

Basic to Clinical

Disparities

Overlapping Conditions

Pain Mechanisms

Surveillance & Human Trials

Tools & Instruments

Basic to Clinical

Fatty Acids Reduce Diabetic Nerve Pain without Side Effects in an Animal Model

[*Acute augmentation of epoxygenated fatty acid levels rapidly reduces pain-related behavior in a rat model of type I diabetes. Inceoglu B, Wagner KM, Yang J, Bettaieb A, Schebb NH, Hwang SH, Morisseau C, Haj FG, Hammock BD. Proc Natl Acad Sci USA. 2012 July 10; 109\(28\): 11390-11395.*](#)

Nearly half of all diabetics will develop diabetic neuropathy, nerve damage caused by high glucose (blood sugar) levels, with care costs projected to exceed \$150 billion annually. Current treatments, which include opiates, have limited effectiveness and are accompanied by unwanted side effects. Previously, inhibition of an enzyme that leads to stabilization of a class of lipids (fats), epoxygenated fatty acids (EpFAs), has been shown to counter increased pain sensitivity in models of inflammatory pain and regulate pain signaling. To develop a more effective pain management therapy for diabetics with neuropathy, researchers investigated whether stabilization of EpFAs through enzyme inhibition affects glucose levels and reduces pain. They used three different inhibitors to stabilize EpFAs, all of which reversed or eliminated the pain-related behavior without sedation or sensory and motor impairment in a rodent model. Furthermore, the inhibitors did not alter normal glucose levels or insulin signaling/response. Researchers also found that the normal lipid balance was dysregulated in their rodent model of diabetic neuropathy. Their results point to a potential mechanism, which may allow for the future identification of lipid biomarkers for painful conditions in diabetics and the development of therapeutics to treat them.

Functional Brain Changes Predict Transition from Acute to Chronic Back Pain

[*Corticostriatal functional connectivity predicts transition to chronic back pain. Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields HL, Apkarian AV. Nat Neurosci. 2012 Jul 1; 15\(8\): 1117-9.*](#)

Researchers have used brain imaging to understand what brain changes occur when people experience acute pain. Through these studies, a number of important brain regions have emerged as part of a 'pain signature.' However, studying persistent (or chronic) pain has been more elusive and considerably more complex. Studies in chronic pain patients reveal that the brain undergoes reorganization - changes in brain structure and function. Therefore, research is underway to determine how this reorganization is involved in the transition from acute to chronic pain. In this study, patients with back pain lasting between 4-16 weeks were followed over the course of a year, and pain and brain measurements were collected. Researchers discovered that persistent pain patients had stronger connections in a particular pathway known as the 'reward' pathway, whereas healthy or recovering pain patients did not. The increased positive connections in these patients correlated with pain ratings. The reward pathway is important for reinforcing learned behaviors (such as food- or drug-seeking), which has important implications for developing a persistent disease, such as chronic pain. This study is the first to demonstrate brain changes over time during the development of persistent pain and suggests that the reward pathway is a critical component of the transition from acute to chronic pain.

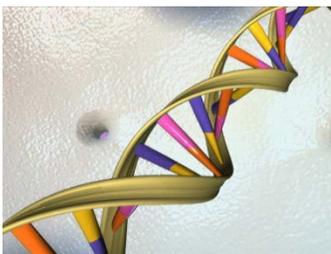
Neuron Transplants Treat Neuropathic Pain in a Model of Spinal Cord Injury

[Forebrain GABAergic neuron precursors integrate into adult spinal cord and reduce injury-induced neuropathic pain. Bráz JM, Sharif-Naeini R, Vogt D, Kriegstein A, Alvarez-Buylla A, Rubenstein JL, Basbaum AI. Neuron. 2012 May 24; 74\(4\): 663-75.](#)

Neuropathic pain, caused by damage to or dysfunction of the nervous system, is not readily treatable by common pain medications, including opioids. Researchers have proposed that certain chronic pain conditions, such as neuropathic pain, may occur due to dysregulation of the normal system, leading to overactivation of excitatory neurons (causing persistent pain); the inhibitory neurons that usually counteract these excitatory neurons are not sufficient to suppress the overactivation. Previous studies have shown that in animal models of neuropathic pain, activation of inhibitory neurons can relieve pain. Excitatory neurons release the neurotransmitter glutamate and are referred to as glutamatergic, whereas inhibitory neurons release the neurotransmitter GABA and are identified as GABAergic. In the current study, researchers tested whether increasing the inhibitory GABA signal would counteract the overactive glutamatergic signal and reduce pain from spinal cord injury. Embryonic GABAergic neurons expressing a green fluorescent protein (GFP) for visualization were extracted and transplanted into the spinal cord of adult mice and left to grow for several weeks. The neurons that survived in the new 'host' environment took on the properties of mature GABAergic neurons. Specifically, the transplanted neurons were able to make connections with other neurons in the spinal cord and could be activated by painful and non-painful stimulation. To test whether the introduction of these neurons would improve persistent pain, they were transplanted into mice with a spinal cord injury caused by damage to the sciatic nerve. Within 30 days of transplantation, the pain threshold of these mice returned to pre-injury levels, whereas mice without the transplantation had persistently lower pain thresholds, indicating persistent pain. These data show that transplanted embryonic neurons can survive and function in the adult mouse spinal cord, and that transplantation of GABAergic neurons was able to reverse the inflammatory pain caused by spinal cord injury. Since standard drug therapy is associated with widespread side effects, this method of transplanting GABAergic neurons into specific locations, such as the spinal cord, presents a novel potential treatment for neuropathic pain.

