



Perspectives on Chronic Pain Management

Michael Rowbotham, MD and Aimee Chagnon, MD

Despite phenomenal progress in basic research, managing chronic pain remains as much art form as science. The first step, as always, is to make a diagnosis. Unfortunately, some of the most difficult chronic pain problems have diagnostic criteria that are based solely on history and physical examination.

Two excellent examples are fibromyalgia and complex regional pain syndrome (CRPS type I, formerly known as RSD or reflex sympathetic dystrophy). Laboratory, radiological, or other diagnostic tests cannot establish either diagnosis, but they can help in excluding the diagnosis (by finding another disorder that fully accounts for the symptoms and presentation). Establishing a reason for initiation of the disorder is important for both CRPS and fibromyalgia, but especially CRPS because there may be a fully treatable underlying pathology, usually orthopedic. Because the diagnostic criteria for some chronic-pain problems are vague, a more specific diagnosis than warranted is assigned in order to give patients a name to attach to their suffering. Optimally, evaluation of a complex chronic pain problem includes obtaining and then thoroughly reviewing records of all prior evaluations and treatments, a careful and detailed history and physical examination, appropriate diagnostic studies and, in most cases, a psychological evaluation and physical therapy evaluation.

With a firm diagnosis or provisional differential diagnosis, a treatment plan can be implemented. It is unlikely that any single modality will be completely effective. The advantage of a multidisciplinary approach comes from the additive and synergy. Keep cost effectiveness in mind; it remains to be proven in a prospective study that expensive and highly invasive treatments are superior to more conservative function-oriented plans. Patient education is not only inexpensive, but the benefits can continue for a lifetime. Chronic pain sufferers need to have a working understanding of their pain problem, including both what is known and what is not (or cannot be known) about its pathophysiology. Learning effective self-management skills empowers patients and lessens the burden on the health care system.

The number of oral medications shown effective for chronic pain continues to gradually increase. However, in placebo-controlled clinical trials, the best result has been satisfactory pain relief in about two-thirds of the research subjects. Moreover, side effects are a problem with all the medications. In the next section, major medication classes are briefly described.

Opioids

Morphine and similar potent opioids remain the "gold standard" for managing moderate to severe pain. However, physicians often fear abuse and addiction, diversion to non-medical use, and the burden of complying with regulatory restrictions (including fear of investigation of the prescribing physician). Although the risk of creating drug addiction appears very small and no other oral medication has been proven to be better, opioids will probably continue to be used to treat chronic pain only when other treatments fail. Loss of efficacy over time (tolerance) is a major concern of clinicians that has received surprisingly little prospective study. Schedule III drugs, all of which are short-acting and contain an adjuvant such as acetaminophen, are easier to prescribe in California, but most pain management experts feel the longer-acting single agent Schedule II opioids are more effective.

Antidepressants

Tricyclic antidepressants (TCAs) were the first medication category proven effective for chronic neuropathic pain in double-blind placebo-controlled trials. Tricyclics remain first-line treatment for fibromyalgia, migraine prophylaxis and many other chronic pain disorders. Contrary to initial beliefs, their analgesic effects are independent of their effects on mood. Unfortunately, tricyclic side effects are often intolerable and an overdose can be deadly. The newer, non-tricyclic drugs appear safer. Although many of the selective serotonin reuptake inhibitors (such as fluoxetine) have been ineffective in clinical trials, mixed reuptake inhibitors (such as venlafaxine) and norepinephrine selective drugs (such as bupropion) have shown promising results.

Gabapentin

Gabapentin, released in 1995 as an anticonvulsant, is used even more frequently for a variety of chronic-pain disorders. For neuropathic pain alone, five large randomized controlled trials have been performed, more than for any other pharmacological therapy. Statistically, it is comparable to the tricyclics in analgesic efficacy and has a favorable

side-effect profile. Drug-drug interactions are not a significant problem and it is excreted unmetabolized, important for chronic pain patients in whom polypharmacy is often the rule and not the exception.

