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Learning Objectives

After reading the three-part newsletter series for 2005, participants should be able to:

- Differentiate chronic pain from acute pain and describe the mechanisms of pain and sites of activation.
- Address common barriers that limit effective pain management for patients with chronic pain.
- Determine the recommended components for comprehensive assessment of pain and function in patients with chronic pain.
- Select more varied pharmacologic and nonpharmacologic strategies for initial and ongoing management of chronic pain.
- Describe therapeutic approaches to minimize potential adverse effects and drug interactions and identify safety issues and precautions.

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Dr Rosenthal has indicated that he has received unrestricted educational grants from Endo Pharmaceuticals Inc.

This is the **second issue of a three-issue CME newsletter series**. To receive credit, read all three issues, complete the post-test and evaluation included in the third issue (to be released Winter 2005), and mail the evaluation form to Thomson Professional Postgraduate Services®, CME Dept. #B082, 150 Meadowlands Parkway, PO Box 1505, Secaucus, NJ 07094-1505. Within 6 to 8 weeks of receipt of the evaluation form, participants will be sent a credit letter.



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Pain Management in the Decade 2010-2020: Déjà vu du Jour



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The quest to control pain dates back to pre-historic times. Ancient skulls display man-made holes that may signify the earliest known surgery. Whether these holes were “drilled” to relieve pain is unknown; however, some African tribes continue this practice of “trephening,” which produces similar anatomic features, as a way to relieve pain. Perhaps the first written account of a pain treatment appeared in the Ebers papyrus¹ dating back over 6,000 years. In the papyrus, the goddess Isis prescribes opium to relieve the god Ra’s headache. Acupuncture as part of traditional Chinese medicine has been used to control pain for nearly 5,000 years and was described in detail in the *Yellow Emperor’s Classic of Internal Medicine*² published in 25 AD. Over 2,400 years ago, Hippocrates³ recommended the use of extract of willow bark to treat pain. The analgesic effects of a class of eels

(“electric eels”) and torpedo fish were described in ancient medical texts where the electrical discharge was believed to provide analgesic benefit.⁴ Additionally, bathing in hot springs, sulfur baths, and mud baths have been advocated for their therapeutic properties dating back 6,000 years to the Sumerians’ Nippur Tablet.⁵

The current pain management armamentarium relies heavily on the ancient one: *déjà vu du jour*. Opioids, nonsteroidals, surgery, thermal agents, and physical modalities continue to be the mainstay of pain management. What has changed, however, has been the development of new routes of administration of pharmacologic agents (eg, implanted pumps with reservoirs filled with various medications diffused continuously or on demand, topical agents), electrical current (eg, spinal cord stimulators, transcuta-

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Unraveling the Mechanisms of Neuropathic Pain



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Broadly speaking, there are three types of pain. If pain were a movie, it would be called “The Good, the Bad, and the Ugly.”¹

Physiologic Pain. The first type of pain, and perhaps least important for clinicians, is physiologic pain. This is the good pain that warns us of actual or impending damage to our body. The intensity of physiologic pain corresponds with the intensity of the stimulus causing it, and its duration is only as long as the stimulus itself. This is the pain we experience when we touch a hot stove or step on a sharp object, and which physiology we learned in medical school (if we learned anything at all about pain). Until recently, physiologic pain was the most studied in research laboratories. Ironically, this is the pain we want least to diminish, except in the context of surgery, invasive procedures, and childbirth. Physiologic pain is always evoked by a stimulus; it is never spontaneous.

Inflammatory Pain. In contrast to the good pain described above, inflammatory pain is a bad pain. It is the pain caused by injury that lingers until healing is complete, or pain that persists because of ongoing tissue-damaging diseases such as arthritis and cancer.

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Why Be Aware of Pain?

Although pain is one of mankind's oldest problems, pain management is one of medicine's newest "specialties." Why is it important, particularly from the vantage point of the primary care physician (PCP), to be aware of the ramifications of pain management?

Not only is pain one of our oldest problems, it is one of the most common problems, causing significant morbidity and disability. A recent ABC News/USA TODAY/Stanford University national poll estimates that nearly 4 in 10 American adults suffer from pain on a regular basis, and one third of those rate their pain as moderate to severe. These figures are consistent with the American Chronic Pain Association's estimate that 75 to 150 million Americans suffer from chronic pain. Although the poll noted that many respondents had not seen a physician, nearly one third of those with pain reported using prescription drugs on a daily basis. For individuals with chronic pain, the use of safe and effective pharmacologic agents can result in meaningful reduction of pain that can be clinically measured by a physician using tools such as pain rating scales. It is likely that PCPs were consulted most often, particularly by the 50% of the participants in this survey who live in rural areas. Dr Charles S. Cleeland, who assisted in creating the poll, is interviewed in this newsletter. For his reaction to these data and the complete study results, see page 6.

This year has seen unprecedented media coverage concerning pain and its management, much of it negative. The legal woes of Dr William E. Hurwitz ended in a conviction of second degree murder and a life sentence for criminal conduct related to prescribing of opioid medications. Three pain medications (Vioxx®, Bextra®, and Palladone®) were withdrawn because of safety concerns. A Supreme Court decision is pending on the use of the Controlled Substance Act relating to Oregon's assisted suicide law, and two bills relating to pain and palliative care are awaiting Congressional action. Pain and its treatment are thoroughly in the public eye.

As physicians, we have a responsibility to engage in policy discussions and inform the public. We urge you to take advantage of resources from the National Initiative on Pain Control® and www.painedu.org as well as from other professional societies dealing with pain and palliative medicine, and participate in these very important discussions. The well-being of our profession and (most importantly) our patients demands no less.

Richard Payne, MD
Co-Editor

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NIPC EDUCATION STATEMENT

This educational activity is a component of the NIPC® and is designed to heighten the knowledge of physicians and other healthcare providers about the serious impact of unresolved pain on patient care. Some of the agents included in this newsletter are discussed in the context of uses for which they have not been approved by the FDA.

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ABOUT THE NIPC

The National Initiative on Pain Control® (NIPC®) is an integrated CME education initiative that was established in 2001 to help physicians improve outcomes for their patients who have pain.

Living with pain has deleterious effects on many aspects of the patient's life, including deterioration of physical functioning, the development of psychological distress and psychiatric disorders, and impairment of interpersonal functioning. Of special concern, less-than-optimal training of physicians in pain disorders has led to the underassessment and undertreatment of patients who are living with pain. The program heightens physician awareness of the impact of pain on patient's daily living in terms of quality of life, lost workdays, and societal/familial consequences.

NIPC addresses the barriers to achieving pain control by providing potential pathways for action and expected amelioration of their patients' pain. By providing physicians with the latest advances and strategies in pain management, they will be better able to translate clinical data into clinical practice.

All NIPC programs are developed and continuously evaluated by the NIPC Education Council, an expert, multidisciplinary team of specialists, researchers, and practicing physicians in pain management. The NIPC Faculty includes nationally respected experts in the pain management field.

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Pain Management in the Decade 2010-2020

Continued from page 1

neous electric nerve stimulation (TENS), electrical stimulation of acupuncture needles), and the development of newer pharmacologic preparations (eg, antidepressants, anticonvulsants). Despite the long history and advances in knowledge of the neuroanatomy, neurophysiology, and neurochemistry, not much has changed in the classes of treatment for pain management from ancient times.