Clinical Trial Shows Gene Therapy is a Safe and Effective Treatment for Pain

[Gene Therapy for Pain: Results of a Phase I Clinical Trial. Fink DJ, Wechuck J, Mata M, Glorioso JC, Goss J, Krisky D, Wolfe D. Ann Neurology. 2011 Aug; 70\(2\): 207-212.](#)



One substantial limitation to developing pain medications is their potential for unwanted side effects, even at or below the dosage required to provide pain relief. Previously, scientists found that release of peptides (essentially, small proteins) and molecules with pain-reducing properties from neurons in a section of the spine called the dorsal root ganglion (DRG) reduced pain-related behaviors in rodent models of cancer, inflammatory, and neuropathic pain. Here, scientists performed a study to assess the safety and efficacy of a potential new treatment for pain – injection of a defective version of the herpes simplex virus (HSV) carrying a gene that encodes for a protein involved in the production of opioid peptides. This modified HSV was injected into the skin surrounding DRG nerves in patients with difficult to treat, severe pain due to cancer. The injections were shown to be safe and effective, as patients receiving the injections in higher doses reported reduced pain and pain-related behaviors. However, those receiving low doses showed little change in their pain scores.

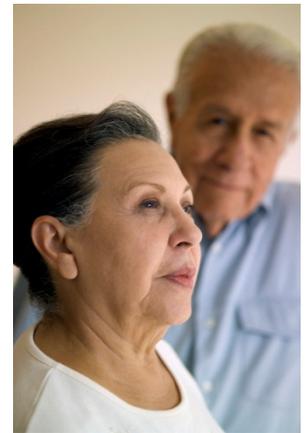
Based on the results from this study, a randomized, placebo-controlled phase II clinical trial has been initiated to investigate this potential treatment further.

Disparities

Women Report Higher Pain Intensities than Men for Many Diseases

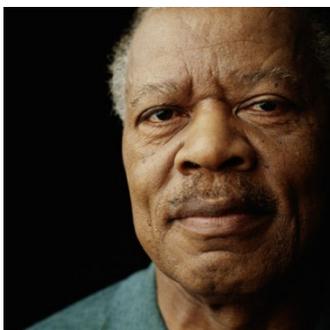
[Sex differences in reported pain across 11,000 patients captured in electronic medical records. Ruau D, Liu LY, Clark JD, Angst MS, Butte AJ. J Pain. 2012 Mar; 13\(3\): 228-34.](#)

Previous research has shown that certain groups of people are more susceptible to pain than others. In fact, some clinical studies suggest that women, who are typically undertreated for pain, have a higher prevalence of many pain conditions than men. However, little is known about the sex-related differences in the perceived intensity of pain. Here, researchers utilized electronic medical records (EMRs) from more than 11,000 patients to investigate sex differences in disease-associated pain levels. The reported pain intensities from women and men with 47 different diseases were analyzed in this large, data-driven study. In multiple diseases and disease categories, researchers found that women subjectively rated their pain intensity higher than men. The largest sex-specific differences in pain intensity were observed for musculoskeletal, circulatory, respiratory, and digestive system diseases. Of particular note, women reported higher pain scores in acute sinusitis, an inflammatory condition, which was previously unreported. This research supports the existence of sex differences in clinical pain intensity across a variety of diseases and underscores the importance of increased attention and treatment for women with pain.



Cancer-Related Chronic Pain Disproportionately Impacts the Quality of Life of Minority Cancer Survivors

[Cancer-related chronic pain: examining quality of life in diverse cancer survivors. Green CR, Hart-Johnson T, Loeffler DR. Cancer. 2011 May 1; 117\(9\):1994-2003.](#)



Improved cancer treatments have increased survival rates. However, approximately two-thirds of patients with advanced, incurable or metastatic cancer as well as nearly half of cancer survivors report chronic pain, lowering the quality of life (QOL) of these populations. Unrelieved chronic pain is associated with greater and more severe symptoms, including depression and poor functioning. Despite a growing awareness, disparities exist among racially and ethnically diverse cancer survivors with respect to pain management for cancer-related chronic pain. By examining patients' current and past pain, health, and QOL, researchers determined the impact of cancer-related chronic pain on the QOL of racially diverse cancer survivors. Overall, they noted that those experiencing pain reported decreased QOL, more non-pain-related symptoms, and heightened financial burdens. While

the pain prevalence is similar, they discovered that blacks with cancer-related chronic pain have increased pain severity and more disability than their white counterparts. Researchers also found that women experience more pain, pain flares, and depression, and have greater pain-related disability than men. Because of the high prevalence of cancer-related chronic pain among diverse cancer survivors, particularly blacks and women, this study lays out new research, clinical care, and health policy opportunities. Future research can build upon these results to develop interventions to improve pain care quality and optimize pain care in diverse cancer survivors.

Racial and Ethnic Disparities Exist in Pain Care

[*Racial and ethnic disparities in pain: causes and consequences of unequal care. Anderson KO, Green CR, Payne R. J Pain. 2009 Dec; 10\(12\): 1187-204.*](#)

Racial and ethnic disparities are widespread throughout the health care system at the same time that there is growing diversity in the United States population. A 2002 report by the Institute of Medicine identified acute and cancer-related pain management as an area where disparities are prevalent. Here, researchers surveyed the scientific literature published between 1990 and early 2009 to evaluate the current studies and results, determine the progress that has been made, and provide recommendations for eliminating racial and ethnic disparities in pain assessment and treatment. They found distinct differences in acute, chronic, cancer, and palliative pain care among racial and ethnic groups across the life span and treatment settings. Compared to non-Hispanic whites, minorities receive lower quality pain care. Acculturation, discrimination, and racial and ethnic group differences are important factors that may lead to this inequality and the researchers emphasized that further study is necessary to determine their impact on pain management and care. They also suggested that the processes by which pain care is provided may need to be altered to include approaches that educate and empower the patient to become more involved in their pain management regimen. Considering the growing prevalence of pain and its increasingly large associated socioeconomic burden, more efficient policies and practices must be designed to lessen and eliminate disparities in pain care.