Anticonvulsants and Antiarrhythmics

Other anticonvulsants, including carbamazepine, oxcarbazepine, lamotrigine, levetiracetam, topiramate and valproic acid, as well as the antiarrhythmics mexiletine and flecainide are used, especially for neuropathic pain.

Anticonvulsants have varying modes of action-some work on sodium channels, others on calcium channels and still others via GABA and glutamate. With the exception of carbamazepine for trigeminal neuralgia, all are currently second-line medications awaiting more controlled trial evidence of efficacy.

Invasive Therapies and Implanted Systems

Local anesthetic nerve blocks and epidural catheters are highly effective for acute pain, including the pain of acute herpes zoster or "shingles." For chronic pain, short-term pain relief is frequently achieved and injections can facilitate more conservative therapies. However, the long-term benefit of repetitive nerve blocks remains somewhat controversial because so few prospective randomized and appropriately controlled trials have been performed. For some types of low back pain, a short series of epidural steroid injections can be highly effective, but again the evidence is less than definitive. The two most expensive techniques for management of chronic pain, implanted intrathecal drug delivery systems and spinal cord stimulators, are best reserved for carefully screened patients who have failed more conservative therapies but remain active participants in a function-oriented multidisciplinary pain management program. The technology for spinal stimulator systems continues to steadily improve and a variety of medications (including baclofen, SNX-111, and clonidine) are available to either supplement or replace intrathecal opioids.

Research

Development of new analgesics remains a priority of pharmaceutical companies large and small. Animal research has led to the identification of new chronic-pain mechanisms and thus new drug targets. Although few of the new compounds have made it to market, many are in the pipeline. Research on new drug delivery systems also continues at a rapid pace. A large, soft, stretchy patch containing the local anesthetic lidocaine has received FDA approval as therapy for the neuropathic pain of post-herpetic neuralgia that frequently follows shingles. Opioid delivery systems include the familiar transdermal fentanyl patch but new techniques, including tiny subcutaneous implanted titanium capsules to provide very long-term delivery of the opioid sufentanil, are in development.

At the UCSF Pain Clinical Research Center (PCRC), the research agenda includes healthy volunteer studies to test new analgesics using the heat/capsaicin sensitization model developed at UCSF. More traditional clinical trials of experimental analgesics in chronic-pain sufferers are in progress, with a broad focus that includes neuropathic pain, post-herpetic neuralgia, CRPS, and fibromyalgia. Studies supported by research grants from the National Institutes of Health address many fundamental questions. These include studies of the responsiveness of various types of chronic pain to opioids, and the clinically important but little studied process of loss of drug response (tolerance). Acute herpes zoster (shingles), caused by reactivation of the chicken pox virus, affects nearly 1 million people in the U.S. each year. The elderly are especially likely to continue to suffer in the form of post-herpetic neuralgia, one of the most important neuropathic pain problems in this age group. The PCRC is using a variety of novel techniques to study the process of nerve injury and recovery in acute shingles sufferers over the age of 50. The study includes double-labeling immunofluorescence of skin punch biopsy specimens to visualize the sensory nerve fibers in the skin during and after shingles. Findings from this study may identify new targets for future therapies and explain why some patients develop relentless chronic pain while others recover completely.

Dr. Robowtham is director of the UCSF Pain Clinical Research Center, an associate professor of neurology and anesthesia and the associate director of the UCSF-Mount Zion Pain Management Center. He is a dedicated neurologist-teacher and runs a post-doctoral fellowship program for clinical research and clinical care in the pain area. Dr. Robowtham is also a hard-core surfer and an active member of the Surfers' Medical Association and their health care and health education projects around the world.

Dr. Chagnon graduated summa cum laude, Phi Beta Kappa with a degree in biochemistry and cell biology from the University of California at San Diego before attending medical school at the University of California at San Francisco. She completed a residency in neurology at Harvard Medical School-Beth Israel Deaconess Medical Center in Boston and is currently the clinical research fellow in pain in the Department of Neurology at UCSF. Her particular area of interest is reflex sympathetic dystrophy.