Perhaps true advancement in pain management began in the 1960s when Bonica⁶ fostered the involvement of multiple disciplines in the treatment of pain, Melzack and Wall⁷ articulated the gate control hypothesis, and Fordyce⁸ extended the principles of operant conditioning to chronic pain. These three streams, which provided the impetus for the explosion of knowledge of the complexity of chronic pain and the role of psychosocial and behavioral factors along with physical ones in understanding and treating chronic pain patients, culminated in the creation of the first multidisciplinary pain treatment centers.

Rehabilitation-oriented multidisciplinary pain centers (MPCs) exploded onto the healthcare scene between the 1970s and 1990s. The prototype of MPCs was the one founded by Bonica at the University of Washington. However, numerous variants evolved. There are several features that capture the essence of these facilities. They include a range of healthcare professionals (eg, physicians of different specialties, physical therapists, psychologists); some emphasis on a biopsychosocial model in treatment planning; diverse healthcare professionals working as an integrated team; emphasis on rehabilitation and accompanying self-management and not on cures; and emphasis on functional outcomes and not just on decreasing pain.⁹

Since the development of rehabilitation-oriented MPCs, there have been a large number of studies¹⁰ and meta-analyses¹¹⁻¹³ supporting the clinical effectiveness and cost-effectiveness of these integrated programs. Paradoxically, despite the fact that there are more published studies substantiating the effectiveness of MPCs than any other treatment for pain,⁹ these programs are becoming endangered. Contributing to the paradox is that, given all the calls for “evidence-based medicine” and the buzz phrase “pay for performance,” third-party payers are refusing to reimburse for treatment at MPCs or they are trying to “carve” parts out and are therefore potentially diluting the effectiveness. Part of the problem is associated with the fact that despite general descriptions there are no standards regarding what constitutes an MPC. So there are all types of solo practitioners promoting themselves as MPCs even when they consist of a single modality even though “multiple disciplines” may be involved (ie, provider and nurse). The result is that third-party payers have little basis for judging whether a facility that labels itself as such is, in fact, a multidisciplinary center.

plinary center.

Another contributing factor to the decline, if not complete demise, of MPCs is the perception that these programs are expensive. After all, if multiple disciplines are involved, they all need to be paid and the amount of space required is larger than what would be required for a solo practitioner. However, even the most advanced single modality treatments for pain (eg, surgery, implantation of spinal cord stimulators and drug administration systems, neural blockade, and even state-of-the-art pharmaceutical treatments) are expensive, especially when the cost for maintenance and treatment for iatrogenic consequences are factored into the equation. Consideration of the cost factors involved for rehabilitation-oriented MPCs and the alternatives has led some to conclude that MPCs are substantially more cost-effective than surgery, implantable devices, and neuroaugmentation procedures.¹⁰ This message has not been acknowledged or processed by third-party payers.

The consequence of lack of awareness of outcome studies and erroneous perceptions by third-party payers is resulting in a return to the earliest treatments of chronic pain where a solo practitioner utilizes a preferred method of drugs, surgery, electrical modalities, physical modalities, and the like. Examination of the literature on the effectiveness of these approaches, however, leaves much to be desired. For example,

- The most potent medications available reduce pain by only about 30% to 40% in fewer than 50% of patients. Although these levels may be clinically meaningful they do not indicate complete eradication of pain.
- Based on the observation about the limited effects of single pharmacological treatments, a number of commentators have advocated for the use of multiple medications, or “rational polypharmacy,” to treat patients with chronic pain. However, there has been a dearth of controlled clinical trials evaluating the effectiveness and potential adverse effects of using drugs in combination. Physicians need to be constantly mindful of safety when using drugs in combination.
- A substantial proportion of patients who are exposed to spinal surgery continue to report considerable pain, functional impairment, and complications associated with the treatment.
- Implantable devices are expensive, and even carefully selected patients may not be pain free and only show modest improvements in physical and emotional functioning.
- The long-term benefits of any treatment for chronic pain are largely unknown due to the brief duration of clinical trials.

What of the future, the decade of 2010–2020? As Niels Bohr acknowledged, “prediction is very difficult, especially about the future.” There are some areas where predictions can be made with some confidence. With advanced knowledge of neurophysiology, neuroanatomy, and neurochemistry, we will see the development of new classes of

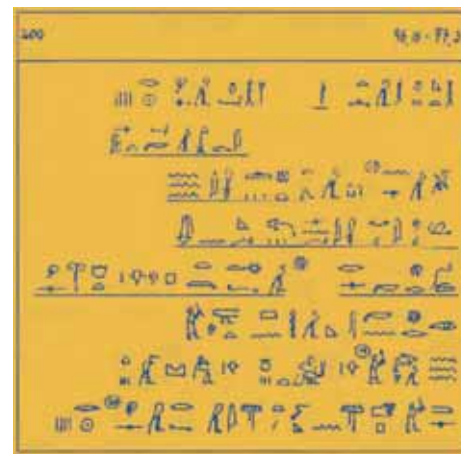


Figure. An excerpt from the Ebers papyrus.

medications and more sophisticated surgical and other invasive approaches. Understanding of genetics will likely permit the customizing of treatment to individuals' genetic codes. It is my belief that there will continue to be multidisciplinary teams involved in pain management. The composition, however, will be different than from the past when they were made up exclusively of healthcare providers. To be crassly cynical, the new multidisciplinary teams will consist of one or more healthcare providers along with an accountant and a financial analyst! Coverage for rehabilitation programs and psychosocial services will be an uphill battle despite evidence supporting their importance, clinical effectiveness, and cost-effectiveness.

* This article reflects the opinion of Dr Turk (and not of the American Pain Society, of which he is president).

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Physical Pain Aggravates Majority of Americans

Results of a National Survey

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Dr Passador has indicated that he has no relevant financial relationships.

Americans are in pain. That's the overriding message of a recently released, ABC News/USA TODAY/Stanford University Medical Center telephone poll of 1,024 randomly selected adults that provides significant insight into the prevalence and impact of that pain.¹

The survey data reveal that pain—ranging from acute to chronic and from slight to severe—is prevalent among Americans, with nearly 4 of 10 respondents stating they suffer from pain frequently. Overall, more than half of all Americans suffer chronic or recurrent pain. Nearly 60% of those surveyed consider their pain to be of moderate intensity or worse and 20% reply that they endure severe pain. Although all age groups are susceptible, the incidence and severity of pain appears to increase as people age. Among seniors, 57% admitted to experiencing pain often, compared with 43% of individuals between 30 and 65 and 17% of respondents under age 30.

Furthermore, the respondents reported that their pain has substantial impact on quality of life by limiting activities, alter-

ing moods, and reducing overall enjoyment of life in general.

So what hurts and why? Results from the survey point to back pain as the leading complaint among all demographic groups except for women under age 50. The women in this group were just as likely to report headache or migraine as they did back pain. Back pain complaints appear to be more prevalent among men, especially those between ages 30 and 49. Rounding out the top complaints were knee pain, headaches and migraine, shoulder pain, and leg pain. Together with back pain, these locations account for 60% of all pain complaints. Reasons for pain vary among specific age groups. Younger respondents, especially men under age 30, were more likely to cite sports injuries and older respondents were more likely to blame arthri-

tis. Approximately half of all respondents said their pain is the result of a specific injury or medical condition such as broken bones, arthritis, and sports injuries. Those experiencing chronic or frequent pain are more likely to cite specific injuries or medical conditions than others who do not.