Sex-Related Influences on Pain Reveal a Greater Prevalence of Pain in Women

[*Sex, gender, and pain: a review of recent clinical and experimental findings. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL 3rd. J Pain. 2009 May; 10\(5\): 447-85.*](#)

The importance of sex-related differences in health, wellness, and disease progression has long been acknowledged in research. However, over the past two decades, a number of publications investigating the sex differences in pain and response to pain treatment have emerged. Scientists comprehensively reviewed and summarized the recent literature on sex differences in clinical and experimental pain, responses to pain treatments, and biological, psychological, and social mechanisms of pain. They concluded that, while the relationship between sex, gender and pain is complex, the most common forms of pain, including musculoskeletal and neuropathic pain, are more prevalent among women. Compared to men, women also report increased pain following invasive procedures and exhibit greater sensitivity to most experimentally-induced pain. Studies on pain-related brain activation and responses to treatment with pain medication remain inconclusive, however. In this review, the scientists suggested several potential mechanisms that may contribute to sex differences in pain and response to treatment such as gender roles, cognitive factors, and hormonal influences. Further, they recommended that preclinical studies in



laboratory animals should include subjects of both sexes and that human clinical studies should evaluate sex differences. Continued focus on this area of research could result in sex-specific advances in pain management, especially where diagnostic assessments, medication, and/or interventions differ between men and women.

Overlapping Conditions

Vulvodynia Diagnosis Increases Likelihood of Other Chronic Pain Conditions

[*Reed BD, Harlow SD, Sen A, Edwards RM, Chen D, Haefner HK. Relationship between vulvodynia and chronic comorbid pain conditions. Obstet Gynecol. 2012 Jul; 120\(1\): 145-51.*](#)



Certain pain conditions are known to co-occur and it is hypothesized that there may be common mechanisms that underlie these conditions. Vulvodynia (vulvar pain), irritable bowel syndrome (IBS), fibromyalgia (characterized as pain in the muscle and connective tissues), and interstitial cystitis (characterized as bladder pain) are all underdiagnosed chronic pain conditions that have similar physiological features, such as sensitivity to touch, and show similar brain pattern activation. This study sought to determine the extent to which these four conditions co-occur. Over 1800 women (with an average age of 50 years old) in Michigan were surveyed at two time points, 6 months apart. The prevalence of the four conditions ranged from 7.5% to 11.8% in the group. Researchers found that women who reported having IBS, fibromyalgia, or interstitial cystitis were more likely to screen positive for vulvodynia. If more than one of these conditions were reported, the likelihood of screening positive for vulvodynia increased further. Vulvodynia is also more likely to co-occur with IBS or interstitial cystitis than with fibromyalgia. Factors such as age, marital status, education, ethnicity, and difficulty paying for basics were assessed to determine if these contributed to increased odds of having more than one of the four conditions. Of these factors, it was found that the odds of having a higher number of disorders were associated with difficulty paying for basics (such as food, clothing or housing). This study is the first to describe co-occurrence of vulvodynia with other chronic comorbid pain conditions in a population. Studies such as these will help address the question of whether these conditions share common mechanisms and ultimately whether preventions or treatments can be used to target multiple pain conditions that co-occur.

NIH Initiative Aims to Identify Risk Factors for Developing Temporomandibular Disorders (TMD) and Other Overlapping Conditions

[*Orofacial Pain prospective evaluation and risk assessment study – the OPPERA study*](#)

In 2006, the National Institute of Dental and Craniofacial Research (NIDCR) funded the Orofacial Pain: Prospective Evaluation and Risk



OPPERA

Orofacial Pain: Prospective Evaluation and Risk Assessment
A Study of Muscle, Joint and Jaw Function

Assessment (OPPERA) study. This multi-year observational study was designed to test a candidate panel of genes and identify the physiological, psychological, and clinical factors causing first onset Temporomandibular Disorders (TMD), a set of conditions that affect jaw muscles, the jaw joint, or both. The OPPERA Study is being conducted with volunteers from four separate study sites: the University of North Carolina at Chapel Hill, the University of Florida at Gainesville, the University of Maryland at Baltimore, and the State University of New York at Buffalo. A second study, embedded in OPPERA and examining the same risk determinants, but instead for chronic TMD, found that females had a four-fold higher risk than males and individuals with greater face pain and limitations in jaw function were at higher risk for

developing chronic TMD. Researchers also discovered that those individuals with a higher frequency of other overlapping pain conditions were more likely to have chronic TMD and that increased psychological stress and heightened self-awareness of pain. In addition, increased mechanical pressure pain sensitivity and increased heart rate were associated with a higher incidence of chronic TMD. A five year follow-up study, OPPERA-II, was recently funded. It includes aims to identify risk factors that predict whether TMD will develop as a single condition or in conjunction with other pain conditions, including headache, low back pain, irritable bowel syndrome, and widespread body pain. As part of the OPPERA-II study, genome wide association studies (GWAS) on TMD and at least one other co-morbid pain condition will be conducted. These studies may help researchers identify new therapeutic treatments for TMD.

NIH Supports a Whole-Body Approach to Study the Relationship Between Two Painful Urological Syndromes and Other Chronic Conditions

MAPP (Multi-disciplinary Approach to the Study of Chronic Pelvic Pain)



The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, sponsored by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), was launched in 2008 to advance the understanding of the causes of the two leading chronic urological pain syndromes, interstitial cystitis/painful bladder syndrome (IC/PBS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). The MAPP Research Network is a multi-center, multidisciplinary study that employs a systemic (i.e. whole body) approach to study IC/PBS and CP/CPPS, and investigates the potential relationship between these two conditions and other pain disorders, such as fibromyalgia and chronic fatigue syndrome. A total of eight sites are involved in the MAPP Research Network – six Discovery sites that conduct research experiments and two Core Sites that analyze samples, coordinate data collection, and supply technical support. Through novel, complementary approaches, the MAPP Research Network aims to provide new insights into the underlying causes, natural history, risk factors, and contributions from co-morbid pain disorders that may lead to improved therapeutic treatments and more effective clinical management. Recently, a new round of studies, MAPP II, was funded to further the understanding of how those with IC/PBS or CP/CPPS respond to various treatments.

