



Pain Management

A Series by REALWORLDHEALTHCARE.org

May 2017

An estimated 100 million adult Americans experience chronic pain every year. Although pain is universal, it is experienced uniquely by each person and care often requires a combination of therapies and coping techniques. Successful treatment, management and prevention of pain requires an integrated approach that responds to all the factors that influence pain.

Pain Management is a recently published series of articles that brings you the stories behind the research and treatment of pain. It recognizes the researchers, clinicians and organizations committed to improving pain management therapies and techniques. Please accept this complimentary copy as our way of thanking you for your commitment to advancing medicine and improving people's lives.

founding sponsor



HEALTHWELL
FOUNDATION®

co-sponsor

biotechPrimer

www.RealWorldHealthCare.org

CONTENTS

A Big Pain	3
<i>Emily Burke, PhD, Biotech Primer</i>	
Assessing Chronic Pain	6
<i>Bryan Jensen, PhD, VA Salt Lake City Health Care System</i>	
Calling for an Integrative Approach to Pain Management	9
<i>Bob Twillman, PhD, FAPM, Academy of Integrative Pain Management</i>	
Pain Management for Cancer Survivors	13
<i>Judith A. Paice, PhD, RN, Northwestern University Feinberg School of Medicine</i>	
Multiple Sclerosis: Overcoming Pain	16
<i>Dawn Ehde, PhD, University of Washington School of Medicine</i>	
Challenges in Pain Management for MS Patients	20
<i>Theodore R. (Ted) Brown, MD, MPH, Evergreen Health Multiple Sclerosis Center</i>	
Pain Management: Opioid Adherence in Cancer Patients	23
<i>Salimah H. Meghani, PhD, MBE, RN, FAAN, University of Pennsylvania School of Nursing</i>	
APS Calls for Pain Management Funding	26
<i>David Williams, PhD, American Pain Society</i>	

A Big Pain

By Emily Burke, PhD, Director of Curriculum Development, BiotechPrimer.com

Editor's Note: This article originally appeared in [Biotech Primer Weekly](#). For more of the science behind the headlines, [please subscribe](#).



The Science Behind Opioids

The opioid addiction epidemic gained attention at the highest levels of U.S. policy circles this past year, as presidential candidates that disagreed on nearly everything else vowed to make fighting the problem a priority if elected. In July, the U.S. Senate overwhelmingly approved a bill to strengthen prevention, treatment, and recovery efforts. And no wonder – according to the Center for Disease Control, opioid overdose deaths are at an all-time high – a stark reality that highlights the dark side of a class of treatments serving a vital need. Opioid pain medications manage the severe short-term or chronic pain of millions of Americans. While these medications mitigate needless suffering, joining forces are the government, corporations, and medical community to battle against opioid abuse and addiction.

We wonder: what is the science behind the headlines? So, let's talk about how pain medications work, the different types on the market, and the approaches to developing less addictive versions of opioid drugs.

Opioids vs. NSAIDS

There are two main categories of pain medications, opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Although these two categories of drugs work differently, they do share one thing in common: both are derivatives of natural products. The NSAID Aspirin is a synthetic version of an extract from willow tree bark, and opioids are synthetic versions of opium and morphine, which come from poppy flowers.

Aspirin works by inhibiting an enzyme called cyclooxygenase 1 (COX-1). Once stopped, COX-1 is no longer able to produce signaling molecules, called prostaglandins and thromboxanes. Prostaglandins and thromboxanes have a wide variety of functions, including mediating aspects of inflammation (fever and swelling) as well as promoting neuronal response to pain. Other NSAIDs, such as ibuprofen and naproxen, also work by inhibiting COX-1 or its sister enzyme COX-2.

Opioid pain medications, such as Oxycontin and Percocet, work by binding to mu receptor proteins on the surface of cells in the central nervous system (CNS)—think brain and spinal cord. While the CNS is tasked with relaying pain signals, opioids decrease the excitability of nerve cells delivering the message, resulting in pain relief—along with a feeling of euphoria in some users.

Lessening the Pain

Short term medical use of opioid pain killers rarely leads to addiction—when properly managed. Due to the euphoria-inducing effects of the drugs, long-term regular use, or use in the absence of pain, may lead to physical dependence and addiction. And because regular use increases drug tolerance, higher doses are required to achieve the same effect, leading abusers to consume pain pills in unsafe ways such as crushing and snorting or injecting the pills. According to the **Centers for Disease Control**, 44 Americans die every day due to prescription painkiller overdose. At the same time, chronic pain is also a serious problem, affecting approximately 100 million U.S. adults, while millions of others suffer acute pain due to injury or surgery. The medical need for these drugs is very real despite the dark side.

The answer to developing less addictive drugs may be found in a drug that blocks pain without inducing euphoria. These new drugs will need a different mechanism of action than traditional opioid drugs, which bind to the mu receptors of cells inside the CNS. Drugs under development include those that bind to a different type of opioid receptor, the kappa opioid receptor. These receptors are present on sensory nerves outside of the CNS. Preclinical studies suggest that targeting these receptors could be effective at reducing pain without driving addictive behaviors. A lead candidate, CR845, is currently in Phase 3 clinical testing for post-operative pain and pruritus (severe itching), and in Phase 2 clinical testing for chronic pain. Also under development are compounds that selectively activate cannabinoid (CB) receptors outside of the CNS. CB receptors inside the CNS are linked to the psychoactive qualities of marijuana; those outside the brain are found on white blood cells and have been shown to be involved in decreasing pain and inflammation. A lead CB receptor activator, CR701, is in preclinical development.

Also under development are small molecule inhibitors of ion channels – proteins on the surface of nerve cells that help to transmit pain signals by allowing positively charged calcium ions to enter the nerve. This plays a critical role in sending the pain signal to the brain, yet because it works on nerves outside of the brain, it has less of a potential for addiction. Phase 1 clinical studies are currently underway of HX-100 for the treatment of painful diabetic neuropathy.

