with their personal preferences and values. This requires patients to have honest discussions with their healthcare providers.

"These low back guidelines are among the first to really emphasize the importance of shared decision making, and we hope that clinicians and patients start to understand that there isn't one right answer when it comes to treating low-back pain," said Dr. Chou.

While surgery often provides quick relief, the benefits tend to wane over a period of time; and patients who opt not to have surgery tend to improve with noninvasive therapies, according to Dr. Chou. "For herniated discs and spinal stenosis, it's true that people initially do better after surgery compared to continuing non-surgical therapy. But if you follow people long enough, both groups may ultimately end up about the same," he said. "So it's important for patients to consider whether quicker pain relief is worth the additional risks and costs of surgery."

Dr. Chou says he hopes the guidelines will allow people to have more realistic expectations about what certain therapies can and can't do.

"Some people report being told that their low-back pain is going to be cured



by an interventional therapy or by surgery," he added. "For a number of interventional therapies, these claims just haven't been borne out, and we're beginning to see that the more aggressive treatments don't necessarily make people better."

Dr. Chou says that more research is needed to figure out how to effectively treat low-back pain and minimize risks to patients.

Americans spend at least \$50 billion each year on low-back pain. It is the most common cause of job-related disability and a leading contributor to missed work, according to the National Institute of Neurological Disorders and Stroke.

The new guidelines were published in the May 2009 issue of the journal *Spine*.

Participants stressed the need to:

- Develop ongoing relationships with providers
- Identify and allocate a single provider to serve as care coordinator; this person would be in regular communication with other specialists so that patients' care plans are integrated and less time is spent briefing each doctor on changes to individuals' health status or treatment regimens
- Have convenient access to providers by telephone, email or in-person for questions only
- Have written plans so they do not have to rely on their memory or sketched notes
- Include shared decision making when creating care plans

Researchers say more research is needed to map out comprehensive systems that are less burdensome on patients, but are not overly labor intensive for the health system. Future research is needed to help determine how more personalized care plans can be implemented, who would benefit most and when it should be started.

Sources: AHRQ (www.ahrq.gov); Bayliss EA, Edwards AE, Steiner JF, Main DS. "Processes of care desired by elderly patients with multimorbidities." *Family Practice* 25(4):287-293.

FROM BENCH TO BEDSIDE: ASPIRING RESEARCHERS SEEK TO UNRAVEL PAIN MYSTERIES

Compared to other medical specialties, pain medicine is still in its infancy and vastly underfunded. To help solve the pain riddle, the field must attract up and coming researchers and clinicians. Here is a look into some of the work being done by two researchers.

RESEARCHER PROFILE



Gregory O. Dussor, PhD

Assistant Professor, Pharmacology, University of Arizona
Associate Editor, PAIN

Gregory Dussor, PhD, likes to solve problems. He is trying to unravel a small piece of the pain puzzle in his lab at the University of Arizona, Department of Pharmacology.

Dussor is studying two types of nerves: those that send pain signals from the skin into the spinal cord and central nervous system and others from the meninges (membranes covering the brain) into the brain stem.

Dussor and his team are able to identify the nerves with a fluorescent tag, take them out of animals and then study them in a petri dish under a microscope.

They hope to learn more about the properties of the nerves that target the skin so they can determine what goes awry in conditions like diabetes or shingles in which patients can feel intense, stabbing or burning pain in the skin.

Dussor says there appears to be an interaction between these nerves and the cells of the skin that may result in pain.

"We're trying to characterize how the nerves and cells are talking to each other, so we can design new drugs to

block their communication and treat pain in ways that aren't currently possible," he said.

Dussor is conducting similar experiments on the nerves that target the brain membranes (meninges) in an effort to better understand migraine headaches, a neurological condition that affects up to 30 percent of women and 10 percent of men at some point in their lifetimes.

He is looking specifically at the types of changes in the nerves' environment that may activate them to initiate the pain signals that result in a migraine.