Pain Mechanisms

Uncovering the Itch

[*A subpopulation of nociceptors specifically linked to itch.*](#) Han L, Ma C, Liu Q, Weng HJ, Cui Y, Tang Z, Kim Y, Nie H, Qu L, Patel KN, Li Z, McNeil B, He S, Guan Y, Xiao B, Lamotte RH, Dong X. *Nat Neurosci.* 2013 Feb; 16(2):174-82.

And:

[*The cells and circuitry for itch responses in mice.*](#) Mishra SK, Hoon MA. *Science.* 2013 May 24; 340(6135):968-71



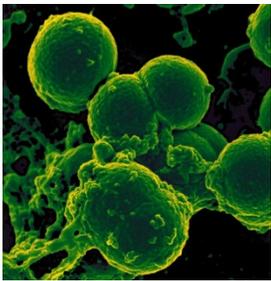
Orrling and Tomer Scheib

The pathways that mediate pain and itch are interconnected, and there has been uncertainty about whether they utilize distinct neuronal pathways. Agents that induce itch, for example the anti-malarial drug chloroquine, also activate capsaicin-sensitive neurons. Capsaicin is the chemical responsible for the burning sensation in chili peppers. Researchers are investigating whether the mechanisms for these two sensations differ at the cellular level. In the first study, Han et al., discovered that a

population of neurons which express the receptor *MrgprA3* (called *MrgprA3+* neurons), located in the skin, respond specifically to chloroquine and other itch-inducing agents. When *MrgprA3+* neurons were deleted in knockout mice, itch-associated behaviors (i.e. scratching) were significantly reduced, but pain-associated behaviors (i.e. facial wiping) were unchanged. Additionally, capsaicin caused scratching, but not wiping, in mice with *MrgprA3+* neurons that lacked the TRPV1 ion channel, which mediates pain responses. These findings indicate that whether a stimulus causes a pain sensation or an itch sensation largely depends on the specific neuronal pathway that is being activated. In the second study, researchers Mishra and Hoon found that the molecule natriuretic polypeptide B (Nppb) plays a role in itch-associated responses in mice. Administration of Nppb induced scratching behavior in mice, while mice missing Nppb were rendered unresponsive to multiple itch-inducing agents, suggesting Nppb acts as a neurotransmitter for itch signaling. Based on their findings, the researchers hypothesize that Nppb acts as a secondary signal in response to itch. Taken together, the two studies suggest a potential itch pathway in which itch-inducing agents activate specific neurons that innervate the skin, the *MrgprA3+* neurons, which then activate second level neurons leading to release of a neurotransmitter, Nppb, that mediates additional signaling in the spinal cord. Distinguishing pain and itch pathways is an important breakthrough because it may lead to the discovery of specific treatments for itch.

Newly Identified Mechanism for Bacterial Infection Pain

[Bacteria activate sensory neurons that modulate pain and inflammation.](#) Chiu IM, et al. *Nature*. 2013 Sep; 501(7465): 52-7.



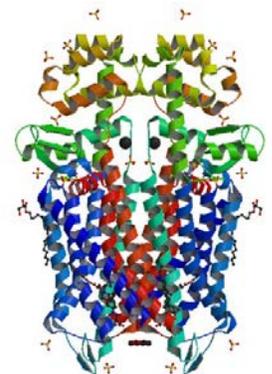
National Institute of Allergy and Infectious Diseases

While bacterial infections can be quite painful, it isn't clear why this is so. Most investigators have attributed this pain to proteins and other mediators released by our immune system. Using an animal model, scientists funded by the National Institute of Health studied the mechanisms by which *Staphylococcus aureus* (otherwise known as staph) infections trigger inflammatory pain. Following bacterial injection, scientists found that the time course of the pain associated with infection does not follow that of tissue swelling or immune activation, but instead parallels bacterial expansion or growth. They also noted that the immune response – the secretion of various factors by immune cells – does not appear to cause infection-induced pain. Instead, bacteria directly activate pain receptors by secreting a toxin called α -haemolysin (α HL) and molecules known as N-formylated peptides. Thus, their data suggest a novel pathway for bacterial infection-induced pain, whereby bacteria directly interact with and activate pain receptors to modify the immune response.

Endorphins May Play a Role in the Development of Chronic Pain

[Constitutive \$\mu\$ -opioid receptor activity leads to long-term endogenous analgesia and dependence.](#) Corder G, et al. *Science*. 2013 Sep; 341(6152): 1394-9.

The μ -opioid receptor (MOR) is the main site of action for opioids, such as morphine, that relieve pain. Chronic use of opioids can produce tolerance (in which more drug is needed to get the same effect) and dependence (characterized by symptoms of withdrawal when the drug is stopped). Endorphins are natural opioids that are produced in humans and are released in response to pain as well as during certain activities such as exercise. Investigators have hypothesized that chronic opioid use may alter the endogenous opioid system so that it is constitutively activated. In this study, researchers tested whether chronic pain did, in fact, alter the endogenous opioid system. They found that tissue injury in mice produced constitutive activation of MORs that decreased pain sensitivity for months. An opioid blocker was used to prevent the activity of the endogenous opioids, which resulted in increased pain sensitivity and symptoms of withdrawal in mice. These findings indicate that chronic pain causes continuous activation



Protein Data Bank

of the endogenous opioid system which, while contributing to reduction in pain, may also contribute to dependence. These findings have important implications for understanding the development of chronic pain.