Another development is a derivative of capsaicin, a naturally-occurring compound found in chili peppers. Capsaicin has pain relieving properties and has been used as a natural remedy. The lead candidate, CNTX-4975, is a highly potent, synthetic form of capsaicin designed to be administered via injection into the site of pain. CNTX-4975 targets the capsaicin receptor, an ion channel protein on the surface of nerve cells. When CNTX-4975 binds the capsaicin receptor, the influx of calcium ions results in desensitization of the nerves, making them unresponsive to other pain signals. This effect

can last for months, and only affects nerves near the site of injection. CNTX-4975 is currently in Phase 2b clinical studies for knee osteoarthritis, and Phase 2 clinical studies for Morton’s neuroma, a sharp pain in the foot and toe caused from a thickening of the tissue around one of the nerves leading to the toes.

Earlier this year, researchers at Tulane University published a paper that shows great promise for the development of effective yet non-addictive pain medications. They have developed a compound that is derived from the endogenous opioid endomorphin. Endogenous opioids are chemicals produced naturally by the body that bind to and activate the mu opioid receptors, resulting in pain relief and mild euphoria without the detrimental side effects associated with opioid drugs such as depressed respiration, motor impairment, and addiction. Scientists have tried before to develop safer pain medications based on endogenous opioids, but have not been successful, due to the instability of these molecules. The Tulane team created a derivative of endomorphin that is stable and binds to the mu receptor in such a way that pain relief occurs, but not the negative side effects listed above. Clinical testing is expected to begin by the end of 2017.

An Antidote to an Overdose

Overdosing can be fatal since respiratory failure occurs at high blood concentration levels of opioids. If an overdose is suspected, the individual should be treated as quickly as possible with naloxone—a “competitive antagonist” of the mu opioid receptor. Simply put, a competitive antagonist binds the receptor without activating it. Since naloxone doesn’t activate the receptor, it doesn’t have any pain-relieving or euphoria-inducing qualities; rather, it prevents the opioid drugs from binding. It may also displace opioids that have already bound the mu receptor, aiding in the stoppage of an overdose.

Cocktail Fodder: Runner’s High

Some folks love to run; others avoid it at all costs. This might be explained by inherent differences in sensitivity to the natural opioids called endorphins that are released during exercise. Not everyone experiences the “runner’s high” — feelings of calm and mild euphoria – just like not everyone experiences euphoric feelings from pain medications. These differences may help to explain why some people enjoy exercise and others don’t, and why some people get addicted to opioids—while others can take them or leave them.

[Read this article](#) on Real World Health Care.

Assessing Chronic Pain

Our series on Pain Management continues this week with insight on how clinicians assess pain. We spoke with Bryan Jensen, PhD, a clinical health psychology postdoctoral fellow at the [VA Salt Lake City Health Care System](#), where he treats inpatients and outpatients with chronic pain as well as facilitates primary care chronic pain recovery groups. Dr. Jensen recently graduated with his doctorate in clinical psychology from [Virginia Commonwealth University](#), where he focused his clinical and research work serving patients with chronic disease in both inpatient and primary care populations, most notably underserved patient populations and those with high levels of co-morbidities.



We asked him about his recent [Translational Behavioral Medicine](#) article on [chronic pain assessment within a translational framework](#) and the challenges facing researchers and clinicians who are studying and treating chronic pain.

Real World Health Care: Can you provide a summary of your recent article in *Translational Behavioral Medicine*?

Bryan Jensen: As researchers and clinicians seek to treat pain, we first need to understand if we are assessing pain accurately. The article is a review of how pain is assessed across the translational continuum. It starts by exploring the basic science of animal models of pain and the types of methods used in that setting to assess pain. Clearly, these methods are not the same methods we use in clinical practice — a rat is not the same as a human — but they must translate. We are starting to understand that older models of pain assessment may no longer be adequate, so we are looking at newer models and seeking to determine a more accurate definition of pain across clinical and research settings. Other translational issues are outlined with a focus on how providers are using pain assessment tools and how they can implement newer evidence-based tools for more evidence based assessment.

The article points to three main areas that hold promise to bridge current gaps. One is using computer adapted technologies to obtain self-reported measures of pain. Because we can't take a "thermometer reading" of pain, we rely on patients' assessments. But pain is multi-dimensional, and asking patients to go through a 100-question survey is daunting and time-consuming, so scientists have developed computer programs that evaluate how patients respond to clinicians' questions and adapt those responses so clinicians can more efficiently and effectively get the information they need.

The NIH has been rolling out these [tools](#) over the past decade.

The second promising area is lab-based, for example, using a blood draw to look for proxy measures of pain. This is more of a downstream method to assess the patient. These tools still require further research to understand how to directly translate into clinical practice.

The third promising area is observational. In animal models, we poke a rat and watch its response. With very few exceptions — such as needle prick tests for diabetic neuropathy — we're not going to go poking human patients. But there are observation-based methods that allow clinicians to accurately measure pain and pain behaviors. For example, the University of Alabama at Birmingham developed a [pain behavior scale](#). Unfortunately, it isn't widely used, even though it has demonstrated excellent validity in terms of helping providers easily and quickly measure pain and pain behaviors like grimacing, holding one's back, and limping. It really does an excellent job giving a complete picture of a patient's experience.

RWHC: What are some of the important implications for patients and for the field of pain management?

BJ: The whole point of accurate pain assessment is to allow for more effective treatment. If patients are more aware of various pain assessment methods, they can advocate for themselves and request clinicians to widen their scope of assessment. Informed patients always help the clinical process.

The goals are improved assessment and treatment, which would lead to better patient care, higher patient satisfaction, and a reduced burden on patients, their families, and our nation. Economically, the cost of chronic pain is over \$600 billion a year. If we can chip away at that, we would be making a huge impact.

RWHC: What are the biggest challenges facing researchers when it comes to studying pain assessment, and how can those challenges be overcome?