"Migraine is a common, sometimes debilitating condition that we know very little about and current drugs are only effective in up to 40 percent of patients, so we have a lot of people who are still suffering," said Dussor. "We hope that our research will pave the way for better, more effective treatments that will block nerve activation and positively impact the large numbers of people who experience migraine."

Dussor says his own experience with pain was the driving force behind his interest in pain management.

"I'm lucky enough not to have the intense chronic pain that many people suffer from, but I've had various sports injuries where the pain lasted for weeks, even months, so I can at least partially relate to what these people might be feeling every day of their lives," he said.

Dussor's ability to empathize with people in pain keeps him focused when doing experiments in the lab.

"While it would be a great accomplishment to see a new drug come directly out of this research, my ultimate reward comes from asking questions and finding new answers and knowing that somewhere down the line these discoveries might contribute to improving people's lives," he said.

Dussor would eventually like to see pharmaceutical companies take an interest in his research so they can carry it to the next level by developing compounds to be tested in humans. His research is currently funded by the University of Arizona and a grant from the American Pain Society, and was a recipient of the Future Leaders in Pain Research Award from the American Pain Society in 2008.



Ajay Wasan, MD, MSc

Assistant Professor of Anesthesiology and Psychiatry, Harvard Medical School

Ajay Wasan, MD, MSc, is trying to crack the mystery of why individuals with pain respond differently to the same treatment.

In his lab at the Harvard Medical School Brigham and Women's Hospital Pain Management Center, Dr. Wasan is studying various pain treatments, ranging from acupuncture to medications and other interventions, and looking at different groups of people to see how they respond to each type of treatment.

"Pain medicine is a very young and developing field, and we see a huge variability in how people respond to pain treatments, and we still don't know why that is," said Dr. Wasan. "It's crucial that we gain a better understanding so we can decide which treatments to give depending on the characteristics of each patient."

Dr. Wasan is looking specifically at characteristics like depression and anxiety levels to see whether or not they predict success or failure for different pain treatments.

"Many patients with pain experience a lot of sadness and frustration, and they have trouble coping," said Dr. Wasan. "Several studies have confirmed that psychiatric factors can explain the differences in how patients respond to treatments, but no one has really broken it down treatment by treatment until now."

In Dr. Wasan's first study, patients with very few psychiatric symptoms responded to a treatment of intravenous morphine for low back pain at least 50 percent better than the patients who had more psychiatric

problems. Individuals with more depression and anxiety responded significantly worse.

"You would never use IV morphine as a treatment for chronic low back pain, but it's a good way of looking at the impact of depression and anxiety in a laboratory setting," he said.

With funding from the National Institutes of Health and the Arthritis Foundation, Dr. Wasan is conducting a series of similar studies looking at patient response to a number of current pain treatments. He'll also be using functional Magnetic Resonance Imaging (fMRI) imaging tests to

"It's crucial that we gain a better understanding so we can decide which treatments to give depending on the characteristics of each patient."

illustrate how the brain functions differently in pain patients with and without anxiety and depression.

Dr. Wasan hopes his research will help the most vulnerable people who aren't responding well to treatment.

"We want to design interventions for patients who are prone to depression and anxiety symptoms so that we can treat them appropriately and improve their ability to respond right from the beginning," he said. "It's important that all physicians and practitioners—not just pain specialists—understand the need for a comprehensive assessment of patients prior to prescribing pain treatments, because the same treatment isn't going to work for everyone."

With diverse interests and training in orthopedic surgery, psychiatry, medical anthropology, family medicine, chronic pain management and anesthesia, Dr. Wasan describes himself as a "one-man multidisciplinary clinic." But he admits that he can't carry out his research alone.

"I am blessed to have five incredible collaborators and mentors who have helped me push my own work forward tremendously. Gone are the days of the mad scientist working alone in the lab," he said. "I couldn't do this without the support of my colleagues."

