WEINER'S PAIN MANAGEMENT

A Practical Guide for Clinicians

SEVENTH EDITION

Edited by
Mark V. Boswell
B. Eliot Cole

AMERICAN ACADEMY OF PAIN MANAGEMENT

CRC Press
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CRC Press
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Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

ISBN-13: 9780849322624 (hbk)

Library of Congress Cataloging-in-Publication Data

Weiner's pain management : a practical guide for clinicians.-- 7th ed. / edited by Mark V. Boswell, B. Eliot Cole.
p. ; cm.
Rev. ed. of: Pain management / editor, Richard S. Weiner. 6th ed. c2002.
Includes bibliographical references and index
ISBN 0-8493-2262-6 (alk. paper)
1. Pain--Treatment. 2. Analgesia. [DNLM: 1. Pain--therapy. 2. Pain--diagnosis. 3. Patient Care Management. WL 704 W423p 2005] I. Title: Pain management. II. Boswell, Mark V. III. Cole, B. Eliot. IV. Weiner, Richard S., Ph. D. V. Pain management.

RB127.P33233 2005
616'.0472--dc22 2004065101

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and the CRC Press Web site at
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Dedication to Richard S. Weiner, PhD

While standing upon the shoulders of giants helped advances to occur, the genius of Richard S. Weiner, PhD was that he could see the finished puzzle within the constituent pieces. He took pre-existing parts and ideas that others had overlooked, pulled them together in altered ways and created new results. He created harmony from the chaos others perceived. He did more than talk about the developing field of pain management; he walked the walk and co-founded the American Academy of Pain Management with Kathryn A. Weiner, PhD. Together, the Weiners created a new organization that finally met the needs of its pain practitioner members through pain-related education, practitioner credentialing, pain program accreditation, outcome measurement, and many other offerings. Bringing together leaders in the field of pain management to create the American Academy of Pain Management's textbook, *Pain Management: A Practical Guide for Clinicians,* was one of his greatest accomplishments and was a continuing source of pride for Richard. Revising six editions became his commitment to the advancement of the pain management profession.

For Richard editing each edition of the textbook was a challenging process that required more than a year of preparation. Richard weathered this process six times in 12 years to make certain that the American Academy of Pain Management's textbook was clinically useful, current, and the best source for multidisciplinary information about the assessment, evaluation, and treatment of pain. For Richard, this was his labor of love and he gave his very best to this process.

Many might say that authoring textbooks is just too much work. It is far more effort than most people would ever willingly take upon themselves. Richard never saw the textbook as too much work for himself. He looked forward to the revision process and the updating of the chapters with each new edition. He enthusiastically called authors, new and old alike, to talk with them about their submissions, suggested points to discuss, and then called up others to tell them about what he had learned in the new chapters when he received them. No matter how many hours or how many authors were involved, he treated each of the authors with consideration, excitement, and respect. He asked of the authors more than some knew that they had within themselves, but always knew what they could accomplish if properly motivated. Richard was the consummate manager, who not only managed ideas, but the people bringing the ideas to fruition.

Knowing that he was quite seriously ill in 2001, Richard began to consider future goals for the American Academy of Pain Management. He knew that in another couple of years the seventh edition of the textbook would need to be written to maintain the currency associated with the book. In his own amazing way, and in his attempt to find goodness and humor even in the worst of circumstances, he speculated that he wouldn't have to edit any more textbooks if he didn't respond to his anti-cancer therapies. He even tried to cheer up those who were so concerned about him by telling us that the chemotherapy was easier than editing the textbook. He helped to identify the principal editor for the seventh edition of the textbook before his death in May 2002.

Practitioners fortunate enough to have personally known Richard, continue to mourn his passing. His hundreds of personal friends and members of his immediate family remember all that he gave to our evolving profession. Always the gentleman in his dealings with others, he shall best be remembered as the man who gathered together the many disciplines that constitute the modern field of pain management to improve the treatment of pain for so many unfortunate sufferers he never met. He never wanted special recognition, but wanted the profession to mature and to see the "mainstreaming" of pain management services.

We miss Richard. Not a day goes by when we do not think about something he said to one of us, some lesson he taught us, or some opportunity he created for all of us who now follow in his footsteps. Few men pass through our lives and have as significant an impact as he did for each of us personally and for so many of our colleagues. While his life was far too short, his accomplishments more than filled his lifetime and left a permanent legacy for all of us. It is only fitting that this *Seventh Edition* be dedicated to the outstanding work and life of Dr. Richard S. Weiner.

Mark V. Boswell, MD, PhD and B. Eliot Cole, MD, MPA


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Preface

PLEASE READ THIS PREFACE!

Few people ever bother to read the preface of a textbook, much less the preface of a book on the subject of pain management. This completely revised Seventh Edition is the most comprehensive rewrite of *Pain Management: A Practical Guide for Clinicians.* Unlike the previous six editions, every attempt has been made to offer evidence-based, clinically relevant information. This book is intended for pain practitioners and busy practitioners from other disciplines trying to provide relief for those suffering with pain.

Uniquely, the book unfolds the "story" of pain and its management just as those suffering present themselves to clinicians for help. Major perspectives and challenges are initially identified, leading to an appreciation of the various disciplines providing care. Common pain problems and diagnostic methods used in pain management next give "flesh" to the skeletal story. Treatment options unfold from least invasive to most invasive as we explore behavioral approaches, pharmacotherapy, procedural techniques and the integrative options. The needs of special populations, along with the legal aspects of care, belief systems and spiritual matters, and practice issues finally complete the book.

While no textbook is completely able to cover the entirety of a subject, the intent of this book is to give any reader the "fast take" on pain-related information needed for the next patient, the upcoming examination, or to satisfy some academic question. This book intends to be the "first and last" source for most clinicians needing to know something about pain management. The book has ample references to guide future self-inquiry, allowing readers to know the original source work and independently reach conclusions about the material presented.

The American Academy of Pain Management's textbook remains a work in continuous development. As the Seventh Edition becomes available, budgeting and planning begin anew for the eighth edition to follow in five years. No one holds all of the truth, and the leadership of the Academy expects that in years to come this book will continue to evolve from one editor to the next, always fresh and current in its presentation, and true to the original charge given to each of us practicing in pain management by our late, founding Executive Director, Richard S. Weiner, PhD.

Please enjoy the material included within these pages. Make note of areas that were covered superficially and need more detail. Be willing to help your colleagues "push the envelope" in future editions by writing chapters, providing peer review, and offering suggestions for continuous improvement.


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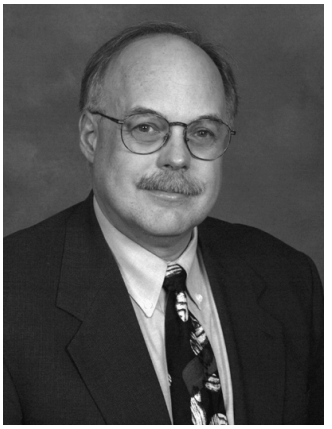
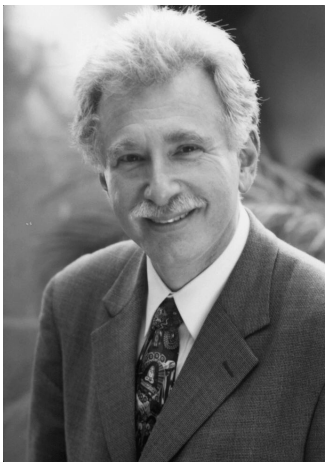


Mark V. Boswell, MD, PhD is chief of pain medicine, director of the Pain Medicine Fellowship Program, and associate professor of anesthesiology at Case Western Reserve University in Cleveland, Ohio. Trained in interventional pain management, medical acupuncture and end-of-life care, Dr. Boswell has been actively involved in clinical pain management, pain-related research, and academic medicine for more than 15 years. Dr. Boswell is editor-in-chief for *Pain Physician*, the official publication for the American Society of Interventional Pain Physicians (ASIPP).

Dr. Boswell earned his PhD in experimental pathology and MD from Case Western Reserve University. He completed an anesthesia residency after a categorical surgical internship, a research fellowship in neuroscience, and additional training in interventional pain management. Dr. Boswell was named the Outstanding Clinical Teacher in Anesthesiology in 1992 from CWRU School of Medicine and received the Outstanding Educational Achievement Award from ASIPP in 2004.

Dr. Boswell was vice-chair of the School of Medicine of CWRU, serves on numerous committees at University Hospitals of Cleveland, including pharmacy and therapeutics, QualChoice Medical Policy and the Rehabilitative Services Advisory Committee. He is a frequent presenter at local, national and international meetings, an accomplished author, and committed member of his community, family, and church.

Dr. Richard S. Weiner personally asked Dr. Boswell to serve as the principal editor for the Seventh Edition of the American Academy of Pain Management's textbook. Under Dr. Boswell's editorial leadership the Seventh Edition has been revised entirely to embrace the evidence basis for pain diagnosis and management. Dr. Boswell has introduced many new sections and made this edition the most diverse in the disciplines involved, the most comprehensive in scope of practice, and the most clinically relevant.



Dr. B. Eliot Cole earned his undergraduate degree in bacteriology from the University of California, his medical doctorate from Wake Forest University School of Medicine, and his master's in public administration from the University of Nevada, Las Vegas. He performed residencies in psychiatry and neurology at North Carolina Baptist Hospital, and completed an anesthesia-based fellowship in pain management at the University of California, Los Angeles, Center for Health Sciences. The American Psychiatric Association awarded Dr. Cole Fellow status in 1995 and Distinguished Fellow status in 2002.

Dr. Cole has been active in pain management since 1985, as a pain management fellow, a clinician, and as an active member of many pain-related organizations. He served on the American Academy of Pain Management's Board of Advisors, Board of Directors, numerous committees, was the organization's President from January 1, 1994 until December 31, 1995, and was the Interim Executive Director from March 1 until December 31, 1998.

Currently, Dr. Cole is a consultant in pain management for the Hawaii Permanente Medical Group and for the American Academy of Pain Management, serves as the Executive Director for the American Society of Pain Educators, and vice-president for medical and scientific affairs for Aventine HealthSciences. Dr. Cole is the program dean for pain studies at the University of Integrated Studies. Dr. Cole enjoys lecturing and writing about pain management, care of the terminally ill, medical policy-making, and ethical issues.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Acknowledgments

The Editors wish to sincerely thank the people who directly and indirectly helped with the development of the seventh edition of this book. Without the help of all these people, and many others not formally mentioned, it would not exist. In addition to thanking every single author, the Editors especially want to thank and recognize the extraordinary efforts of:

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Section 2
Discipline Specific Approaches
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Section 3
Common Pain Problems
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Section 4
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Section I

Perspectives of Pain

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A Brief History of Pain from a Personal Perspective

B. Berthold Wolff, PhD

Pain — The Fifth Vital Sign? Pain is a natural phenomenon of all humankind. Yet, until recently, it has been a sadly neglected field of behavior and medicine. In 1958, when I started to study human pain behavior, I was amazed to find how little knowledge of pain and its treatment was available. At that time, most clinicians believed that "real" pain had an underlying physical or physiological basis. Therefore, treating this underlying cause by appropriate therapeutic methods would cure or at least control the basic problem and the patient's pain would be alleviated. Should the patient continue to complain of pain following "successful" treatment, except for malignancies, the patient was often told "it is all in your head" — or worse he would be called a malingerer. Actually, this may still occur occasionally.

In the 1950s, there existed no gate control theory, no real understanding of endogenous morphine-like substances (endorphins), no awareness of differences between acute and chronic (intractable) pain, and there was no generally accepted definition of pain. There also existed no national, international, or regional pain associations.

The ancient philosophers, such as Plato and Aristotle, placed pain together with pleasure among the passions of the soul. In his 1939 review, Dallenbach suggested that Aristotle's great influence on Western scientific thought delayed the recognition of pain as a sensation for almost two thousand years. Eventually, however, the 19th century permitted much research into the neurophysiological basis of pain. In 1884, both Blix and Goldscheider, independently of each other, finally established that pain was a sensation by demonstrating specific pain points in the skin. In contrast, however, some other physiologists and psychologists believed that pain resulted from "overstimulation" of receptors (Wundt, 1874). Thus, at the end of the 19th century, three different "pain" theories co-existed. The old emotional (pain–pleasure) theory and two neurophysiological theories, the "specificity" theory (i.e., pain-specific receptors/fibers) and the "intensivity" theory (i.e., too much stimulation).

The early 20th century saw a shift toward specificity theory, such as Sherrington (1906), indicating that there are specific nerve endings for pain. Zotterman (1959) observed that in several "classical" experiments during the 1930s pain was apparently subserved by A-delta and C fibers. The faster-conducting A-delta fibers yield sharp and well-localized pain, whereas the slower C fibers yield dull and poorly localized pain sensations. This type of information led Lewis (1942; Lewis & Kellgren, 1939) to postulate the existence of two separate sensory pain systems, one transmitting pain from the skin and the other from deeper and visceral tissues. However, subsequent work by others, especially that of the Oxford group of anatomists (Weddell, Sinclair, & Feindel, 1948), indicated that the differences observed by Lewis, suggesting a two-pain system, could also be adequately explained in terms of pattern and density of innervation, which differ between skin and deeper tissue. Our own early work in my laboratory (Jarvik & Wolff, 1962; Wolff & Jarvik, 1961) demonstrated that two different pain responses could be elicited from the same tissue locus (gluteus medius muscle) and also tended to refute Lewis's two-pain systems theory. Further work by the Oxford group (Feindel, Weddell, & Sinclair,

1948) suggested that pain sensation may depend upon central analysis of space–time pattern of neural activity.

Eventually, this type of research led to the important gate theory of pain, published by Melzack and Wall in 1965, which revolutionized the field of human pain mechanisms. Simply stated, the gate theory postulated a "gating" mechanism that controlled the feedback of fast-conducting fibers from the central nervous system to advancing slower-conducting fibers either inhibiting or allowing progress through the "gate." Thus, a central nervous system analysis is required allowing both physiological and psychological influences. Four decades have passed since the introduction of the gate theory and like all good science, progress has been made and the theory further modified. However, this chapter is not concerned with current concepts but with a historical background from my personal perspective.

It is relevant at this point to mention an interesting problem. While our knowledge of pain and pain mechanisms has significantly increased during the 20th and early 21st centuries, we still lack a generally accepted definition of pain. A century ago, Sherrington (1906, p. 229) defined pain as "the psychical adjunct of an imperative protective reflex." Nearly all 20th-century pain researchers disagree with his definition, but they have eschewed defining pain themselves (Beecher, 1959). More recently, Merskey and Bogduk (1994) for the International Association for the Study of Pain defined pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (p. 210). This definition, while passable, is in my opinion not completely adequate. Many years ago, I had the pleasure of personally discussing the problem of an adequate definition of pain with Dr. Harold Merskey and I applaud his courage and persistence in eventually coming up with a definition.

There are several problems. Pain, while almost always unpleasant, is not necessarily so. Occasionally, one pain may serve as a relief for another pain (e.g., counter-irritation). In an experimental study, we have observed that white noise is generally reported as more aversive than pain (Wolff et al, 1976). Another problem is that it is often difficult to communicate pain to others because we may lack appropriate words and may thus resort to analogy. This problem has recently been highlighted in a review by Schott. (2004). Both clinically and in the laboratory, pain tends to be defined operationally, such as withdrawal from a noxious stimulus, the patient or subject saying "pain," marking a point along a line, relaxing tense muscles. However, pain defined in this manner can strictly speaking only refer to the specific situation rather than act as an absolute. Consequently, it is yet premature to define pain in absolute terms.

My own work started in 1958, while I was a member of the New York University Rheumatic Diseases Study Group. Specifically the question was raised whether it is possible to (1) measure a patient's pain level objectively and (2) predict a given patient's ability to tolerate (clinical) pain during physical rehabilitation and postoperative exercises of an operated joint. Obviously, with that background and at that time, the emphasis was on deep somatic arthritic pain rather than on cutaneous or visceral pain. Consequently, I chose to utilize a strictly psychophysical approach to devise a technique and measure the patient's pain response. Pain threshold determinations had been made by earlier investigators, such as von Frey (1897), on the skin, culminating in the "heroic" studies of Hardy, Wolff, and Goodell (1952), who used themselves as guinea pigs to measure pain threshold and pain discrimination with radiant heat on the skin. They developed the Dol scale of pain and introduced the radiant heat dolorimeter. Their work can be regarded as the first major psychophysical study of human pain. However, at that time, less psychophysical information existed for deep somatic tissues.

Kellgren (1937–38, 1938) had published some studies on muscle pain although his work was not strictly as psychophysical as that of Hardy et al. However, Kellgren's studies served as a beginning for our own deep somatic pain research. After experimenting with several different body loci, we chose the gluteus medius muscle as the most suitable site (Wolff et al, 1961). We developed a single-blind psychophysical technique permitting the insertion of 32 hypodermic needles in rosette fashion through eight anesthetized blebs of the overlying skin. The muscle was stimulated at each different needle point with 0.2 ml of sterile iso-, hyper-, or hypotonic saline in randomized fashion and a lower and upper pain threshold was measured (Jarvik & Wolff, 1962; Wolff & Jarvik, 1951). We were able to demonstrate, as briefly mentioned previously, that the same body locus could produce two different pain responses, namely, well-localized, sharp pain intensity of short duration (from hypotonic saline and water) and a diffuse, dull ache after a relatively long interval of onset and long duration. This technique, while of scientific value, is rather cumbersome to be used routinely in a pain center. Therefore, few other studies had been published on human muscle pain until the 1980s (Capra & Ra, 2004).

Numerous studies involving experimentally induced pain in humans have been done during the second half of the 20th and the start of the 21st centuries. Different types of noxious stimuli have been employed, such as electrical, mechanical, thermal, and chemical. In the laboratory, attempts are usually made to have the noxious stimulus simulate clinical pain of some kind or other and then to investigate whatever parameter is relevant to the purpose of the experiment. In the mid-20th century a major stumbling block for experimentally induced pain studies in humans was the criticism that such laboratory pain was artificial and bore no resemblance to "real" (pathological) clinical pain, especially in terms of the emotional/psycho-

logical components of clinical pain, which were lacking in the experimental model. Dr. Henry K. Beecher (1959) of Harvard was one of the chief critics of experimental human pain and for years carried on a (published) dispute with the Cornell group of Hardy et al. on the latters' dolorimetric work with humans. At that time, Beecher was an important figure with great influence in the pain arena and clinical pharmacology, who, in my opinion, had a major negative impact on human laboratory pain work. Eventually, Beecher changed his mind and announced that he and Smith et al. (1966) had developed an experimental method — the submaximum effort tourniquet technique — which had validity for clinical pain and could be used to study analgesic agents. Consequently, with Beecher's "blessing," experimental human pain studies became "respectable" again.

In our own work with experimentally induced pain in humans, we focused on several pain response parameters and not only on the pain threshold. In psychophysical terms, the latter is the point at which pain is first reported 50% of the time; i.e., it is really a measure of minimal pain. We applied experimental procedures that also allowed us to collect reports of maximal pain tolerated by the subject — the pain tolerance level. (There is some confusion in the literature about terms such as *pain tolerance*, but we use this term to denote the upper threshold). A third parameter, which we called pain sensitivity range (PSR) is the difference between the pain threshold and the pain tolerance, i.e., pain tolerance – pain threshold = PSR. A fourth response parameter is the just-noticeable-difference between successive levels of stimulus intensity.

Hardy et al.'s Dol scale is based on these just-noticeable differences. In a number of experimental studies in our laboratory using several different pain-induction techniques, we were able to demonstrate that the pain tolerance is the most sensitive parameter for analgesic assays with both mild and potent drugs, such as aspirin and morphine; i.e., it is a valid tool (Wolff et al, 1969). Some investigators have used yet another response parameter, namely, the drug request point, i.e., the stimulus intensity level at which the subjects would have requested a pain killer, had it been clinical pain. Single dose, as well as cross-over designs, have been used in these experimental studies. While the latter are statistically more powerful than single-dose designs, they suffer from an interaction effect, such as order of presentation or expectancy. In recent years, experimental pain in humans has been used less frequently for drug (analgesic) studies but animal models are still widely used.

The important contribution of Dr. W. Crawford Clark (1969) should be mentioned at this point, as he was the first to introduce signal detection theory or sensory decision theory (SDT) to the field of human pain studies in 1969. Clark's approach originally was based on Swets's work (1961) who publicized SDT in 1961. SDT was developed to detect a weak signal above background noise and essentially challenged the sensory threshold of classical psychophysics. In turn, Clark criticized the classical pain threshold as being contaminated by both sensory and judgmental components, while SDT permits separation. SDT caused considerable excitement among many pain researchers resulting in numerous publications, both pro and con. I reviewed this area (Wolff, 1978) discussing classical as well as "new" psychophysical parameters.

In human pain studies, both clinical and experimental, differences in pain behavior have been observed between and within various groups. Frequently, observed differences have been ascribed to ethnic differences, Afro-American, Irish, Scandinavian, Jewish, etc. Unfortunately, such "ethnic" differences have implied "racial" (a dirty word) or "genetic" differences for some authors and are eschewed politically. A good and brief review has been published by Morris (2001) in which he questions the scientific validity of so-called ethnicity. Many years before this publication, I also was interested in ethnocultural factors of pain and published a review with an anthropologist (Wolff & Langley, 1968). On the basis of our own studies, as well as those of several other investigators, it is my belief that pain behavior and pain responses are largely learned responses, molded by many variables, especially sociocultural, and that so-called "ethnic" differences simply reflect such learned behavior. Consequently, it is possible to modify such response under appropriate conditions (Horland & Wolff, 1973). This is not to deny that physiological and genetic differences may exist, but more evidence is required. Within homogeneous groups, age and gender differences are often observed, but again how much is learned and how much (if any) is genetic? We have also noted apparent lateral dominance differences in the same individual. The nondominant side appears to be more sensitive to noxious stimuli than the dominant side, but the latter is more discriminative (Wolff et al., 1965).

In recent decades ethical considerations have played an increasingly important role in experimental and clinical pain studies — both human and animal. Strict standards have been set by both institutional and governmental bodies to guard the rights of animal and human subjects, and funded investigations require approval from various "independent" and "impartial" committees. This is most laudable in spite of greater "red tape." In the "old" days, many investigators paid little heed for the suffering of conscious animals being experimented upon. Now, the animal must be able to escape (avoid, terminate) the noxious stimulus. In laboratory human pain studies, it was considered appropriate for the experimenter to be his or her own first guinea pig, such as Hardy et al. in their radiant heat work, previously mentioned. In my personal experience, I was my first guinea pig when we tested various muscles for the hypertonic saline method. I well remember hobbling

around for a few days after we used the gastrocnemius muscle and obviously decided against this muscle. The ethical problem in general is that the experimenter is not the best judge of noxious procedures to be "inflicted" on human volunteers. Historically, the famous Dahlem Konferenzen sponsored a symposium on "Pain and Society" in November 1979 in Berlin to which I was privileged to be invited and selected to be the rapporteur of a small group of other invited pain mavens, including Drs. Ronald Melzack, Hans Kosterlitz, Sir Michael Bond, Kenneth Craig, Giancarlo Carli, Jane Dum, Hartmund Brinkhus, and Wei-ming Tu. In terms of ethics, our group recommended that the Golden Rule, which states, "Therefore all things whatsoever ye would that man should do to you, do ye even so to them," should be amended to "Do not do unto others what you would not have done to yourself, and do not do unto others what they would not have done unto themselves" (Wolff et al, 1980). It is only 25 years ago that such a statement had to be made, which may surprise many current pain specialists. Another major ethical problem in clinical studies is the use of placebo when there is pathology. A "good" experimental study with a new or untested treatment, e.g., an analgesic drug, should be double-blind and include placebo. Yet, if the experimental modality is therapeutically effective, what ethical right is there not to use it with the placebo group?

Historically, two animal techniques for measuring pain have been standard procedures in analgesic assays, namely, the Eddy hot plate method and the radiant heat tail flick method. In the former, the pain response is measured when the mouse lifts its hind paw and in the latter when the rat flicks its tail. In human experimental pain studies both verbal and nonverbal (e.g., withdrawal) responses are used. What about clinical pain? Obviously, both verbal (e.g., "I am in pain," "Ouch!") and nonverbal (e.g., wincing, rubbing, tensing) responses have been observed and are in daily use by the practitioner. However, for human analgesic studies, two methods have become standard, namely, a numerical rating scale (NRS) or the visual analogue scale (VAS). The former requires the patient to state his or her pain level along a numerical scale, usually from 5 to 10 points. Incidentally, many investigators consider a larger scale (e.g., 10 points) to be more accurate and discriminative than shorter ones. However, scaling has several inherent errors well known to psychophysicists, such as clustering, and therefore, a shorter (say, 5 points) scale may often be more valid because it is easier for the patient to do the ratings. The VAS has become very popular. I remember its being introduced into the field of human pain by Dr. E. C. Huskisson in 1974. It consists of a straight line, generally horizontal and 10 cm in length. One end represents no pain and the other the most extreme pain. The patient is requested to mark a point along the line to represent his or her pain level. An unmarked rather than a graded line tends to be more valid for human analgesic assays. There are many other measures of human pain, such as questionnaires, among which the McGill pain questionnaire is probably the best known.