BJ: From a research perspective, there's less emphasis on assessing pain than there is on treating pain. The main challenge is a financial one, with fewer research dollars dedicated to studying pain measurement. Another challenge is a theoretical one. There's been some exciting, cutting-edge research on neurological measures, focused on neurosignatures that act as a thermometer to measure pain, but there's been some discord in the field as to whether this is a useful pursuit. We also need better uniformity across the literature in terms of methods and measurement. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials ([IMMPACT](#)) has been working for well over a decade to develop consensus and establish best practices for measuring pain in clinical trials, but these best practices aren't always followed.

RWHC: What are the biggest challenges facing clinicians in assessing pain, and how can those challenges be overcome?

BJ: Making clinicians aware of the latest research is a big challenge. I hear lots of clinicians express that they don't have the training to fully assess and treat pain — especially chronic pain. Many providers approach treating someone with chronic pain with some trepidation as we have seen political, societal, and clinical swings in the use of opiates and other pain medications. Many clinicians will opt to not treat chronic pain or to seek out clinics with non-opiate policies. This is problematic, because the fact is that some patients do benefit from opiates.

We need more focus on early medical training. Medical schools are just starting to employ an integrated approach to pain, by combining the fields of primary care, psychology, pharmacy and social work. Trainees and residents are now being exposed to a broad-based perspective on how to approach and treat chronic pain, but additional course work is needed.

Clinicians also have a practical challenge. Most cases of pain are managed in primary care practices, and these clinicians are time-strapped. They default to the model of assessing pain by asking patients what their pain is on a scale of one to ten without looking at how pain impacts a patient's functionality and quality of life. Those quality of life measures, like being able to get back to work or play with your kids, are important goals for treatment.

RWHC: What initially attracted you to this field and what continues to inspire you?

BJ: I initially became interested in the field of pain assessment when my daughter was born. She had an early medical condition — which fortunately turned out to be benign— and I was struck by the integrated team at the Shriner's hospital who cared for her and our family. Since then, I've had wonderful opportunities to do clinical work with chronic pain patients. I continue to be inspired by my patients and the impact pain has on their lives. It's gratifying to help them go from being essentially disabled to the point where they can regain their lives and take part in meaningful activities.

[Read this article](#) on Real World Health Care.

Calling for an Integrative Approach to Pain Management

This week, Real World Health Care continues our series on pain management with an interview with Bob Twillman, PhD, FAPM, Executive Director of the [Academy of Integrative Pain Management](#). Dr. Twillman is responsible for overseeing federal and state pain policy developments and advocating for those supporting an integrative approach to pain management. He also serves as chair of the Prescription Monitoring Program Advisory Committee for the Kansas Board of Pharmacy. Dr. Twillman previously served as a faculty member at the University of Kansas School of Medicine, where he founded and directed the inpatient pain management program and was a co-founder of the hospital's Palliative Care Team.



Improving People's Lives

Real World Health Care: Can you describe the mission of the Academy of Integrative Pain Management?

Bob Twillman: Our mission is to improve the lives of people with pain by advancing a person-centered, integrative model of pain care through evidence-guided education, credentialing, and advocacy. In essence, we want to promote an integrative, multimodal, multidisciplinary approach to pain management because we believe such an approach is more effective and more cost-effective in treating all types of pain, both chronic and acute. Our educational opportunities teach clinicians how to provide this kind of care, and our advocacy efforts — which are unparalleled in the pain management sphere — promote policies that encourage provisions of this type of care.

Clinician Training & Challenges

RWHC: Why is it important for clinicians to be well-versed in integrative pain management?

BT: The traditional biomedical approach to pain management doesn't always work well for a good number of people with pain. We know — and it's been confirmed by the [Institute of Medicine](#) and in the recently-issued [National Pain Strategy](#) — that pain is a complex biopsychosocial phenomenon, and that an integrative approach is the only safe and sane way to care for people with pain. The only way to achieve the best possible pain control for every person with pain is to use an integrative approach that addresses all aspects of this complex phenomenon, as they play out for each individual person. There is no cookbook for pain care, and one size doesn't even fit most, so we need to use an integrative approach that permits maximum flexibility in providing care.

RWHC: What are some of the biggest challenges that clinicians face in dealing with patients' pain management issues?

BT: Undoubtedly, access to all the treatments we need in order to provide integrative pain care is our biggest challenge. Access to integrative non-pharmacological treatments such as acupuncture, massage therapy, biofeedback and others has never been good because insurance reimbursement is poor, causing people with pain to have to pay out of pocket for these treatments — something many of them can't do. Adjunctive treatments such as physical therapy and behavioral health care might be more readily available, but they also are subject to inadequate insurance coverage that makes true access less than optimal. And now, even the medications that have been so ubiquitous as primary treatments of pain are under fire and both insurers and policymakers are restricting access to those as well. It's really challenging to provide the kind of care that even key governmental agencies like the CDC have been calling for.

RWHC: How is the Academy addressing these challenges?

BT: AIPM continues to advocate for appropriate access to all of the treatments we need in order to provide comprehensive integrative pain care. Often, that means we have to battle inappropriate restrictions on pain medications, but we also advocate extensively for policies that promote improved access to non-pharmacological pain treatments. Recently, we have been advocating for enhanced Medicare and Medicaid coverage of integrative pain treatments, while also advocating for more opportunities to carry out Medicaid demonstration projects that we believe will show how much can be gained if those treatments were covered. And of course, we continue to educate clinicians about ways they can provide integrative pain care even if they don't have a large multi-disciplinary staff and insurance coverage for all the treatments they need.

Pain Management Therapies

RWHC: What are the most promising non-pharmaceutical approaches for pain management and why are they important?

BT: Consider what the pain management experts at the Department of Defense and the Department of Veterans Affairs have listed as the five evidence-based, non-pharmaceutical approaches they think every current and former service member with chronic pain should be able to access: chiropractic and osteopathic manipulations, acupuncture, massage therapy, biofeedback, and yoga. And it's important to note here, in follow up to my previous comment on inadequate coverage, that only some types of chiropractic and osteopathic manipulation are covered by Medicare, and only for some diagnoses. None of the rest of this list of five are covered.