Of special interest is the manner in which respondents deal with their pain. While 60% of people do talk to their doctors or healthcare professionals about their pain, it is still surprising that almost 40% of respondents never do. Why this may be is not evident from the survey results but one might reason that patients and their families, the healthcare professionals, and the healthcare system can all foster misconceptions and place barriers in the way of effective treatment.²⁻⁶ Ethnic and cultural practices can sometimes interfere with the medical care. Stoicism is often regarded as an admirable quality and some might see complaining of pain as a sign of weakness. Language barriers, mistrust of physicians, religious beliefs, or fear that the pain might indicate a serious medical problem can all hinder the reporting and necessary treatment of pain. The survey did indicate, however, that persons with chronic pain are much more likely to speak to their doctor than those with acute pain.

Even if patients do acknowledge their pain, it appears that good pain relief may be hard to find. It appears most respondents feel that the treatments they receive could

KEY FINDINGS

PREVALENCE

- More than half of all Americans suffer chronic or recurrent pain.
- Almost half of all Americans suffered pain 2 weeks prior to the survey with nearly 4 of 10 people experiencing pain on a regular basis.
- Approximately 60% of respondents consider their pain to be of moderate intensity or worse, with 20% replying that they endure severe pain (Figure).
- Among seniors, 57% admitted to experiencing pain often, compared with 43% of individuals between ages 30 and 65 and 17% of respondents under age 30.

SOURCE AND LOCATION OF PAIN

- Approximately half of all respondents said their pain is the result of a specific injury or medical condition such as broken bones, arthritis, and sports injuries. This is especially true for those experiencing chronic or frequent pain.
- Younger respondents, especially men

under the age of 30, were more likely to blame sports injuries as the cause of their pain while older respondents were more likely to blame arthritis.

- Back pain is the most prevalent reported source of pain (25%), especially among men between the ages of 30 and 49.
- Back pain is the primary pain reported across all demographic groups, but women under age 50 were just as likely to report headache or migraine (20%) as they were back pain (18%).
- Along with back pain, knee pain (12%), headaches and migraines (9%), shoulder (7%) and leg (7%) pain account for 60% of all pain by location.

SEVERITY

- Chronic pain is very rare in young adults between ages 18 and 29 (3%), but this group is more apt to report acute or specific injury-related pain (70%). Complaints increase after age 30 and are

highest in those older than 65 (29%).

- More than 60% of all respondents indicated that their pain was moderate or worse in intensity and 20% classified their pain as severe.
- Women were more likely to report recurrent pain, whereas men were more likely to report acute pain.

IMPACT

- Persons suffering from pain reported an impact on their lives, whereas more than 40% of respondents admitted to pain interfering with their ability to work or perform day-to-day activities. This was especially true for those suffering from chronic or frequent pain.
- Just under 40% stated that pain interfered with their enjoyment of life and led to sleep disturbances.
- Pain significantly affected interpersonal relationships for 24% of all respondents.
- Women were more likely to admit to pain

be better, with approximately half stating that they were reasonably satisfied with the level of pain relief. Of those who did report their pain, less than 6 of 10 said they obtained a great deal or good amount of pain relief. Also surprising is the finding that when pain relief is obtained, prayer is cited as the source of the relief just as frequently as are prescription medications. The survey did note that those who used prayer were likely to rely on other pain treatments as well. While the majority of the respondents use over-the-counter (OTC) therapies, prescription medications, or home remedies to obtain pain relief, some do turn to alternative methods including the use of alcohol or marijuana. The use of compounds such as alcohol and marijuana can be especially problematic, as they may simply mask the pain, which may lead to disregarding of the pain source—a potentially serious mistake.

One striking result is that many Americans are becoming dependent on pharmaceuticals to help them make it through the day. Of those respondents who have used OTC medications, 10% use them daily. Furthermore, 20% of people use prescription pain medications daily. Taken together, these findings indicate that more than 10% of Americans use pain medications daily.

What is clear from this survey is that pain is a prevalent part of our everyday life. The results of the survey also underscore a great need for more effective education of patients, healthcare professionals, and the

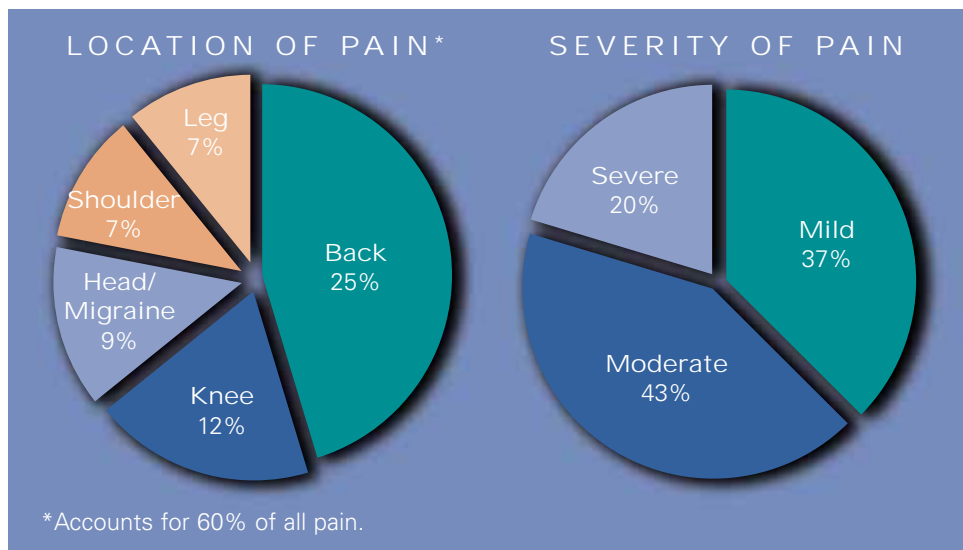


Figure. Key findings of national pain survey.

healthcare industry with regard to pain. Patients need to become more open about their pain and actively seek out effective treatment. At the same time, clinicians need to become proactive in asking their patients about pain and then treating it effectively. This is especially true for those patients with chronic pain. Of course this is an additional burden on time-constrained physicians who must also be cost-conscious in today's healthcare environment. Nonetheless, the large impact in terms of health, lost productivity, and increased utilization of healthcare services make recognition and treatment of pain a socioeconomic imperative.

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interfering with their mood, sleep, enjoyment of life, and ability to work.

PHYSICIAN INTERACTION

- Sixty-three percent of respondents have spoken with a doctor about their pain. Women were more likely than men to speak to a doctor.
- Approximately 90% felt the doctor understood their problem, yet only 60% indicated they obtained a good amount of pain relief. Thirty-one percent felt they obtained a great deal of relief.
- Chronic pain sufferers are more likely to report their pain to their doctor. Unfortunately, only about half reported their pain relief improved following their visit to a medical professional.
- Doctors appear to be better able to manage acute pain. Almost 80% of respondents with acute pain felt the doctor understood their problem very well compared with chronic pain sufferers (63%).