The discovery of morphine-like opiates in the brain in the 1970s was another major advance in the second half of the 20th century. Endorphins, as these endogenous opiates were named, have been studied extensively since that time. A number of investigators in different laboratories across the Western world pursued this line of chemical investigation making it difficult to pinpoint the originator. Many of us in the pain field felt that this work deserved a Nobel prize, but perhaps there were too many researchers. The endorphins are involved in various aspects of analgesia and a variety of receptors have been identified. Pharmaceutical companies have and are studying a variety of potential drugs that may act upon such receptors or modify related chemical processes to produce better analgesics.

The use of opiates, such as morphine, for clinical pain has been practiced for a long time. They have been used for immediate postoperative acute pain as well as for palliative care in cancer patients. However, morphine or other opiates were not considered suitable for long-term treatment of nonmalignant intractable pain. In the mid-20th century, when I first started to study pain, many physicians were afraid to prescribe adequate doses of morphine for patients for fear they would become addicted. In fact, this fear also permeated the nursing profession and occasionally a nurse would question a doctor's prescription of morphine. In other words, patients were frequently undermedicated as far as opiates were concerned. Yet, the irony is that undermedication can still produce addiction under certain circumstances. Fortunately, in recent years, pain practitioners have attempted to change this medical attitude and insist that if morphine or other opiates are prescribed, it should be done in adequate doses to relieve pain properly.

A newer question relates to the use of opiates for long-term care of nonmalignant chronic pain. Some pain specialists advocate the use of opiates for such patients, claiming good results. However, other practitioners have seriously questioned such an approach. I like to mention aspirin at this point. This non-narcotic, nonsteroidal, anti-inflammatory drug has been around since the late 19th century. It has serious side effects; it can certainly burn holes in tissue because it is an acid and can cause Reye's syndrome in children. Yet, in spite of that, aspirin is an effective analgesic for many pain conditions. Acetaminophen is now used more frequently and tends to replace aspirin in pain management.

Historically, it is worth mentioning amitriptyline, a tricyclic antidepressant, which has been used by psychiatrists for a very long time to treat depression. In the 1960s and 1970s, several clinicians experimented with various psychotropic drugs including amitriptyline to control pain.

Amitriptyline in low doses appeared to have analgesic effects. Originally, many psychiatrists criticized pain physicians for using such low doses for pain management, well below the generally recommended doses for depression. In fact, I know some psychiatrists who refered to such low doses as producing nothing else but a placebo effect. It took several years for the analgesic effect of amitriptyline to be "officially" recognized, although many clinicians still prescribe the higher psychiatric doses rather than the lower analgesic doses. Other tricyclics for pain relief have also been studied and are used frequently. The American Pain Society publishes a short guide on "Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain," at the time of writing already in its fifth edition, which is very useful for the practicing clinician.

I indicated at the beginning of this chapter that in the mid-20th century, we lacked knowledge in several areas. As stated before, at the time, pain was generally regarded as what we now call acute. Dr. John J. Bonica was one of the first to stress that acute and chronic pain must be differentiated. He termed chronic pain as a malefic state and said that it makes no sense to talk about "benign" chronic pain to separate it from cancer pain. While it may now seem obvious to classify pain into three major groups, namely, acute, cancer (or malignant), and chronic (or intractable) nonmalignant, it is Bonica who must be credited for promoting such distinctions. Many pain mavens call Bonica the "father of chronic pain," although I am not sure if he really would have liked that title. Recent and current research on pain based on neurophysiological and chemical investigations has demonstrated the plasticity of the brain and neural circuits involved in pain behavior. However, the above classification still has practical value.

I have always stressed the importance of communication both within and between professions for clinical practice and research. Initially, I worked in the field of arthritis and rheumatology and learned about the important contributions of nurses, physical therapists, orthopedic surgeons, and other health professionals in addition, of course, to the rheumatologists. In 1965, I was privileged to become a charter member and later president of the now-called Association of Rheumatology Health Professionals, joining forces with the rheumatologists in the American College of Rheumatology. As the name implies, the association brings together professionals from many fields working in arthritis and the rheumatic diseases. I considered this to be a good example for pain professionals. In 1964, just before the creation of the Association of Rheumatology Health Professionals, my colleague Dr. Thomas Kantor and I invited several pain "specialists" of whom we knew and who worked within a radius of about 100 miles from New York City to come to monthly luncheon sessions at New York University School of Medicine in order to network. We thus formed the New York Pain Group. It was disappointing, however, that only about 30 individuals, who were actively engaged in pain management and research, participated. Therefore, after 4 years of seeing each other, we stopped these meetings. It must be noted that at that time in the 1960s, there was still little interest in pain and the above group essentially comprised all then-active pain investigators in the greater New York City area. It was also a really interdisciplinary group with neurosurgeons, nurses, psychologists, physiatrists, rheumatologists, neurologists, statisticians, and others.

It was with great interest that I learned in 1973, that Dr. Bonica had invited many pain investigators to a meeting in Issaquah, Seattle, which eventually led to the formation of the International Association for the Study of Pain (IASP). This was indeed a very courageous and highly significant endeavor by Bonica to bring together pain clinicians and researchers from all across the world to exchange knowledge and communicate with each other. The first International Congress of IASP was held in Florence, Italy, in 1975 and was highly successful; other congresses are now held every 3 years in different countries. The IASP also publishes a journal, *Pain*, originally under the editorship of Dr. Patrick Wall, which has become the most influential scientific journal in the field of pain.

Stimulated by Bonica's success in forming an international pain organization, I decided to review what had originally been the New York Pain Group, especially after receiving enthusiastic support from many colleagues in the greater New York City area. Therefore, in 1974, I started the New York Pain Society, which almost immediately became the New England Pain Association following strong urging from Bonica. Rapidly thereafter, we enlarged to become the North-Eastern Pain Association and, as such, supported the IASP as one of its first chapters. Concurrently, the West Coast pain scientists formed the Western Pain Association and also joined the IASP as a chapter. In view of the steadily increasing interest in pain across the United States, both American societies enlarged, the Western including states west of the Rockies while the Eastern included states east of the Rockies. The latter again changed its formal name to Eastern Pain Association and has been functioning as such ever since.

In view of the rapidly rising interest in pain, I continued to feel that we should have a national pain organization in the United States in addition to the regional societies, a view shared by many of my Eastern colleagues. We considered it important that we have support for such a national U.S. organization from our Western U.S. colleagues as well as from the IASP. In 1975, during the First International IASP Congress, Dr. Pierre L. LeRoy and I discussed this issue with Dr. Bonica. The latter was concerned that an American pain organization might overshadow the IASP both financially and numerically and recommended that we wait some time until the IASP became a stronger organization. However, the success of the IASP, as well as the need to have a national society

that could represent pain scientists nationally rather than regionally, encouraged me to form a national U.S. pain organization. Therefore, I started informal discussions with Dr. Bonica, mainly by telephone, and we had Dr. Arthur F. Battista and Dr. B. Raymond Fink negotiate on our behalf — successfully. Thus, with Dr. Bonica's support, a national society could be started in the United States. In 1977, a meeting was arranged in Chicago to which Dr. Bonica and I invited 12 participants each, representing various interests. This meeting successfully supported the idea of a national organization and the American Association for the Study of Pain, shortly thereafter changed to the American Pain Society (APS), was formed, and I was elected as its first president. The Eastern and Western groups became chapters of the APS, which now has several regional chapters.

The APS has steadily grown and is representative of U.S. pain clinicians and researchers. The APS is truly multidisciplinary and includes all professions involved with pain. In view of its multidisciplinary structure, I decided that it could not have "trade union" functions but had to be predominantly scientific and educational. However, some physicians felt pain medicine had become important and that there should be a new specialty (or subspecialty) and eventually this led to the formation of the American Academy of Pain Medicine (AAPM). Fortunately, this did not pose a threat to the aims and goals of the APS. Furthermore, other professions can have pain specialists with their own guidelines within their profession. There always has been and still is concern that the APS is too scientific and research oriented and fails to cater to the practicing clinician while at the same time basic scientists often complain that the APS is too clinical. It is difficult to satisfy both views.

Because the APS gives no certificates or diplomas for proficiency in pain control, Dr. Richard Weiner years ago decided that there should be an organization to do so. Dr. Weiner had discussions with APS Board Members, including myself, and realized that this could not be a function for the APS. He thus formed the American Academy of Pain Management — the other AAPM — which focuses on the practicing health professional, provides education, and awards credentials of proficiency. It has now become one of the major pain organizations in the United States.

In this chapter, I have rambled along various historical paths often associated with my own functions and role. It is thus a little autobiographical although I hope not too boring. Detailed histories of pain may be found in other publications. Here I have cursorily reviewed the historical background leading up to the Melzack and Wall gate theory of pain and focused on the mid- and second half of the 20th century. In my opinion, the gate theory and the discovery and role of endorphins were the two most significant scientific contributions to pain in the latter half of the 20th century. Clinically, the realization that pain is a specialty of its own and requires a multidisciplinary as well as multimodel approach should be regarded as another significant contribution. Associated with both the clinical and scientific contributions has been the much greater interest in pain, its mechanism, and management. Better communication and networking, largely due to the formations of regional, national, and international pain societies followed by the publications of several pain-oriented journals, have also contributed to our constantly increasing better understanding of pain — now often regarded as the Fifth Vital Sign.

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Fibromyalgia: Patient Beliefs and Expectations

Lynne Matallana

Yes, when I see a healthcare professional, I am a fibromyalgia "patient," but more importantly I am a human being — a living, breathing, feeling person who must face, on a daily basis, a constellation of distressing symptoms that cause both physical and mental anguish. Like millions of others with fibromyalgia, not only do I have to live with the consequences and challenges that its chronic symptoms cause, I have to live with the fact that there are many people who give no credence to my condition, dismissing my suffering because they don't understand it or don't want to get involved with those of us who are seen as "difficult patients who constantly complain."

Ten years ago I believed that if you became sick, all you had to do was go to a doctor, get a diagnosis, be given the appropriate treatment, and within time (hopefully not a long period of time) you would feel better and your life would return to normal. Yes, a naive concept, but one that had been my experience. We live in a world that possesses more scientific medical knowledge than ever before. We place physicians on pedestals as they transplant hearts, cure cancers, and remove brain tumors. These acts are truly incredible, almost incomprehensible feats of accomplishment. So when only a few days after having had surgery for endometriosis I started to experience a variety of disturbing symptoms, including widespread body pain, unrelenting fatigue, migraine headaches, and the inability to easily organize my thoughts, I felt certain that a visit to my doctor would solve the problems. Instead, it marked the beginning of my passage into a new life. A journey that would mean learning to live well despite chronic pain, one of the most desperate of human conditions, yet one that still in many ways remains challenging and mysterious to the medical community.

Although it took me some time to come to accept the fact that doctors don't possess a magic wand to make pain disappear and that my expectations of their "God-like" ability to cure me was not only unfair but silly, I couldn't accept their conclusion that there was nothing wrong with me and that there was nothing that could be done to help. Was there truly no hope for my future? Although even at times I questioned my sanity, wondering if my pain was "real," I believed that no matter what the cause of my suffering, I deserved to be treated with respect as a human being and that my experience could not and should not just be dismissed because others didn't understand it. My pain didn't fit into their reality, but my pain was very much my constant reality.

When I first became ill scientific *proof* of my condition lagged behind my state of misery, but I believed that *I* shouldn't be seen as a pariah, a nuisance to the medical community and valueless to humanity. However, that is how I felt. I wanted and needed help, so that I could regain my worth and continue to contribute to society. Pain is not new, so how could the medical community not accept my pain as real or help treat it as something that truly existed? Was I naïve to also think that a physician should be *compassionate* to my distress no matter what the illness? Was it simply because the *type* of pain that I experienced did not yet have evidence of organic pathology, unlike pain from a broken limb or a cancerous growth, that made it unworthy of concern? Without empirical evidence, my pain was invisible to everyone except me. And my frustration with the situation made me frantic, and I turned into that "difficult and constantly complaining patient." I hated what I had become. I hated the looks of frustration on the faces of my family and doctors. I felt like the little baby who cries and cries, trying to let others know that there is something wrong, but no one can figure out the reason for the screams. I couldn't imagine a life

where I was supposed to just quietly disappear. Like the women of my grandmother's generation whose complaints were dismissed as one of those "middle-age women's things," which left them retreating to their beds for days, weeks, and years at a time. I valued life too much not to fight for a life of quality, despite fibromyalgia. I tried to be understanding of the frustrations that everyone around me was feeling. I felt guilt because *I* had caused them distress and yet angry that they couldn't take away my pain.

I remember as a child the first time I looked through a microscope and a drop of water from a pond turned into a world of small invisible creatures that hadn't existed in my reality a few seconds earlier. Even though my fibromyalgia pain weighed me down with frustration, fear, disillusionment, guilt, and even anger, I wanted to fight the temptation to believe the cluster of preconceived negative assumptions that were attached to *my* illness. I wasn't crazy, I wasn't just stressed, I wasn't lazy, or just a negative person. Why was I supposed to suffer because of other people's ignorance and lack of acceptance? Of course it was easier to just turn away than to try to make sense out of something that didn't fit into the way the medical community *currently* looked at and accepted things. But we *can't* be reluctant to look through the microscope and discover new truths, to recognize that we can't *see* everything easily, so we must take a closer look, refusing to turn a blind eye, especially when it involves a large community of people who are truly suffering.

Unlike most patients with fibromyalgia who do not have the circumstances that allow them the opportunity to keep searching for answers, I had the emotional and financial support that allowed me to continue to seek out help. Although there were times that I began to lose faith, my pain urged me on, a constant reminder that there was no room for self-doubt. My pain was real and it wasn't something that could be ignored. It wasn't just the medical community that had left me feeling stranded and isolated; it was friends, employers, and society who questioned my pain and fatigue. Even the media talked about a *new* illness that was thought to affect people who were "lazy and out of physical condition." What had I done that was deserving of *abandonment and judgment*? I kept telling myself — I did nothing wrong. This was an *illness*, not a punishment. So there had to be answers and there had to be people out there who *did* care. I just had to find them.

Unfortunately, today and even more so ten years ago, knowledgeable physicians on fibromyalgia are rare. Thirty-seven doctors and two years later, I found my compassionate, open-minded, knowledgeable doctor. I came to understand that my quality of life was going to be influenced by our doctor–patient relationship. I realized that it was going to take time to build this relationship and that we both had to make a commitment to working hard and doing our part as *a team*. I couldn't have expectations that my doctor was going to cure me, and my doctor couldn't expect me to not share my suffering with him. I trusted him to keep me informed of the most recent treatment options available to people with fibromyalgia, and he trusted me to try to keep a positive attitude and to be willing to take his medical advice while making personal life-style changes that would help improve my overall symptoms. We both made a commitment — he to treating and encouraging me to the best of his ability, and I to being a pro-active patient, implementing a multidisciplinary self-management plan, working to achieve both physical and mental balance. Even though much of the "responsibility" did fall on me, the patient, his willingness to diligently keep up with new research findings that led to the implementation of new treatment options encouraged me and resulted in treatments (both pharmacological and alternative) that helped reduce my symptoms.

When asked, most individuals with fibromyalgia express above all else the need to feel "normal" and understood. Living with an "invisible" illness can strip away people's self-confidence and make them feel isolated and alone. All need and feel better when they receive validation, whether it is for what they have accomplished, what they think, or what they feel. When you are told that what you are feeling is not real, it is like being told that *you and your feelings* have no value. We as individuals need our lives to have value, a purpose, without which we feel cast out, alone, and even abnormal. Pain that is not validated causes one to feel guilt, fear, and hopelessness, which in turn can even become disillusionment and depression. Referring to fibromyalgia as being a "waste basket" diagnosis alludes to the fact that the diagnosis has no value, again discrediting and belittling the personal experience. It is evident that even before pursuing efforts to reduce their symptoms, people with fibromyalgia can greatly benefit from acts of compassion, acceptance, and the gift of hope.

In pain states that are caused by injury, the treatment protocol is to treat the injury, thereby eliminating the problem that is causing the pain. However, fibromyalgia is a condition of central sensitization and neuroendocrine dysfunction, so the pain experience becomes chronic. For a person living with constant pain it is an ongoing challenge to find ways to achieve a better quality of life. The actions taken and avenues pursued by a person with fibromyalgia are based specifically on the chronic nature and idiosyncrasy of the syndrome. Each individual's personality affects the way in which he or she approaches the problem. With the lack of reliable treatment options, the individual can feel that there is nothing available to help and can become depressed and withdrawn, while others spend hours searching for solutions, becoming overwhelmed with a countless selection of unreliable treatments touted to "cure" or help relieve symptoms. Desperation can sometimes outweigh common sense and one can

become compulsive in the attempt to find relief. Those of us who were once independent and self-sufficient can find ourselves needy and desperate for others to concentrate only on our dilemma, at times not even recognizing that our neediness can actually push others away.

In that fibromyalgia is a syndrome of multiple symptoms and overlapping conditions, the extent of the complaints can seem questionable to those on the "outside," and patients often find themselves trying to explain, as well as understand, a myriad of ever-changing ailments. One day you'll be suffering with a burning pain sensation all over your body and the next day you'll experience cognitive dysfunction, dizziness, and anxiety. Then you'll find yourself gaining confidence as things slowly start getting better, and then the next day you'll be experiencing nagging unrelenting pain that seems to come from nowhere. Living in a world where we look at things in relationship to cause and effect, people with fibromyalgia can become disheartened by the inability to find this type of relationship when it comes to their pain and symptoms.

Overanalysis of the situation can lead to nothing but confusion, and therefore, it is important to realize that with our current limited understanding of central sensitization, it is often impossible to predict a cause/effect relationship when it comes to symptoms. In those situations where one can identify a "trigger" for a specific symptom, a small sense of control can emerge, helping one to better self-manage the condition. However, when one expects a certain reaction, for example, spending several days in bed in order to relieve pain and exhaustion, and that result does not occur, the sense of control becomes elusive and the ensuing frustration is not surprising.

It is important to realize that our "cause and effect" expectations are based on our existing experiences and knowledge of the reactions of a healthy body or one with a specific disease or trauma. But in the case of fibromyalgia, we are learning that the problem is "system failure," or in other words, symptoms that are caused by disordered sensory processing at a central level. For a person experiencing "pain amplification," the existing cause-and-effect "rules" do not apply. It is only with additional research that we will be able to assist the person with fibromyalgia by better understanding the cause(s) of this illness. We as patients will experience more control over symptoms when we come to understand the new relationship of cause and effect, which produces fibromyalgia symptoms.

It is at this point that one realizes yet another challenge confronting those of us living with fibromyalgia. Not only must we adapt to living with disruptive, disabling symptoms for which there is often little relief, but we must also live with an illness that produces symptoms that don't "react" like our preconceived expectations. Besides the physical pain that must be endured, this lack of control and resulting feelings of abnormality cause extreme emotional suffering. Until we understand the cause(s) of the "system breakdown," and we can find ways to correct that problem, patients must find ways to feel a sense of control over their illness through limited existing avenues — usually consisting of options that involve extensive self-motivation and patience. In the past, the focus has been on the patient's learning to accept and live with the pain (and other symptoms) through means of counseling, cognitive behavioral therapy, biofeedback, etc. These are excellent ways to deal with the situation, but they are not solving the actual problem so as to eliminate the symptoms. For years patients have had to learn ways to adapt and adjust to their illness rather than have options that will "fix" them. Today, there are more options available to help people with fibromyalgia cope with their symptoms. But the continuous waxing and waning cycle still robs certain individuals of the freedom to plan daily activities and move forward with their life.

Fibromyalgia obviously affects the patient in numerous ways, but it must be pointed out that fibromyalgia also affects the lives of all who share the patient's life. As with any chronic illness, individuals find themselves in roles that they are not comfortable with or even refuse to accept. Spouses and family members must become caregivers, employers are asked to make work accommodations, physicians are asked to treat patients with exceptional needs, and friends are relied upon to provide support and assistance. When one or more of these people decide that they cannot or will not accept the responsibilities that go along with their new role in their relationship with this person, more emotional trauma ensues. Often fibromyalgia can make a person dependent on others for various aspects of their livelihood. When an individual becomes chronically ill there are people around that person who will not be able to cope and will remove themselves from the situation. In the case of a person who is chronically ill with fibromyalgia, an "invisible illness" that is difficult at best to understand and doesn't have the "credibility" of other chronic illnesses, the chances of disassociation become even greater. Living with fibromyalgia all alone is something that far too many people have to face.

Fibromyalgia is not just a problem that affects a specific group of people. It is a health condition that touches the lives of millions and millions of people every day. The negative implications of this illness are far reaching and must be given the attention necessary to ensure that we will find the answers that will allow us to eliminate the suffering caused by this disorder. Education is the key to providing a future that guarantees hope for those who live with fibromyalgia. As a patient, I can live with an illness that causes pain, but as a person, I can't live with the knowledge that others have dismissed this pain and find it unworthy of their concern and acceptance.


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3

The Neuroscience of Pain and Analgesia

James Giordano, PhD

By definition, pain is a noxious sensation that evokes perceptions of dysphoria and illness. The linkage of sensory phenomena with cognitive processes is important to the strong avoidant motor reflexes, autonomic events, and emotional responses that are co-terminal with both the pain experience and its expectation (Cazzullo & Gala, 1987). The scientific perspective has evolved to characterize pain as a heterogeneous entity that may be classified by temporal (i.e., acute, chronic), mechanistic (i.e., nociceptive, inflammatory, neuropathic), and phenomenologic (i.e., eudynia, maldynia) factors. Far from being mutually exclusive, these classifications are both overlapping and interactive and can be useful when elucidating the qualitative, quantitative, and pathologic variables that contribute to a particular clinical pain syndrome (Woolf & Max, 2001). The neural substrates that are involved in processing noxious input contribute to both the sensation and cognitive–emotional phenomena of pain.

NOCICEPTORS

The first step in the nociceptive sensory pathway is the transduction of noxious thermal, mechanical, or chemical stimuli to a relevant neural electrophysiologic signal. In cutaneous, muscle, and visceral tissues, free nerve endings of nocisponsive primary afferents are responsible for this transduction step. Cationic channels on free nerve endings respond to noxious stimuli directly and to evoked changes in the innervated tissues.

Two nonselective cation channels, molecularly similar to vanilloid receptor-1 and vanilloid receptor-like protein 1, are responsive to noxious heat (>45°C) and thermal sensitization (Davis, 2000). A related cation channel, the cold- and menthol-receptor-1 (CMR1/transient receptor potential M8) is responsive to noxious cold (8 to 25°C) and menthol (McKemy, Neuhausser, & Julius, 2002). In both cases, thermal change produces an ungating of the channel(s) to induce cationic flux.

Noxious mechanical input (i.e., compression, shear, tensile distortion) is subserved by a nonspecific cation channel that is gated by mechanical linkage to bridging elements of the free nerve ending membrane and the matrix of surrounding tissue (Mannsfeldt, Carroll, Stucky, & Lewin, 1999). Transduction occurs as these stimuli distort the mechanical field of the neural membrane, transforming channel configuration and producing an inward Na^+, K^+, or Ca^{2+} current. The receptor potential for free nerve endings appears to be a graded response, with time- and intensity-dependence of the membrane polarity. Once the conductance threshold for Na^+ is achieved, activation of voltage-gated Na^+ channels occurs, leading to a propagation of the depolarization along the membrane of the primary nociceptor. As well, the influx of both Na^+ and Ca^{2+} elevates the concentration of intracellular Ca^{2+} that activates a variety of intracellular signaling systems capable of producing short- and long-term changes in neuronal function (and perhaps microstructure; *vide infra*).