Additionally, we know that many people with pain benefit from physical and occupational therapy and from behavioral health interventions. If we had full access with adequate insurance coverage for these treatments, we would be delighted. Being able to get these treatments for people with pain would mean that more of them would have less pain, better functioning in a number of areas, improved

quality of life, and increased likelihood of being able to work. Plus, we would spend less money achieving those improved outcomes.

Opioid Addiction

RWHC: How is the rising opioid addiction issue in America changing how clinicians address and treat their patients' pain?

BT: For much of the past two decades, pain treatment has been primarily associated with opioid prescribing. While I think increased opioid prescribing was a well-intended attempt by the medical profession to provide better pain care, it may have been misguided due to lack of evidence, lack of access to alternatives, and the influence of a number of market forces and cultural beliefs. Now that this increased prescribing has been implicated in the parallel and sharp increase in overdose deaths involving prescription opioids, policymakers are extraordinarily active in pushing legislation and regulation intended to reduce excessive prescribing. Unfortunately, this is happening in the context of the non-pharmaceutical treatment access problems I outlined previously, without concomitant attempt to improve that access. All of that leaves primary care clinicians, who deliver the majority of pain care in this country, struggling to figure out what to do.

We are hearing from people with pain that some clinicians are responding by either setting an arbitrary dose limit for opioids, or by establishing policies that they will not prescribe opioids, regardless of the circumstances. That may be harming people who benefit from those medications, in service of benefitting those who use opioids inappropriately and in a harmful manner. I think it's going to be a while before all of this shakes out and we can arrive at a balanced approach that maximizes the benefits and minimizes the harms for everyone.

Pharmaceutical Industry Efforts

RWHC: What should be the role of the pharmaceutical industry in addressing the rising opioid addiction issue in America? How can they work with clinicians and groups like the Academy?

BT: The pharmaceutical industry has been engaged in efforts to make their products safer, by developing abuse-deterrent opioids. These medications make it much harder to abuse prescription opioids by means of altering them to permit snorting or injecting the opioid medication. This is an important step, because it will protect people who misuse these medications — the vast majority of whom are not people with pain. If we are able to do that, then perhaps we won't see as much of a reactionary backlash that causes people with a legitimate medical need for prescription opioids to have their prescriptions denied or taken away.

The industry can also help us by increasing funding for our education and advocacy efforts. We have so many needs for education — both for new clinicians who are now in school and for experienced clinicians who are in practice — that meeting the need is an enormous and extremely expensive task. Due to mandates for Risk Evaluation and Mitigation Strategies (REMS) education imposed by

FDA, much of this funding has been redirected away from organizations like ours that can provide integrative pain management education — and without discernible benefit. We desperately need FDA to revise the REMS program blueprints so we can teach clinicians about more than just the pharmacology of opioids and so we can teach about non-pharmacological approaches to pain care. It's really challenging for the industry to adhere to FDA mandates and to go beyond those, but we need to find a way to encourage that to happen.

[Read this article](#) on Real World Health Care.

Pain Management for Cancer Survivors

This week, Real World Health Care continues our series on Pain Management by speaking with [Judith A. Paice](#), PhD, RN, who is the lead author for the [American Society of Clinical Oncology's](#) guideline, [Management of Chronic Pain in Survivors of Adult Cancer](#). Dr. Paice is Research Professor of Medicine, Hematology/Oncology, at [Northwestern University's Feinberg School of Medicine](#) and a full member of the Robert H. Lurie Comprehensive Cancer Center. Dr. Paice's clinical work focuses on the management of cancer-related pain, and her research focuses on the study of chemotherapy-induced peripheral neuropathy. We spoke about the ASCO guideline and the need for clinicians to balance pharmaceutical and non-pharmaceutical approaches to pain management.



Real World Health Care: Why did ASCO issue a guideline for the management of pain in survivors of adult cancer?

Judith Paice: The oncology field has evolved tremendously in recent years. Not only are people living longer with cancer, but they're being cured of their disease thanks to some fantastic treatments. These treatments provide good clinical responses, but they can also cause significant toxicity, some of which may lead to chronic pain syndromes. The goal of the guideline was to alert oncologists to the presence of these long-term, persistent pain syndromes. A secondary goal was to provide support for chronic pain syndrome treatment.

Clinician Guidance

RWHC: What are the most important take-aways for clinicians?

JP: First are ASCO's recommendations for screening and assessment. Second are recommended treatment options, both pharmacological and, equally important, non-pharmacological treatments. The guideline also provides insights and risk mitigation strategies for clinicians around the long-term use of opioids.

Today's oncologists are faced with a very different pain management phenomenon than they were 20 years ago, when opioids were primarily used at end of life. Opioids are now being used for patients with a much longer survival trajectory — 20 to 30 years or more. As clinicians, we need to ask if such long-term use of opioids is appropriate and safe. How do we go about determining that? The guideline helps oncologists with those types of assessments and decision making.

RWHC: What do you feel are the biggest challenges facing oncologists in managing chronic pain in cancer patients, and how is ASCO helping clinicians manage those challenges?

JP: Our society is facing a serious public health problem in the opioid abuse and misuse epidemic. As a result of this problem, we've seen regulations at both the state and federal level that are having a chilling effect on the availability of opioids, even for those in desperate need of these medications. ASCO has a position paper on protecting access to treatment for cancer-related pain that I encourage all clinicians to read. ASCO also advocates for better third-party reimbursement for physical therapy, occupational therapy, cognitive behavioral therapy and mental health counseling. These are crucial therapies for patients facing the "new normal" of cancer survivorship, yet most third party payers provide little or no support for these treatments. As clinicians, we need to help our patients maintain function and cope with the fact that their lives are going to be very different. For patients, it's more than surviving cancer. It's about finding their own inner strength in survivorship.

New Pain Management Treatments

RWHC: Where do the biggest opportunities lie for new pharmaceutical pain management treatments?