The Inhibitor Naloxone Reverses Chronic Neuropathic Pain in Rats

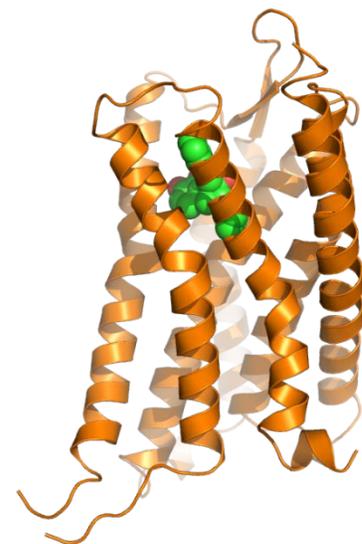
[*\(+\)-Naloxone, an Opioid-Inactive Toll-Like Receptor 4 Signaling Inhibitor, Reverses Multiple Models of Chronic Neuropathic Pain in Rats. Lewis SS, Loram LC, Hutchinson MR, Li CM, Zhang Y, Maier SF, Huang Y, Rice KC, Watkins LR. The Journal of Pain. 2012 May; 13\(5\): 498-506*](#)

Chronic pain affects at least 100 million Americans, at a national economic cost of approximately \$600 billion per year. Many patients continue to receive inadequate pain relief. Thus, identifying potential new medications is critical. Recent evidence indicates a pivotal role for the receptor known as toll-like receptor 4 (TLR4) in regulating the activity of microglial cells in the spinal cord, a type of cell critically involved in the development and maintenance of chronic pain. A drug that inhibits TLR4 could inhibit the activity of microglial cells and thereby produce pain relief. Previous work has shown that inhibiting TLR4 does produce pain relief in animal models of neuropathic pain; however, these were specifically models of short-duration pain, and wouldn't necessarily model how TLR4 inhibitors might affect chronic pain in patients. In this study, scientists showed that (+)-naloxone, a drug that inhibits TLR4, produced pain relief in two animal models of persistent, long-duration neuropathic pain. This research supports TLR4 as a potential therapeutic target for treating chronic pain in patients, and, as the establishment of a completely new class of pain-relieving medication, would be a remarkable advance in pain treatment.

Scientists Unlock the Structure of Opioid Receptors

[*Structure of the \$\delta\$ -opioid Receptor Bound to Naltrindole. Granier S, Maglik A, Kruse AC, Kobilka TS, Thian FS, Weis WI, Kobilka BK. Nature. 2012 May 16; 485\(7398\): 400-4.*](#)

Opioids, like morphine, are commonly prescribed to patients to relieve pain. However, opioids cause many undesirable side effects and have the potential to be abused. Scientists are studying how to design new opioids that still relieve pain, but have less potential for side effects and abuse; such a discovery would transform the field of pain medicine. This effort requires an understanding of the structure of the receptors that opioids interact with in the brain to relieve pain. These receptors are of a particularly complex type called G-protein coupled receptors (GPCRs), and their structures had long been impossible to study in the lab – these large and floppy molecules are incredibly difficult to stabilize as crystals, a necessary first step in order to analyze their molecular structures by the 'gold standard' X-ray crystallography. However, the structures of the four known opioid receptors were all published this year in the high-profile journal *Nature*. Brian Kobilka, who worked for over twenty years to show in 2007 the first high-resolution structure of a GPCR bound to a hormone, won the 2012 Nobel Prize in Chemistry for his work (with Robert Lefkowitz) on how GPCRs function in the body.



Proteins Involved in Painful Touch Identified as Potential Targets to Treat Pain and Other Disorders

Piezo Proteins Are Pore-forming Subunits of Mechanically Activated Channels. Coste B, Xiao B, Santos JS, Syeda R, Grandl J, Spencer KS, Kim SE, Schmidt M, Mathur J, Dubin AE, Montal M, Patapoutian A. *Nature*. 2012 Feb 19; 483(7388):176-81.
and:

The Role of Drosophila Piezo in Mechanical Nociception. Kim SE, Coste B, Chadha A, Cook B, Patapoutian A. [Nature](#). 2012 Feb 19; 483(7388): 209-12.



*Photograph of drosophila by
André Karwath*

One important area of pain research investigates the biological processes involved in the sensation of painful touch. Many of these processes involve pressure-detecting channels – pore-forming proteins present in the membranes surrounding all cells – but only a few of these types of channels have been described to date. These milestone papers, working in a mouse model system and a fruit fly (*Drosophila*) model system, identified and characterized Piezo proteins, a family of channel proteins that are essential to the sensation of painful touch. This research gives scientists a new type of target for treating pain in patients, and also has significant implications for other aspects of human health, including regulation of blood pressure and hearing sound. This is because Piezo proteins detect squeezing and stretching of cell membranes *in general*. So, for example, Piezo proteins

embedded in the walls of blood vessels might act as ‘detectors’ of blood pressure, and disruption of this function could contribute to the development of high blood pressure. Similarly, Piezo proteins in the ear might act to detect the pressure of sound waves, producing normal hearing; disruption of this function could contribute to deafness. Thus, targeting the function of Piezo proteins with new drugs could be an important strategy not only for relieving pain, but also for treating hypertension and deafness.

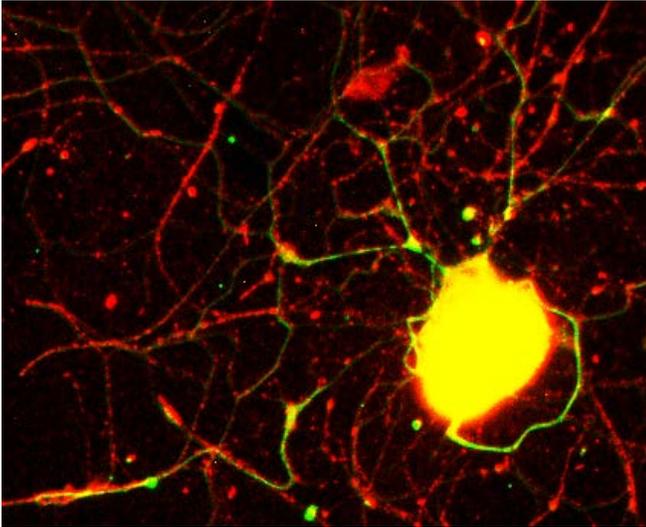
Potent Opioid Analgesic May Provide Pain Relief without the Side Effects

Truncated G protein-coupled mu opioid receptor MOR-1 splice variants are targets for highly potent opioid analgesics lacking side effects. Majumdar S, Grinnell S, Le Rouzic V, Burgman M, Polikar L, Ansonoff M, Pintar, J, Pan Y-X, and Pasternak GW. Proceedings of the National Academy of Sciences. 2011; 108(49): 19778-19783.