In addition to the direct action of noxious stimuli upon nociceptors, high-intensity input may incur local tissue disruption or membrane damage to evoke the release of fatty acids and free ions from cell membranes. The enzyme phospholipase-A2 catalyzes free membrane fatty acids to produce the omega-6, arachidonic acid, that then serves as the initiative substrate for (latent) induction of the isoenzyme cyclooxygenase 2 (COX-2) to induce the inflammatory cascade, subsequently mediated by the for-

TABLE 3.1
Algogenic Substances/Stimuli and Substrates Mediating Effects

Algogenic stimulus	Substrate(s)	Effect(s)
H^+ ion	VR1 receptor	Na^+, Ca^{2+} influx
Protons	Acid-sensitive ion channel (ASIC)	Na^+ influx
Noxious heat >45°C (and capsaicin)	VR1, VRL-1 receptor proteins	Na^+, K^+, Ca^{2+} influx
Noxious cold 8–25°C (and menthol)	CMR1/trpM8	Na^+, K^+, Ca^{2+} influx
Mechanical distortion	Nonselective cation channel	Na^+, K^+, Ca^{2+} influx
BDNF	Trk-B receptor	MAPK activation–transcription effects
Prostaglandin-E_2	Prostanoid receptor	Metabotropic activation of protein kinase
Serotonin	5-HT_3 receptor	Na^+ influx
		NK-1 receptor sensitization
		NO production
Adenosine (or ATP)	A_2 purinoreceptor	Sensitization of Na^+ channels
Glutamate	AMPA receptor	Na^+ influx
	NMDA receptor (GluR)	Ca^{2+} influx
	mGlu receptor	Phospholipase-C-induced rise in intracellular Ca^{2+}
		Protein kinase-C phosphorylation/sensitization of trk-B
Bradykinin	Bradykinin B_2 receptor	Cationic influx

mation of biologically active prostaglandins, most specifically prostaglandin synthase–generated prostaglandin-E2. Prostaglandin-E2 acts upon the free endings of nociceptors to produce a receptor-mediated increase in adenyl cyclase to elevate cyclic adenosine monophosphate (cAMP) and engage specific protein kinases. Protein kinase A and C can phosphorylate membrane proteins to affect the sensitivity of prostanoid, kinin, or amine receptors as well as increase the sensitivity and/or modify the configurational state of ion channels (McClesky & Gold, 1999). Such changes can produce a leftward shift in nociceptor membrane thresholds, which can sensitize the affected primary afferents to subsequent stimulation by increasing the number and frequency of nociceptor depolarizations produced by both noxious stimuli (e.g., contributing to hyperpathic responses) and perhaps innocuous stimuli (i.e., allodynia; Gold, Levine, & Correa, 1998; Ji, Kohno, Moore, & Woolf, 2003). Table 3.1 presents an overview of noxious stimuli and the substrates that transduce their neural activity.

Subsequent to transduction, the nociceptive signal is conducted from free nerve endings in the periphery (or viscera) along the membrane of primary nociceptive afferents via depolarization induced by sodium influx subserved by $Na_v1.8$ and $Na_v1.9$ subtypes of Na^+ channels, that are specific to nociceptor membranes (Amaya et al., 2000). There are two types of primary nociceptive afferents, A-delta and C-fibers. These subtend distinct types of noxious input (e.g., thermal, mechanical, polymodal) and are strongly contributory to the differing subjective sensory qualities of fast (i.e., "first") and slow (i.e., "second") pain, respectively (Ochoa & Torebjork, 1981).

PRIMARY AFFERENTS

A-Delta Fibers

These fibers are small, thinly myelinated neurons, 1 to 5 μm in diameter, with conduction velocities in the range of 5 to 30 m/s. The rapid rate of conduction is responsible for the initial sensation of pain, "first pain," typically described as sharp, localized, and well defined. A-delta fibers have small receptive fields and are relatively modality specific. This latter quality is a function of specific, high-threshold ion channels on the free endings of A-delta afferents that are differentially activated by distinct high-intensity thermal or mechanical input (Julius & Basbaum, 2001). A-delta thermosponsive fibers respond to extremes of temperature. One population is activated by noxious heat, with an initial response threshold in the range of 40 to 45°C. Response function increases directly, although not necessarily linearly, as a consequence of temperature elevation, with maximal responses occurring at temperatures of 46 to 53°C. These responses subserve both the rapid, demonstrably painful response to an initial presentation of noxious heat and the ability to quickly discriminate extent of thermal pain as a function of heat intensity. A second population, high threshold cold afferents, responds to cold temperatures at or below a threshold of approximately 8°C, with increasing cold sensitivity to temperatures less than 25°C (Price & Dubner, 1977; see Table 3.1).

A-delta mechanoreceptive afferents are activated by high-intensity mechanical stimulation (deep pressure, stab, pinch, stretch), although these fibers may be sensitized by, and become secondarily responsive to, noxious heat. Unlike A-delta thermal afferents, sensitized A-delta mechanoreceptive afferents respond to suprathreshold heat (usually in excess of 50 to 55°C) and/or repetitive presentation of noxious heat, rather to a singular exposure to a heat stimulus at or above the nociceptive threshold (Kumazawa & Perl, 1976). The sensitization of this second population of nociceptive A-delta afferents may contribute to the hyperalgesia observed following heat and mild to moderate burn injury.

C-Fibers

C-fibers are small, unmyelinated afferents with broader receptive fields than A-delta fibers. C-fiber diameters range from 0.25 to 1.5 µm, and the absence of myelin leads to slower conductance velocities that vary from 0.5 to 2 m/s. This slower conductance together with the broad receptor fields subserve clinical "second pain," a diffuse, poorly localized burning, throbbing, or gnawing sensation that follows and that is temporally and qualitatively distinct from the initial sensation of "first pain" (Torebjork, 1974). Numerically, C-fibers constitute the majority of primary nociceptive afferent innervation of cutaneous tissue. C-fibers are polymodal, and can be activated by thermal, mechanical, and chemical stimuli. This latter quality reflects the direct engagement of C-fibers by specific chemicals that perfuse the neuronal microenvironment of C-fiber free endings following cellular disruption. Free H^+ ion (i.e., lowered pH), protons, and adenosine triphosphate (ATP) are all capable of activating C-fibers. H^+ acts by sensitizing the VR1 vanilloid receptor (that is also responsive to noxious heat) and enhancing Na^+ and Ca^{2+} influx (Caterina et al. 1999). Protons stimulate C-fibers by acting at an acid-sensitive ion channel to evoke an inward Na^+ current (Waldman & Lazdunsky, 1998). Adenosine, liberated from ATP by hydrolysis, binds to an A_2 purinoreceptor, to sensitize Na^+ channel excitation (Gold, 1999; see Table 3.1).

In addition to responding to noxious (thermal, mechanical, and chemical) stimuli, C-fiber polymodal afferents may be sensitized by substrates of the inflammatory cascade (e.g., prostaglandin-E2, bradykinin) that are released following thermal or mechanical insult (Gold et al., 1998; Levine & Reichling, 1999). Once sensitized, these C-fibers can be activated by certain types of non-noxious, low-intensity stimulation. This may account for the persistent second pain and hyperalgesia that occurs following burn injury or other inflammatory states (Rowbotham & Fields, 1996). In this light, C-fibers may contribute to multiple sensations from a painful region.

C-fibers also innervate muscle tissue, localized to the intrafibril matrix, tendons, and areas surrounding the vascular walls (Iggo, 1974). C-fiber muscle afferents are polymodal and are responsible for the nociceptive response to intense mechanical stimulation (Jones, Newham, Obletter, & Giamberardino, 1987) that produces numerous substances as a consequence of both aerobic and anaerobic metabolism. C-fibers innervating muscular tissues are activated by H^+ ions as a constituent of the acidic postmetabolic environment (Mills, Newham, & Edwards, 1982) as well as end products of inflammation due to exercise-induced micro- or macrotraumatic insult (including bradykinin, histamine, and 5-HT; Vecchiet, Giamberardino, & Marini, 1987), mechanical distention of microedema (Newham & Jones, 1985), and heat (Mense, 1977). Although not directly activated by muscular contraction or the stretch reflex, intramuscular C-fibers can be sensitized (under ischemic conditions) to respond to even small myofibril contraction and may respond vigorously to excessive stretch (Vecchiet et al., 1987). It appears that ischemia yields an increased concentration of free adenosine that acts at A_2 purinoreceptors to produce G protein–mediated modulation of Na^+ channel thresholds (Gold, 1999). This sensitization helps to explain the diffusely painful response to both passive and active movement of over-exerted, traumatized, or ischemic skeletal muscle.

Visceral Primary Nociceptive Afferents

Numerous stimuli are capable of producing visceral pain (see Gebhart, 1995, for review). Distention, compression, and chemical and tactile irritation of several visceral structures have all been shown to elicit distinct and quantifiable pain responses in humans (Willis, 1985), that are often accompanied by reports of localized somatic and cutaneous pain. The diversity of response to various types of noxious stimuli suggests the presence of afferents with polymodal qualities. Taken with the diffuse, poorly localized quality that often accompanies visceral pain, such findings implicate the involvement of C-fiber-type innervation (Dubner, 1985; Gebhart, 1995). C-fiber-type afferents innervate several visceral structures, even though studies have also demonstrated presence of A-delta fibers with polymodal sensitivity, particularly in the testes and structures surrounding the heart (Paintal, 1972; Uchida & Murao, 1974). As well, a small, unmyelinated J fiber has been identified in the parenchyma of the lung (Paintal, 1972). J fibers have structural properties, receptive fields, and conductance velocities similar to C-fibers and respond to high-intensity mechanical changes in lung volume (i.e., distention and compression), inflammation, and exogenous chemical irritants (e.g., acidic and basic substances; Coleridge, Coleridge, & Luck, 1965).

TABLE 3.2
Physiologic and Neurochemical Properties of Primary Afferent Nociceptors

Type	Stimulus	Anatomy	Diameter	Conduction/Properties	Chemistry
A-delta fiber	High threshold Mechanical Thermal (>45°C) (<20°C) Mixed-sensitized	Free endings Myelinated Punctate fields	1–5 μm	10–30 m/s Fast; First pain; Well localized	Glutamate Substance-P CGRP (?) VIP Postsynaptic activation of AMPA receptors Short-term NK-1 receptor activation
C-fiber	High threshold Polymodal Thermal Mechanical Chemical	Free endings Unmyelinated Diffuse receptive fields	0.5–1.5 μm	0.5–2 m/s Slow; Second pain; Chronic; Poorly localized; Sensitized	Glutamate Substance-P CGRP Postsynaptic activation of NMDA, Glu receptors Potentiated NK-1 receptor activation May induce neural plasticity

Nociceptive afferent innervation of visceral structures has several characteristics that are markedly distinct from those in cutaneous and muscle tissues. First, nociceptive afferent innervation of the viscera is relatively sparse, with considerable diffusion at projection sites at second-order neurons within the spinal dorsal horn (Cervero & Iggo, 1980). Thus, nociceptive input from the viscera may not evoke strong, well-localized volleys of excitation capable of spatially or temporally summating at spinal relays. Second, the nature of visceral afferents is such that sensitization by chemical mediators and/or sympathetic activity (see below) appears to be required for their sustained firing. Given the sparse distribution of these fibers throughout the viscera and the diffuse connections with nociceptive units of the spinal cord, it appears that this sustained firing is responsible for the activation of second-order spinal afferents and, ultimately, the transmission of visceral nociceptive signals. The perception of visceral nociception is vague, becoming more intense (and better localized) as increased painful activity in the innervated structure(s) sensitizes the involved afferents (Dubner, 1985). Third, nociceptive afferent innervation of the viscera is often structurally co-localized with sympathetic afferent (and perhaps efferent) neurons. Noxious stimulation from the viscera can lead to concurrent excitation of both visceral nociceptive afferents and sympathetic innervation, capable of producing retrograde sympathetic outflow and sympathetically maintained regional hyperalgesia and altered autonomic tone. However, such sympathetic alterations are not exclusive to visceral pain; sympathetic effects are strongly contributory to the constellation of nociceptive, vasomotor, and sudomotor features of complex regional pain syndromes (CRPS) that can affect somatic innervation, as well. In such cases, excessive stimulation of sympathetic axons or endings (either by ephaptic transmission from adjacent nociceptive afferents or directly by peripheral tissue insult) can induce increased synthesis of high-affinity adrenoceptors, thereby perpetuating the cycle of peripheral adrenergic sensitivity, sympathetically-maintained pain, and alterations in peripheral autonomic regulation (Campbell, Meyer, & Raja, 1992, for an overview). Last, visceral nociceptive afferents are often anatomically integrated with somato-cutaneous nociceptive afferents within dorsal root ganglia or within the aggregate of primary afferent synaptic fields at second-order afferents of the spinal cord (Willis, 1985). Reciprocal sensitization within the dorsal root ganglion and the overlap of second-order receptive fields for both visceral and somato-cutaneous input subserve the somatic referred component that is characteristic of much of visceral pain. It is clinically relevant to understand the convergence of visceral and somato-cutaneous afferents when attempting to predict involvement of visceral structures in patterns of referred somatic pain.

Projections to the Spinal Dorsal Horn

Although a small number of nociceptive afferents synapse within the ventral spinal cord, the vast majority of somato-cutaneous and visceral nociceptive primary afferent fibers project to defined areas of the superficial dorsal horn (Gobel, 1976). This area has been anatomically distinguished into discrete zones, the laminae of Rexed. The laminae are numbered consecutively from dorsal to ventral regions (Rexed, 1952). Both A-delta and C-fibers terminate on specific populations of second-order spinal neurons in laminae I, II, IIa, and V that are the origin of the ascending spinal pathways critical to pain transmission. Specifically, A-delta fibers terminate in laminae I, II, and to a lesser extent, IIa (Gobel, 1976), while C-fibers project to laminae II, IIa, and V (Torebjork, 1974). The anatomic, physiologic, and neurochemical properties of primary nociceptive afferents are presented in Table 3.2.

Neurochemistry of Primary Afferent Pain Transmission

The principal neurochemical mediator at the synaptic cleft between primary afferent nociceptors and dorsal horn cells is glutamate. Postsynaptically, glutamate is capable of binding to two types of discrete receptors (Woolf, 2004). The first, the AMPA (alpha-amino-3-hydroxy-5-methyl-isoxazole-4 propionic acid) receptor, appears to be the initial or first molecular target for glutamate binding. Glutamate-induced AMPA receptor activation evokes a ligand-gated sodium current in postsynaptic second-order neurons of the dorsal horn that produces a rapid depolarization. AMPA receptor-mediated depolarization modulates glutamate-induced activation of the second class of receptor, the *N*-methyl-D-aspartate (NMDA) receptor, by allosteric modulation of magnesium binding to a shared or cooperative domain of the NMDA receptors. With persistent AMPA receptor activation, the rise in intracellular sodium displaces a magnesium "gate" from the NMDA receptor, thereby increasing its sensitivity or releasing it from an inaccessible configuration to actively bind glutamate (Woolf & Salter, 2000).

There are two types of NMDA receptor: a fast-on, slow-off, ionotropic, Ca^{2+} channel site (GluR) that subserves a durable calcium influx and a metabotropic, G protein–coupled receptor (mGluR). Of the eight identified mGluR sites, three are positively coupled to phospholipase-C (PLC). In nociceptive neurons, one type of mGluR engages PLC to induce inositol triphosphate (IP3) to release calcium from intracellular stores. These effects elevate the level of intracellular calcium; this activates a Ca^{2+}-sensitive protein kinase-C (PKC) to phosphorylate serine and threonine residues in the submembrane pool of NMDA and AMPA receptors, thereby inducing post-translational changes that subsequently increase the number and sensitivity of these receptors (Luo et al., 2001; South et al., 2003). Metabotropic glutamate receptors can also act through intracellular diacylglycerol (DAG) to activate PKC to phosphorylate the tyrosine kinase-B (trkB) receptor for brain-derived neurotrophic factor (BDNF; Kerr et al., 1999). BDNF, a secretory protein, is produced and released by primary nociceptive afferents (McMahon & Bennett, 1999). The action of BDNF at postsynaptic trk-receptors initiates mitogen-activated protein kinase (MAPK) capable of affecting gene transcription (Friedman & Greene, 1999).

Taken together, these glutamate-dependent reactions may be responsible for the sensitization of second-order afferents to input from nociceptors. There is further evidence to suggest that prolonged activation of newly synthesized NMDA receptors may instigate PKC-mediated activation of transcription factors to affect genomic elements to facilitate ongoing alteration of cell membrane components (e.g., sensitized ion channels, additional upregulated receptors) and produce durable changes in second-order nociceptive afferent function (Stubhaug, Breivik, Eide, Kreunen, & Foss, 1997).

While brief, suprathreshold primary nociceptor activity causes the release of glutamate, prolonged and/or intense C-fiber activation induces the release of the undecapeptide tachykinin, substance-P (Cao et al., 1998). Initially, substance-P binds postsynaptically to neurokinin-2 (NK-2) receptors on second-order dorsal horn neurons. However, with more prolonged excitation, substance-P also binds to NK-1 receptors to activate G protein–mediated, metabotropic, slow onset, durable shifts in membrane potential (Woolf, 2004). The continued activation of NK-1 receptors induces DAG-dependent activation of protein kinase (A and C) to phosphorylate NMDA receptors, leading to enhanced intracellular calcium levels (Thompson, Dray, & Urban, 1994). Latent (i.e., 30 to 60 min) calcium-mediated phosphorylation of transcription elements stimulates production of the early-phase proto-oncogenes, *c-fos, c-jun,* and *Krox-24* (Jin et al., 2003; Lanteri-Minet, Isnardon, de Pommery, & Menetreu, 1993). The induction of these proto-oncogenes produces protein products that both act as metabolic regulatory units and produce late-gene effects that may be responsible for transcribing and translating novel (and perhaps aberrant) proteins involved in functional and microstructural remodeling of second-order neurons that are actively processing chronic pain (Jin, Zhuang, Woolf, & Ji, 2003). According to Doubell, Mannior, & Woolf (1999) such remodeling characteristically results in a reduced firing threshold, increases in durability and frequency of response, expansion of the functional postsynaptic region (i.e., the receptive field), and a suppression of inhibitory potentials (subserved by both downregulation of receptors for inhibitory transmitters and a loss of inhibitory synapses). These processes are similar to long-term potentiative (LTP) and depressive (LTD) mechanisms, respectively, and it is likely that they play a role in central sensitization and directly contribute to neuropathic pain syndromes (Ji et al., 2003; Randic, Jiang, & Cerne, 1993).

Additionally, sensitized primary afferents are capable of antidromic or retrograde release of neurochemical mediators of the inflammatory response (Fitzgerald, 1989). Substance-P provokes degranulation of mast cells in peripheral tissue leading to the release of several potent vasoactive and proinflammatory mediators including histamine and serotonin (Holsapple, Schnur, & Yin, 1980). Substance-P may also act directly as a vasodilator. In addition to antidromic release of substance-P, primary afferent nociceptors release calcitonin gene-related peptide (CGRP) from terminal branches to affect distal peripheral (and/or visceral) tissues. CGRP activates the enzyme NO (nitric oxide) synthase from

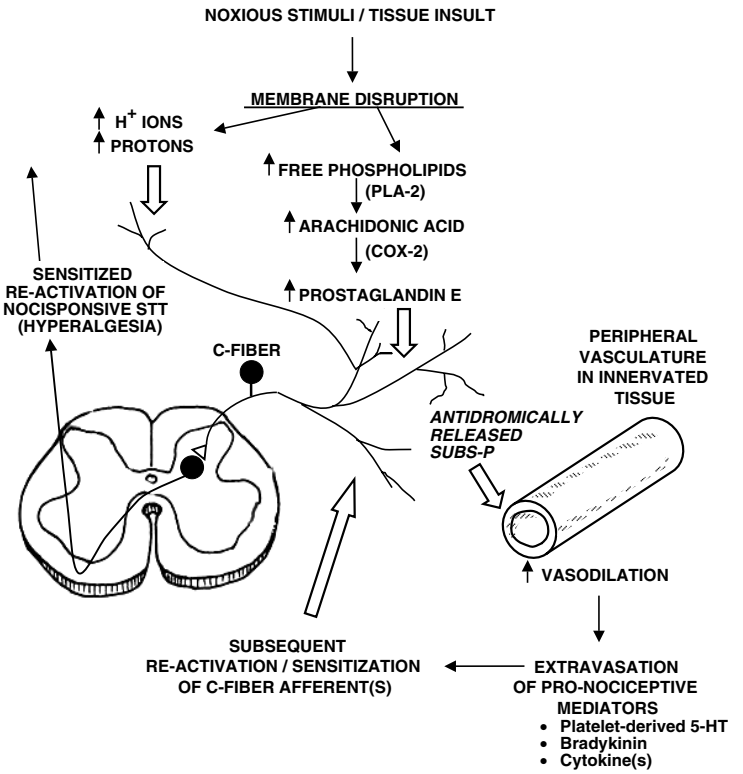

FIGURE 3.1 Schematic depiction of mechanisms subserving inflammatory pain and subsequent neurogenic inflammation. Although noxious stimuli (e.g., heat, high-intensity mechanical stress, and/or chemical irritants) can act directly at nonselective cationic channels on free nerve endings, such stimuli can also disrupt membrane integrity and evoke the formation of prostaglandin-E_2 (via initiation of the arachidonic acid cascade) and liberation of H^+ ion and protons. These substances induce depolarization of C-fibers, causing both an orthodromic and antidromic release of substance-P. Antidromically released substance-P acts as a vasodilatory agent, both directly and through nitric oxide–mediated mechanisms. Extravasation of blood-borne substances (e.g., 5-HT, bradykinin, cytokines) stimulate and/or sensitize C-fibers, perpetuating both nociception and inflammation. PLA-2: phospholipase-A2; COX-2: cyclo-oxygenase-2.

the vascular endothelium leading to an increase production of NO and ultimately vasodilatation. Taken together, the effects of histamine, mast cell–derived serotonin, substance-P, and CGRP produce potent peripheral vasodilatory effects that lead to extravasation of chemical mediators that both propagate the neurogenic inflammatory response and are directly pro-nocisponsive (Figure 3.1). These include vasoactive intestinal peptide (VIP), bradykinin, and platelet-derived serotonin (Gupta & Bhide, 1979; Handwerker, 1976). Of particular interest is the effect of rising concentrations of serotonin in extravascular tissue from mast cells and degranulated platelets. As peripheral serotonin concentrations rise, serotonin 5-HT_3 receptors on terminals of C-fiber primary afferents are engaged to produce a rapid Na^+ influx, depolarizing C-fibers and leading to continuity of this cycle (Giordano & Dyche, 1989; Sufka, Schomburg, & Giordano, 1992). Additionally, locally concentrated free serotonin appears to sensitize both 5-HT_3 and NK-1 receptors on C-fiber afferents, thereby increasing subsequent responsivity to serotonin and substance-P (Giordano & Gerstmann, 2004).

SECOND-ORDER AFFERENTS

The dorsal horn of the spinal cord is a critical site for the convergence and neural processing of nociceptive information from peripheral primary afferent fibers. A-delta and C-fibers form synaptic connections on wide dynamic range (WDR) and nociceptive-specific (NS) neurons within the spinal cord whose functional properties contribute to both spatial and temporal transformations of the afferent input. As depicted in Figure 3.2, the majority of these second-order neurons aggregate in the dorsal horn, project contralaterally, and ascend within the anterolateral quadrant(s) as the spinothalamic tract (STT) to sites within the brainstem, midbrain, and thalamus. The unique physiologic characteristics of WDR and NS neurons encode specific qualities of intensity, modality, and localization to the nociceptive signal that is transmitted to supraspinal targets.

Wide Dynamic Range Neurons

WDR neurons are localized with highest concentrations in laminae I, II, V, and VI, with greatest numbers found

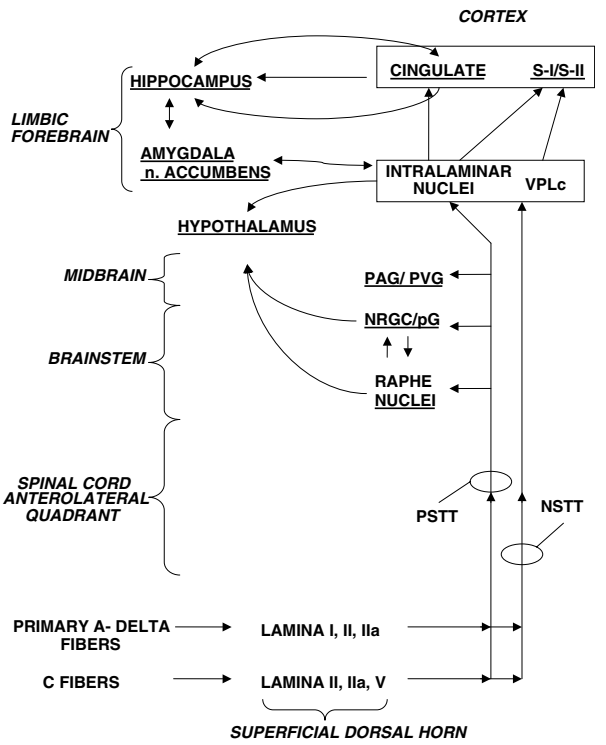

FIGURE 3.2 Diagrammatic depiction of afferent pathways subserving nociception. Primary afferent (A-delta and C) fibers synapse upon second-order neurons in the superficial laminae of the dorsal horn. These units decussate and ascend in the contralateral anterolateral column as the spinothalamic tract(s). The NSTT is a relatively direct pathway that projects to the VPLc nucleus of the thalamus. Thalamo-cortical projections from VPLc are predominantly to S-I, subserving stimulus discriminatory functions. The PSTT comprises the spinoreticular pathway, which projects to monoaminergic nuclei of the brainstem, and the spinotectal pathway that projects to the midbrain PAG. The PSTT projects to thalamic intralaminar, medial, and latero-dorsal nuclei. Connections among the brainstem, intralaminar nuclei, and hypothalamus mediate autonomic and neuroendocrine responses to nociceptive input. Projections from the intralaminar nuclei to the cingulate and from the cingulate bilaterally to S-II and the hippocampus are involved in associative and evaluative domains of pain processing. Refer to text for further description of afferent processing of pain sensation and cognition. NRGC: nucleus reticularis gigantocellularis; NRpG: nucleus reticularis paragigantocellularis; NSTT: neospinothalamic tract; PSTT: paleo-spinothalamic tract; PAG/PVG: periaqueductal/periventricular gray; S-I/S-II: somatosensory cortices I and II; VPLc: ventroposterior laterocaudal nucleus of the thalamus.

in the latter levels. Although WDR neurons receive input from low-threshold cutaneous mechanoreceptor afferents (A-beta type), they are also a site of convergence for both A-delta and C-fiber nociceptive afferents. WDR neurons that are driven by nociceptive input are hierarchically organized within the dorsal horn, with the majority of primary A-delta and C-fiber afferent input occurring in laminae V (Maixner, Dubner, Bushnell, Kenshalo, & Oliveras, 1986). The size and responsivity of WDR neuron receptive fields increases progressively from laminae I to V: WDR units in laminae I and II have smaller receptive fields that are sensitive to gentle mechanical stimuli; those of laminae V have larger, overlapping receptive fields with graded sensitivities containing small, discrete regions excited by non-nociceptive input and broad regions that are maximally sensitive to high-threshold nociceptive stimulation (Mayer, Price, & Becker, 1975).