JP: Several new findings in the laboratory may lead to novel agents that do not produce opioid related adverse effects. This is promising, assuming the findings can be translated into a clinical setting. There have also been numerous compounds that proved effective in animal models of pain, but when moved into the clinical setting, they either had adverse effects that weren't seen in animals, or they didn't have the efficacy they presented in the lab. It is very difficult to develop a model of cancer pain in animals.

Unfortunately, there haven't been many completely new drugs. Most of the agents approved recently are slight variations of existing compounds or an update in the delivery method: a spray instead of a tablet, for example. The industry has been more focused recently on abuse-deterrent compounds. This is a somewhat controversial area because while such formulations prevent people from crushing, snorting or injecting the drugs, they don't keep people from taking more than what is prescribed.

Non-Pharmacologic Therapies

RWHC: What should the role be for non-pharmaceutical pain management therapies in treating cancer patients?

JP: For quite a long time, there was a tendency in medicine to rely only on pharmaceutical therapies. This made sense when patients did not have long-term survival prospects and when managing pain meant helping the patient get from their bed to a chair. Today, cancer patients are living longer. They want to get back to work and function safely without the risk of falls and other complications. We've seen good data around the usefulness of physical therapy, occupational therapy and cognitive

behavioral therapy for many chronic pain situations, including cancer-related pain. These non-pharmacologic therapies must go hand-in-hand with pharmaceutical therapies.

Part of the challenge with non-pharmacologic therapies is limited reimbursement. The other big challenge is getting buy-in from patients. Most of us want a quick fix. Redefining expectations can be difficult. Physical and occupational therapy can be demanding, and access to specialists who understand the special needs of those surviving cancer are in short supply. Also, there remains a stigma attached to seeing a mental health counselor. It's important for cancer patients to know that they aren't "weak" if they need support to help them cope with the physical and emotional challenges of being a cancer survivor. Our field needs to do a better job educating our patients about the importance of including non-pharmacologic therapies as part of our pain management repertoire.

[Read this article](#) on Real World Health Care.

Multiple Sclerosis: Overcoming Pain

Real World Health Care continues our series on pain management by speaking with [Dawn Ehde](#), PhD, [Department of Rehabilitation Medicine, University of Washington School of Medicine](#). Dr. Ehde serves as a clinical psychologist and professor at UW. She conducts research evaluating the efficacy of various behavioral, exercise, and pharmacological interventions for chronic pain, depression, and/or fatigue in adults with multiple sclerosis (MS) and other acquired neurological conditions.



Dr. Ehde discusses some of her recent clinical and research work on cognitive-behavioral interventions for MS-related pain.

Living with MS and Pain

Real World Health Care: In 2015, you published an article: [Utilization and Patients' Perceptions of the Effectiveness of Pain Treatments in Multiple Sclerosis](#). Can you summarize the key results of your study and the implications for patients with MS?

Dawn Ehde: We conducted this survey to learn more about pain management from the perspective of people living with MS and pain. We found that people with MS and pain try a lot of different treatments to manage pain, but few treatments provide adequate pain relief.

Nonprescription medications such as nonsteroidal anti-inflammatories and physical modalities such as massage were some of the most common methods used. Many use more than one treatment to manage pain. Some of the treatments that individuals rated as most helpful, such as hypnosis, were infrequently used. In fact, we found that very few people surveyed had tried or accessed behavioral pain treatments such as training in mindfulness meditation, cognitive behavioral self-management, or self-hypnosis. This was the case even though there is good evidence that these types of treatments are beneficial to many people with chronic pain, including MS, and have few or no negative side effects. This study highlighted for me the need to improve access to these types of non-pharmacological pain management.

Integrated Care Approach

RWHC: Are you currently involved in any other research relating to pain management in MS patients?

DE: We have several studies in various stages that address pain management in MS. We recently published a [study](#) that found that an eight-session telephone-delivered self-management intervention was effective in reducing pain (both its severity and its interference with activities) and fatigue. It also was effective in improving mood, quality of life, and resilience. The benefits were maintained at 6- and 12-month follow ups. Patient satisfaction with the treatment was high as well.

The study I am most excited about is the [MS Care study](#), which is a comparative effectiveness trial that evaluated the benefits of an integrated care approach to pain and depression management in the clinic called “collaborative care.” The MS version, called “[MS Care](#),” aims to improve the quality of pain care in the clinic by adding an MS Care manager to coordinate care, deliver brief behavioral treatments, initiate or adjust other medical treatments, and ensure patients do not slip through the cracks. We also offer patients the choice of getting their care management by phone or in person. Seventy-five percent chose the phone. We found that patients with chronic pain and/or depression randomly assigned to MS Care had significantly improved pain and depression symptoms, including less severe pain, less interference, less disability, and less fatigue. Additional details on the results are available at <http://www.uwm scare.org/background>.

Opportunities in MS Pain Research

RWHC: What are some of the biggest challenges facing researchers who are studying pain management in MS patients? How can those challenges be overcome?

DE: I actually see a lot of opportunities as an MS pain researcher. The MS community is interested in improving pain management and supporting research in this area. For example, the [National MS Society](#) has named pain as one of its research priorities. We also often find people with MS are willing participants in our research, both as participants as well as stakeholders who guide us in our research. For example, we used [stakeholders](#) to guide our MS Care study. At times, we have had to work hard to convince potential funders that pain is an issue that warrants funding and study, but that has improved in the time that I’ve been doing research. We have come a long way since I first started in this area, when pain was not always recognized as an important problem deserving attention in MS.

Challenges for MS Clinicians

RWHC: What are some of the biggest challenges facing clinicians who are treating MS patients with pain management problems?

DE: MS presents many different symptoms to manage, and thus both patients and clinicians have a lot to discuss and manage in the typical clinic appointment. One challenge is that pain management is often only one of several issues being addressed. As such, it may be difficult to fully manage a complex issue like chronic pain. I think these challenges may be overcome by rethinking how we approach and deliver pain care. We need to look at harnessing technology — including telehealth technologies — to improve care. We also need to empower patients and the MS community to

recognize that pain management is something that requires active self-management and multimodal strategies.