PAIN RELIEF

- Prayer was used by 58% of Americans to deal with their pain, almost equal to those who tried prescription drugs. Half of those using prayer state that it worked very well, again equivalent to those using prescription drugs for efficacy.
- Women (66%) were more apt to have tried prayer than men (49%).
- People who use prayer are also more likely to take prescription drugs or try other pain therapies. Hence, prayer appears to be an adjunct to other pain therapies.
- Those who suffered severe and/or chronic pain were more likely to use prayer as an approach.
- OTC medications and home remedies are the most commonly used pain therapies among Americans, with over 80% stating they have used one or both.
- Approximately 60% of respondents have used prescription drugs, prayer, or bed rest. In other categories, respondents have

tried massage (28%), a chiropractor (28%), homeopathic/herbal remedies (16%), yoga/meditation (14%), alcohol (12%), marijuana (6%), and acupuncture (5%).

- Over 25% of respondents cited concerns about the possibility of serious health risks from the use of both prescription and nonprescription drugs. Related to this, 75% stated that the FDA was justified in the actions against Bextra® and Vioxx® and in requiring other medications to add warning labels.
- Fifteen percent of respondents have taken COX-2 inhibitors, which have since been removed from the market. Twelve percent reported experiencing self-defined negative side effects whereas 85% percent said they would not take those drugs again.
- The number of respondents (60%) taking naproxen-containing drugs is far higher, with few people reporting serious side effects and 62% stating they would take them again.

Pain Survey Impressions

An Exclusive Interview With Dr Charles S. Cleeland

DAVID E. HARTREE, PhD

Medical Writer, Thomson Professional Postgraduate Services®

Dr Hartree has indicated that he has no relevant financial relationships.

Dr Cleeland has indicated that he has no relevant financial relationships.



Charles S. Cleeland, PhD, a leading specialist in the field of pain assessment, assisted in the creation of the Physical Pain Aggravates Majority of Americans survey that was conducted in April 2005. In this exclusive interview, Dr Cleeland discusses his motivation for developing the questionnaire and his impressions about the important findings. Dr Cleeland is currently Chair of the Scientific Advisory Committee, American Pain Foundation and McCollough Professor of Cancer Research and Chairman, Department of Symptom Research, Division of Internal Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, Texas.

What was your own motivation for taking part in the survey?

At the American Pain Foundation we had for some time realized that there was an important need for a large-scale, gold standard population survey of pain in the United States. At the same time ABC News and USA TODAY were planning a series of stories on pain medicine including topics such as who suffers from it, what kind of treatments are used, and what kind of research is being undertaken. The collaboration we formed with ABC News was very helpful because of their general experience with conducting public opinion polls.

How did the survey obtain a representative sample in view of the fact that patients suffering from pain are more likely to be at home than the general population?

The survey used the standard polling methodology of ABC News, which is quite sophisticated. Their methods are designed to obtain a representative sample of the US population. They target specific households and call the household phone number evenings and weekends and make repeat call attempts if there is no answer. This seems to produce accurate sampling because the percentage of employed persons in the surveys is identical to the percentage of employed persons in the United States.

What did the people in the survey use to treat their pain?

They used a variety of treatments. The top five were over-the-counter (OTC) drugs, home remedies (not otherwise defined), prescription drugs, bed rest, and prayer. Patients with chronic pain often used more than one treatment. About one third of subjects used prescription drugs a few times a month or more, and a fifth used prescription drugs on a daily basis. Experience with questionnaires has shown that most patients will report satisfaction with treatment. What is much more important is whether they report relief of pain.

Were the people in the study being treated by primary care physicians or specialists?

The survey did not contain any questions to

identify any particular specialty. It is most likely that primary care physicians were treating most of the patients. This is especially likely to be the case for the subjects from rural communities who constituted nearly 50% of the survey participants.

What do you consider to be the main take-home message from the survey findings?

The fact that a third of the subjects in the survey were experiencing bothersome (ie, moderate-to-severe) pain is particularly noteworthy. The finding is consistent with studies of the prevalence of pain from other countries. For such a common symptom, pain needs to be discussed between doctors and patients far more than is currently the case. A front-end fault of the system is that the patient is not asked about pain. There have been some improvements in the right direction. For example, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) now requires that hospital patients be assessed at least once daily for the duration of their stay, and pain assessments are made using a 1 to 10 pain rating scale.

A second shortcoming is the general lack of follow-up in pain management. For most other treatable conditions such as diabetes or dyslipidemia, the need for follow-up seems obvious to all. A similar curiosity needs to be established in pain management because patients are not often asked to rate their pain after receiving treatment.

There is a clear need for medical schools and residencies to cover pain management much more in depth than is currently the case, where there is rarely even a week of instruction on how to manage pain. Some improvements are being made, and California now requires some pain management training as part of recertification.

For patients, the overall message is that they need to be more proactive in reporting pain. It is true that some patients do over-report pain because of psychological reasons, but for the most part, patients do not take the initiative when it comes to describing pain levels.

Are there any particular surprises from the study findings?

One surprise is that a third of those reporting moderate-to-severe pain in the survey had never been to a physician for the pain. There are different possible reasons for this neglect including "the macho factor" or a feeling that there is no effective treatment. The questionnaire did not include any questions about the reasons for not reporting pain.

Also surprising was the widespread use of prescription medications for pain. Certainly the widespread advertising of prescription COX-2 inhibitors to the public may have had an influence in the current use of prescription drugs. Unfortunately, there was no equivalent survey 10 years ago; it is not possible to gauge the effect of such promotion.

Do safety concerns with prescription and OTC pain medications influence patients?

Patient anxiety about drug safety exists in several areas. The survey results show that patients are discontinuing use of COX-2 inhibitors and some NSAIDs in reaction to news coverage of serious side effects. Many feel they have run out of options for pain medication because of these concerns.

With prescription opioids, there has been plenty of sensationalist news coverage of drug abuse and diversion. This has undoubtedly resulted in patients with moderate-to-severe pain failing to get the treatment they need or even failing to report their pain to their physicians, whether through their own misgivings or through physician concerns of excessive government scrutiny. Undertreatment due to opioid avoidance is probably more widespread for patients with severe noncancer pain than with cancer patients.

Are there additional surveys planned for the future?

It is hoped that the interest generated from the survey will prompt the funding of a much larger survey with up to 10,000 respondents, which will gather much useful additional data. It would be helpful to know the prevalence of pain and accessibility to pain management in underserved and/or minority populations. A larger survey could also measure the prevalence of different types of pain, such as neuropathic pain. As with the ABC News survey, telephone polling would be used and the study completed in a relatively short time. Though the current survey demonstrates that pain is widespread and that many people are not receiving sufficient relief, a larger study would help pinpoint those who are at greatest risk for poorly managed pain. It would also help identify the types of pain that are most resistant to treatment, as well as help prioritize a research agenda. At the same time there is a need for a separate survey on the prevalence of pain in children because such a study requires a different set of experts and a greater emphasis on face-to-face interviews.

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Sometimes, this inflammatory pain is called nociceptive pain (as distinguished from neuropathic pain), although that is a misnomer. Inflammatory pain is felt when actual or potential tissue damage occurs. In a sense, it may be called an “accurate” signal of events.

Neuropathic Pain. Neuropathic pain is referred to as ugly pain. Neuropathic pain arises from damage to the nervous system itself. Although a patient with neuropathic pain reports feeling as if the body is being squeezed, burned, or jolted, there is, in fact, no ongoing or threatened damage to tissue. Neuropathic pain is a “false” signal such as in phantom limb pain, in which the patient feels pain in a limb that has been amputated.