WDR neurons are not individually sensitive to specific types of stimuli. Rather, individual WDR neurons, based on response properties within their receptive fields, function to discriminate stimulus intensity. Increases in stimulus intensity activate coexistent areas of receptive fields of numerous WDR neurons. This pattern of engagement would involve slight differences in temporal activation, with individual WDR responses becoming phase shifted. The activation of greater numbers of WDR neurons by high-intensity nociceptive stimuli would therefore result in both spatial and temporal summation of these responses (Hayes, Price, & Dubner, 1979).

Nociceptive-Specific Neurons

In contrast to the anatomical distribution of WDR neurons, NS neurons are found in highest concentrations in laminae I and II, with lesser numbers in laminae V (Dubner & Bennett, 1983). NS neurons receive excitatory input from A-delta fibers and polymodal C-fiber afferents. Generally, NS neurons have small, non-overlapping receptive fields with a well-defined, center-surround organization. The central region is maximally excited by high-intensity stimuli, while the outer region is differentially excited by frequency-based repetitive stimulation. This outer region may be inhibited by non-noxious input. The homogeneity of input from nocisponsive primary afferents and the small size and nociceptive selectivity of their receptive fields provide evidence that NS neurons appear to function in localization, and perhaps qualitative discrimination of particular types of noxious input (i.e., noxious pressure and heat; Willis, 1979).

Although painful sensations and responses can be evoked by WDR neuron excitation alone, both WDR and NS activity appears to be necessary for the constellation of spatial and temporal qualities ascribed to pain (Mayer et al., 1975). This becomes apparent when the convergent inputs of A-delta and C-fibers upon WDR and NS neurons are considered. The unique properties of the primary afferents and the second-order neurons essentially "assemble" the neurologic pain signal. For example, the sensation of first-pain as punctate, well localized, and temporally well defined is a function of the response characteristics of both rapidly conducting A-delta primary afferents and their excitation of WDR and NS neurons. In contrast, second-

pain, a more diffuse, long-lasting nociceptive sensation that follows the initial stimulus, is the result of the threshold, firing, and conduction properties of C-fibers sustained by local tissue damage and/or chemical change, as well as patterns of temporal and spatial summation of C-fiber inputs by WDR and NS neurons (Mayer et al., 1975; Price & Dubner, 1977). Both WDR and NS neurons are capable of after-responses that persist as a consequence of the number and frequency of nociceptive afferent volleys (Willis, 1979), factors that are related to nociceptive stimulus intensity and continuity.

The anatomic and physiologic properties of second-order afferents also subserve the phenomenon of referred pain. As previously discussed, primary afferent innervation of visceral and deep muscular structures is organized so that these fibers converge upon WDR and NS neurons that also receive input from primary nociceptive (and non-nociceptive) afferents from specific somato-cutaneous regions (Selzer & Spencer, 1969). The convergence of visceral and cutaneous afferents from a given somatotome upon second-order WDR and NS neurons underlies patterns of referred pain. Thus, sensory information from the viscera is often subjectively interpreted as afferent information from a cutaneous structure within the corresponding somatotome.

SPINOTHALAMIC TRACT(S)

The majority of WDR and NS neurons project contralaterally within the spinal cord and ascend within the anterolateral quadrant, forming the spinothalamic tract(s) (STT). A minority of fibers remain ipsilateral and ascend outside of the STT within the ventrolateral white matter to supraspinal sites that correspond to the contralateral anterolateral quadrant projections (Appelbaum et al., 1975). Anatomically, axons from second-order neurons in the superficial dorsal horn (laminae I and II) are segregated from those of deeper laminae (lamina V). This provides anatomical separation between the neospinothalamic (NSTT) and paleo-spinothalalmic (PSTT) tracts. While both the NSTT and PSTT may be considered "labeled-lines" for the transmission of pain signals, the differential localization of NS neurons to laminae I and II, in contrast to a greater abundance of WDR neurons in lamina V, subserves functional distinctions in the type of nociceptive information that is transmitted in these pathways (Giesler, Yezierski, Gerhart, & Willis, 1981).

The NSTT projects directly to the ventroposterior lateral (VPL) nuclei of the thalamus and is composed predominately of NS neurons from lamina I and II (Kenshalo et al., 1980). WDR neurons are in smaller numbers within these laminae, and they comprise only a minority of NSTT fibers. NS neurons receive almost completely homogeneous input from A-delta and high-threshold polymodal C-fiber afferents, and encode stimulus localization and modality. Therefore, the main role of the NSTT appears to involve transmission of these signal qualities to the thalamus (Price, Hayes, Ruda, & Dubner, 1978).

The PSTT is composed of axons from second-order neurons arising in lamina IIa and V of the spinal cord. WDR neurons constitute the majority of cells from this lamina, with only a smaller number of NS neurons contributing to the axonal pool of the PSTT (Appelbaum, Beall, Foreman, & Willis, 1975). Heterogeneous input to lamina V WDR neurons from both nocisponsive and non-nocisponsive primary afferents contributes to the transmission of some non-nociceptive signals along the PSTT. WDR neurons of lamina V also send axons ipsilaterally to ascend within the dorsal column medial lemniscal tract (Boivie, 1980; refer to Figure 3.7 later in the chapter). This latter pathway is responsible for the transmission of light touch, vibration, and other low-threshold stimuli. Given the role of lamina V WDR neurons to encode noxious stimulus intensities, the co-localized transmission of both nociceptive and non-nociceptive afferent information within the PSTT appears to serve a stimulus discriminatory function (Price & Dubner, 1977). This is further supported by the properties of PSTT WDR neurons to accumulate strong after-responses following nociceptive input. Such after-responses override weaker impulses evoked by non-nociceptive afferent stimuli and produce temporally summated volleys within the PSTT. These events are correlated to, and appear to subserve, the qualities and subjective characteristics of second-pain.

Unlike the NSTT, the PSTT is not a direct thalamic pathway. PSTT fibers project to several supraspinal sites that are involved in (nociceptive) sensory processing and that exert pain modulatory control. The PSTT is divided into spinoreticular, spinotectal, and ultimately spinothalamic projections. Spinoreticular pathways project to areas of the brainstem reticular formation. These include the raphe nuclei of the rostro-ventral medulla and the nuclei reticularis gigantocellularis (NRGC) and paragigantocellularis (NRpG) of the caudal pons (Basbaum & Fields, 1978).

Spinotectal projections terminate within the tectum and periaqueductal gray (PAG) region of the midbrain (Beitz, 1982). The spinoreticular and spinotectal circuits function in centrifugal pain control, and ascending neurons from these sites serve as relays between spinal pathways and higher centers that mediate the cognitive and affective dimensions of pain. Of particular note are defined tracts from the reticular formation to several regions of the limbic forebrain, and a reciprocal neuraxis involving the PAG, periventricular gray region (PVG), hypothalamus, and brainstem (Guilbaud, Bernard, & Besson, 1994). Thalamic projections of the PSTT differ from those of the NSTT; PSTT fibers project diffusely to the thalamus, with terminations at the intralaminar nuclei (Ralston, 1984), the centro-median parafascicular complex, and the latero-

dorsal and the mediodorsal nuclei (Mancia et al., 1987). (Refer to Figure 3.2 and Figure 3.6, later in the chapter).

BRAINSTEM NOCICEPTIVE NEURAXES

As depicted in Figure 3.2, PSTT neurons differentially project to specific sites within the brainstem. Some stimulus-specificity exists in PSTT activation of raphe and/or NRGC/NRpG neurons. Input from NS and/or WDR units excited by thermosponsive primary afferents appears to evoke greater excitation of raphe circuitry, while WDR and NS neurons driven by mechanosponsive input elicit somewhat greater activation of the NRGC/NRpG (Giordano & Barr, 1988; Kuraishi, Hirota, Satoh, & Takagi, 1985). Both circuits are apparently engaged by chemosponsive or polymodal C-fiber afferent activation of WDR or NS neurons. It has been suggested that such stimulus specificity is maintained at the midbrain level and may be involved in the differential activation of PAG-raphe or PAG-NRGC centrifugal analgesic systems (as described further in this chapter). Whether these distinctions actually subserve modality specificity or reflect differential activation based upon stimulus intensity remains speculative (Craig, 2003). Of note is the existence of specific cells that respond differentially to PSTT input. One group of brainstem cells, "on" cells, depolarizes in response to PSTT input driven by noxious stimulation. These cells appear to augment transmission of pain via facilitation of spinal afferent output. Another group, the "off" cells, hyperpolarizes upon PSTT activation and reduces nociceptive transmission along spinally originating PSTT pathways (Heinricher, Morgan, Tortorici, & Fields, 1994). The net actions of these cells appears to augment or suppress the pain signal and may play a role in frequency-dependent or intensity-dependent encoding for given types of noxious stimuli. Additionally, PSTT excitation of "on" cells activates hypothalamic, cingulate, insular, and septal systems involved in pain-related aversive and arousal responses (Kalivas & Barnes, 1993).

MIDBRAIN NOCICEPTIVE MECHANISMS

There is anatomical evidence to demonstrate that PSTT fibers project to the midbrain PAG both directly and through interneuronal pathways from the reticular formation. The PAG is somatotopically and perhaps stimulus-specifically organized. Somatotopic organization corresponds to the ascending hierarchy of PSTT afferents from progressively rostral somatotomes: the posterior PAG receives input from PSTT fibers of the caudal spinal cord while the anterior PAG receives PSTT projections from more rostral regions.

Stimulus-specific organization of the PAG seems to be a function of characteristics of populations of PSTT WDR or NS neurons that are selectively excited by mechanical, thermal, or polymodal primary afferents. While it is difficult to determine whether absolute stimulus-specific organization exists, it is likely that regions of the PAG respond to somatotopic innervation of the periphery and would thus be maximally excited by input from a particular modality or intensity.

Although the function of the PAG in centrifugal pain control is clear, the role of the PAG in afferent processing of the nociceptive signal remains more enigmatic. Pathways exist between the PAG and hypothalamus and several structures of the forebrain, including the septal nuclei and amygdala (see Figure 3.2). Stimulation of the PAG or fibers within this pathway elicits an array of arousal and behavioral activation responses that have distinct aversive or frightening emotional content (Cailliet, 1993). Such responses have significant conditioning potential, primarily by activating "upstream" neuraxes involving the mammillo-thalamic tract, anterior thalamic nucleus, and subsequent involvement of the cingulatum and ultimately the hippocampus (Ploghaus et al., 1999). It is not completely understood whether the PAG can evoke these responses alone or acts in concert with the reticular system, cingulate gyrus, insula, and frontal cortex.

THE THALAMUS

The NSTT and PSTT project to different regions within the thalamus. NSTT neurons project to a caudal area of the ventroposterior lateral nucleus (VPLc). Nociceptive inputs from the NSTT are arranged in columnar zones that are somatotopically organized. Thalamic neurons within these zones retain many response characteristics of WDR and NS units. Thalamic wide-range neurons have center-surround receptive fields with distinct, small areas sensitive to low-threshold excitation and a broad area that is excited by high-threshold nociceptive input. Thalamic NS neurons, like their spinothalamic counterparts, have smaller receptive fields that are excited by high-intensity mechanical or thermal input (see Albe-Fessard, Condes-Lara, Sanderson, & Levante, 1983, for review).

Both WDR and NS neurons of the VPLc summate responses as a function of stimulus frequency and intensity (Gerhart, Yezierski, Fang, & Willis, 1983). Slow temporal and spatial summation is accompanied by a prolonged firing phase that exceeds the actual noxious stimulus and primary and secondary afferent discharges. It is probable the temporal aspects of pain *perception* reflect serial processing of afferent information from the peripheral to the thalamic levels, with progressive extension of after-discharges along the pathway (and perhaps subsequently to cortical sites; see below). It is temping to speculate that such effects may "match" sensory, arousal, and environmental cues in establishing conditioned responses to circumstances surrounding painful stimuli.

The PSTT projects to the intralaminar thalamic nuclei, the dorsal nucleus centralis lateralis, and medialis dorsalis (see Figure 3.6). Most of the neurons within these thalamic areas are of the wide range type, sensitive to both nociceptive and non-nociceptive activation and with extensive overlapping input from cutaneous and visceral innervation (Curry, 1972; Dong, Ryu, & Wagman, 1978). These units do not have the adaptive properties of neurons of the VPLc; intralaminar neurons summate responses, but response patterns do not reflect direct spatial or temporal transformation of increments in stimulus frequency or intensity (Guilbaud, Caille, Besson, & Benelli, 1977). Unlike neurons of the VPLc, intralaminar neurons appear to be arranged in a "looser" somatotopic pattern and project diffusely to S-II, as well as the anterior and posterior cingulate gyrus regions of the cortex, and a reciprocal pathway to the amygdala has been described (Burton & Jones, 1976; see Figure 3.6). The response patterns of individual intralaminar neurons, together with their anatomic distribution to cortical and amygdalar projections, suggest that PSTT-intralaminar thalamic pathways act to engage these systems in behavioral activation, aversive-emotional, and nocifensive responses.

CORTICAL PROJECTIONS

Neurons from the NSTT project to the VPLc of the thalamus; thalamo-cortical fibers from this region terminate in S-I (and to a lesser extent S-II areas) of the somatosensory cortex. Thalamo-cortical fibers from the intralaminar, lateral, and medial dorsal nuclei, driven by the PSTT, project more diffusely, with a smaller number terminating in S-I, while the majority project bilaterally to S-II (Figure 3.6) (Albe-Fessard, 1983). The somatotopic organization of the thalamus is preserved in S-I and to some extent S-II; nociceptive input contributes to distinct regions of somatosensory activation within the cortex (i.e., the sensory "homunculus," the spatial representation of bodily structures across the cortical sensory field).

Somatosensory cortical regions are arranged in vertical dominance columns in which hierarchical processing of afferent input occurs. Only a small percentage of nociceptive input constitutes each given cortical column (Kaas, 1993). Nociceptive thalamo-cortical input is differentially distributed within each column. Superficial cortical layers receive thalamic input from non-nociceptive pathways, while WDR- and NS-activated inputs are concentrated throughout the deeper cortical layers (Kaas, 1993). Thus, for any given bodily region represented in a cortical column there is an array of non-noxious information (relayed through medial lemniscal tracts) and nociceptive information (relayed through the STTs) that creates the "depiction" of sensations that determine the subjective sensory experience (Ralston & Ralston, 1994). The integrity of the pain signal and unique qualities of its duration and intensity are a function of additive transformation of afferent volleys from primary nociceptors through multiple processing ultimately terminating in cortical neurons. The slow adaptation, long after-discharges, and highly modifiable spatial and temporal summation of cortical S-I and S-II neurons contribute to the subjective, temporospatial, discriminative dimensions of pain sensation (Mayer et al., 1975).

As depicted in Figure 3.6, there are projections from S-II to the anterior cingulate via the insula and to the posterior cingulate through a direct, reciprocal pathway (Vogt, Finch, & Olson, 1992). The role of the anterior cingulum in pain sensation and pain-related behavioral responses is well documented (Devinsky, Morrell, & Vogt, 1995), such that the superior, anterior cingulate is commonly referred to as the nociceptive cingulate area (NCA). Anterior cingulate–hypothalamic projections mediate components of neuroendocrine and autonomic responses to pain sensation (Bromm & Desmedt, 1995). The involvement of the hypothalamus is initiative in engaging multiple, non-opioid, hormonally mediated forms of pain modulation (Bodnar, Kelly, Steiner, & Glusman, 1978; Lewis, Cannon, Stapleton, & Liebeskind, 1980; Lewis, Chudler, Cannon, & Liebeskind, 1981; see Watkins & Mayer, 1982, for review). Diagrammatic depiction of putative hormonal mechanisms of pain modulation is shown in Figure 3.3. Additionally, Losel et al. (2003) suggest that the nongenomic action of steroid hormones on neurotransmitter receptors may be a mechanism that alters hypothalamic function to affect the activity of other supratentorial structures. This may subserve distinctions in pain presentation and responses that occur in various neuroendocrine (and perhaps psychiatric) states (e.g., premenstrual disorder, depression; Kalin & Dawson, 1986).

Efferent connections that project from the anterior cingulate to the caudate, putamen, and nucleus accumbens mediate motor responses to pain (Kalivas & Barnes, 1993) and may be involved in repetitive and/or stereotypical behaviors observed in (chronic) pain states. Afferent pathways from the hippocampus via the subicular complex and entorrhinal cortex (together with efferent input from the posterior cingulum) mediate cognitive and memory-based aspects of pain (Vogt et al., 1992).

Afferent and efferent connections exist between the posterior cingulate, the lateral dorsal thalamic nucleus, and the amygdala. As well, the posterior cingulum receives efferent input from the inferior temporal, mediotemporal, and inferior parietal cortices. These pathways appear to subserve the higher cognitive-emotional dimension of pain sensation (Bromm, 2001). The anatomy of these pathways well illustrates that the subjective experience of pain may vary according to myriad combinations of extero- and, perhaps, interoceptive circumstances for each individual.

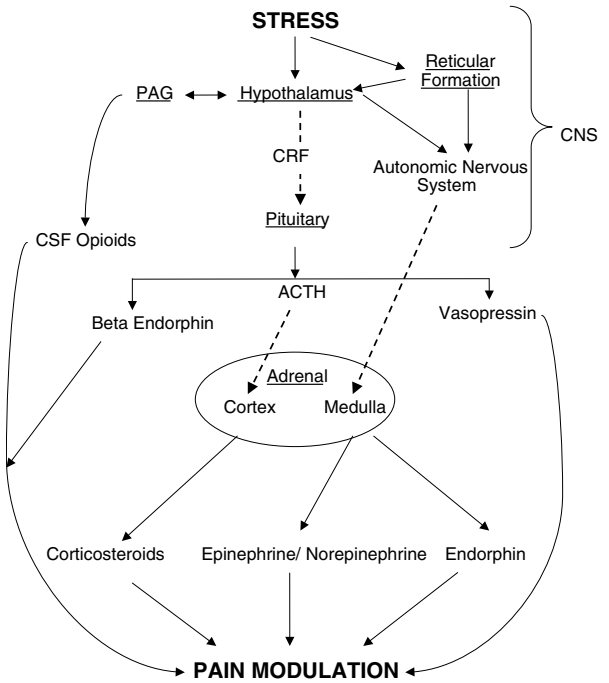

FIGURE 3.3 Representation of certain stress-induced analgesic mechanisms. Exogenous stress can engage the reticular system and hypothalamus to heighten the activity of the autonomic nervous system. As well, hypothalamic involvement in the stress response can engage the hypothalamic–pituitary–adrenal axis. Together, these mechanisms synergistically lead to a systemic increase in glucocorticoid and epinephrine/norepinephrine level(s). The pituitary, adrenal medulla, and midbrain periaqueductal grey region (PAG) release opioids, which act on populations of opioid receptors in the central nervous system (CNS) and periphery. These opioid and non-opioid pain modulatory systems can be engaged together or distinctly, dependent upon the type, intensity, and duration of the provocative stress(or). It is interesting to note that prolonged or acute disturbance of this system may be contributory to altered patterns of pain modulation and an alteration in pain sensitivity (see text for details). ACTH: adrenocorticotropic hormone; CRF: corticotropin releasing factor; CSF: cerebrospinal fluid.

The assemblage of sensory input together with memory, emotional response(s), and cognitive state creates conscious experience of pain that contributes to its perception. However, there is a considerable philosophical debate whether pain can be completely defined as a perception (Wikler, 1979). The complexity and strongly subjective nature of pain strengthen the hypothesis that the hierarchical neural processing that expands the sensory signal into an aggregate of combined awareness of internal state, circumstances surrounding the event, and memory and emotional components that impart contextual "meaning" to the experience qualifies pain as a discrete event of consciousness. This becomes significant in light of the involvement of nonsensory central nervous system structures in nociceptive processing. Thus, it may be that the experience of pain represents both a conscious interpretation of the sensory experience caused by activation of neural pathways and an epiphenomena of higher-order consciousness resulting from the change in brain state.

PAIN MODULATING SYSTEMS

Intraspinal Pain Modulation

Pain modulation can occur through the activation of local circuits within the spinal dorsal horn. Interneurons that receive collateral projections from primary A-delta and C-fibers are found in laminae I, II, and V. These interneurons form reciprocal synapses upon primary afferent(s) and, in certain cases, second-order WDR and NS neurons. The majority of such interneuronal connections are found within a given horizontal section of the spinal cord, although Willis and Coggeshall (1991) have shown that some interneurons have terminal fields that are trans-segmental. Pharmacologic and electrophysiologic evidence has demonstrated that these interneurons are inhibitory; many produce and release the inhibitory transmitter gamma amino butyric acid (GABA), as well as the opioid peptides dynorphin and leu- and/or met-enkephalin (Fields, Heinricher, & Mason, 1991). Acting at postsynaptic $GABA_B$ receptors on primary and second-order afferents, GABA induces a chloride ion flux to produce hyperpolarization. Dynorphin binds post-synaptically with kappa-opioid receptors (Corbett et al., 1982). There is some heterogeneity in kappa receptor populations; however, most found in the spinal cord are negatively coupled to N-type calcium ionic channels. Dynorphin binding at these kappa sites on primary or second-order afferents closes the calcium channel, thereby producing a hyperpolarizing inhibitory current, essentially "tuning down" or "shutting off" the transmission of nociceptive information along this neuraxis (Han & Xie, 1982). In contrast, leu- and met-enkephalin act at delta, and to a lesser extent mu opioid, receptors to engage G protein–mediated kinases to phosphorylate and open K^+ channels, enhancing K^+ influx and producing graded hyperpolarization (Duggan & North, 1983). Recently, endogenous cannabinoids, including anandamide and 2-arachadoylglycerol, have been shown to exert spinal anti-nociceptive effects by acting at type-1 cannabinoid (CB1) receptors in the dorsal root ganglion and superficial spinal cord (Hohmann & Herkenham, 1999; Pertwee, 2001; Rice, 2001). Cannabinoid CB1 receptors are also expressed in cortical and subcortical brain regions where anandamide (and exogenous *cannabis sativa* and 9-tetrahydrocannabinol) exerts pain modulatory effects, as well (Rice, 2001).

This local circuit inhibition modulates firing of primary A-delta and C-fibers afferents; a particular frequency pattern of primary afferent firing may excite populations of local interneurons to exert recurrent inhibition. Simi-

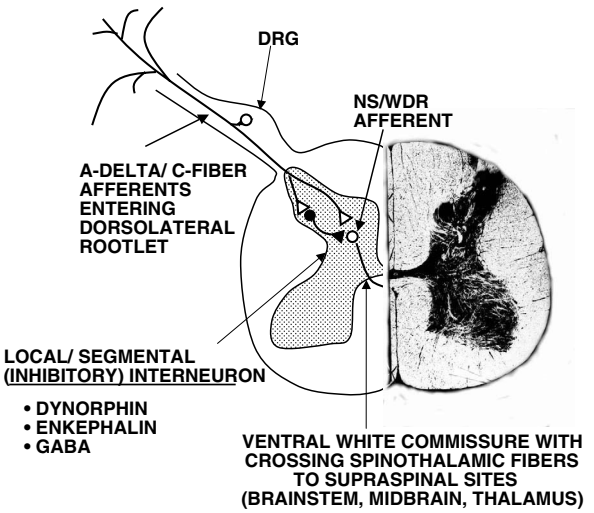

FIGURE 3.4 Local/segmental inhibition producing pain modulation within the dorsal horn of the spinal cord. A-delta and C-fibers synapse upon interneurons that release dynorphin, enkephalin, or gamma amino butyric acid (GABA) to postsynaptically suppress/modulate the activity of second-order nociceptive specific neurons (NS) and wide dynamic range neurons (WDR) afferents. As well, the endogenous cannabinoid anandamide may act at specific cannabinoid (CB1) receptors to inhibit nociceptive transmission within the dorsal root ganglion and superficial dorsal horn (not illustrated). The level of local spinal inhibition may be dependent on the spatial and frequency intensity of incoming nociceptive afferent volleys. Increased primary afferent activity is capable of overcoming local inhibition. As well, these spinal inhibitory interneurons can be driven by descending bulbospinal activation. Complete description of these mechanisms appears in text. (*Note*: Not to scale.)

larly, primary afferent activity may evoke local spinal inhibition of certain populations of second-order WDR and NS neurons to limit the "gain" of mild nociceptive input (Figure 3.4).