Pain remains a pervasive public health problem. Despite significant advances in our understanding of the basic mechanisms underlying pain, there has been a lack of major breakthroughs in development of drugs to treat pain, called analgesics. The Institute of Medicine reported that between 2005 and 2009, only a few of the hundreds of new drugs approved by the U.S. Food and Drug Administration were for pain conditions. Opioids (such as morphine and codeine) and non-steroidal anti-inflammatory drugs (such as aspirin and ibuprofen) are two classes of analgesics commonly used to treat pain, yet both classes are associated with undesirable side effects and risks. In this paper, scientists describe an opioid analgesic they developed, called IBNtxA. They showed that, in mouse models, IBNtxA is a potent analgesic and, unlike classical opioids such as morphine, does not produce addiction-like behaviors, constipation, or depressed respiration. Further, the scientists show that IBNtxA produces analgesia via a naturally occurring variant of the opioid receptor, mu-opioid receptor-1 (MOR-1). Because this MOR-1 receptor variant also occurs in humans, this study suggests that analgesics targeting MOR-1 variants could produce pain relief with reduced potential for side effects and abuse.

Signaling Molecules, Resolvins, Reduce Pain and Inflammation in Animal Models

Resolvins RvE1 and RvD1 Attenuate Inflammatory Pain via Central and Peripheral Actions. Xu Z-Z, Zhang L, Liu T, Park JY, Berta T, Yang R, Serhan CN and Ji R-R. Nat Med. 2010 May; 16(5): 592-7.



Co-localization of ChemR23 with TRPV1 in a cultured dorsal root ganglion neuron

Inflammation is the body's way of protecting itself from injurious stimuli, such as infectious agents, and initiating the healing process. Without inflammation, wounds and infections would never heal. However, inflammation must be tightly regulated because in excess it causes tissue destruction and pain – this is what occurs in arthritis. Resolvins are signaling molecules naturally produced in the body that act to “resolve” inflammation, allowing inflammation to happen on a short-term, but not permanent, timeframe. In this study, scientists showed that administering resolvins in animal models of inflammatory pain produced a decrease in pain-related behaviors and also reduced markers of inflammation. Resolvins may represent a possible new analgesic drug for treating inflammatory pain, which would not only alleviate pain, but also directly limit inflammation and, potentially, the tissue destruction associated with it. Also, resolvins could represent a

significant improvement over currently used therapies (mainly, opioids such as morphine and inhibitors of the enzyme cyclooxygenase (COX)), because opioids and COX inhibitors have undesirable side effects that limit their use. Resolvins would be expected to produce fewer or at least less adverse side effects in patients, because they would not produce the off-target side effects that opioids do, such as sedation and nausea, and they would not interfere with the body's ability to initiate the short-term inflammation necessary for healing from wounds and infections.

Surveillance & Human Trials

Opioid-Related Pharmaceutical Overdose Deaths Rise Dramatically

[Pharmaceutical overdose deaths, United States, 2010.](#) Jones CM, Mack KA, Paulozzi LJ. *JAMA*. 2013 Feb; 309(7): 657-9.

And:

[National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999-2009.](#) Calcaterra S, Glanz J, Binswanger IA. *Drug Alcohol Depend*. 2013 Aug; 131(3): 263-70.

In the past, fatal drug overdoses from illicit drugs such as heroin and cocaine were more common than overdoses from prescription medications. In recent years however, as death rates from drug overdoses have increased, pharmaceutical drugs have become a major contributor. These two articles focus on prescription opioid-related drug overdoses, and the role of other pharmaceutical agents that are subject to abuse, such as benzodiazepines. In the first study, researchers looked at the data trends from unintentional drug overdose death rates at ages 15-64 from 1999-2009. Overall, the death rate across all ages increased by 400%. The increases were most concerning for the 15- 24 year old age group, which increased by 600% overall. For example, deaths related to sedative hypnotics increased 5-fold in all persons aged 15-64, but increased 10-fold in persons aged 15-24. Males had higher death rates than females for all substances; the sex difference was less for pharmaceutical opioid and sedative hypnotics than for



Centers for Disease Control & Prevention

heroin, cocaine, and psychostimulants. The second study focused on pharmaceutical overdose deaths in 2010, and also demonstrated a predominant role of opioid analgesics in overdose deaths. The death rate related to pharmaceutical opioids was the highest among users of combinations of substances, particularly when opioids were taken in combination with benzodiazapines, antidepressants or antipsychotics. It is important to note that the non-opioid drugs that contribute to overdose deaths are drugs taken for mental health issues, a reminder of the challenges of treating pain susceptibility in the mental health population. The researchers suggest evaluation of tools, such as drug monitoring programs, as well as the need for better management of mental health and chronic pain disorders.

Spinal Manipulation Therapy and Home Exercise with Advice Are More Effective than Medication for Treating Neck Pain

Spinal Manipulation, Medication, or Home Exercise with Advice for Acute and Subacute Neck Pain. Bronfort G, Evans R, Anderson AV, Svendsen KH, Bracha Y, Grimm RH. Ann Intern Med. 2012 Jan 3; 156(1 Pt 1): 1-10.