There is an overlap in the pathophysiology of inflammatory pain and neuropathic pain and some analgesics will work for both types of pain, but with significant differences as well. Recognizing the major types of pain the patient has facilitates treating it. By analogy, there are two major types of diabetes; one is characterized by insufficient insulin and the other by insulin resistance. (I recognize that this is a simplification of the pathophysiology of diabetes.) Some treatments are useful for both, and others for only one type. A good clinician would not embark on treating diabetes without investigating which type of diabetes the patient has. Similarly, a good clinician will try to ascertain which type of pain a patient has, or whether he has a combination of pain types, before beginning treatment.

Physiology of Pain Perception

Pathology is simply physiology gone awry, therefore, a brief review of how normal pain works will provide the background information necessary for understanding the pathophysiology of neuropathic pain. Using the pain schema applied above, we start with the “good” before proceeding to the “ugly.” Normal pain perception involves a series of steps outlined below.

Transduction

Physiologic pain is experienced in response to noxious stimuli. The most common of these are pressure and heat on our exterior surfaces, and stretching in our viscera. (Keep in mind that the pain we feel as sharp or cutting is in fact simply a noxious pressure applied to a very small area.) In order for us to feel this pain, the physical force must first be transduced to a neurological signal. In other words, there must be a mechanism by which we move from the realm of physics to that of biology. This role of transducer is played by a family of nonspecific cation

channels that are found on the surface of high-threshold nociceptors. This family is called transient receptor potential (TRP) ion channels.²

Probably the best known of these is TRPV1, formerly known as the vanilloid receptor type 1 (VR1). It also serves as the receptor for capsaicin, the pungent ingredient of chili peppers. When exposed to a temperature above 43 degrees Celsius, TRPV1 undergoes a conformational change, allowing ingress of cations into the nociceptive neuron.³ This is the first step in the generation of an action potential that will ultimately be interpreted as hot pain. When capsaicin binds to TRPV1, it too opens the ion channel. No wonder, then, that chili peppers taste “hot.”

A related TRP may be responsible for transducing mechanical noxious stimuli. TRPA1 opens its ion channel as a result of mechanical deformation rather than heat. It is present in the hair cells of the inner ear, where

it contributes to hearing.⁴ A TRP very similar to TRPA1 is responsible for mechanical nociception in fruit flies, encouraging researchers to speculate that this is a major element in mechanical nociception in humans too.⁵

Transmission

The transmission of information along a nerve is often likened to an electrical signal. There is an important difference, however, between the electrical signals that run at nearly the speed of light along a copper wire and those that move at a far more leisurely 0.5 to 10 meters per second in an unmyelinated neuron. The copper wire carries a current due to the motion of electrons in the wire. A neuron carries a signal due to current flow effected by the movement of cations, mostly sodium, across its membrane. The transducing element described above initiates the flow of cations

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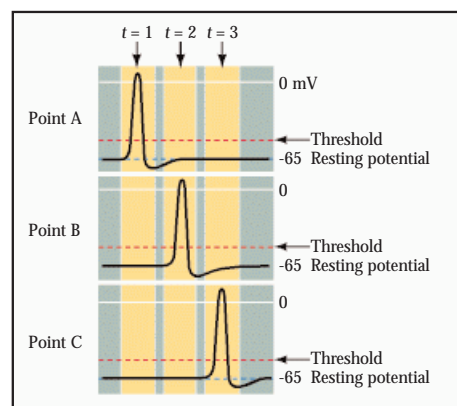
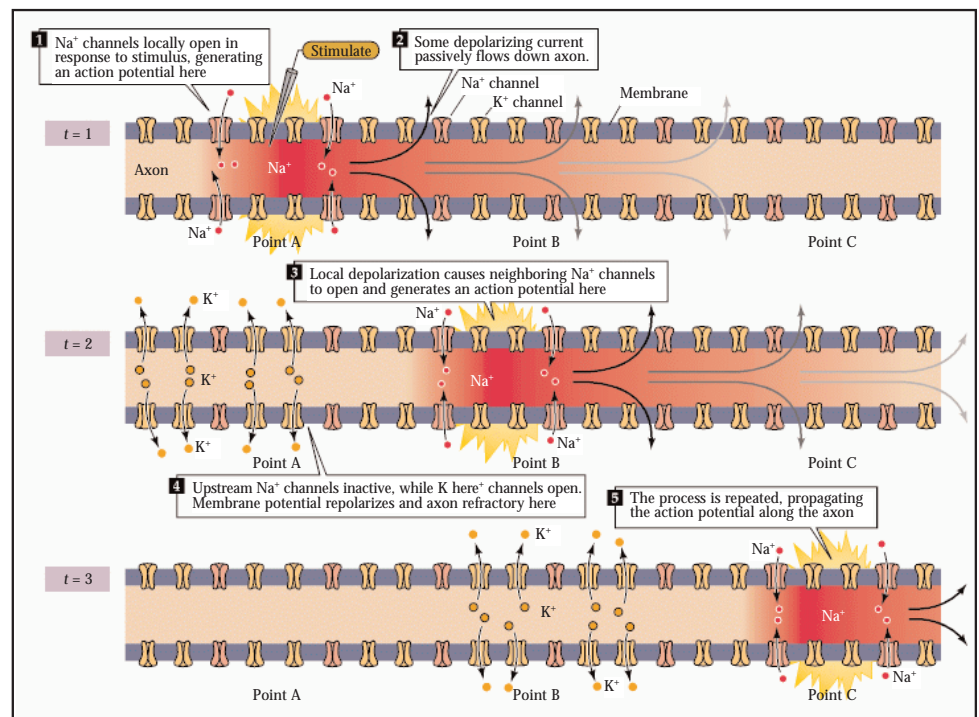


Figure. Action potential conduction requires both active and passive current flow. Depolarization at one point along an axon opens Na^+ channels locally (Point 1) and produces an action potential at this point (A) of the axon (time point $t=1$). The resulting inward current flows passively along the axon (2), depolarizing the adjacent region (Point B) of the axon. At a later time ($t=2$), the depolarization of the adjacent membrane has opened Na^+ channels at Point B, resulting in the initiation of the action potential at this site and additional inward current that again spreads passively to an adjacent point (Point C) farther along the axon (3). At a still later time ($t=3$), the action potential has propagated even farther. This cycle continues along the full length of the axon (5). Note that as the action potential spreads, the membrane potential repolarizes due to K^+ channel opening and Na^+ channel inactivation, leaving a “wake” of refractoriness behind the action potential that prevents its backward propagation (4). Panel to the left of the figure legend shows the changing membrane potential as a function of time at the points indicated. Reproduced with permission from Purves D, Fitzpatrick D, Williams SM, et al. *Neuroscience*. 3rd ed. Sunderland, Mass: Sinauer Associates, Inc.; 2004.

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across the neuron's cell membrane. That causes a decrease in voltage across the membrane at that site. Many sodium channels embedded in the neuron's membrane are voltage-dependent. As the voltage near a sodium channel drops, it tends to open more. This allows the influx of even more sodium ions at that site in the neuron. Of course, the sodium channels near this area of dropping voltage are likewise affected. The result is a wave of depolarization moving up the neuron to the spinal cord. In many ways this is similar to "the wave" that fans sometimes perform at a sports arena. Fans in the stand do not wave because other fans far away in the stadium are waving. They wave because those fans nearby them are waving. Similarly, the neuron transmits a "wave signal" of information as sodium channels in the neuron sequentially respond to the activity of other sodium channels near them.