Bulbospinal Pain Modulation

Projections from the (P)STT synapse upon neurons in the rostro-ventral medulla and ventromedial pons (Basbaum & Fields, 1978). In the rostro-ventral medulla, the projection fields include neurons of the raphe nuclei, including the nuclei raphe alatus, dorsalis, and raphe lateralis. These sites are combined when referring to the nucleus raphe magnus (NRM). In the caudal pons, the PSTT projects specifically to the subcerulear nuclear group, consisting of the nucleus reticularis gigantocellularis, nucleus reticularis paragigantocellularis, and the nucleus paragigantocellularis lateralis (NpGL). These sites are often referred to as the reticular magnocellular nuclei (RMC). The NRM and RMC also receive efferent input from the PAG as well as this afferent input from the PSTT. Both neuraxes are capable, either alone or in concert, of exciting NRM or RMC neurons to elicit centrifugal or bulbospinal pain modulation, respectively (see Fields & Basbaum, 1999, for review). Mixed inhibitory and excitatory connections between these groups of brainstem nuclei exist (Stamford, 1995); this inter-brainstem inhibition appears to determine the relative participation of NRM, RMC, or both groups in bulbospinal analgesia. Moderate levels of activity within the RMC inhibit the NRM. In contrast, higher levels of RMC activity excite certain NRM neurons. The NRM maintains tonic modulation of the RMS, and phasic, "burst" activity of NRM cells can engage activity within the RMC (Fields, 2000).

As previously discussed, two distinct subtypes of neurons exist throughout the rostral medulla. These are referred to as "on" or "off" cells, with reference to their electrophysiologic response patterns to noxious afferent input. "On" cells become active with noxious afferent stimulation and appear to potentiate afferent transmission. "Off" cells become quiescent in response to afferent noxious input, and the lack of facilitatory input to the spinal cord decreases the frequency and duration of nociceptive transmission. "On" cells suppress "off" cells; thus, once sensitized, "on" cells can potentiate nociception by driving volleys of transmission within the spinal cord. Opioid projections from the PAG inhibit the activity of "on" cells, and thereby eliminate their capacity for facilitating the pain signal and also disinhibit "off" cells to exert an analgesic effect (Fields & Basbaum, 1999; Heinricher et al., 1994.)

Axonal projections from the NRM and RMC descend in the dorsolateral funiculi (DLF) of the spinal cord and terminate in dense synaptic fields within laminae I, II, and V of the dorsal horn (Basbaum & Fields, 1979). Synaptic connections within these layers involve polysynaptic circuits of multiple spinal interneurons, as well as monosynaptic contacts with WDR, NS, and primary afferent neurons. Spinal interneurons receiving efferent projections from the brainstem synapse on WDR and NS second-order neurons as well as the terminals of primary afferent fibers. As previously described, these interneurons are neurochemically heterogeneous, releasing the inhibitory transmitters GABA, enkephalin, dynorphin, and/or anandamide. These interneuronal contacts provide selective, multifocal inhibition of specific groups of nociceptive afferents.

Synaptic connections between bulbospinal and WDR, NS, and perhaps primary afferent neurons exist in laminae I, II, and V (Fields et al., 1991). A single fiber from the brainstem may synapse on several second-order afferents within a given lamina. The differential projection of NRM or RMC terminals onto discrete populations of mechanosponsive, thermosponsive, or polymodally driven WDR and NS neurons in laminae I, II, and V further suggests that some stimulus or modality specificity may exist in the analgesic axis that originates from these brainstem nuclei (Abbott & Melzack, 1982; Giordano & Barr, 1988; Kuraishi, Harada, Aratani, Satoh, & Takagi, 1983; Kuraishi et al., 1985).

Midbrain Pain Modulation

There is considerable evidence to show that the midbrain PAG is a principal site for endogenous pain control. Efferent projections from the cingulate gyrus, limbic forebrain structures, and hypothalamus are capable of exciting opioid (i.e., endorphinergic, enkephalinergic, and orphaninergic) neurons of the PAG, as do inputs from the PSTT (Fields & Basbaum, 1999). The PAG exerts pain modulation by centrifugal inhibition of the spinal second-order afferents that comprise the PSTT and NSTT. This effect primarily involves disinhibition of bulbospinal projections from the NRM and NRGC/NRpG (Fields, Bry, & Hentall, 1983). Defined pathways from the PAG to the raphe nuclei and NRGC/NRpG are activated by high-threshold, high-frequency afferent volleys from the PSTT. Mechanical, thermal, or polymodal nocisponsive units of the PSTT appear to differentially stimulate discrete areas of the PAG to activate the raphe nuclei, NRGC/NRpG, or both (Fields et al., 1983; Fields & Basbaum, 1999). It is not fully understood whether selective PAG engagement of raphespinal or NRGC/NRpG spinal neuraxes is dependent on the modality, frequency, or intensity of the evoking afferent input (Abbott & Melzack, 1982; Giordano & Barr, 1988; Kuraishi et al., 1985).

The former system involves a release of opioids from the PAG that enhances the output of serotonergic cells of the raphe nuclei, thereby causing an increased turnover and release of serotonin in pathways that descend in the dorsal lateral funiculi (Fields & Anderson, 1978). These serotonergic fibers synapse heterogeneously in lamina I, II, and V, where serotonin may postsynaptically bind to heterogeneous populations of serotonin (5-HT_1, 5-HT_2) receptors on processes of primary and/or second-order nociceptive neurons (LeBars, 1988, see also Fields & Basbaum, 1999, for review). As well, serotonin may bind to postsynpatic 5-HT_3 receptors on an interneuron pool in several laminae of the dorsal horn to evoke the release of the inhibitory transmitters GABA, dynorphin, and enkephalin to produce graded inhibition of second-order pain transmitting afferents (Giordano, 1991). PAG-NRGC connections involve a release of opioids from the periaqueductal gray that suppress GABAergic interneurons, thereby disinhibiting noradrenergic neurons of the reticular formation (whose axons similarly descend in the dorsal lateral funiculi) to evoke a release of norepinephrine in lamina II and V. Norepinephrine binds to postsynaptic alpha_2 receptors on primary (and perhaps second-order) neurons to produce a graded hyperpolarizing inhibitory current, thereby "toning down" these neurons and producing a reductive modulation of volleys from nociceptive primary and second-order afferents (Dostrovsky, Shah, & Gray, 1983; Dubuisson & Wall, 1980).

The described connections between the PAG and brainstem are polysynaptic, involving pools of both excitatory glutaminergic and inhibitory GABAergic interneuronal relays. Tonic glutaminergic excitation of the brainstem produces low-level modulation of STT volleys and appears to have a "band-pass filtering" effect upon the nature and extent of low-level noxious sensory input that is transmitted to higher centers (Behbehani & Fields, 1979; Fields & Basbaum, 1999). In contrast, spatially or temporally summated high-frequency volleys from PSTT cells activate opioid systems of the PAG that suppress the tonic activity of inhibitory GABAergic interneurons that terminate upon descending neurons of the RMC and/or NRM (Dostrovsky et al., 1983). This suppression of tonic inhibition releases (i.e., disinhibits) the brainstem, thereby facilitating descending inhibition of nociceptive afferent transmission within the spinal cord. Such "volume control" is a function of the nature of the afferent nociceptive stimulus, the extent of PAG activation of PSTT (and perhaps cortical, hypothalamic, and mesolimbic) neurons, and the relative degree of excitation or inhibition of specific neural circuits to the brainstem. Thus, the PAG can discriminably recruit (or suppress) bulbospinal substrates whose net output determines the extent and properties of centrifugal pain modulation (Figure 3.5). These subcortical pain modulatory systems are summarized in Table 3.3.

Cortical Inhibitory Processing

The pathways through which cortical pain modulation occurs are presented in Figure 3.6. Neurons of the sensory cortex are capable of inhibitory control over the thalamocortical units of STT origin that project to them (although cortico-thalamic inhibition can also occur over neurons of the medial lemniscal tract that are non-nocisponsive). The extent of inhibition appears to vary with frequency and intensity of thalamo-cortical input. For nociceptive input that is both rapidly temporally and spatially summating, there is a greater level of inhibition (Guilbaud et al., 1994). Sensory cortical inhibition involves "normalization" or "stabilization" of afferent volleys. This compensates for differences in response characteristics between thalamic and cortical neurons and ultimately enhances the input–response function of thalamically driven, nociceptive cortical inputs. In this way, a more direct transformation of the incoming sensory signal is generated without oversummation. Cortical neurons can also excite both thalamocortical fibers and STT units directly. This inhibition and excitation serves a modulatory role over afferent information that affects cortical circuitry. Thus, cortical neurons can discriminately amplify or reduce the extent of nociceptive input (Sawamoto et al., 2000). Such modifications strengthen the signal-to-noise ratio of particular afferent volleys and facilitate discrimination of sensory input. This alternate excitation/inhibition may also subserve changes in the nociceptive sensorium as a consequence of levels of cortical activity (e.g., sleep, hypnosis, biofeedback), and

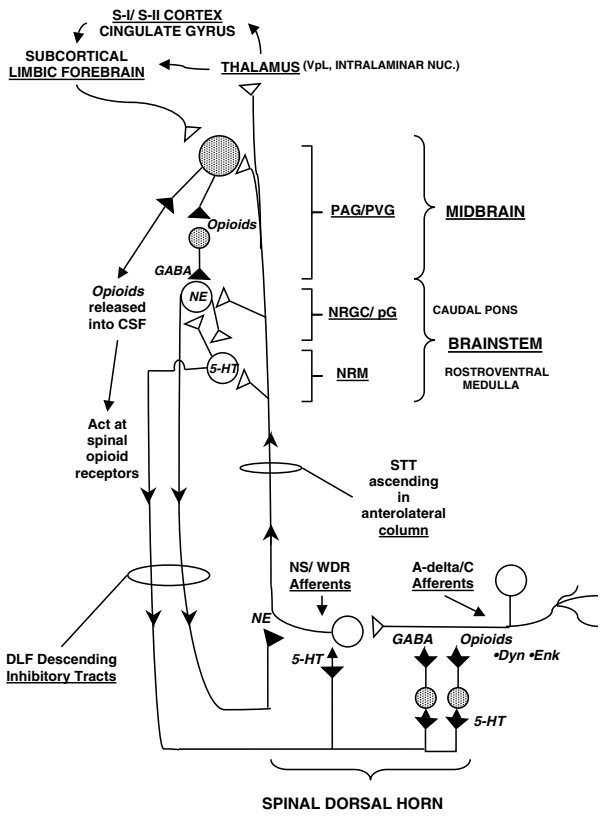

FIGURE 3.5 Representation of pathways involved in bulbospinal and centrifugal analgesia. Afferent volleys from the STT can activate 5-HT and/or NE systems of the brainstem and cause the release of these monoamines within the dorsal horn. Postsynaptically, 5-HT can directly inhibit the activity of nociceptive afferents and may act by stimulating inhibitory interneurons within the superficial cord to (indirectly) suppress nociceptive afferent output. NE acts directly to inhibit the firing of nociceptive afferents. Both 5-HT and NE systems can be engaged by the release of opioids from the PAG (through suppression of GABAergic inhibition of bulbospinal output). Opioids are also released into the cerebral spinal fluid and act at spinal opioid receptors to produce antinociception. Descending influences from the limbic forebrain can also stimulate the PAG. A complete description of brainstem and midbrain pain modulatory systems is provided in the text. Excitatory synapses are depicted by open endings/icons. Inhibitory synapses/neurons are depicted by shaded icons. CB1: cannabinoid-1 receptor; CSF: cerebrospinal fluid; Dyn: dynorphin; DLF: dorsolateral funiculus; Enk: enkephalin; GABA: gamma amino butyric acid; 5-HT: serotonin; NE: norepinephrine; NRM: nucleus raphe magnus; NRGC/pG: nucleus reticularis gigantocellularis/para-gigantocellularis; NS: nociceptive specific neurons; NUC: nucleus; PAG/PVG: periaqueductal/periventricular gray; STT: spinothalamic tract; VpL: ventroposterior lateral nucleus of the thalamus; WDR: wide dynamic range neurons.

may be contributory to the elicitation of pain by cognitive expectation or anticipation (Fields, 2000).

It is of interest to note that changes in higher-order consciousness (i.e., cognitive changes) can alter the appreciation, extent, or contextual "value" of sensory phenomena. While the pain-modulatory role of acute sympathetic arousal has long been known (Pribram & McGuinness, 1975), more recent studies have revealed that events that engage cortical and limbic areas to produce alterations of first- and second-order consciousness may have significant pain suppressive effects as well (Hugdahl, 1996; Lou et al., 1999). The long-held "placebo response" is better described as a patient-centered response, in which the participation in some event (e.g., relaxation, types of patient–clinician interaction, meditation, prayer) induces neurochemical change(s) in reticular and mesolimbic/cortical areas (d'Aquili & Newberg, 1993; Levine, Gordon, & Fields, 1978; Saver & Rabin, 1997). Such changes can affect neuraxes to alter nociceptive processing, as well as other physiological events (e.g., immune function, autonomic tone; Amanzio & Benedetti, 1999; Petrovic, Kalso, Petersson, & Ingvar, 2002). This concomitantly activates higher-order consciousness to interpret the interoceptive state (and its effects) and circumstantially "frame" this interpretation relative to environmental, behavioral, and cognitive events that are temporally antecedent and/or coincident. The pairing of these phenomena can have profound conditioning effects. In this way, such inductive events (and awareness of their biological effects) assume both salutogenic value to the patient and "noetic" value that is rich in subjective interpretation of the event itself (Giordano & Engebretson, 2004; Newberg, Tashner, both in this volume).

Dorsal Columnar Pain Modulation

Low-threshold mechanosponsive dorsal column afferents, driven by A-beta mechanoreceptors, also exert modulatory influence over WDR and NS neurons that make up the STT. Interneurons in laminae IIa, III, and IV with synaptic fields linking the dorsal columns and STT evoke brief inhibitory postsynaptic potentials (IPSPs) in STT cells following dorsal column excitation by low intensity mechanical stimuli (Lee, Chung, & Willis, 1985). These IPSPs persist after termination of the low-intensity stimulus and cause a short-lasting, rightward shift in both the time- and threshold-based stimulus response function of the affected WDR and NS cells within the STT. In other words, low-level mechanical stimulation of the dorsal column tract is capable of "overriding" or "de-sensitizing" WDR and NS activity within the STT. As well, the dorsal column projects to the nuclei cuneatus and gracilis of the medulla, and as the medial lemniscal pathway, decussates to terminate in the VPL of the thalamus (Willis, 1985; Figure 3.7).

Continuous, low-level phasic or high-frequency repetitive stimulation of the medical lemniscal pathway can produce selective activity within the VPL that can suppress STT-induced input(s) and reduce thalamo-cortical transmission of nociceptive information (Campbell, 1982; Sweet & Wepsic, 1968; Willis, 1985). These phenomena

TABLE 3.3
Physiologic and Pharmacologic Properties of Selected Pain Modulating Systems

System	Anatomy	Chemistry	Physiology/Properties
Intraspinal	Interneurons, laminae II, V	Opioid	Acts upon κ-receptors
Segmental	Synaptic contact with recurrent processes of A-delta fibers	Dynorphin	Acts upon δ (and perhaps μ) receptors
		Leu/met-enkephalin	Acts upon $GABA_B$ receptors: potentiates chloride flux hyperpolarization
		GABA	
		Anandamide	Acts upon CB1 receptors
Bulbospinal	Descending fibers from NRM of medulla	5-HT	Acts on postsynaptic $5\text{-}HT_{1b}$ receptors on (presynaptic) primary afferents and (postsynaptic) second-order neurons
NRM	Fibers descend via DLF		Hyperpolarizing; inhibitory
	Mono- and polysynaptic contacts with primary and second-order units of dorsal horn		Acts on postsynaptic $5\text{-}HT_3$ receptors on GABA and opioid spinal interneurons; excitatory; evokes release of inhibitory modulators
	Synapse upon interneurons		
RMC	Descending fibers from NRCG/NRpG of pons	NE	Acts on postsynaptic α_2 receptors on (presynaptic) afferents and second-order afferents
	Fibers descend via DLF		Graded hyperpolarization, inhibitory
	Mono- and polysynaptic contacts with primary and second-order afferents of dorsal horn		
Midbrain	Multilevel connections: inputs from	Opioid	Acts on μ and δ sites
PAG	hypothalamus, limbic system, cortex	Leu/met-enkephalin	Acts on μ-receptor subtypes
PVG	Activated by STT	Endorphin	Some direct opioid release into CSF
	Polysynaptic contact with brainstem to disinhibit centrifugal modulatory systems	Orphanin	Graded slow hyperpolarization; inhibitory

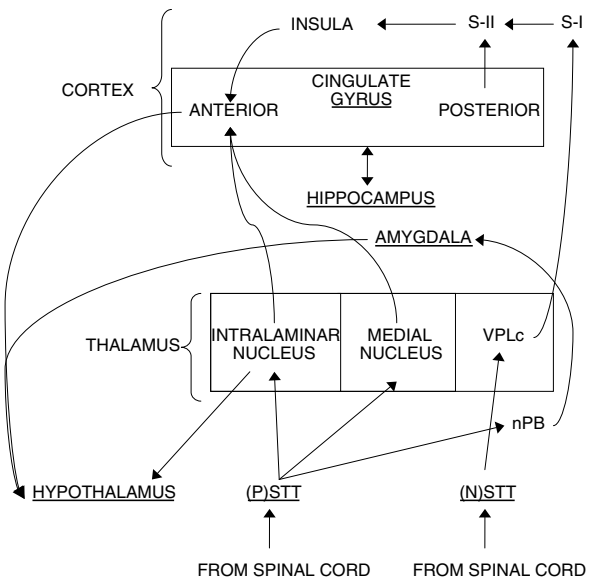

FIGURE 3.6 Schematic diagram of projections from the spinothalamic tract and thalamus to higher centers mediating the emotional, executive, and cognitive dimensions of pain processing. As described in the text, the PSTT diffusely projects to the intralaminar and medial nuclei of the thalamus. Projections from these nuclei to the anterior cingulum subserve emotive aspects of pain. The anterior cingulum also receives input from the posterior cingulum and S-II associative cortex, both via the insula. Reciprocal connections exist between the cingulum and hippocampus. The integrative role of the cingulate gyrus becomes evident in light of these pathways. The PSTT engages the amygdala via the parabrachial nucleus. Hypothalamic activation by the PSTT occurs both through this pathway and by a PSTT-intralaminar nuclei neuraxis. This neural circuit is involved in activational and arousal dimensions of pain. The NSTT projects to the VPLc thalamic nucleus, from where thalamo-cortical pathways project to both S-I and S-II. This pathway is primarily involved with sensory discriminative aspects of the pain signal. However, the interaction of S-I and S-II, and the contribution of S-II input to the cingulate (via the insula) play a synergistic role in cognitive–emotional dimensions of pain consciousness. nPB: parabrachial nucleus; (N)STT: neospinothalamic tract; (P)STT: paleospinothalamic tract; S-I/S-II: primary and associative somatosensory cortex; VPLc: caudal ventroposterior lateral nucleus of the thalamus.

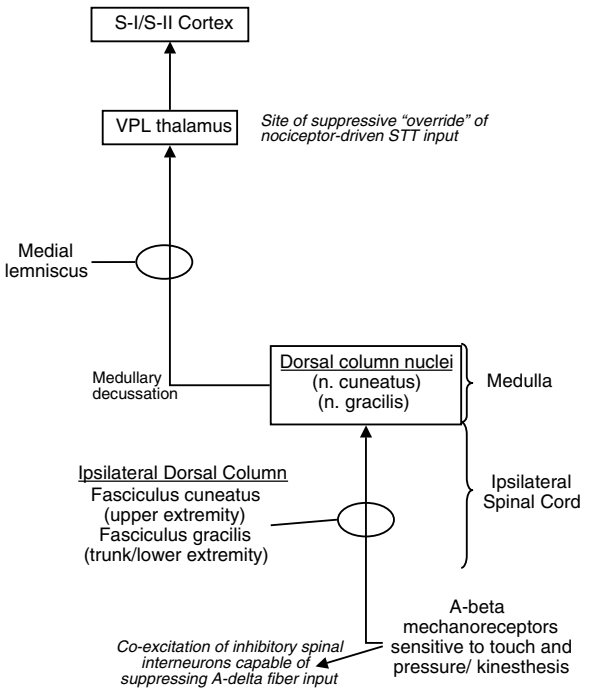

FIGURE 3.7 Schematic depiction of the dorsal column/medial lemniscal pathway and its role in pain modulation. As described in text, A-beta mechanoreceptors can excite inhibitory neurons within the dorsal horn to suppress low-level A-delta nociceptive fiber activity. As well, A-beta mechanoreceptor input can stimulate medial lemniscal pathways from the dorsal column nuclei. Lemniscal projections to the VPL nucleus of the thalamus can modulate coterminal nociceptive input from the STT.

subserve the clinical efficacy of dorsal column electrostimulation (DCS) and help to explain the somewhat beneficial effect of rubbing a painful area. The effects of dorsal column stimulation, however, seem to be relatively temporally limited in circumstances of long-standing, durable, or progressively increasing pain. With continued A-delta and C-fiber activity, the function (and perhaps microstructural architectural re-modeling) of the STT and/or supraspinal nociceptive neuraxes enhances the transmission of the pain signal, thereby overcoming the viability of spinal or thalamic suppression by dorsal column input (Erickson & Long, 1983). Augmented dorsal column stimulation is then required to regain suppression over STT input, and clinically there appears to be an asymptotic (i.e., ceiling or plateau) pattern to the relative efficacy of serially incremented DCS against progressive neuropathic pain.

SUMMARY

The anatomical and physiologic systems that subserve pain and analgesia are complex. Heterogeneous populations of neurons from the periphery, through the spinal cord, brainstem, thalamus, and ultimately cortical and limbic systems, with discrete neurochemical and physiological properties all contribute to the amalgam of sensations and the cognitive phenomena known as pain. By understanding the structure and function of this system, we may develop enhanced therapeutic approaches for chronic pain that target these substrates more effectively and selectively, thereby reducing deleterious side effects while facilitating an enhanced quality of life.

ACKNOWLEDGMENTS

The author wishes to acknowledge the untiring, cheerful technical and graphic artistic assistance of Sherry Loveless in preparation of this manuscript. As well, the author is appreciative of ongoing collaborative and intellectual exchanges with Drs. Tom Schultea, Robert Barkin, B. Eliot Cole, Philipp Lippe, Pierre LeRoy, and Scott Raven.

This chapter is dedicated to the memory and work of Dr. Richard Weiner: a mentor, supporter, colleague, and friend.

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4

Overview of Pain: Classification and Concepts

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Pain is generally described as an unpleasant sensation. Pain, as a concept and symptom, is discussed and described throughout professional and lay medical literature. Pain is the reason for initial contact with any physician for the vast majority of medical problems, e.g., abdominal pain, chest pain, limb pain, low back pain. As such, pain *condition* classification is very sophisticated and advanced, as demonstrated by the IASP Chronic Pain Classification system (Merskey & Bogduk, 1994) and others (Derasari, 2000; Waldman, 2003).

The foundation for the history of physiological pain (mechanism) classification essentially started with Descartes (Melzack & Wall, 1965) in the 17th century but has not been framed in these terms until recently (Thienhaus & Cole, 1998, 2001). The history of pain condition classification is synonymous with the history of pain in humankind.

Only recently have physician neuroscientists and medical doctors begun to focus on pain mechanisms that are the foundation for understanding pain conditions and, therefore, for pain classification (Dallel & Voisin, 2001). This effort should proceed rapidly because much information is already available. However, this progression is hindered by the difficulties of transferring scientific knowledge to medical practice.

The main reason to classify (i.e., label or name) clinical presentations of symptoms centered around pain is to facilitate communication between patient and doctor for better pain care outcomes. The goal of therapy is to reduce suffering and increase function, which is the overriding purpose for practicing pain management and is at the core of this textbook and of medicine itself (Fields & Martin, 2001).