Neck pain is one of the most commonly reported symptoms in primary care and afflicts nearly 70% of people at some point in their lives. Commonly, home exercise programs, medications, and spinal manipulation, a manual therapy, are prescribed as treatment. Despite frequent and widespread use, the effectiveness of these interventions has not been investigated thoroughly. In this study, researchers examined which treatment option – spinal manipulation therapy (SMT), home exercise with advice (HEA), or medication – is more effective at reducing pain in patients suffering from transitory (< 7 days) or short-term (8 days - 3 months) neck pain. Over the course of 12 weeks, 272 patients were randomly assigned to one of these treatment options and their pain scores were measured at intervals for 52 weeks. While patients in the SMT and HEA groups reported similar and significant pain reductions, both treatments were more effective in the short- and long-term at decreasing pain compared to treatment with medication. SMT and HEA treatments, which have relatively few side effects, have been shown here to be successful intervention therapies for patients with neck pain.



Knee Pain and Knee Osteoarthritis is on the Rise

Nguyen US, Zhang Y, Zhu Y, Niu J, Zhang B, Felson DT. Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. Ann Intern Med. 2011 Dec 6; 155(11): 725-32.

Knee pain affects a quarter of the adult population and significantly reduces quality of life. One major cause of knee pain is knee osteoarthritis. Knee pain and knee replacements have increased over the years, particularly in older adult populations. Obesity is a significant risk factor for both knee pain and knee osteoarthritis and the rising rate of obesity in the US population could be contributing to the increased incidence; an aging population could also be impacting the incidence of knee osteoarthritis. This study sought to investigate what factors contribute to the increased prevalence of knee pain and knee osteoarthritis. Data were collected from two nationally representative cohorts: (NHANES: National Health and Nutrition Examination Survey) and FOA (Framingham Osteoarthritis Study) periodically over a 30 year span (1971 – 2005). A diverse group of participants over the age of 50 were included. The prevalence of knee pain and knee osteoarthritis increased over time in both studies, regardless of the age of the individuals. While obesity (measured by body mass index) did play a role in the increase in knee pain and knee osteoarthritis, it only partially accounted for the rise, since increases were still seen even after controlling for BMI. These findings point to an increasing burden of knee pain in the U.S. adult population and help to explain the increased number of knee replacements.

Chronic Joint Pain Is Associated with Elevated Rates of Falls in Older Adults

Chronic musculoskeletal pain and the occurrence of falls in an older population. Leveille SG, Jones RN, Kiely DK, Hausdorff JM, Shmerling RH, Guralnik JM, Kiel DP, Lipsitz LA, Bean JF. JAMA. 2009 Nov 25; 302(20): 2214-21.

In the United States, falls are the leading cause of death from injury among older adults, at an estimated economic cost of \$30 billion in 2010 alone. While the evidence supporting associated risk factors is growing, few fall prevention strategies have proved successful. Chronic pain, while prevalent in older adults, remains undertreated and contributes to limited physical mobility, decreased attention, and increased distraction. However, the impact of chronic pain on the risk of falls remains unclear. As a result, researchers investigated whether chronic musculoskeletal pain increased the number of falls in older, community-living adults. They found that participants with two or more sites of joint pain, increased severity of pain, or greater pain interference with activities have elevated rates of falls than those with no joint pain. Even those reporting very mild pain have a higher risk of falling than those with no pain. Thus, improved pain management may reduce the frequency of falls in older adults.

Emergency Department Visits and Prevalence of Common Pain-Relieving Drug Use

Emergency department visits attributed to selected analgesics, United States, 2004-2005. Willy M, Kelly JP, Nourjah P, Kaufman DW, Budnitz DS, Staffa J. Pharmacoepidemiol Drug Saf. 2009 Mar; 18(3): 188-95.

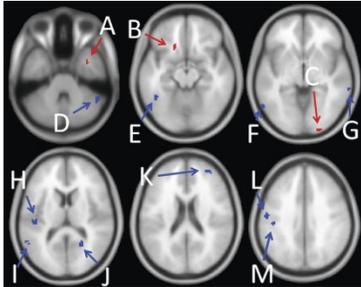
Nearly 147 million American adults use analgesic (pain-relieving) drugs every month. Common analgesic drugs include acetaminophen, ibuprofen, aspirin and naproxen. Additionally, combination drugs, which may include a narcotic drug such as opioids, are used. However, it is not well-known how the use of analgesic drugs correlates with the number of emergency department (ED) visits that are attributed to analgesic use. Researchers sought to address this question using national data on the use of analgesics in households and ED visits due to analgesic adverse events. From 2004-2005, analgesic use was quite common and varied by age group. Adults over 65 years of age predominantly used single-ingredient aspirin. In adults aged 18-64, ibuprofen, single-ingredient aspirin, and single-ingredient acetaminophen were the most common medications, followed by non-narcotic-acetaminophen combinations, naproxen, and narcotic-acetaminophen combinations. Children 12-17 years of age most commonly used ibuprofen and children 0-11 years of age most commonly used single ingredient acetaminophen and ibuprofen. Over 180,000 visits to the ED in 2004 and 2005 were attributed to an adverse drug event requiring urgent care. In nearly 75% of those visits, analgesics were thought to be the sole medication used. These data did not include cases of intentional self-harm. Acetaminophen-containing products, particularly narcotic-acetaminophen combination products, had the highest rate of ED visits among adults aged 18-64. For children, single-ingredient acetaminophen product overdoses were a common reason for ED visits. Side effects from aspirin use were a common reason for ED visits, whereas allergic reactions were more common for naproxen and ibuprofen use. Although the rate of ED visits due to analgesics is low and do not usually result in hospitalization, the public health impact is still great based on the number of individuals who use analgesics.



Tools/Instruments

Brain Imaging and Machine Learning Identify Brain Changes in Chronic Low Back Pain Patients

[Multivariate Classification of Structural MRI Data Detects Chronic Low Back Pain](#). Ung H, et al. *Cereb Cortex*. 2014 Apr; 24(4): 1037-44.