Pain Management Therapies

RWHC: What do you see as the most promising pharmaceutical therapies for treating pain in MS patients? What are the caveats that must be understood by clinicians when prescribing such therapies?

DE: As a psychologist, I'm less able to speak to promising pharmaceutical therapies on the horizon. However, I think there are promising practices for how we deliver pain care, including medications and other rehabilitation interventions. We did manage medications in our MS Care study, and our goal within that was to promote the appropriate and effective use of pain medications and other medications that can benefit pain management, such as some of the antidepressants which have analgesic benefits. We know from our research that too often, patients get started on a treatment, perhaps at a "low dose," and for whatever reason, they don't have adequate follow up to adjust, intensify, or change treatment plan. In the MS Care study, we closely and quickly followed patients' pain and adjusted treatments to optimize their benefits or switched treatments if needed. We also know that physical activity — whether it is physical therapy or encouraging physical activity — benefits people with MS and likely helps with pain management.

RWHC: Do you see a role for non-pharmaceutical pain management therapies in treating pain in patients with MS?

DE: Certainly. This is where I've spent most of my energy, not only because I am a psychologist, but also because many people with MS want to use non-pharmacological therapies and strategies. The people with MS I know and our stakeholders are eager to advance our understanding and use of non-pharmacological treatments such as mindfulness meditation, relaxation, and cognitive behavioral coping skills.

Partnering with Patients

RWHC: What initially got you interested in this field? What continues to inspire you?

DE: I have had family and friends with MS, and thus was drawn to learning more about MS. I started out conducting chronic pain research in people where chronic pain such as headaches was the primary problem. When I started working with patients with MS clinically, I was struck by how little we knew about MS pain management and how people with MS pain were not accessing care we knew was helpful in other pain populations.

I've been inspired and continue to be inspired by the people with MS whom we've partnered with to conduct our research. Our best research has resulted from partnering with people living with MS.

They've also taught me a lot about resiliency. Although MS can present many challenges like pain, many people with MS and pain live full, meaningful and happy lives.

I also have been fortunate to have training grants from the National MS Society, which have allowed me to train postdoctoral fellows in MS and rehabilitation research. They represent the next generation of clinical researchers in pain and symptom management in MS.

[Read this article](#) on Real World Health Care.

Challenges in Pain Management for MS Patients

This week, Real World Health Care interviews [Theodore R. \(Ted\) Brown](#), MD, MPH, about pain management in patients with Multiple Sclerosis (MS). Dr. Brown is director of neuro-rehabilitation at the [EvergreenHealth Multiple Sclerosis Center](#), which cares for about 800 patients. His clinical duties include managing patients with established MS through a total wellness approach that involves drug therapy, exercise, stress management, diet and sleep. His research work focuses on developing new studies to investigate treatments for symptoms of MS and minimizing the side effects of MS drugs.



Duloxetine Study

Real World Health Care: In spring of 2016, you published a [study](#) on the use of duloxetine for central pain management in MS, which received the [2016 Herndon Award](#) for best paper published in the [International Journal of MS Care](#). Can you summarize the results and the implication of the study for MS patients?

Ted Brown: Pain is common in MS. Duloxetine is a serotonin-norepinephrine reuptake inhibitor that has a potential therapeutic role in treating MS-related pain. We conducted a single-center placebo-controlled, double blind trial of duloxetine involving thirty-eight MS patients. The dosing regimen was 30 mg daily for 1 week, then 60 mg daily for 5 weeks. The primary outcome measure was change in worst pain for week 6 relative to baseline recorded on a daily pain diary.

Of 38 randomized patients, 14 (78%) patients randomized to duloxetine and 19 (95%) randomized to placebo completed treatment. These participants had an average age of 55.5 years, 27% were male, and 64% had relapsing-remitting MS (RRMS). Baseline characteristics were similar. Discontinuations were due primarily to drug intolerance (nausea, headache, no serious treatment-related adverse events).

Among those who completed treatment, worst pain at 6 weeks was reduced by 29% ($\pm 20\%$) for duloxetine versus 12% ($\pm 18\%$) for placebo ($P = .016$). Average daily pain at 6 weeks was reduced by 39% ($\pm 29\%$) on duloxetine compared to 10% ($\pm 18.8\%$) in the placebo group ($P = .002$). Change in subject global impression favored duloxetine ($P = .048$). There were no significant changes (week 6 vs. baseline) or between-group differences for Beck Depression Inventory or sleep quality score. This suggests that the benefits we found were due to a direct pain-relieving effect, not due to change in mood or sleep.

The implications are that duloxetine may have a role for treating central pain due to MS, that effects can be seen within 4-6 weeks, and that not all patients are able to tolerate the drug.

Research Perspective

RWHC: What are some of the biggest challenges researchers face in studying pain control in MS patients, and how can those challenges best be addressed?

TB: Studying MS pain is difficult for many reasons. Pain makes patients uncomfortable, so they need relief. This is a challenge for recruitment into a study that is placebo-controlled. There are many treatments available by prescription. So, patients may prefer to get a quick fix from a prescribed drug instead of volunteering for a study.

Funding for pain studies also is difficult, since most trials may involve drugs that may already be generic or non-drug interventions. Funding sources for such studies are scarce. The study design must be as brief as possible to limit patient discomfort, should provide some contingency for rescue treatment in case of severe pain, and must be as cost-effective as possible.

Clinical Perspective

RWHC: What are some of the biggest challenges that clinicians face in treating pain in MS patients, and how can those challenges best be addressed?

TB: We tend to assume that all pain in MS is caused by the disease itself. We may overlook non-MS factors that may be causing the pain, such as orthopedic, vascular, infectious or oncological problems. Every case requires thorough assessment, which can be difficult when patients may have several other active problems to address.

Physicians must treat the MS patient to provide pain relief and maximize quality of life. However, pain can very rarely be eliminated completely. State agencies and national organizations discourage prescription of opioid medications for nerve pain. These drugs are not all that effective and carry a host of potential side effects and problems with dose escalation and dependency. Anticonvulsant medications are usually first-line.