THE PRESENT STATE OF PAIN THEORY AND THOUGHT

Pain is described in a myriad of ways:

- In temporal terms: chronic pain, subacute pain, and acute pain
- In characterizations: intermittent pain, intractable pain, lancinating pain, referred pain, burning pain, and dull pain
- In medical diagnoses: phantom pain, cancer pain, vascular pain, arthritic pain, nerve pain, muscle pain, fibromyalgia, myofascial pain, sympathetically maintained pain, and complex regional pain syndrome
- In mechanistic/etiologic terms: neuropathic and nociceptive pain
- In anatomic perceptional terms: headache, back pain, neck pain, facial pain, limb pain, abdominal pain, etc.
- In source or origin terms: central pain as originating in the spinal cord or brain, or peripheral pain
- In psychiatric/psychogenic terms: psychosomatic ("all-in-the-head") pain, etc.

Caudill (1995) analyzed pain from different angles to emphasize its complexity:

- Biologically — Serves as a signal that the body has been harmed.

- Psychologically — Is experienced as emotional suffering.
- Behaviorally — Alters the way a person moves and acts.
- Cognitively — Calls for thinking about its meaning, its cause, and possible remedies.
- Spiritually — Serves as a reminder of mortality.
- Culturally — Tests a people's fortitude or forces their submission.

DSM-IV-TR Pain Disorders

Pain Disorders are coded for their medical conditions in the *DSM-IV-TR* (American Psychiatric Association, 2000; First and Pincus, 2000) as follows:

307.80 Pain Disorder Associated with Psychological Factors
307.89 Pain Disorder Associated with Both Psychological Factors and a General Pain Condition

Elsewhere, the *DSM-IV-TR* (First & Pincus, 2000) attributes neural dysfunction to pain. Again, these are only descriptive categories and do not provide insight into underlying pain mechanism. Suffering, or the affective component, is not separated.

Pain Classification Characteristics

Pain has been classified by anatomic location, body system, duration, severity, frequency, and etiology (Cole, 2002). Merskey and Bogduk (1994) have done a prodigious job of compiling numerous pain conditions, basically all pain conditions mentioned in modern medical literature. Refer to Table 4.1 for a summary of the characteristics of this and other current systems of pain classification.

To add complexity, many factors, such as culture, personality, psychosocial stressors, nutritional status, and other disease states, can be involved to influence the degree of perceived pain and to confound understanding of the causal factors of the pain.

Healthcare professionals and the general public tend to think of location first for most pain classification systems. Waldman (2002, 2003) did so in listing and describing many locations for both common and uncommon pain conditions.

The simplest traditional categorization of pain has been "acute" and "chronic." Acute pain is usually just a result of the stimulation of a normally functioning pain detection system and serves to allow us to avoid or minimize tissue damage. Chronic pain merely means that pain is perceived over a long period of time, which is often arbitrarily set at 3 to 6 months.

However, while the chronology of pain has further subdivided pains basically into "acute" and "chronic," there is a mechanistic relationship, i.e., acute pain is simple nociceptive pain and chronic pain is a complex mix of pathologies along the neural pathways. Dr. Lippe (1998) has suggested the useful terms, *eudynia* (good pain) and *maldynia* (bad pain). As a generalization, many would describe eudynia as acute, and maldynia as chronic, although actual, individual cases tend to be more complex in both cases.

"Biopsychosocial" considerations are one step up from the "traditional" classification. The "pathogenetic"

TABLE 4.1
Pain Classification Systems

Categories	I	II	III	IV	V
Traditional	Acute	Subacute	Chronic		
Biopsychosocial	Acute	Recurrent acute	Cancer related	Chronic nonmalignant	
Pathogenetic	Primary	Secondary	TX. Effect (chemotherapy, tissue trauma, edema, etc.)		
ICD-9[a]	Disease process	Pain location	Secondary		
Dickerson (special case adapted by Brookoff, 2000, who elaborates the various subtypes)	Neuropathic	Inflammatory	Long-term		
IASP[b,c]	Region	System	Chronology	Intensity	Etiology

Note: The "traditional" classification scheme addresses chronology, location, and gross mechanisms.

[a] International Classification of Diseases, 9th edition.
[b] International Association for the Study of Pain.
[c] Merkey & Bogduk, 1994.

TX = therapy; Effect = therapy effect.

system grossly indicates the cause, primary or secondary, as major disease classifications. Inflammatory and long-term designations can involve both nociceptive and neuropathic pain. The IASP system provides a more detailed description of the pain, but fails to approach the cause, except generally in Etiology; the IASP definition of pain avoids linking pain to a specific stimulus.

The biopsychosocial model includes four categories: acute, recurrent acute, cancer-related, and chronic nonmalignant pain. The first two categories deal with timing issues; the latter two categories speak to whether cancer is involved. Although useful in incorporating the issue of suffering, we suggest that these categories bear little relationship to mechanisms of pain. Except, perhaps, for vascular headaches, identifying the location of the pain is not necessary to basic understanding. The basic pain mechanisms are the same — whether for arm, leg, abdominal, or ear pain. Further, we think that the mechanisms of pain and pain pathways are the same, whether or not cancer is involved.

The most advanced concepts are expressed by Craig (2002), who states that pain is just one manifestation of the mind–body homeostasis system. From the patient's point of view, the spectrum of pain control spans temporary treatments (usually pharmaceutical) in suppressing pain to permanent remission or cure of underlying pathology/disease.

Obviously, these are all very useful concepts; but, are still generally academic in nature and do not provide much practical help to a physician. Concepts of pain pathophysiology, and thus classification, are abundantly available in the scientific and medical literatures. There is a need to refine and clarify all of this information and apply it as simply as possible to the treatment of pain in the physician's office.

Pain and Suffering

Pain is an unpleasant sensation appreciated as suffering. Most of the present pain classification systems actually include suffering as an essential part of the pain condition described. If suffering is removed, then, theoretically, pain can occur without suffering and would then logically seldom come to medical attention.

Suffering, as a separate life experience, may remain in the psychopsychiatric realm and not be objectively measurable for some time. There is an implied linkage between pain and suffering, which we disconnect here.

PAIN IS A MICROSCOPIC EVENT

Certainly, the first step is to understand that nociceptive pain is not a psychological event; it is a microscopic physical, chemical, or thermal event.

Acute, noxious stimulation of nociceptive pain (detecting something at the pain nerve ending), which may also precede neuropathic pain (hypersensitive transmission pathways), occurs at microscopic pain nerve endings as a signal that something is wrong, physically, chemically, or thermally. The neurotransmitters across synapses and endogenous and exogenous neurotoxic substances are microscopic. The upstream normally functioning peripheral and central neurons are microscopic. Then, neuropathic pain is, by definition, pathology of neurons. Because neurons are microscopic, peripherally or centrally, neuropathic pain can be likewise nothing but a "microscopic" event.

The presence of macroscopic pathology may or may not explain local pain, nociceptively or neuropathically. Macroscopic pathology, in other words, is not necessary, and may even be unrelated, for pain to occur or pain to be perceived. However, many patients and clinicians seek macroscopic pathology as *the* explanation for pain and suffering, e.g., most low back pain patients think of a "slipped disc" first, even though at least 85% of low back pain is nonspecific and, indeed, microscopic.

Functional MRI (Coghill et al., 1994) or PET scans (Iadarola et al., 1995) can show characteristic areas of activation in response to noxious stimuli in both nociceptive and neuropathic pan states. While not yet used in daily clinical practice, this information illustrates that pain is measurable in that it cuases physiological brain phenomena akin to "perception." Suffering is likely to be manifested in different patterns, sometimes with the areas activated by pain, and sometimes without the coincidence of pain. Thus, there are some cases that theoretically could have pain without suffering. Lepers have no pain and no direct suffering (Brand, 1993).

PAIN MECHANISMS

It has been known in medical science for decades that evolutionally advanced somatic A-delta fibers and primitive sympathetic C-fibers transmit pain signals under specific circumstances. In addition to transmitting cold information, the A-delta fibers also transmit thermal and mechanical pain information relatively quickly and with precise locational information to the central nervous system. The C-fibers, on the other hand, transmit thermal and mechanical pain information relatively slowly and rather imprecisely to the central nervous system, i.e., warm pain and achy/burning pain are seen by the central nervous system as "through fogged glass."

Perception may be defined as the localization and quantification by the central nervous system of signals from the A-delta and C-fiber pain pathways. Present pain *condition* classification systems are helpful, but these classification systems are complex and do not seem to be organized to provide the practicing physician with handles

TABLE 4.2
Peripheral Nerve Fiber Types/Characteristics

Class\Units	Stimuli/Function	Perception	Conduction Velocity (m/s)	Diameter (microns)	Myelinated
A-alpha fibers	Motor contraction Efferent transmission	None direct	30–85	12–22	Yes
A-beta fibers	Vibration, pressure Afferent transmission	Vibration, pressure	30–70	5–12	Yes
A-delta fibers*	Cold sensation, pain Fast pain, localized touch Afferent transmission	Cold sensation, pain Localized touch	5–30	1–5	Yes
C-fibers**	Hot sensation, pain Slow pain, generalized touch Afferent transmission	Hot sensation and pain Generalized touch	0.5–2.0	0.3–1.3	No

Note: Based on Haines, 1997; Cousins & Bridenbaugh, 1998; Ganong, 2003.

* Spinal laminas I and V.
** Spinal laminas I and II.
*** C-fibers can still be clumped and embedded in other nonconducting tissue.

that can help the physician more effectively treat those patients presenting with pain — particularly chronic pain. Medical doctors depend on knowledge of the pathophysiology, or at least a diagnosis, to decide on treatment. Thus, to maximize likelihood of a correct and effective treatment and a positive outcome, physicians need to understand where and what the pain mechanism is and how the pain is perceived.

A relatively recent trend has been to look at basic mechanisms of pain (Dallel & Voisin, 2001). By doing so, we are seeking to look one level deeper at the underlying mechanisms so treatment can be facilitated. Dallel and Voisin (2001) recognize the need for a clear roadmap: "Once pain-generating mechanisms are known, it becomes possible to establish the appropriate treatment of pain." We suggest that refining these concepts is a giant step in the right direction and propose to present a simple, clear pathophysiologically based classification model. We contend that pain treatment should primarily focus on reversing pathologic mechanisms that cause the pain in the first place.

Any one or combination of the microscopic mechanisms can contribute to pain: nerve pain ending/"sensor" stimulation, neural "wire" misfiring, and central nervous system/"perceptron" dysfunction (Woessner, 2002a).

RELEVANT NEUROANATOMY AND NEUROPHYSIOLOGY

It appears that the locational patterns of disease, including neuropathology, and the mixture of these mechanisms that are dynamic over time make understanding the basic neuroanatomy and neurophysiology important.

Nerves, or neurons, are long tubes of protoplasm (rather than a series of sausage links), which may, or may not, be surrounded by poorly conducting myelin (insulation). Nerves generally come in various sizes and characteristics and have numerous branches to other neurons. Neurons interact/communicate via numerous electrical (gap junction) and chemical synapses. There are motor (efferent) neurons, which primarily carry signals from the brain to muscles, and sensory (afferent) neurons, which primarily carry signals from the periphery to the brain.

The primary focus for investigation by pain practitioners should be the small sensory nerves, which carry unpleasant signals to the brain that may or may not be perceived by the brain. Descartes depicted a noxious stimulus causing information to flow along a pain pathway to the brain that is then perceived as pain in his famous illustration of a boy's foot touching the edge of a fire (as in Melzack & Wall, 1965). Characteristics of nerve fibers, including classification and conduction velocities, are listed in Table 4.2.

There are three types of fibers that carry pain signals to the brain — A-beta, A-delta, and C-fibers. The first two are evolutionarily modern fibers that are myelinated (insulated) and carry nerve impulses rapidly to the cortical regions of the brain (Haines, 1997).

Neural signals are conveyed by sodium and potassium ions moving out and into neurons via voltage-gated channels in specific patterns to form a relatively slow (see Table 4.2; not 186,000 mi/sec) moving wave of information to, from, and within the central nervous system. These voltage-gated channels are concentrated in "holes" in the myelin (nodes of Ranvier) of the somatic nerves (A fibers),

but are more evenly distributed in the more primitive, unmyelinated nerve fibers (C-fibers).

In the absence of neural wire damage, there is a continuum across various numbers of synapses (switching stations) from the source or place of stimulation to the site of perception. At the distal end of sensory nerves, there are various types of nerve endings. When it comes to pain nerves, those endings are so-called "free" nerve endings. At the proximal end are the perceptor areas of the brain (Haines, 1997).

The A-beta fibers are probably reserved for deep, lancinating pain; certainly these carry vibratory signals. The A-delta fibers are somatic, myelinated fibers that have primary connections to the cortical regions of the brain. These fibers convey sharp, lancinating, easily localized pain signals; these pain sensations usually pass quickly unless constant or recurrent stimulation occurs.

Then, a more generalized, burning/aching pain sensation is perceived in the brain. This latter pain takes longer to pass. The C-fibers are relatively primitive and are not covered by myelin and conduct rather slowly to the subcortical part of the brain (Haines, 1997). Thus, when one experiences a paper cut, one quickly appreciates a "zing" followed by a "burning" pain. You know exactly where the "zing" comes from (A-delta pain pathways), but the brain "sees" the burning pain through "fogged glass" (C-fiber pain pathways).

Now that we know generally how these small nerves work, we need to know where these nerve endings and small pain nerves reside. Our standard anatomy books often do not depict or describe these networks of nerves. Dr. Fishman (2000), an insightful pain doctor, has described in his book entitled *The War on Pain* that these nerve fibers cover and line most of the tissue plane surfaces throughout the body.

HOW PAIN IS MEASURED

If pain is separated from suffering, it is easy to understand that pain is then measurable physiologically. As indicated in Table 4.2, neurophysiologists have assigned identifiable physiological functions to different nerve types. As with large-fiber functional testing, the small fibers, i.e., the A-delta and C-fibers, can be tested electrically and thermally. Measurement of small pain fiber function by preferred frequency transmission measurements (= current perception threshold [CPT]) has been clinically available for more than ten years. Thermal testing is as old as neurology itself; the basic physical examination includes qualitative testing with the handle of a reflex hammer as is for comparative cold sensation and heated for comparative warm sensation. In the laboratory, neuroscientists have been able to quantify thermal nerve, i.e., A-delta and C-fiber, function for decades. Machines are available now to test the function of pain nerve pathways in clinical settings. Testing pain nerves thus provides valuable information for diagnosis, and more effective treatment (Woessner, 2002b).

Imaging of pain perception has also been accomplished with transcranial magnetic stimulation (Gale, 2004), positron emission tomography (PET) (Iadarola, et al., 1995), single photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI) (Coghill, et al., 1999) and near infrared spectroscopy techniques (NIRS) (Cope, 2000). "Research in diagnostic imaging of neuronal activity is … endemic at many academic medical centers. … The ability to map transmission of pain and other disorders not only to block but to alter and reprogram neurotransmission is now a very active and ever-changing research area (Cope, 2000)."

An interesting question arises from this research: Can a human being perceive pain without suffering? My clinical experience indicates that this is exactly so. Most clinicians, indeed, do understand that patients suffer for a variety of reasons. Thus, what medicine really needs is Suffering Relief Specialists rather than Pain Medicine Specialists per se. With the proper mindset, a pain specialist should be able to tackle the broader, and sometimes separate, issue of suffering. Thus, measuring and understanding physiological pain and comparing the results to perceived pain allow the clinician to more precisely treat "pain patients."

PROPOSED PHYSIOLOGICAL PAIN MODEL

This physiological pain model (Woessner, 2002a) focuses on underlying causative mechanisms, as opposed to the pain condition classification systems listed in Table 4.1. To review terms, nociceptive pain is merely normal functioning of the neural sensor/wire/perception system. This system serves useful purposes in alerting the brain to bodily injury. Neuropathic and central pain, however, is a manifestation of true dysfunction and can be the "disease" itself.

If we consider a bundle of axons, neuropraxia, axonotmesis, and neurotmesis represent points along a complex continuum of damage to axons and nerves. The three possibilities for individual axons are normal function, hyperfunction (hyperesthesia, hyperalgesia, hyperpathia, and allodynia), and hypofunction (hypoesthesia, hypoalgesia, and conduction block). Hyperfunction can also be thought of as sensitization or irritation. The ultimate hypofunction is axon death without regrowth. Free nerve endings can also be sensitized or irritated, which is considered here to be in the neuropathic category.

Understanding neurophysiology of pain pathways is helpful. Further, we propose that all pain can be understood by considering problems of stimulation of sensors, conduction along nerves, and/or perception in the spinal cord and brain. The perception then may involve feedback, either positive or negative (i.e., release or not of native painkiller, e.g., endorphins). If negative, the result

is, by and large, a dysfunction that conceptually could stand alone.

Haines (1997) describes an electronic schematic of the nerve cell membrane and forms the basis of concepts discussed below. A key concept is that the neural pain system follows basic electrochemical principles.

The analogy of the neural net in complex electrical circuitry seems to be an accurate one. The pain sensors (free nerve endings) are relatively simple. The wires (peripheral nerves) are even simpler. The central nervous system is incredibly complex. We are discovering that the spinal cord is not just a transmission device; complex interactions can occur here also. Finally, the complexity of the brain is difficult to imagine with millions of neurons and billions of synapses (Haines, 1997).

Stimulation of the sensors is nociceptive or eudynia. Malfunction of the wires and perceptron is neuropathic. Note that neuropathic pain is divided into central and peripheral parts of the pain nervous system because, while relatively little is known about either, these two parts of the pain pathways are clearly distinguished from each other.

Essentially no pain condition is unifactorial. For the actual pain conditions that the practicing physician encounters, it is useful to assess the pain using a conceptual framework. This approach is useful as a tool in assessing an individual patient's pain and deciding on treatment within the conceptual pain model.

STIMULATION OF PAIN SENSORS (NOCICEPTION)

Normal stimulation of pain sensors is the "good" pain described in *The Gift Nobody Wants* (Brand, 1993). It is termed "eudynia" in that the free nerve endings of pain pathways are working perfectly and normally — giving good information to the body and brain that tissue is being damaged — or is about to be damaged — and that the body needs to do something about it. Impact on mechano(noci)ceptors, heat or cold stimulation of thermo(noci)ceptors, or caustic chemicals on chemo(noci)ceptors start the process of perception of pain. In other words, this type of pain is based on mechanical, thermal, and/or chemical stimulation of normally functioning pain nerves; nerves that detect pain as a signal indicating impending or active tissue damage.

MISFIRING OF WIRES (NEUROGENIC OR NEUROPATHIC PAIN)

During the normal transmission of neural signals to the central nervous system, any damage to the neural pathway itself may manifest itself analogously to "static" in radio transmissions. This neural "static" alters the neural signal and is then perceived as pain. Nerves can be damaged just as any soft tissue, in which these nerves occur, can be damaged. Neuropathic pain, therefore, is a result of damaged and malfunctioning wires/nerve fibers. One can also conceive of similar damage to nerve fibers in the central nervous system. As long as those fibers are not the end of the pathway, the phenomenon is the same. Damaged nerve fibers follow a course of anatomic and physiologic change involving irritation (hyperactivity) and dysfunction/death (hypoactivity) (Iadarola et al., 1995). Upon nerve death, of course, signals can no longer be transmitted along the neural pathway.

Mechanisms of hypersensitive or pain neuropathology include "rapid repriming" of sodium channels or "electrical bursting in pain signaling neurons." These sodium channels are specific to the "spinal sensory neurons" (Waxman, 2001, p. 382). Waxman et al. (2001) provide significant detail of this mechanism without indicating the nerve type; we assume that a similar mechanism works for both the A-delta and C-fiber pain nerves and, at least, is related to local microscopic mechanical and chemical occurrences.

DYSFUNCTION OF PERCEPTION (CENTRAL PAIN)

The most complex, and very difficult to study, part of the pain pathway(s) is in the central nervous system and occurs at the end of the neural pathway, where these signals are interpreted. Perception and consequences can occur in the dorsal horn. If central neurons malfunction in any part of the pain perception pathway, one possible consequence is that the brain perceives "pain." The environment of the central nervous system can also play a part. This complex system can be considered together to be a *perceptron* (Woessner, 2002a). This word has been chosen to convey the true complexity and computer-like nature of these central nervous system phenomena. If the "perception" is the cause of the perceived pain, this pain pathology can also be called central neurogenic pain.

ANTINOCICEPTIVE DYSFUNCTION

The human body possesses antipain (antinociception) systems including endorphins, enkephalins, etc. that are utilized as natural pain killers and neural feedback modulation to reduce perception of pain and the quantity of pain signals arriving at the "perceptron." In normal function, the human body releases these painkillers to modulate or mollify pain. At the very least, if these chemicals are not released or do not arrive at the affected receptors, the perceptrons will appreciate pain or greater pain, in the presence of pain signals (Craig, 2002).

Pain experts have also recognized that pain is nociceptive and/or neuropathic (Abrams, 2000), which are

commonly thought to be equivalent to "acute" and "chronic," respectively. The difficulty is that most acute and chronic pain conditions are a combination of both nociceptive and neuropathic pain, which can and do change over time. An acutely damaged nerve can result in acute neuropathic pain, and chronic arthritis can result in a chronic recurrent nociceptive pain.

Antinociceptive dysfunction (Brookoff, 2000) occurs in the perceptron (brain and/or spinal cord) and can worsen both nociceptive and neuropathic pains; antinociceptive pain, in other words, is dysfunction of the natural pain modulation system (Heinricher, 2002). Then, externally delivered painkillers are antinociceptive, as well.

Then, there are natural pain modulations that can malfunction resulting in more pain (hyperalgesia) or even pain without a noxious stimulus (allodynia). In this physiological manner, pain can be better understood. Each possible mechanism is dynamic in anatomical location, along pain pathways, and over time; each mechanism is individual and unique according to the underlying pain condition.

COMPLEX PAIN FROM A MIXTURE OF MECHANISMS

Over time and with the presence of widespread and/or severe causal factors, more than one aspect of the pain perception system may be malfunctioning at the same time. For example, it is common for patients to develop pain in a limb due to trauma that injures small pain fibers in addition to the other soft tissue. One can have stump pain along with phantom pain, possibly not coincidentally. Central sensitization can develop over time in a patient with ongoing peripheral disease. Dysfunctional efferent reflexes or reactions can change the physical and chemical environment of pain sensors, which then causes nociceptive pain as in complex regional pain syndrome (CRPS).

REFERRED PAIN AND NONTENDER SYNDROMES

Likewise, clinicians should be aware of pain perceived in body areas that are not tender on palpation. In other words, referred pain is pain that is perceived separately from the true pain generator and was first discussed in publications by Sturge (1883), Ross (1887), and others (Bonica and Loesser, 2001; Coda & Bonica, 2001). Local acute pain is relatively easy to understand, and physicians usually appreciate radicular pain, which is one type of referred pain. The concept of referred pain can be difficult for clinicians and patients alike.

Physicians strive to achieve the best possible understanding of pain conditions and try to find an acceptable label or diagnosis, even for conditions and presentations that are uncommon and/or difficult to understand. As the patient's presentation becomes more complex and as pain conditions become more chronic, physiologically legitimate presentations may not be understood.

Understanding referred pain requires specialized and diverse knowledge along with wide clinical experience. Suggesting that complaints are "non-anatomic" or "non-physiologic" may very well be a clear indication of the diagnostician's ignorance rather than a negative reflection on the motives of the patient. Individual variations in the presenting pain patterns complicate interpretation. Even well-known and classic pain patterns may be difficult to diagnose in the face of complex disease and multiple causes of pain. There are other complex, and poorly understood, pain conditions defined below.

Referred Pain Mechanisms

Kosek and Hansson (2003) have specifically found that "referred pain is most likely a consequence of misinterpretation of the origin of input from the stimulated focal pain area, due to excitation of neurons somewhere along the neuraxis with projected fields in the referred pain area … [this] suggests that the divergence of the input is not reciprocally arranged."

The best-known referred pain patterns may originate from viscera and myofascial trigger points. Each type is presented below. Other pain syndromes, with different names, however, also fall within this general category with the broad definition given above, where the pain is perceived at a site separate from the pathology.

Ombregt et al. (2003) have provided more precise principles limiting and defining referred pain:

1. Radicular pain is directly related to spinal segments.
2. The perceived pain site and causative pathology are usually on same side of midline.
3. The main pain is usually felt deeply.
4. The referred pain is referred distally within a dermatome, but not necessarily throughout that dermatome.
5. Referred pain may be contiguous with or may be separated from pathology.

The author proposes a sixth principle (Woessner, 2003): that the site of perceived pain is not tender, whereas the site of pathology is tender. Central pain phenomena do not necessarily fit completely within these general principles, but it is still useful to understand the similarities.