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Chronic low back pain (cLBP) is the leading cause of activity limitation in individuals over 45 years old with an estimated annual economic burden of \$100-200 billion in the US. The origin of cLBP, however, is unknown for the majority of patients. Imaging studies had previously identified changes in brain structure and function in those with chronic pain but the results were inconsistent for cLBP. Here, researchers investigated the density of gray matter (GM) – the portion of the brain that contains most of the neuronal cell bodies – in un-medicated patients with cLBP and compared it to that of healthy controls. A machine-learning algorithm, in which a machine was trained to distinguish distributed patterns of changes in GM density, was utilized to distinguish

cLBP patients from healthy controls. They found that, whereas total GM volume is similar, patients with cLBP display unique distributed patterns of GM density throughout the brain, particularly in areas associated with pain. Changes in areas of the brain less commonly associated with pain were detected as well. The researchers validated the use of GM density imaging and machine-learning to classify cLBP (76% accuracy). The results from this study advance the understanding of the brain's role in cLBP and provide a tool to aid in identifying the disease.

Pain in the Brain: A Brain Signature for Pain

[An fMRI-based neurologic signature of physical pain](#). Wager TD, et al. *N Engl J Med*. 2013 Apr; 368(15): 1388-97.

There is substantial interest in understanding the central brain circuitry responsible for pain perception. One valuable tool for studying the brain in humans is functional magnetic resonance imaging (fMRI), which measures brain activity in specific regions by detecting associated changes in blood flow. Wager and colleagues conducted a series of fMRI studies using different subject groups to identify a neurological signature that is specific and sensitive to physical pain. They used fMRI to detect the brain's response to painful heat and non-painful heat in normal subjects and evaluated the results with machine-based learning which permitted the identification of a distinctive response, or a pain signature, consistent across multiple individuals. In their first study, machine-learning analyses were used to identify the activity patterns measured by fMRI in specific brain regions associated with heat-induced pain and with non-painful warmth. These signatures were so distinct that they reliably discriminated painful heat and warmth. Subsequent studies that compared the pain signature associated with physical pain to that associated with social pain (in which subjects reported intense rejection due to a recent romantic breakup) revealed that they also were sufficiently distinctive to be predictive of the stimulus. In addition, they showed that administration of the analgesic agent Remifentanyl reduced the strength of the physical pain signature response. This study demonstrates the ability to use fMRI to assess the pain response in healthy persons. The findings from these studies ultimately may help to provide more standardized, reproducible and less subjective measures of pain which could facilitate the development of more individualized and better treatments.

Brain Imaging and Machine Learning Used to Distinguish Painful and Non-Painful Heat Stimulation

Towards a physiology-based measure of pain: patterns of human brain activity distinguish painful from non-painful thermal stimulation. Brown JE, Chatterjee N, Younger J, Mackey S. PLoS One. 2011; 6(9): e24124.

Pain is commonly accepted to be an individualized experience; thus, self-reporting is considered the gold standard of pain measurement. However, self-reporting can fail certain vulnerable populations such as older individuals or those with mental health disorders. Therefore, researchers are actively seeking an assessment of pain that is based on physiological changes. Brain imaging non-invasively measures brain activity that is closely associated with physiologic events. The addition of machine learning algorithms allows researchers to develop models in which known stimuli can be used to test novel stimuli. This study examined whether a machine could be trained to accurately distinguish painful from non-painful heat stimulation based on brain imaging. Eight individuals self-reported pain levels following application of varying heat intensities on their forearm to determine average non-painful and painful temperatures. Brain imaging, functional Magnetic Resonance Imaging (fMRI), was then performed during presentation of a non-painful heat stimulus or a painful heat stimulus (temperature that was consistently rated 7 out of 10 on the pain scale). Data from these individuals were then used to train the machine to distinguish non-painful from painful heat stimuli. To test the model, sixteen previously untested individuals were presented with various heat stimuli during fMRI testing and the machine assigned a classification of painful or non-painful. The trained machine was able to distinguish painful from non-painful stimuli with an average accuracy of 81%. Further analysis revealed that the brain regions which most influence the machine's classification were different in the non-painful versus the painful stimuli. This study demonstrates the utility of brain imaging and machine learning for assessing pain levels without requiring any communication from the person. In the future, other painful stimuli such as electrical or mechanical pain may be tested.



Brain image depicting active areas during stimulation

Federal Agencies Partner with Public Groups to Optimize Pain Treatment Development and Clinical Trials

ACTTION/IMPACT (Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks/Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials)



The Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) is a multi-year, multi-phase public-private partnership with the United States Food and Drug Administration (FDA). This initiative is designed to optimize clinical trials and other activities that will accelerate the discovery and development process

and improve the efficacy and safety of new analgesic, anesthetic, and addiction treatments. The FDA's Critical Path Initiative, which is designed to drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured, is closely aligned with ACTTION. ACTTION aims to initiate and support data sharing, innovative thinking, and strategic collaborations among a wide range of partners, including academia, government agencies, industry, professional organizations, patient advocacy groups, foundations, philanthropic organizations, and others, to improve the evaluation and expedite the development of novel therapeutics and benefit the public health. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMPACT), an ACTTION initiative, is an international consortium designed to develop consensus recommendations to enhance the design, execution, and interpretation of clinical trials of pain treatments. To date, fifteen consensus meetings have convened with participants from academia, US and international regulatory agencies (FDA and European Medicines Agency), the National Institutes of Health, the Veterans Administration, consumer groups, and industry. Pain clinical trial topics have included chronic pain in adults, acute pain in adults, and pediatric acute and chronic pain. Thus far, the recommendations and reviews put forth by IMPACT have informed clinical trial design, other clinical research, and a national survey. Additional consensus meetings are planned on an annual basis and ongoing research initiatives focused

on the assessment of pain and the design and interpretation of clinical trials continually are making progress to improve the understanding of pain and its treatment.