Non-drug treatments, such as physical activity, massage, meditation and complementary treatments should be explored. Some level of pain that is tolerable, and does not interfere with sleep and daily activities, may be the best that can be achieved in many cases.

Range of Treatments

RWHC: What are some of the most important pharmaceutical developments in treating pain in patients with MS? Is the field poised for a breakthrough?

TB: Good question. I believe that the incorporation of duloxetine in the treatment algorithm of MS pain is an important development. Some patients find medical marijuana beneficial for MS pain, yet it is very difficult to do clinical research with cannabis in the United States. This treatment is not available in all states, and where available, it is expensive and difficult to instruct patients on how to use it without taking too much or experiencing adverse effects, including cognitive dysfunction. I am not aware of any breakthroughs on the horizon. The danger is that MS pain is overlooked in the vital effort to develop drugs for neuro-protection and neural repair. Certainly, more research in MS pain is needed.

RWHC: Do you think there is a role for non-pharmaceutical pain management therapy in patients with MS?

TB: Yes, absolutely. In every case, physical exercise should be included in the pain management program. Depression is very common in MS. Treating depression and stress may help in treating the pain. We are conducting a study of laughter therapy at the moment and are hopeful that this is one of many complementary approaches that may help with pain management.

Inspiration and Dedication

RWHC: What initially attracted you to this field, and what continues to inspire you about it?

TB: Initially, I was attracted by the newness of the field. We only had a few approved drugs at that time and the MS professional community was relatively small. Now, it is the rewards of patient care that keeps me motivated. I have patients whom I have been following for more than ten years. You become friends with patients and visits can be fun and joyful. When patients have a decline in function, or health, or spirits, it is so important to stay involved as their care provider. Often just being accessible gives patients the trust and reassurance that they need to help them to cope.

[Read this article](#) on Real World Health Care.

Pain Management: Opioid Adherence in Cancer Patients

This week, Real World Health Care speaks with [Salimah H. Meghani](#), PhD, MBE, RN, FAAN. Dr. Meghani is an associate professor and term chair in Palliative Care at the [University of Pennsylvania School of Nursing](#). She is also associate director, [NewCourtland Center for Transitions and Health](#). Her main research interest involves palliative care, specifically understanding and addressing sources of disparities in symptom management and outcomes among vulnerable patients.



We asked her about her study on analgesic adherence and health care utilization in outpatients with cancer pain, recently published in [Patient Preference and Adherence](#). We also discussed the role of non-pharmacological approaches in treating cancer pain.

Opioid Adherence Patterns

Real World Health Care: Last year, you published an article: Patterns of analgesic adherence predict health care utilization among outpatients with cancer pain. Can you provide a brief summary of the article and talk about the study's implications for cancer patients with pain management issues?

Salimah Meghani: This is the first study to understand how opioid adherence patterns, over time among cancer patients, relate to health care utilization outcomes. We used objective measures of adherence (Medication Event Monitoring System - MEMS) and novel adaptive methods recently validated by the co-author, [Dr. George Knaf](#) from UNC-Chapel Hill. We found that inconsistent adherence patterns of analgesics over time was significantly associated with hospitalization over a 3-month observation period. The interaction of inconsistent adherence and strong opioids (WHO step 3 opioids) was one of the strongest predictors of health care use. It should be noted that this was a serendipitous finding. We did not plan to study adherence patterns and health care utilization. It therefore needs validation in hypothesis-driven study.

RWHC: Are you currently involved in any new research programs studying pain management in cancer patients? If yes, can you briefly describe?

SM: Yes, I am studying outcomes of opioid adherence and adherence patterns among cancer outpatients. This is an important topic as few recent U.S. based studies exist on the topic despite all

the recent guideline contentions (e.g., [CDC guidelines](#) for managing chronic pain including chronic cancer pain and ASCO response) and national policy debates on opioids.

How Patients Manage Cancer Pain

RWHC: What do you think are the biggest challenges facing researchers studying pain management in cancer patients? How can those challenges be addressed?

SM: One of the biggest challenges is that we know very little about how patients manage their cancer pain. We know that opioids are widely prescribed, but we also know that there is poor adherence to prescribed opioids. Other treatments such as acupuncture are not consistently covered by health insurance or lack data on clinical effectiveness. There is a need to understand how patients are managing their cancer pain and what health care systems can do better to address the great burden on unrelieved cancer pain. Future work should also include improving access to effective non-opioid treatments for cancer patients. My previous research has also documented racial and ethnic disparities in cancer pain treatment for African Americans, which requires continued attention.

Safe Opioid Use

RWHC: What do you think are the biggest challenges facing clinicians treating pain in cancer patients? How can those challenges be addressed?

SM: There is a lot of confusion among clinicians about the role of opioids and the safe and rational use of opioids among cancer patients. Unfortunately, there is little empirical evidence base about the outcomes of opioid treatment among cancer patients. A look at the recent CDC guidelines on managing chronic pain would indicate that cancer patients frequently, if not invariably, have been excluded from the studies of the outcomes of chronic opioid therapy. More empirical evidence is needed to help clinicians develop comfort in opioid prescriptions.

Non-Opioid Treatments

RWHC: What do you think is the role of non-pharmaceutical pain management therapies for cancer patients? How can clinicians integrate both pharmaceutical and non-pharma therapies for cancer patients?

SM: I think access to non-pharmacological treatments is the biggest problem. While the [NCCN](#) guidelines for cancer pain identify a number of non-pharmacological modalities, they are not readily accessible to cancer patients. I have argued this in a recent [letter to JAMA Oncology](#) about the CDC opioid guideline that recommends that non-opioid treatments should be the first line therapy for chronic pain. This paradigm assumes easy and consistent access to non-opioid treatments. Also, access to effective non-pharmacological treatments are very different among poor, minorities, those with limited literacy.

Global Disparities

RWHC: What initially attracted you to this field? What continues to inspire you about it?