Modulation

The first synapse along the pain pathway is in the dorsal horn of the spinal cord. The signal that has come in along the nociceptor culminates in the release of neurotransmitters into the synaptic cleft that separates that neuron from the projection neuron of the dorsal horn. The dorsal horn of the spinal cord is organized in layers, and much of normal pain processing occurs in the first and second layers of the dorsal horn. Broadly speaking, neurotransmitters are of two varieties: small molecules that have an immediate effect on a neuron's ability to generate an action potential, and peptides that affect the activity of target neurons over a longer time frame. Glutamate is the most important small molecule neurotransmitter involved in physiologic pain perception, but the peptide substance P also plays an important role, especially in the case of particularly noxious stimuli. Glutamate is an excitatory amino acid (EAA). It can bind to a variety of different receptor types. They are named according to the ligand with which they are assessed in the laboratory. Thus, AMPA receptors and NMDA receptors are plentiful in the spinal cord, although no human has AMPA or NMDA. These are merely types of glutamate receptors.

The projection neuron, which will carry the signal up the spinal cord to the brain, is not a mere automaton. A variety of inputs to that neuron will either augment or diminish its signaling. For example, it is commonly known that soldiers injured in battle, although aware that they have been wounded, may feel little or no pain for several minutes or more after their

injury. This phenomenon is not merely because of courage or bravado. Rather, the life-threatening situation of battle has generated a strong attenuating descending signal from brain to spinal cord, blocking the upward transmission of pain information. Gamma-aminobutyric acid (GABA) and opioids, both endogenous and administered, act at the cord level (among other sites) to attenuate pain signals.

Interpretation

Pain information arriving at the brain does not make a beeline for the cortex. A significant projection of pain information goes to the thalamus—the part of the brain involved, among other tasks, with mediating the experience of emotion. (This is why one of the major pathways of pain information is called the spinothalamic tract.) It is no wonder, therefore, that pain is almost always an emotion-laden experience. We are designed (or have evolved) to experience emotion with pain. Emotion is not an epiphenomenon added after the fact. It is an essential aspect of the pain experience, and one ignored by the clinician, if not at his own risk, then certainly to the patient's detriment. Neuroscientists believe that the meaning of pain is adduced in the cerebral cortex. Thus, the pain after a breast biopsy that showed cancer may cause more suffering than the pain that follows a long-desired childbirth in a previously infertile woman.

Behavior

While acute pain is sometimes accompanied by changes in vital signs, chronic pain is usually not so obvious. The only way to know if a patient is in pain is by observing the patient's behavior. (Behavior, in this context, includes speech and its contents.) It would be naïve to believe that pain-related behavior is a function only of factors within the person in pain. In fact, interpersonal and social factors such as differences in gender, social status, and race between the observer and the person in pain can significantly affect pain-related behavior.⁶⁻⁹

Pathophysiology of Neuropathic Pain

The above outline—it is little more than an outline of such a complex subject—of pain physiology can serve as a framework for understanding some of the pathological changes that occur in neuropathic pain.

In considering the impact of nerve damage on pain perception, it is important to note that a nerve is not merely a neuron. A nerve is composed of many neurons, and many more support cells, such as glia, Schwann cells, and blood vessels. These other cells are not physiologically inert, and they too play an important role in neuropathic pain.¹⁰ Damage or death of some neurons within a nerve may lead to functional changes in other intact nerves within the

same neuron. Of course, damage to peripheral nerves also causes a host of secondary changes in the spinal cord and brain. The mechanisms cited below are merely a sampling of the complex pathophysiology of neuropathic pain.

Transduction. TRPV1 levels decrease in damaged nociceptive neurons. However, the intact neurons (in the same nerve) adjacent to the injured neuron showed an increased amount of TRPV1. This increased expression of TRPV1 is seen not just in unmyelinated neurons, but even in high-threshold myelinated A-fibers, a type of sensory neuron that usually does not express this transducing ion channel. In other words, there is a phenotypic shift as a consequence of the nerve injury. Neurons that formerly did not carry pain-related information now do so.¹¹ Since lidocaine is an inhibitor of TRPV1 activity, it is possible that part, at least, of the benefit of topical lidocaine for neuropathic pain is because of its inhibitory effect on the transducer.¹²

Transmission. The important role of sodium channels in propagating action potentials along nerves was outlined above. Nerve injury leads to derangements of sodium channel activity in several ways. First, the injured nerve itself expresses an increased number of sodium channels proximal to the site of injury. Thus, neuromas are particularly rich in sodium channel activity.¹³ Just as important, the uninjured neurons in the partially injured nerve also express an increased quantity of sodium channels.¹⁴ Not only that, but the type of sodium channel expressed after nerve injury is abnormal. After nerve injury, dorsal root ganglion neurons express a kind of sodium channel otherwise only seen during fetal life.¹⁵ This newly expressed sodium channel has faster kinetics than normal sodium channels; it is able to recover more quickly after depolarization, thus being ready more quickly to depolarize again.¹⁶ The role of tricyclic antidepressants in the treatment of neuropathic pain may be, at least in part, modulation of sodium channel activity.¹⁷ Calcium ion channels, too, are important in pain transmission and are deranged in neuropathic pain. Gabapentin, an antiepileptic agent with analgesic effect in neuropathic pain, is active in modulating the activity of abnormal calcium channels.¹⁸

In addition to the changes in ion channel expression described above, neuropathic pain is associated with a number of changes in neuropeptide expression.¹⁹ As noted above, neuropeptide neurotransmitters change the long-term function of the target neuron. Thus, changes in neuropeptide expression lead to the facilitation of pain processing, even the generation of spontaneous (that is, not evoked by a

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What's Hot in Pain Control

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Dr Hartree has indicated that he has no relevant financial relationships.

The International Association for the Study of Pain® (IASP®) held its triennial scientific meeting, the 11th World Congress on Pain®, from August 21-26, 2005, in Sydney, Australia. The Scientific Program included every aspect of acute and chronic pain, from basic science to clinical practice. Several of the NIPC® faculty members participated in workshops and seminars, and presented their studies at the meeting. Four are summarized below.

New Patient-Completed Screening Tool for Use in a Primary Care Setting

Dr Miroslav Backonja, Associate Professor at the University of Wisconsin Medical School, was part of a team that developed the patient-completed screening tool (ST) that is capable of differentiating nociceptive and neuropathic pain in primary care settings. In a multicenter study, 586 patients who visited general practitioners for nonheadache chronic pain completed an 89-item questionnaire on chronic pain and then underwent assessment from pain specialists for benchmark diagnosis. From the 89 questions, six were chosen for the ST on the basis of regression analysis and the advice of an expert panel. The ST identified nearly 70% of patients with neuropathic pain as being likely or very likely to have pain with a neuropathic component. Twenty-five percent of patients with nociceptive pain were incorrectly categorized as likely or very likely to have neuropathic pain. A second study was used to validate the ST. Sensitivity, specificity, and concordance were tested in a sample of 308 patients with neuropathic, nociceptive, and mixed pain enrolled at pain specialists' offices. The ST showed a similar concordance with expert diagnosis to that observed in the original development study. In conclusion, the ST shows promise in two studies as an instrument for making an initial probable diagnosis of neuropathic pain, and it can be used in the primary care setting.

Griesing T, Portenoy R, Cleeland C, et al. Development and validation of a new patient-completed neuropathic pain screening tool for use in a primary care setting. Presented at the 11th World Congress on Pain; August 25, 2005; Sydney, Australia. Abstract 1451-P321.