Selzer and Spencer (1969) suggest five underlying mechanisms involved with referred pain:

1. "Convergence-Projection" describes one neuron receiving impulses from two sources; i.e., peripheral neurons, resulting in the central path-

ways not being able to distinguish between the sources (Ruch, 1960).
2. "Peripheral Branching of Primary Afferent Nociceptors" involves the fact that single neurons are very long narrow tubes that may have various branches that come from different peripheral sources, again making it impossible for central pain pathways to distinguish the source.
3. "Convergence-Facilitation" is ephatic transmission that occurs where nerves from two different body areas are in close proximity and results in signals from the viscera being transmitted along an associated spinothalamic tract to be perceived in the brain as coming from various skin areas (originally proposed by Ruch, 1960).
4. "Sympathetic Nervous System Activity," which is suggested to restrict blood flow to an area causing pain in that area or by releasing substances that sensitize nerve endings in the area of perceived pain such that hyperesthesia or allodynia occurs. Except as illustrated elsewhere, this possibility does not make much sense.
5. "Convergence or Image Projection at the Supraspinal Level" describes ephaptic transmission in central locations rather than at the dorsal root, or some similar mechanism to be perceived as being pain in one area while the stimulation comes from another.

There are, of course, other possibilities and/or contributing factors to referred pain:

1. Note that when nerve root pathology affects only the nerve root surface pain nerves, we expect local pain to be perceived and local tenderness to be elicited. For more severe pathology that extends physically as pressure and chemically to the pain nerves inside the nerve root, we expect that the brain would perceive the pain more distal to nontender locations in the feet or hands, understood as "radicular" pain. This mechanism is likely for all non-central syndromes considered here.
2. Mistransmission or ephatic transmission solely in the central nerve system, as in the phantom pain phenomenon discussed in the labeled section below.
3. The embryologic relationship of the internal organs to spinal levels, which is then directly related to sympathetic chain levels. The importance of the embryologic levels must reflect organization in the central nervous system. In addition, the main nerve fiber type of the sympathetic nerve system is the C-fiber, the primitive, unmyelinated pain fiber, emphasizing that ontogeny follows phylogeny.
4. Along these pathways, neuropathic pain can also be referred and, in some cases, may indicate that the nerve is "trying" to normalize, to heal. Certainly, dead neurons do not transmit pain signals or any other impulse.
5. Central pain syndromes could very easily fit into the same category as phantom pain. Deafferent pain syndrome is consistent with "total body amputation" from the head/brain and represents a pain syndrome without nerve impulses of any sort coming from the periphery. In other words, the pathology or dysfunction is in the neurons of the central nervous system, but not necessarily just in the brain.
6. Wide dynamic range (WDR) neurons and interneurons of the spinal cord represent neuropathic dysfunction that could by specific, complex mechanisms end with the perception of pain where there is no pathology; the pathology, in this case, is in the spinal cord.
7. Sympathetic chain pathology is the same as the spinal cord pathology. We may eventually identify WDR neurons of the sympathetic chains; we will probably come up with a different name.
8. Patchy brain modulation of pain, i.e., antinociception, could well leave the brain appreciating pain where there is no pain with or without a reason, i.e., nerve impulses of any kind coming from elsewhere.

Certainly, more than one or all of these phenomena could occur together to form the various widespread and complex pain problems that a physician must manage and try to cure.

Embryology and Referred Pain

Various authors (Marcus, 1998; Ombregt et al., 2003) discuss the embryologic basis for referred pain. Certainly, the referred pain mechanisms must have a relationship to nerve pathways and networks. These pathways and networks are geometrically and positionally related to where the precursor structures occurred in early ontogenic stages and how these structures migrate during growth and maturation. Thus, referred pain patterns have an evolutionarily ancient (phylogenic) and developmentally individual relationship (ontogenic) to dermatomes, myotomes, sclerotomes, viscerotomes, etc. Central pathway and network pathology can probably be understood in the same way.

Factors Causing Referred Pain

Ombregt et al. (2003) described factors that predispose to referred pain. Stronger central and/or proximal deep (vs. superficial) stimuli more likely cause the perception of pain beyond the pathology. Sclerotomal referred pain is more likely than myotomal referred pain, and much more likely than bone pain. This order of occurrence may be generally inversely related to intensity and pain-related dysfunction.

Marcus (1998) adds and states differently that "tenacious" pain stimulation is more likely to be referred; superficial pain is more likely to be localizable (less likely referred), deep (excluding bone) is more likely referred; soft tissue referred pain is less localizable, i.e., more likely referred; and distal pathology is more localizable than proximal.

Viscerotomes

Visceral referred pain is probably the most widely recognized, while still being the least understood of all the referred pain patterns. Head (1893) noted disturbances of sensation arising from visceral disorders. Cousins (1987) refers to these patterns as "viscerotomes." Lingappa and Farey (2000), in fact, describe "referred pain" as "the phenomenon in which injury to internal organs causes pain that localizes, in part, to surface structures or other organs clearly distinct from the site of primary injury. Typically, the pain is referred to other structures that have the same embryonic origin" (pp. 798). There are established patterns of referred pain from internal organs. Drewes et al. (2003) have provided a detailed description of the various referred visceral pain distributes, providing basic information to understand the complexities of viscerotomes.

Ephatic transmission is analogous to electrical shorting out. Via these shorts, "many different afferent sensory nociceptive neurons synapse with the same ascending fibers in the spinal cord," which causes the brain to mistake the origin of the pain signals; in other words, the pain feels like it is coming for some typical locations on the skin or nearby subcutaneous tissues and possibly deeper structures, rather than the actual internal organ from which the pain signals are coming (Lingappa & Farey, 2000, pp. 798–799). These scientists also suggest that the brain generally will have more recent memory of surface/subcutaneous pain and will "ignore" deep pain until an inciting event occurs.

With A-delta pain fiber involvement, a skin injury is easily locatable. Visceral pain is difficult for the human brain to locate because the pain is "referred" to the skin and involves sympathetic C-fibers, which subserve poorly localized pain.

Angina pectoris is well known to cause left arm pain, alerting to the possibility of impending myocardial infarction. Abdominal pain that becomes rapidly generalized implies perforation and leakage of fluid into the peritoneal cavity, irritating the parietal peritoneum. Biliary pain can radiate to the right inferior scapula. Pancreatic and abdominal aneurismal pain may radiate to the back. Ureteral colic classically is referred to the groin and thigh (Haist & Robbins, 2002).

The areas of the body to which visceral pain is referred are described in narrative rather in schematics. Note that we expect that each patient will display variations on these generalizations. Word descriptions may actually represent reality better than the various published schematics because each viscerotome schematic is different and inconsistent, with individuals and populations being unique and different to some degree.

Common Pain Radiation Patterns (Woessner, 2003)

Lungs: Pain is referred in a collar-like band completely around the neck from about C6 to T3 levels.

Diaphragm: Pain is referred in a pattern similar to the lungs.

Heart: Pain can be referred to around the mouth, but is more commonly referred over the left chest and contiguously down the anterior left arm and directly to the mid-back between the scapulae from T4 to T7.

Gallbladder: Pain is referred to superior and lateral right shoulder, offset superior similar in size and circular shape to the superficial distribution of the axillary nerve.

Liver: Pain is referred in a similar pattern to the heart, but only on the right hemi-body.

Stomach: Pain is referred just to the right of midline in the epigastric area and to the mid-back, just below the referred angina from T7 to T9.

Ovaries: Pain is referred to the skin area immediately over the ovaries anteriorly and directly posteriorly, but more lateral.

Appendix: Pain is referred to the umbilicus and then to McBurney's point in the right hypogastric area when parietal peritoneum becomes inflamed.

Kidneys: Pain is referred to the skin area somewhat below the kidneys, posteriorly only, and medial to the posterior referred ovarian pain; there is also an area half way down the right lateral thigh, the right chest just to the right of the lower sternum.

Ureters: Pain is referred to an anterior band across the pelvis, including the groin and the genitals, but not extending to the back.

Bladder: Pain is referred to a continuous area encompassing the sacrum from S2 down to the upper medial thighs.

Radicular Pain

Radicular pain originates at the nerve root, cervical, thoracic, lumbar, or sacral, and typically radiates or is referred along a dermatome. Dermatomal pain suggests nerve root involvement from a herniated disc or other physical or chemical irritation at the nerve root exiting from the spinal canal.

Consistent with the definition, there can be various pathologies at the nerve roots, which include (1) nerve root compression from a herniated disc, (2) foraminal stenosis from bone spurs or arthritis irritating the nerve root, (3) nerve root pressure from mass lesions, (4) chemical changes at the nerve roots secondary to diabetes, (5) scarring from previous spinal surgery or chronic disc pathology, and (6) all other nerve root injuries. The radiating component is technically "referred pain." This type of "referred pain" is not a nociceptive process; it is neuropathic, even if momentary. Pain with such a specific distribution seems unlikely to even be central.

Thinking of the distribution of pain nerves in the cross section of a nerve root is instructive. If the pathology is minor, the pain on this surface of the nerve root is most affecting, and thus local pain is appreciate (Woessner, 2002a). With more compression the pain nerve pathways/axons deeper in the nerve root are affected and "fool" the brain into thinking that the painis located more distal toward the limb involved.

Overlapping Distributions

The nerves that innervate dermatomes interdigitate at the borders to some extent, making the boundary edges fuzzy. In addition, the sensory distributions, which characterize and define dermatomes, may not be identical to the pain patterns. Therefore, exact determinations of pain perception distributions are not "cut and dried" (Bonica & Loeser, 2001).

Referred Muscular Pain

Referred muscle pain in voluntary muscles is most often accompanied by secondary hyperalgesia and hypotrophic changes. A schematic of these referral distributions is shown in *Bonica's Management of Pain* (Coda & Bonica, 2001).

"Myotomal" pain involves problems with the fascial tissue planes that surround muscle groups. While "myotomal" may not be the correct description, when muscles were injected with hypertonic saline, which is an experimental substance known to produce pain, mapped patterns of referred pain emerged (Coda & Bonica, 2001). While we would expect that these would be the same referred pain patterns as myofascial trigger points, gross inspections reveal no clear congruence or overlap.

Sclerotomes

Pain referred from tendinous and/or ligamentous interfaces with bone surfaces has no specific, well-recognized name (Hackett, 1958). Sclerotomes are pain referral patterns from sites of enthesopathy, i.e., pathology of the collagenous attachments (tendons, ligaments, cartilage, etc.) to bones generated by inflammation (Bonica & Loeser, 2001).

Dural Pain Patterns

Bogduk (2003) has recognized that the spinal dura is innervated. Cailliet (1988) has further shown that the dura is innervated by sympathetic C-fibers. Ombregt et al. (2003) and Butler (1991) have postulated that certain pain perception patterns occur when the pain nerves on the dura are stimulated.

Certainly, these diffuse patterns do not even vaguely resemble dermatomal distributions. They are much more widespread than the limited zones of referred trigger point pain. For instance, dural nerves stimulated by scar tissue in the lumbar region may result in perceived pain and discomfort throughout the legs.

Kernig's and Brudzinski's signs, i.e., the meningeal signs (Gerard & Kleinfield, 1993), are reminiscent of this same phenomenon. By definition, these are consistent with meningeal irritation, i.e., dural irritation, where A-delta and C-fiber pain nerve endings occur, anteriorly and laterally (Cailliet, 1988).

Thermatomes

There are thermal patterns of pain, which are probably related to the distribution of sympathetic C-fibers nerves and with sympathetic chain pathway components, without shorting, crossing over, emphatically to the A-delta fiber pathways.

Hooshmand (2000) has coined the word *thermatomes* to describe referred pain patterns related to the circulatory distribution of sympathetic C-fiber nerves. These relatively amorphous distributions are consistent with the observation that these C-fiber nerve pathways end up seeing pain "through fogged glass."

If we think of the possible evolutionary origin of the sympathetic chains, which in lower animals transmit all efferent and afferent nerve impulses, those pathways should be able to reestablish transmission pathways in compensation, much like collateral circulation.

Facial Referral Patterns

Pain referral patterns in the innervation of the face and anterior neck are not completely appreciated by healthcare professionals.

Guyton & Hall (2000, pp. 558–560) show that:

Nasal sinus and eye aches radiate to a wide area around the eyes from below the nose and up to mid-fore.
Cerebral vault aches occur frontally to parietally at the ear.
Brainstem and cerebellar vault aches occur from the ear through the entire occiput.

Phantom Pain (Woessner, 2003)

Phantom sensations and pain are well-described phenomena, which means that the brain perceives the existence of a body part, from which no nerve impulses could possibly be emanating.

In a sense, phantom pain is the ultimate "referred pain." Perceived pain location is obviously not where the pain is originating because there cannot be peripheral pain nerve stimulation. Stump and neuroma pains are separate pain phenomena and are not referred pain, and therefore, these pains are not phantom pain. There is surprising confusion about these, i.e., stump and neuroma pains versus phantom pain.

Referred Pain Due to Healing Pain Nerves

Healing nerves and tissue cause pain by the following:

1. Inflammation is part of the healing process; the natural chemicals involved are caustic to pain nerve endings. The treatment dilemma here is if you stop the pain with anti-inflammatory medications, do you not also stop the healing?
2. Consequent muscle spasms occur. Spasm or cramping muscles change, usually decrease circulation; ischemia causes pain by causing a caustic microenvironment around nerve endings. In addition, the spasm/cramping muscles are causing pressure on the A-delta and C-fibers that occur in the myofascial tissue planes.
3. Improper healing of any tissue can reasonably contort it and cause pain and dysfunction; such nociceptive pain is caused by pressure on and/or caustic chemical environment around the nerve endings; neuropathic pain would come from the changed neuroanatomy, thus changed neurophysiology, and also from the changes in the chemical microenvironment.

HOW, IN THE END, DOES PAIN AND REFERRED PAIN CLASSIFICATION HELP?

For nociceptive pain, the primary goal is to resolve ("cure") or remove the stimulant, i.e., the causative pathology, while covering up the pain. For neuropathic pain, the goal is to stop the irritation and promote rebuilding the damaged nerves or normalization of their function. For central pain, the goal is to employ techniques to change the central nervous system neural environment. For antinociceptive pain, the goal is to normalize pain perception and reestablish natural painkiller production and function.

The ultimate approach for effectively treating pain is individualizing and balancing the various approaches for optimal results in complex chronic pain cases. By understanding the underlying mechanisms, physicians clearly have a better chance of effectively serving their patients with better pain relief. Suffering is probably the most difficult part of pain to quantify and treat. However, it is expected that suffering will improve as we improve our abilities to treat pain.

SUMMARY

Pain classification depends on the understanding of pain mechanisms. The more we know about these mechanisms, the more likely we are to apply the appropriate terms to the pain conditions that we see in our clinics. We cannot abandon the time-honored names that we are using.

Basically, there are two categories, i.e., nociceptive and neuropathic pain. Eudynia and maldynia, respectively, may actually be more useful terms because the accepted terminology may be limited by the historical processes involved in pain (condition) classification. Accurate consideration of these basic concepts should be applied to every pain condition encountered by the practitioner in order to plan appropriate treatment of the pain.

Referred pain is neuropathologic, i.e., not nociceptive. Referred pain is important because it may have diagnostic value. Referred pain adds another layer of complexity to the process of making a diagnosis. Making the diagnosis by artfully and systematically combining the findings obtained from the clinical history and physical examination allows the clinician to formulate a coherent treatment plan.

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5

Culture and Pain

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INTRODUCTION

The growing attention that is given to understanding the influence of culture on pain stems from a number of factors that go beyond intellectual curiosity. Growing public interest in the treatment and palliation of pain, advanced technology to manage symptoms, and an increasingly diverse consumer base all combine to prompt culturally mediated issues of whether to relieve pain, for whom, with whom, how, when, and under what circumstances. The national commitment to eliminate disparity in health care outcomes along with the fact that most persons suffering health inequity are culturally and linguistically distinct compels further understanding of the relationship between culture and pain. As evidenced by emerging research, policies, and professional statements on diversity and pain, it is clear that scholars, policy makers, and clinicians are hopeful that advancing understanding of how culture informs pain experiences will contribute to optimal pain-related interventions.

The complexity of both concepts, culture and pain, has encouraged variable interpretations. Although pain is considered systemic, context dependent, multidimensional (e.g., biological, cognitive, emotional, social, and spiritual) and substantially affected by personal values and cultural traditions (Morris, 1998), culture implies an ongoing multilayered dynamic process of accepted ways of seeing, experiencing, interpreting, and expressing experiences affected by social processes and historical epoch (Moore, 1994; Shore, 1996). Models that attempt to explain pain relationship to culture generally assert that (1) pain is more than a simple neurological response to physiological injury and disease; (2) pain has mental-emotional, cultural, spiritual, and historical dimensions; (3) pain can be influenced by personal values and spirituality as well as multiple layers of context including cultural traditions and social dislocation or disharmony; (4) pain is subjective and can only be defined by the individual; and (5) pain can be partly fabricated out of imagined lives and possible social exigencies (Bates, 1987; Glucklich, 2001; Jackson, 1994; Kleinman, 1994; Melzack & Wall,1983; Moore, 1994; Shore, 1996).

In line with current discussions that resist "ethnizing" culture, that is, limiting culture to ethnicity alone, a broader definition offered by the Office of Minority Health (Meadows, 2001, p. 1) is used here: *Culture* refers to integrated patterns of human behavior that include the language, thoughts, communications, actions, customs, beliefs, values, and institutions of racial, ethnic, religious, and social groups. A related concept, *cultural and linguistic competence*, refers to a set of congruent behaviors, attitudes, and policies that come together in a system, in an agency, or among professionals that enables effective work in cross-cultural situations. In turn, *competence* implies having the capacity to function effectively as an individual and an organization within the context of the cultural beliefs, behaviors, and needs presented by consumers and their communities (Meadows, 2000, p. 1).

The focus of this chapter is not to review the broad and complex topic of culture and pain or the accumulated findings on how culture influences pain, as that would require a book of several thousand pages, even for the parsimonious writer. Instead, this chapter focuses on addressing topics that are elementary yet important to current discussions of culture and pain, particularly in terms of appropriate and just responses to pain across cultures and linguistic traditions. This chapter encourages a broader understanding of culture and pain by briefly

addressing current thinking in the analysis of culture and pain and select challenges encountered when attempting to understand culture. Potential areas for cross-cultural tension are considered in this chapter, as is research that points to disparate outcomes on pain relief across sociocultural groups. Other topics addressed in this chapter are the importance of language when addressing culture and pain, standards for cultural and linguistic competence, and multilevel cultural and linguistic competencies that can help anticipate, mitigate, and perhaps prevent cross-cultural tension. Finally, the chapter concludes by considering challenges and opportunities to advance the effectiveness and equity in the treatment or care of pain across cultures. The choice of topics is driven by two notions: (1) better understanding of culture in an increasingly culturally and linguistically diverse world contributes to appropriate and just clinical outcomes; and (2) equity in the treatment of pain requires multilevel cultural and linguistic competencies. While the discussion in this chapter points to classic and current sources, it does not represent the extant literature that addresses culture and pain.

TOWARD A BROADER UNDERSTANDING OF CULTURE OF PAIN

Our understanding of culture and pain has advanced steadily over the last 52 years since Zborowski's classic work (1952) opened the study of pain to cultural comparisons, now regarded superficial in theory and method (see Delvecchio Good, Brodwin, Good, & Kleinman, 1994, p. 2). Our current level of analysis of culture and pain has moved beyond cultural comparisons and explorations of how meaning shapes pain experiences to one that addresses pain as a deeply personal feature of lived experience of individuals in the context of their social world and historical era. Individuals experiencing pain are not regarded as passive to the potential influence that culture can have on their perception and response to pain, but are seen as active in mediating (i.e., accepting, rejecting, modifying) cultural messages and other levels of social context that may or may not be within their control (Janes, 1999). In addition, current thinking on the influence of culture and pain considers all clinical encounters as cross-cultural, relational, and affected by imbalances of power. The multiplicity of factors, including personal values and cultural traditions that influence the attitudes about, perceptions of, and responses to pain take on special significance in clinical settings where pain becomes an interpersonal experience between the consumer and clinician and where therapeutic control is vested in the clinician (Farber Post, Blustein, Gordon, & Dubler, 1996). Current understanding of culture and pain has rediscovered the relationship between culture and voluntary pain. Current thinking reminds us that the experience of pain, whether observed through the athlete who endures, the person who elects to undergo tattoos, the woman who elects child birth without analgesics, can signify something other than disintegration (Glucklich, 2001). Finally, current thinking does not limit culture to ethnicity but considers it to emerge from other sociocultural categories such as age, gender, religion, ablement, sexual orientation, race, national origin, linguistic tradition, and socioeconomic status.

Our broader and deeper understanding of culture and pain has encouraged developments that are certain to enhance the treatment and palliation of pain. This broader understanding of culture and pain discourages the temptation to overassign importance to cultural descriptions of groups, particularly those that are elevated above person, time, and situation and void of culture-bound information on sociocultural categories across the diversity spectrum. Current emphasis on the distinctive intimate experience of pain-in-context prompts clinicians and their sponsoring institutions to acquire multilevel competencies to best understand personal cultures and serve persons-in-their-pain experience. The renewed attention to voluntary pain and the premise that pain can be regarded a good thing that can enable a sense of belonging or connectedness challenges clinicians to think and prepare broadly to respond competently to diversity. Current thinking on culture and power that interact in clinical encounters to produce disparate outcomes has advanced commitment to explore the sources of inequity in pain relief. The emphasis that current thinking places on the complexity of culture in relationship to pain encourages clinical and scholarly engagement across disciplines, interdisciplinary rather than multidisciplinary, to more holistically and appropriately respond to pain.

Despite the advances made in our understanding of culture and pain, this field of study is in an early stage of development. Routes, patterns, and end points of cultural influence are considered complex and to reflect the multifaceted exchanges between culture and individual pain-related cognition, emotion, behavior, and spirit remains a challenge. Deeper understanding of what culture and pain mean and the processes that shape their meaning remain in development. The recent commitment by at least 15 National Institutes of Health (NIH, 2001) to support research on the social and cultural dimensions of health communicates the importance of advancing our understanding of culture and counters the tendency to use the term superficially and mechanically. While better information on how culture influences pain is being obtained, applying what is known can help allay cross-cultural misunderstandings. The following section discusses select aspects of culture that are known to challenge our grasp of its nature and influence.

CHALLENGES IN UNDERSTANDING CULTURE

A number of factors can make our understanding of cultural influences on pain particularly challenging. Understanding some of these factors permits a more accurate understanding of cultural diversity that guards against blind spots in our assessment and response to cultural difference. First, there are a great many cultures and within each single general culture, except for certain minority religious or ethnic groups (Yazar & Littlewood, 2001), there is substantial intracultural of variation, often related to other subcultural categories such as gender, age, religion, race, ablement, national origin, linguistic tradition, sexual orientation, and socioeconomic location (Miller & Eskin, 2001). The value that a specific Latina places on pain, for instance, may not be entirely a function of her ethnicity, but related to the cultural underpinnings of her religion and age, as well as the cultural construction of womanhood that assigns meaning to some of her pain. In contrast, this Latina woman's sister, who is agnostic, 10 years younger, resentful of culturally mediated messages of womanhood, and relatively removed from her Latina origins, considers all pain dehumanizing and requiring relief.

Second, due to its dynamic nature, culture changes across time. For example, discourse on the history of pain reminds us that pain lost much value after anesthetics were invented and applied in the 20th century (Cusick, 2003; Glucklich, 2001; Morris, 1991). In most general terms, this cultural shift transformed pain into a medical problem, of physical matter, and one devoid of meaning and function, thus relegating voluntary pain to deviant status.

Third, cultures intersect and persons acculturate. Defined as a multidimensional, multidirectional, developmental, interactive, and adaptive process of cultural adjustments experienced by individuals (Cuellar, Arnold, & Maldonado, 1995; Padilla & Perez, 2003) and groups (Berry, 1997; Berry & Sam, 1996), acculturation blurs cultural boundaries and creates variants of all aspects of culture. Individuals, particularly if presented with alternate forms of viewing phenomena, may reject, accept, or adapt culturally mediated messages related to pain (Johansen, 2002), not always in a definable pattern.

Once pain is suffered, it may be experienced differently by the same individual over time. For instance, a Mexican laborer who migrates from a small village in Mexico to the United States confronts an assessment of his pain that is contrary to his own. While in his native village his pain is regarded as a necessary part of living and spiritual transformation, in migration he experiences a society where pain is considered something that should be avoided. This can lead to a transformation of the pain experience, from necessary and meaningful to unnecessary and even destructive. Johansen (2002) shows, from her study of pain associated with infibulation among Somali immigrants in Norway, that the contexts in which pain is originally suffered and subsequently remembered can affect the pain experience and its management. The implication is that not everyone from every culture group conforms all the time to a set of expected behaviors or beliefs, particularly in the face of acculturation. Cultural stereotyping (e.g., assuming that a person of Chinese heritage is stoic about pain) can contribute to inaccurate assessment and treatment of pain.

Fourth, not all behaviors are culturally based. For instance, a First Nations person who remains nonverbal during a clinical interview may not be signaling a cultural or linguistic tendency, but rather his or her resistance to the clinician's poor interviewing skills. Responses related to overwhelming pain may be void of culture as well. Intolerable pain with its mortifying character, referred to as "unmaking" of the world (Scarry, 1985), is considered a noncultural or even an anticultural experience (Jackson, 1994). The "unmaking" or counterpoint to culture that insurmountable pain may evoke is said to be due to the duration, intensity, and meaninglessness of the experience. Developing competencies to skillfully engage and interview for accurate assessment and corroboration across cultures and linguistic traditions guards against inaccurately assigning cultural significance to behavior.