SM: My original research interest was global disparities in opioid availability for cancer pain management and the role of the [International Narcotics Control Board](#). After migrating to the United States, I became familiar with racial and ethnic disparities in pain care and the toll it has for patients and families. This work continues to inspire me.

[Read this article](#) on Real World Health Care

APS Calls for Pain Management Funding

Real World Health Care concludes its series on pain management with an interview with David Williams, PhD, president of the [American Pain Society](#) (APS). Dr. Williams is Professor of Anesthesiology, Medicine (Rheumatology), Psychiatry and Psychology at the [University of Michigan](#), where he also serves as the Associate Director of the Chronic Pain and Fatigue Research Center, co-director of Research Development within the [Michigan Institute for Clinical and Health Research](#) (MICHHR), and is on the senior faculty of the Neurosciences Program.



The APS is a multidisciplinary community that brings together a diverse group of scientists, clinicians and other professionals to increase the knowledge of pain and transform public policy and clinical practice to reduce pain-related suffering. APS was the first multidisciplinary professional society dedicated to pain science and the practice of evidenced-based pain care.

Research Priorities

Real World Health Care: What are the APS's priorities in terms of pain management research?

David Williams: Pain is complex. No one view point is likely to capture such complexity. The APS values interdisciplinary collaboration demonstrated by respect for the value of diverse views and perspectives among professionals. Our society is composed of professionals from the basic sciences who examine pain mechanisms at the level of neurons and neurotransmitters. We're also pharmacologists exploring and developing new drugs for pain. We're psychologists, occupational therapists, nurses, and physical therapists working to refine behavioral, psychosocial, patient-centric, and self-management approaches to pain. We are clinical and translational researchers developing and implementing multi-modal forms of treatment into real-world settings. And we're public policy experts working to improve options for pain care at systemic levels. As a society we try to facilitate the broad-based work of our members while encouraging collaboration across disciplines.

RWHC: Can you provide an example or two of recent or current pain management research programs you are supporting or have supported? Why are those research programs so impactful?

DW: The [Annual Scientific Meeting](#) and the Society's [Journal of Pain](#) are the two best sources to witness APS's commitment to the dissemination of evidence supporting multidisciplinary pain care. APS also financially supports the research of many of its early career professionals in the form of

the [Rita Allen Foundation Award for Pain](#) (basic science), the [Future Leaders in Pain](#) award (in part supported by the MayDay Foundation), and through contributions to the APS Pain Research Fund. This past year, the APS also partnered with Pfizer to offer a [grant program](#) focused on learning and change that will help support the implementation of aspects of the National Pain Strategy.

Research and Clinical Challenges

RWHC: What are some of the biggest challenges facing pain management researchers and how are those challenges being addressed?

DW: Funding is always a big challenge for a society focused on research. Annually, the APS meets with leadership at the National Institutes of Health (NIH) and with the inter-institute leadership of the [NIH Pain Consortium](#). The needs of societal members are expressed, thematic research discussed, and challenges in grant review presented. There is also a need for pain to be viewed as an important national research priority. Currently many APS members have been invited to participate in the creation of the [Federal Pain Research Strategy](#) (FPRS), a document which will serve as a blue print for pain research across Federal agencies.

RWHC: What are some of the biggest pain management challenges facing clinicians, and how are those challenges being addressed?

DW: One big challenge is that as a field, we do not have great treatments for chronic pain. More research is clearly needed. An honest appraisal would suggest that we offer modest benefit for most. Complicating the problem is that relatively more beneficial approaches, such as multi-disciplinary pain care, are difficult to implement both logistically and financially. As such, it is rarely seen in practice. Currently there is research underway to study how best to implement evidence-based approaches in routine care and at a systems level. Such efforts are supported by APS and by the [National Pain Strategy](#).

Approaches to Pain Management

RWHC: How can clinicians integrate pharmaceutical and non-pharmaceutical approaches to pain management in their practice?

DW: Optimal care would suggest integration of both pharmacological and non-pharmacological approaches to pain management. Optimal care would also include a patient-centric approach to care where the patient and provider share decision making about what medications and what non-pharmacological approaches will be utilized. Evidence exists for many medications and many non-pharmacological approaches. Matching the available approaches to the specific needs of an individual patient, however, is the clinical challenge. Informing both the patient and the provider about evidence-based approaches as well as how best to implement those options at the individual level is an area where additional research and training is needed. This important challenge was highlighted by the National Pain Strategy and has been a focus of the APS in its educational agenda.

Opioid Addiction

RWHC: How is the APS working to address the issue of opioid addiction in this country?

DW: The APS is not a practice guild. It is a Society based upon a valuation of science and evidence. As such, we let evidence guide our position rather than politics. For decades, the APS has gone on record as supporting a multi-disciplinary approach to pain management rather than a mono-therapeutic approach (e.g., a solely opioid-based approach). Opioids may or may not have relevance to the care of a given individual and should be viewed in the context of an entire integrated treatment plan designed with input from both the patient and provider. Through the promotion of evidence-based multi-modal care, APS is supporting efforts to find sources of pain relief that go beyond opioids.

Go-To Pain Information Source

RWHC: Is there anything else you would like our readers to know about the work APS is doing?

DW: The APS is the unbiased “go-to” information source regarding pain. We are sought out by governmental representatives, industry, academia, and patient advocacy groups. We support the early careers of young pain scientists and serve as a home for senior scientists, clinicians, and public policy experts interested in changing how chronic pain is managed. Our members have participated in the development of important documents such as the IOM report “[Relieving Pain in America](#),” the “National Pain Strategy”, and the forthcoming “Federal Pain Research Strategy.”

RWHC: How did you get involved in the field of pain management? What continues to inspire you about this field?

DW: Over the years I have studied pain from the perspectives of a basic scientist, a clinical/translational researcher, and currently a clinical trialist. Our understanding of pain continues to evolve and with each finding, new questions arise. It has been both challenging and rewarding to participate in the study of pain. It is also rewarding to see the current field of young scientists taking interest in this topic and taking fresh approaches to problems my generation was not able to solve.

[Read this article](#) online at Real World Health Care.