Efficacy of Opioids and Tricyclic Antidepressants (TCAs) in Mechanism-Based Subtypes of Patients With Postherpetic Neuralgia

Dr Srinivasa N. Raja, Director of Pain Research, Johns Hopkins University School of Medicine, researched the efficacy of opioids and TCAs in mechanism-based subtypes of patients with postherpetic neuralgia (PHN). PHN can be classified either as PHN1 (due to irritable nociceptors) or PHN2 (due to deafferentation). The study recruited PHN patients and classified them as PHN1 (n=36) based on normal or reduced heat pain thresholds and the presence of mechanical allodynia, or as PHN2 (n=32) based on increased

heat pain thresholds and presence or absence of allodynia. The study had a randomized crossover design in which patients received tricyclic antidepressants (TCAs) (nortriptyline/desipramine), oral opioids (morphine/methadone), and placebo for separate 8-week intervals. Pain intensity was reported using a 0-10 scale and pain relief as a percentage. Patients with either PHN subtype experienced greater pain reduction with TCAs or opioids than with placebo ($P < .05$). In PHN1 patients, opioids gave more pain reduction (2.2 vs 1.1, $P = .04$) and pain relief (44% vs 26%, $P = .003$) than TCAs. In PHN2 patients, opioids and TCAs, respectively, gave similar levels of pain reduction (1.4 vs 1.8) and pain relief (27% vs 32%). Responder rates with opioids were statistically significantly greater than placebo in PHN1 patients (59% vs 17%, $P < .002$), but not with PHN2 patients (37% vs 17%). It can be concluded that PHN patients with intact peripheral nociceptor function (PHN1) obtain better relief from opioids than they do with TCAs.

Raja S, Tella P, Agarwal S, Klick B, Max M, Haythornthwaite J. Efficacy of opioids and tricyclic antidepressants in mechanism-based subtypes of patients with postherpetic neuralgia. Presented at the 11th World Congress on Pain; August 23, 2005; Sydney, Australia. Abstract 670-P276.

Combined Treatment of Neuropathic Pain and Inflammatory Pain

Dr Michael C. Rowbotham, Director at the University of California, San Francisco Pain Clinical Research Center, organized and chaired a workshop on the role of central sensitization in chronic inflammatory pain conditions of osteoarthritis and rheumatoid arthritis. He also presented the section on strategies for the management of pain with a neuropathic or inflammatory component. Nerve injury leads to chronic central sensitization to pain and to the state of allodynia. Anticonvulsant drugs are effective in reducing central sensitization, hence their use for treating neuropathic pain. However, the same drugs have not been shown to be effective for pain in osteoarthritis and some types of chronic low back pain. Conversely, COX-2 inhibitors and NSAIDs are effective for pain associated with inflammation, but are largely ineffective for neuropathic pain. Some neurologic mechanisms are common to both inflammatory and neuropathic pain and, therefore, some of the newer pharmacologic agents may be effective against

both pain types. One such possibility is the use of TNF-alpha blockers in pain therapy.

Rowbotham M, Porreca F, Choy E. Role of central sensitization in chronic inflammatory pain conditions of OA and RA—mechanisms and therapeutic implications. Presented at the 11th World Congress on Pain; August 22, 2005; Sydney, Australia. Abstract 4.

Core Outcome Domains in Clinical Trials—The IMMPACT Recommendations

Dr Dennis C. Turk, John and Emma Bonica Professor of Anesthesiology & Pain Research, University of Washington, organized and chaired a workshop presentation on standardizing pain treatment outcomes, and gave a presentation on the "Core Outcome Domains in Clinical Trials: The Initiative on Methods, Management, and Pain Assessment in Clinical Trials (IMMPACT) Recommendations." The purpose of the initiative is to improve the design of clinical studies in chronic pain management and provide a much-needed standardization of outcome measures. IMMPACT recommends six core outcome domains to be used in chronic pain trials whenever feasible.

1 Measures of pain intensity using validated and reliable scales, supplementation of rescue treatment after careful self-report assessments, measures of affective and sensory pain quality, and the temporal aspects of pain such as patients' reports of the time to onset of meaningful pain relief and its durability, and the frequency and intensity of episodes of breakthrough pain should all be considered when assessing pain outcomes.

2 Assessment of physical functioning is very important for evaluating the efficacy of chronic pain treatment because it shows only a limited association with pain intensity. Both disease-specific measures and generic measures of physical functioning should be considered in designing chronic pain clinical trials because each approach provides strengths. Either the Multidimensional Pain Inventory (MPI) or Brief Pain Inventory (BPI) is recommended for clinical trials examining disorders that do not have disease-specific measures already in place; both these interference scales provide reliable and valid measures that have been translated into many languages. Regardless of whether a disease-specific measure or the MPI or BPI scale is used, administration of a generic measure of physical functioning should be considered to obtain data that will allow comparison with other disorders and that could be used in cost-effectiveness analyses.

3 An assessment of emotional functioning is necessary because chronic pain is so frequently accompanied by symptoms of psychological distress and psychiatric disorders. The Beck Depression Inventory (BDI) and the Profile of Mood States (POMS) are recommended. The BDI provides a well-accepted measure of the level of depressed

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noxious stimulus) pain. As just one example, neuropeptide Y is significantly upregulated in some animal models of neuropathic pain. Blocking its activity with an antibody to neuropeptide Y reduces tactile allodynia (pain-related behavior induced by a non-noxious stimulus). Curiously, neuropeptide Y seems to play little role in thermal hyperalgesia, an indication of the complexity of facilitated pain.²⁰

Cholecystokinin (CCK) is another neuropeptide whose expression is upregulated in neuropathic injury, even though it is downregulated in models of inflammatory pain. CCK acts as an antioioid in the spinal cord. It may be one of the mechanisms of opioid resistance in neuropathic pain. It must be remembered, however, that while neuropathic pain is resistant to opioid therapy, it is not completely refractory to it. In fact, opioid therapy can be useful in treating patients with neuropathic pain.²¹

Modulation. A host of changes in the dorsal horn, the site of significant modulation of pain processing, occur after nerve injury. Ordinarily, the small unmyelinated afferent nerve fibers (whose normal function is to carry pain information to the spinal cord) abut on the first and second layer of the dorsal horn of the spinal cord. The larger myelinated fibers, whose usual function is to carry information about light touch, make their synapse at a deeper level. But when peripheral nociceptive neurons are destroyed, the larger afferent fibers sprout new connections, taking the abandoned place of the now-absent nociceptor termini.²² Thus a non-noxious stimulus might be transduced by a low-threshold afferent neuron, but then relayed to a projection neuron whose function is to transmit information about high threshold (noxious) stimuli. This may be part of the pathophysiology of tactile allodynia.