Dr. Wasan says the overlap between seeing patients and doing research is the most rewarding aspect of his job.

"That's where I can put all my skills to work and enjoy myself," said Dr. Wasan. "When I'm seeing patients I can be thinking about what we know and don't know, and that will often give me ideas for my research. And when I do research, it sparks my creativity and gives me new ideas for how I can treat my patients with chronic pain."

His next study will investigate patient response to opioid treatment for low back pain over a period of six months.



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NEW DRUG OPTION APPEARS SAFE FOR CHILDREN WITH SICKLE CELL

Hydroxyurea, which was approved in 1998 to prevent sudden episodes of pain in adults with sickle cell anemia, may also benefit children with the disease. Sickle cell disease is a hereditary blood disease in which the body produces abnormally shaped red blood cells. These cells can clog blood vessels, blocking blood flow and resulting in piercing pain (usually in the chest, stomach and bones) and organ damage.

A recent review of 26 published studies by researchers at the Johns Hopkins Evidence-based Practice Center found that hydroxyurea may be safe and effective for children. One randomized clinical trial showed that children taking the medication had fewer and shorter hospital stays compared to those who received a placebo. The number of crisis pain episodes was also found to be reduced in three out of four observational studies.

The potential benefits of this drug in children were also recognized in 2002 when the National Heart, Lung and Blood Institutes issued a recommendation for its use in the pediatric population. Further research is needed.

Source: AHRQ Research Activities, www.arhq.gov; National Library of Medicine, www.medlineplus.com

ELEVATED LEVELS OF TWO PROTEINS MAY PREDICT RISK OF DEVELOPING RHEUMATOID ARTHRITIS

High levels of two proteins appear to be useful in predicting future risk of rheumatoid arthritis (RA), according to research published in the March 2009 issue of *Arthritis & Rheumatism*. Tumor necrosis factor (TNF) and interleukin-6 (IL-6), which are released by the immune system, are important mediators of inflammation. Sustained inflammation in the body, which usually goes unnoticed at first, has increasingly been linked to a variety of conditions, including all types of

pain, heart disease, diabetes, cancer, Alzheimer's and gum disease.

Researchers at Brigham and Women's Hospital and Harvard Medical School found that even modest increases in these biomarkers have predictive value up to eight years before there are symptoms of RA. Authors are encouraged by the results, stating these findings may help clinicians better identify high risk individuals based on the presence of

certain antibodies and elevated biomarkers of inflammation and might ultimately allow for earlier and more effective treatment. Because RA often hits people between the ages of 25 and 55—a very productive and busy time for professional development and raising families—the ability to predict its onset, treat it sooner and potentially slow disease progression is important.

RESEARCHERS INVESTIGATE NEW DRUG DERIVED FROM SNAIL

Results of a pre-clinical study of leconotide, an investigative calcium channel blocker, show that it has the potential to be safe and effective as a new non-opioid treatment for pain relief, according to research presented the American Academy of Pain Medicine's 25th Annual Meeting. Calcium channels are structures in the body that allow cells to transmit electrical charges to one another, and some types play a role in pain transmission.

When injected under the skin, leconotide

acted on calcium channels to reduce pain, but did not act on other calcium channels to cause negative side effects. The drug, which is derived from a fish-hunting cone snail called *Conus Catus*, appeared to be even more effective when given along with a potassium channel opener (flupirtine).

Unlike currently available treatments of this type, leconotide does not have to be injected directly into the spinal fluid to achieve pain relief, so it has potential for a variety of drug delivery options

including a nasal spray, skin patch or pill.

"There is a tremendous need for non-opioid treatments for neuropathic pain, so the results of this study are exciting for researchers in the field of pain medicine, doctors whom treat pain, and patients who suffer or are undertreated because of the abuse potential and side effects associated with opioid treatments," said Colin Goodchild, PhD, and director of the Centre for Pain Research and Palliative Care, Monash Institute of Medical Research.