In physiologic pain, the neurotransmitter glutamate binds to an ion-channel receptor that opens briefly, then closes again. This allows a

good correspondence between stimulus intensity and pain perception. But in neuropathic pain, a glutamate receptor whose channel stays open much longer is upregulated. This is the NMDA receptor. This allows the influx of calcium into the projection neuron. The calcium, in turn, activates a number of tyrosine kinase signal mediators, leading ultimately to a change in gene expression in that neuron. One of the tyrosine kinases is protein kinase C (PKC). Inhibitors of PKC attenuate expression of neuropathic pain in animals.²³

Inhibition of NMDA receptors has been attempted in human neuropathic pain, too. Ketamine is a powerful inhibitor of that receptor, and has some activity in neuropathic pain,* but its usefulness is limited by its narrow therapeutic index.²⁴ Dextromethorphan is another inhibitor of NMDA, but clinical trials showed little additive benefit of using it with morphine.²⁵ It may be that a subset of neuropathic pain patients can be identified who would benefit from dextromethorphan* therapy.²⁶

An important part of the modulation of pain perception is effected by descending inhibitory pathways. One of the major inhibitory neurotransmitters is GABA. Nerve injury is associated with a loss of this GABAergic inhibition of pain processing. It is not surprising, therefore, that drugs with GABA-like activity, such as lamotrigine, tiagabine and others,* have shown some promise in the treatment of neuropathic pain.²⁷⁻²⁹

Interpretation and behavior. Pain interpretation and behavior are almost certainly functions mediated by the brain. Our understanding of the pathological changes that arise in the brain during neuropathic pain is still in its infancy. Functional MRI and other imaging studies have given some insight into the brain differences in neuropathic pain and inflammatory pain.³⁰ There may be actual reorganization of brain structure in neuropathic pain.³¹ Opioid receptors in the brain may be deficient in some central pain syndromes.³² Finally, the apparent efficacy of magnetic stimulation of brain motor cortex to treat neuropathic pain, an intervention that is anything but intuitive,

*Not FDA approved for this use.

gives evidence of how much more we need to learn to truly understand the ugly business of neuropathic pain.^{33,34}

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What's Hot

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mood in a sample and its response to treatment; the POMS is useful because it includes scales for depression, anxiety, and anger—the three most important dimensions of emotional functioning in chronic pain patients.

4 A patient rating of global improvement and satisfaction with treatment is also stipulated in IMMPACT because the measure reflects patients' individual values and preferences in pain management, and provides

them with an opportunity to aggregate all of the components of their experience into one overall measure. The Patient Global Impression of Change (PGIC)—a single-item rating on a 7-point scale—is recommended for use in chronic pain clinical trials.

5 Symptoms and adverse events need to be recorded. The use of active capture (structured interviews and questionnaires) is preferable to passive capture (spontaneous reports and open-ended prompts) when assessing symptoms and adverse events relevant to chronic pain and its treatment.

6 Information on participant disposition is essential for the adequate evaluation of clinical trial results and for interpreting the trial conclusions regarding efficacy and safety. Records of patient disposition should include relevant data on recruitment and subjects' progression through the trial. Withdrawals because of lack of efficacy or adverse events need to be recorded in sufficient detail.

Turk D, Dworkin R, Kehlet H. Core outcome domains in clinical trials—the IMMPACT recommendations. Presented at the 11th World Congress on Pain; August 23, 2005; Sydney, Australia. Abstract 386.

ASK THE EXPERT

**BRUCE D. NICHOLSON, MD**

Clinical Associate Professor
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Dr Nicholson has indicated that he is a clinical investigator for Endo Pharmaceuticals, GSK, and Elan and a research consultant and investigator for Pfizer Inc and Alpharma.

Question from the field

Are there significant side effects with the use of amitriptyline in treating chronic pain?

Dr Nicholson: Pain practitioners have considered tricyclic antidepressants (TCAs) to be the backbone of systemic therapy for chronic pain for years. Clinical studies clearly demonstrate the efficacy of TCAs such as amitriptyline,* nortriptyline,* and desipramine* for neuropathic pain syndromes.¹⁻³ Although they may be as effective as other therapeutic classes, the adverse-effect profile of TCAs mandates that the agents be used with caution as first-line drugs for the treatment of neuropathic pain conditions.⁴⁻⁶

There are two classes of TCAs: secondary amines (nortriptyline, desipramine) and tertiary amines (amitriptyline, imipramine,* and doxepin*). Generally, the secondary amines demonstrate fewer anticholinergic effects (eg, constipation, dry mouth, blurred vision, cognitive changes, tachycardia, urinary hesitation) and less sedation than do the tertiary amines. All TCAs are reported to cause these adverse events in varying degrees of frequency and severity.⁷ Intolerable side effects are more frequent with amitriptyline, however (Figure). Therefore, the American Geriatrics Society does not recommend its use in patients older than 65 years.⁸ In general, when using TCAs, the secondary amines may be more desirable in the elderly population.

Amitriptyline has a high side-effect profile for cardiovascular problems and must be used very cautiously in patients with cardiovascular disease.^{9,10} Because of these effects, physicians should consider performing a cardiovascular evaluation before beginning or escalating treatment in patients older than 45 years. Amitriptyline inhibits the reuptake of norepinephrine and serotonin, and may cause balance problems and cognitive impairment in older patients. Amitriptyline also has profound effects on the cholinergic system, and should be avoided in patients with dementia. Anticholinergic drugs such as amitriptyline tend to worsen cognitive impairment and precipitate delirium. If patients are being treated for early dementia with cholinergic agents, their positive effects

may be countered if amitriptyline is added to the treatment regimen.

Different TCAs have different potencies; therefore, significant interindividual variability exists in the efficacy, tolerability, and correct dosage. Neuropathic pain generally responds more quickly (3-10 days) than does depression (2-4 weeks) to tricyclic antidepressants, and often with one third to one half the dosage administered for depression. In high doses, they effectively treat anxiety and depression; in lower doses, there is a differential response to pain vs other conditions. Higher doses of TCAs (eg, as typically used for depression) and several weeks of treatment may be necessary for efficacy. Risk vs benefit of effects should be assessed, particularly when using higher doses in the older population.

Additionally, starting TCAs at inappropriately high dosages or titrating too rapidly may produce unacceptable side effects, resulting in treatment failure. Slower dosage titration is recommended for older patients who generally experience a higher frequency of adverse effects. Treatments prescribed twice a day are as effective as once a day (particularly with amitriptyline because of the peak/trough level). The most significant side effect of amitriptyline is sedation; it may therefore be given to patients in the evening before bedtime. Starting with a 10-mg dosage of a secondary amine at bedtime, especially in older patients, and titrating the dosage upward from 10 to 25 mg weekly will help reduce side effects.

Because TCAs appear to be almost equally efficacious, a rational approach for clinical practice is to start with the agents that have the fewest adverse effects,

unless a specific "side effect," such as nighttime sedation, is desired. Desipramine is probably the safest agent with the lowest side-effect profile.^{2,3,6} Because it may elevate mood and increase excitability even at low doses, patients should take it in the morning.

Individual variability in treatment response should be expected. Because several weeks may be needed before benefits are realized, titration can be a slow and frustrating process. There are no shortcuts, and physicians should set appropriate expectations with the patient.¹⁰ The duration of an adequate trial is 6 to 8 weeks with at least 1 to 2 weeks at maximum tolerated dosage.⁶

*Not approved by the FDA for this use.

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Tricyclic Antidepressants: Adverse Effects

• Commonly reported AEs (generally anticholinergic):

- blurred vision
- cognitive changes
- constipation
- dry mouth
- orthostatic hypotension
- sedation
- sexual dysfunction
- tachycardia
- urinary retention

Fewest AEs



Most AEs

- Desipramine
- Nortriptyline
- Imipramine
- Doxepin
- Amitriptyline

AEs = adverse effects.

Unraveling the Mechanisms of Neuropathic Pain

Continued from page 10

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