Finally, in the midst of deterritorialization, the character of modernity whereby ethnic groups and communities, among other social formations, operate according to principles that transcend territorial boundaries and identities (Appadurai, 1991), it is increasingly hard to make specific local cultural assignments. Appadurai suggests that in our deterritorialized world, intertwined by the effects of media, technology, migration, tourism, and global markets, individuals belonging to what were once circumscribed local communities now are invited to imagine and envision alternative lives. Given this aspect of our postmodern world, Appadurai (1991) posits that the notion of symbolic pain may become more extraordinary both for the observer and participants. Among the many implications of Appadurai's forecast, greater cultural variation will require more attention to skillful assessment of personal cultures during clinical encounters. *Personal culture* has been defined by Pack-Brown and Braun Williams (2003) as the "organized, dynamic totality of an individual's identity … comprised of historical, political, and economic dimensions, including religion, work experience, parental status, sexual orientation, gender and so forth" (pp. 230–231).

Understanding culture and its relationship to pain assumes special significance in clinical settings where pain becomes an interpersonal and cross-cultural experience between the consumer and clinician. The culture of Western medicine, prominent and powerful in clinical settings, provides the principal basis for the cross-cultural nature of clinical encounters. The following section briefly

discusses medicine as a culture and potential areas in which cross-cultural tension can arise.

WESTERN MEDICINE AS CULTURE AND POTENTIAL CROSS-CULTURAL TENSION

Most clinical encounters responding to pain can be expected to be cross-cultural and thereby hold the potential for cross-cultural tension. This assertion is more obvious if Western medicine is viewed as the prevalent culture operating in clinical encounters and one that is at odds with those of consumers. Cultures of health care providers, growing in number as many cross national boundaries to fill labor shortages, operate in clinical encounters as well. This section briefly discusses medicine as culture and potential cross-cultural tension as it relates to culture-bound principles.

While some of Western medicine's core values, metaphors, beliefs, attitudes, and themes are not found problematic by some persons, particularly those receiving Western medical training and indoctrination, they may be considered challenging, if not threatening, by persons who are ill and in pain. Persons in pain, feeling highly dependent on others and in-the-present with their pain, may have difficulty accepting medicine's value orientation, which favors activity, mastery over nature, individualism, and future mindedness (see Stein, 1990, for an ethnographical account of American medicine). The potential for tension between clinicians and consumers is appreciated further when key components of Western medicine's world view are considered:

> (1) the "basic sciences": anatomy, physiology, biochemistry; microbiology, pathology; (2) the belief that medical science is and should be based upon rational, scientific, dispassionate, objective, professional judgment; (3) the belief that disease and its attendant suffering are ultimately to be understood in terms of pathological entities, organic in nature, and that treatment optimally consists of a technological procedure or interventions that results in a cure; (4) the belief that medical knowledge and skills are best organized by creating specialties around "organ systems." (Stein, 1990, p. xiv)

Comparing medicine's worldview with that of other groups, particularly those who encounter a disproportionate burden of inequity in the treatment and care of pain, demonstrates that the potential for cross-cultural conflict is substantial. Western medicine's tendency to distinguish illness into distinct mental and physical spheres can lead to conflict with individuals who integrate mind and body with social and natural universes (Ulusahin, Basaglu, & Paykel, 1994). Moreover, the holistic system that is frequently associated with an integrated system of prevention and healing that attributes psychological distress to physical imbalance and conversely assigns the cause of physical illness to spirits or the evil eye challenges Western medicine's world view (Avila with Parker, 2000; Mirdal, 1985). Similarly, religious medicine across cultures that are grounded in beliefs that pain can be spirit-imposed and that the sacred word or touch can lead to healing (Glucklich, 2001; Littlewood and Dein, 1995) is in direct contrast to Western medicine's worldview. Medicine's worldview as outlined is even at odds with the widely held understanding that pain is a subjective experience influenced by multiple factors that fall outside the basic sciences.

The potential for cross-cultural tension is compounded when values and beliefs that surface in clinical encounters involve major philosophical commitment to what is "good" and what is "bad." For this reason, the potential for cross-cultural tension is considered in relationship to select ethical principles that operate in clinical settings, namely, in decision making. The principles that are considered here include those that hold the most potential for generating cross-cultural tension: autonomy, beneficence, nonmaleficence, and fidelity (for discussion on ethics across cultures, see Braun, Pietsch, & Blanchette, 2000; Farber Post, Blustein, Gordon, & Dubler, 1996; Pack-Brown & Braun Williams, 2003).

Autonomy

Autonomy is a central principle in Western cultures that reflects the core values of individual rights, independence, and self-control (Zaner, 1988). Autonomy receives widespread support publicly, administratively, and legally, yet can be at odds with individuals who are family and group oriented. There is growing evidence that a number of groups, distinguished by age, gender, and ethnicity, prefer alternate models of decision making, models that subscribe to communitarian or hierarchical standards. Autonomy in these groups may be shared with their "families" or transferred to others, including clinicians who may be viewed as holding the knowledge and power needed to make the best decisions. Family-centered models of making decisions have found support in a number of studies (Blackhall, Murphy, Frank, Michel, & Azen, 1995; Morrison, Zayas, Mulvihill, Baskin, & Meier, 1998).

An associated cultural script, that of filial responsibility (Berger, 1998), which refers to the expectation that family members are expected to assist in some manner, may also come into conflict with the principle of autonomy and those who support it. Filial responsibility can cue family members to assist the patient in self-care functions that clinicians desire the patient to do on his or her own. Patients and families who prefer to be together for protective, instrumental, or supportive purposes can be regarded as disruptive and interfering by clinicians who endorse autonomy. Culturally competent clinicians

addressing the relief of pain not only assess the patient's and family's moral basis for making decisions, they assess the role that the family assumes in the treatment and care of pain.

Beneficence and Nonmaleficence

While beneficence refers to the principle to do good, nonmaleficence refers to the principle to cause no harm. Because notions of what constitutes "good" and "harm" are value driven and culturally bound, we can expect certain interventions considered "beneficial" by Western standards to be viewed as harmful by some culturally distinct groups. Instances of conflict between varying perspectives of what is "good" and "not harmful" to the consumer system (patient and family) often underlie consumer choice not to take prescribed pain medication or to resist treatment altogether. The clinical challenge is to establish a working relationship built on trust and to rely on strong foundational interviewing skills to accurately assess consumer perceptions of "goodness" and "harm," as well as the basis for their choice to reject treatment. Much research has been committed to examine differing perceptions of what is regarded as "good" and "harmful" treatment (Carrese & Rhodes, 1995; for interesting and detailed account of cross-cultural conflict between Hmong consumers and Western medicine, see Fadiman, 1997).

Fidelity, Veracity, or Truth-Telling

A perceived fundamental duty of clinicians in Western medicine contexts to disclose information of medical status supports values related to self-determination and informed consent (Zaner, 1988). The culture-bound value of "accepting" diagnoses and prognoses, which requires full disclosure of medical status, has encouraged unflinching disclosure by clinicians. Direct disclosure can engender conflict with culturally distinct groups whose members may consider disclosure as inflicting unnecessary pain, such as Latinos (Blackhall et al., 1995), Hmong (Fadiman, 1997), Navajos (Caresse & Rhodes, 1995; McCabe, 1998), and Japanese (Kalish & Reynolds, 1976). Cultural competency calls for accurately assessing consumers' moral code on disclosure (e.g., who determines whether to disclose "truth," when is it shared, who shares it, with whom is it shared, how is it shared, and how much is shared?), in a timely manner. An institutional-level competency related to truth-telling encourages policies that dually protect a consumer's right to determine his or her own moral code on disclosure and the institution's need to guard against potential charges of negligence to disclose.

Attention to the interrelational, cross-cultural, and tension-prone nature of clinical encounters can help anticipate, mitigate, and prevent consumer–clinician conflicts. More importantly, attention to potential cultural misunderstanding and misuse of therapeutic control can help avert inequity in clinical outcomes. The following section summarizes research that addresses inequity in pain relief.

DISPARATE PAIN RELIEF OUTCOMES ACROSS SOCIOCULTURAL GROUPS

A growing body of literature that addresses potential inequity in clinical outcomes related to pain has been evolving and providing evidence that group-based differences, associated with culture, are related to pain-related clinical outcomes. Although this body of literature uses language and ethnicity to reference culture and ignores gender and age as cultural subcategories, its findings are worthwhile noting. A caveat when interpreting these studies is that factors that could help explain disparate outcomes are unknown (e.g., pain attitudes and perceptions, understanding and expectations of treatment, and the nature of patient–clinician interaction).

Select findings from this body of scholarship show that disparities in the treatment of pain by sociocultural categories are not due to chance alone and are evident in fracture treatment (Jones, Johnson, & McNinch, 1996; Todd, Deaton, D'Adamo, & Goe, 2000; Todd, Lee, & Hoffman, 1994; Todd, Samaroo, & Hoffman, 1993), postoperative pain following limb fracture (Ng, Dimsdale, Shragg, & Deutch, 1996), cancer pain (Bernabei et al., 1998; Cleeland, Gonin, Baez, Loehrer, & Pandya, 1997), migraine, and back pain (Tamayo-Sarver, Hinze, Cydulka, & Baker, 2004) and for persons in long-term facilities (Won et al., 1999).

In a particularly notable series of studies, Todd and associates (Todd et al., 1993, 1994, 2000) demonstrated that African Americans and Latinos were significantly less likely to receive analgesia in emergency departments for isolated bone fractures than were Whites, even though physicians rated patients' pain as similar in severity. Findings from a larger-scale study using 1997–1999 National Hospital Ambulatory Medical Care Surveys and involving a substantial sample size (N = 67,487) did not show differential administration of analgesics for long-bone fractures in emergency departments, yet revealed that Black patients with back pain and migraines were less likely to receive opioids in comparison with their White counterparts (Tamayo-Sarver et al., 2004). Relevant research suggests that not only may physicians have more negative perceptions of minority patients, but opioids may raise physician concerns that the patient may be seeking opioids in order to satisfy addiction or to sell them (van Ryn & Burke, 2000). Another study that did not find potentially unjust medication patterns for long-bone fractures in an emergency department suggests that hospitals serving larger ethnic minority populations may be best prepared

to address cultural and linguistic difference (Karpman, Del Mar, & Bay, 1997.)

In a study that examined analgesic administration with patients treated surgically for limb fracture (Ng et al., 1996), significant differences by ethnicity in analgesic administration were found. Based on data gathered from chart reviews, the researchers found that while White patients received 22 mg/day of morphine equivalents, their Black and Hispanic counterparts received 16 and 13 mg/day, respectively. The researchers (Ng et al., 1996) suggest that patient–provider interaction during clinical encounters may partly explain differences in analgesic administration.

Findings from studies that focus on cancer-related pain are equally noteworthy. One study reported that 65% of the patients referred to as minority did not receive guideline-recommended analgesic prescriptions for their cancer-related pain compared with 50% of nonminority patients (Cleeland et al., 1997), with Latino patients at primary risk. Another study reported that older persons of ethnic minority groups who have cancer were at risk of receiving less medication or even no medication for daily pain (Bernabei et al., 1998).

Disparity according to age has been reported as well. In one study that examined analgesic administration with patients with fractures, it was found that persons aged 70 and older received less medication and had to wait longer than patients aged 20 to 50 (Jones et al., 1996). A study involving nursing home residents reported that persons older than 85 years, males, or members of non-European White group were less likely to receive pain medication even when pain was acknowledged in the patients (Won et al., 1999). Pain Management Index scores in a study that examined outcomes of pain management and predictors of patient satisfaction in hospitalized Latino patients reporting pain revealed less effective pain management with older persons (McNeill, Sherwood, Starck, & Nieto, 2001).

Disparity in pain management has also been found to vary according to gender. In a study that assessed pain management across groups (Breitbart, Rosenfeld, Passik, McDonald, Thaler, & Portenoy, 1996), it was found that besides patients with less education and those with histories of drug abuse, women were most likely to be undertreated. In another study, women were given analgesics less often and sedatives more often than men by physicians and nurses because they were seen more emotionally labile and prone to exaggerating pain symptoms (Calderone, 1999).

Inequity in pain relief at the community level has been documented as well. A study that examined the distribution of pain medication in neighborhoods (Morrison, Wallenstein, Natale, Senzel, & Huang, 2000) reported that only 26% of pharmacies in predominantly ethnic minority neighborhoods in comparison with their European American counterparts had sufficient opioid analgesics for someone with severe pain.

Although research examining group-based inequality in the treatment and care of pain is at an early stage of development, findings show that disparate outcomes in pain relief are widespread. The commitment to eliminate inequity in pain treatment outcomes directs our attention to multilevel approaches that can contribute to this goal. The following section briefly addresses the importance of language to the topic of culture and pain and provides resources that support efforts to advance cultural and linguistic competency.

THE IMPORTANCE OF LANGUAGE TO CULTURE AND PAIN

Although it has been proposed that pain is uniquely private, subjective, and beyond the construction of language (Daniel, 1991; Scarry, 1985), prevalent discourse on the topic of pain and culture asserts that pain indeed has language (Asad, 2000; Fabrega & Tyma, 1976; Glucklich, 2001; Jackson, 1994), albeit sometimes muted, silenced, and redirected such as through somatization. The function of language to label and communicate bodily sensations and meaning (Villaruel, 1995), besides delivering messages of empathy and hope, points to the need to give language its scientific and clinical due.

While researchers are called to test communication approaches designed to effectively engage linguistically distinct persons affected with pain, clinicians are called to understand culturally and linguistically distinct consumers who use different gestures and terms, even in English, to convey aspects of their pain experience. Both verbal and nonverbal messages need to be accurately interpreted in order to best respond to the pain experience. In turn, the terminology and communication approaches that are used with consumers and their families must be chosen carefully (Salimbene, 2000), even if they are English speaking. Moreover, the clinician is expected to communicate to the consumer what she or he has understood.

Attention to language is particularly warranted given the expanding linguistic diversity across the world and the disparate health care outcomes that are attributed to linguistic difference. Today, as documented by the U.S. Census Bureau (2000), more than 4.6 million people in the United States report not speaking English as their primary language, and more than 21 million report speaking English less than "very well." More astounding is the U.S. Census report that more than 300 languages are spoken in the United States. Persons who report having limited English proficiency are less likely to have a regular source of primary care (Kirkman-Liff & Mondragon, 1991; Weinick & Krauss, 2001); to undergo surgery, such as cholecystectomy (Diehl, Westwick, Badgett, Sugarek, &

Todd, 1993); and to receive preventive care (Woloshin, Schwartz, Katz, & Welch, 1997) and more likely to experience medical errors (Ghandi, Burstin, Cook et al., 1998). Moreover, persons who report having limited English proficiency report less satisfaction with the care they receive (Carrasquillo, Orav, Brennan, & Burstin, 1999; Morales, Cunningham, Brown, Honghu, & Hays, 1999). Ample evidence suggests that failure to address language and cultural issues can result in inferior quality of care, adverse outcomes, and increased health care costs (Baker, Parker, Williams, Coates, & Pitkin, 1996; Flores, Abreu, Olivar, & Kastner, 1998; Flores, Abreu, Schwartz, & Hill, 2000; Harsham, 1984).

Both federal and state laws mandate that health care organizations provide appropriate linguistic access for consumers with limited English language skills. (*Note:* While current reference to consumers who have limited English language skills is *limited English proficient [LEP] patients*, this author prefers to "place consumers first," followed by the descriptive phrase to avoid risk of labeling. The ideal would be to let consumers communicate their preference for how they would like to be categorized.) Accreditation agencies such as the Joint Commission on the Accreditation of Health Care Organizations (JCAHO) and the National Committee on Quality Assurance (NCQA) set standards and monitor compliance in language services, in addition to other health care services. The Office of Civil Rights' (OCR) "Policy Guidance on the Prohibition Against National Origin Discrimination as It Affects Persons With Limited English Proficiency," which applies to part of Title VI of the 1964 Civil Rights Act, aims to ensure equity in critical health and social services to persons with limited English language skills (Ross, 2001). Signed in August 2000, the OCR policy guidance outlines the legal responsibilities of providers who receive federal financial assistance from Health and Human Services (HHS) including:

- Develop a plan for providing written materials in languages other than English
- Establish policies and procedures for identifying and assessing language needs of the individual provider and its client population
- Provide a range of oral language assistance options, appropriate to each facilities circumstances
- Provide notice to persons with limited English language skills of the right to free language assistance
- Provide staff training and program monitoring (Ross, 2001, p. 2)

There are a number of resources available for clinicians and sponsoring institutions that need support in providing linguistic and cultural competent treatment of care: the Department of Health and Human Services (DHHS) Office of Minority Health (OMH; http:www.omhr.gov); American Translators Association (http://www.atanet.org); National Center for Cultural Competence (http://gucdc.georgetown.edu); Office for Civil Rights (http://www.hhs.gov/ocr); the American Medical Association's Cultural Competence Compendium (http://www.ama-assn.org/ama/pub/category/3066.html); and Cross Cultural Health Care Program (http://www.xculture.org) to list a few. The National Council on Interpreting in Health Care (NCIHC; http://www.ncihc.org), a multidisciplinary organization dedicated to promoting cultural and linguistic competent care in the interest of health care equity, provides a number of valuable Web site resources including working papers that are relevant to linguistic competence, an evaluation tool to assist organizations in assessing their linguistic needs, and links to related Web sites.

The challenge of arriving at approaches that can most appropriately assess and treat pain across cultures and linguistic traditions demands an array of multilevel competencies in various domains including knowledge, skills, and values. While the notion of achieving a *set of competencies* that permits effective work across cultures is commonly regarded as *cultural competency*, the terms are variously defined and designated (Boyle & Springer, 2001). The assortment of definitions of cultural competency and standards for cultural competency that have been drafted, while begging for uniformity, attest to the importance placed on improving outcomes and eliminating inequity in health care. (The terms *competence* and *cultural and linguistic competence* are defined earlier in this chapter.)

STANDARDS AND APPROACHES FOR MULTILEVEL CULTURAL AND LINGUISTIC COMPETENCIES

Most literature on cultural and linguistic competence primarily focuses on conceptual exploration and neglects the assessment of the theorized structure and outcome of cultural and linguistic competency. There is little evidence available on what cultural and linguistic competencies, applied when and in what fashion, work best. There is less information available on what training or background best conditions specific cultural and linguistic competencies.

Despite the limited direction that scholarship provides in the training, measurement, and clinical application of cultural and linguistic competencies, many human service and health care settings seem to be ambitiously working toward cultural and linguistic competency. Approaches and guidelines for cultural and linguistic competency, largely based on practice, observation and wisdom, have emerged in rapid fashion and are too many to reference here. This section briefly discusses national

standards for cultural and linguistic competency and outlines select multilevel competencies.

Standards for Cultural and Linguistic Competency

The first set of national *Standards for Cultural and Linguistic Competence* in health care delivery, released recently by the OMH (Ross, 2001) of the U.S. DHHS, as a result of the its Cultural and Linguistic Competence Standards and Research Agenda Project, represents an important step toward a more uniform and comprehensive approach to culturally and linguistically appropriate services (CLAS). The 14 standards are based on an analytical review of key laws, regulations, contracts, and competence standards and measures used by federal and state agencies and national organizations. The standards' aims are not only to ensure that services are more responsive to the individual needs of all consumers; the standards aim for health care providers, policy makers, and others in the health care community to create accountability within their organizations for providing equitable, quality services (Ross, 2001).

Evolution of instrumentation to measure and assess the status of cultural-linguistic competency has been slow but is gaining momentum (see Boyle & Springer, 2001, for discussion of well-known measures). As mentioned previously, the NCIHC offers a multilevel process by which health care organizations can evaluate their existing structure and capacity for providing linguistically and culturally appropriate care and accessibility. In a report entitled, *Cultural Competency Methodological and Data Strategies to Assess the Quality of Services in Mental Health Systems of Care: A Project to Select and Benchmark Performance Measures of Cultural Competency,* produced by the New York Office of Mental Health, the Nathan Kline Institute for Psychiatric Research, and Center for the Study of Issues in Public Mental Health (2002), a conceptual framework that explains multilevel pathways toward cultural competency, operationalization of all concepts, and data sources for each measure proposed is offered.

Multilevel Cultural and Linguistic Competencies

A number of approaches or guidelines to help advance cultural and linguistic competencies in health care have been offered (Bakker, 1995; Flores et al., 2000; Galanti, 1997; Hizar, Shearer, & Giger, 1997; Koenig & Gates-Williams, 1995; Purnell & Paulanka, 1998; Salimbene, 2000; Spector, 2000) and are too many to fully enumerate here. While these guidelines are designated for specific health care settings, consumers, or health statuses, most are similar in that they propose multilevel competencies in the domains of knowledge, skills, and values. Most guidelines are relevant across cultures, settings, and health or illness focus. This section focuses on summarizing eight competencies that are considered basic for cultural and linguistic competent care. Among the many competencies that have been proposed as important, Table 5.1 provides added information on the competencies that are considered basic by this author:

- Understand self in relationship to others
- Understand culture
- Value cultural beliefs and diversity
- Establish and sustain working relationships
- Recognize linguistic complexity
- Facilitate learning between providers and consumer communities
- Involve community in defining and assessing needs
- Professionalize staff hiring and training
- Institutionalize cultural and linguistic competency

Kleinman's often-quoted set of eight questions (Kleinman, 1988; Kleinman, Eisenberg, & Good, 1978), which is designed to elicit a person's explanatory model for his or her illness, is regarded as a useful guide by many person-centered clinicians who view consumers as experts of their lived-with-pain experience. The questions when addressed and adapted skillfully can be considered a classic approach to cultural competency that holds currency in modernity: (1) What do you call your problem [pain]? (2) What do you think caused your problem [pain]? (3) Why do you think it started when it did? (4) What do you think the sickness [pain] does? How does it work? (5) How severe is the sickness [pain]? Will it have a long or short course? (6) What kind of treatment do you think you should receive? What are the most important results you hope to receive with this treatment? (7) What are the chief problems [and benefits] the illness [pain] has caused? (8) What do you fear most about the [pain]?

CONCLUSION

The moral imperative to treat or palliate pain effectively and appropriately faces the challenge of adjusting to an increasingly diverse consumer base that is not only culturally and linguistically distinct, but subject to a disproportionate burden of disparate outcomes, including inadequate pain treatment. Our commitment to optimally respond to pain and to achieve equity in doing so requires a combination of sustained efforts. Further research on what culture and pain mean as well as on the routes and patterns of cultural influence on pain can provide needed information to improve not only the treatment and care of pain but also its prevention, when appropriate. While efforts to advance cultural and linguistic competency in the treatment and care of pain need continued philosoph-

TABLE 5.1
Approaches to Culturally and Linguistically Competent Care

- Understand self in relationship to others
  - Become aware of our own cultural background
  - Know how our cultural heritage affects our definitions of normality and abnormality
  - Recognize the stereotypes and preconceived notions that we hold of others
  - Understand how we socially impact others
  - Recognize the limits of our competencies and expertise
- Understand culture
  - Acquire broad knowledge of cultural and subcultural groups
  - Regard potential culture-specific information as tentative insight and not an "end point" to understanding
  - Understand how subcultural categories based on shared attributes and shared life experiences contribute to a person's "personal culture"
  - Recognize the challenges present in understanding culture
  - Acquire practical, experience-based knowledge about the community being served (e.g., Chinese teaspoons are generally larger than American ones)
- Value cultural beliefs and diversity
  - Respect cultural orientation, including beliefs of moral goodness
  - Acknowledge decision-making preferences
  - Avoid assuming anything
  - Avoid making judgments
  - Avoid the "golden rule"
  - Trust that pain is whatever the consumer says it is
  - Communicate acceptance
  - Incorporate consumers' models of care with treatment plan
- Establish and sustain working relationships
  - Develop and use communication and facilitative skills (e.g., empathy, genuineness, warmth) to build trust, accurately assess, corroborate clinical observations, and negotiate conflicts
  - Appropriately and accurately assess background, decision-making preferences, and culturally mediated beliefs, theories, and practices related to health, illness, pain, suffering, healing, caring, treatment types, health care providers, families
  - Operate from strengths' perspective
  - Regard consumer as expert and having the best understanding of the pain, what has helped, what has not helped, and what is likely to help
  - Evaluate what beliefs would interfere with your treatment plan
  - Effectively explain culture and orientations from which you are operating
  - Be conservative in relating news or in providing details of potential complications
  - Encourage procedures that affirm consumers' values (e.g., have larger conference rooms and waiting areas for consumers who value family)
  - Avoid a treatment plan that conflicts with person's beliefs and lifestyle
  - Selectively align treatment strategy with consumer's beliefs
- Recognize linguistic complexity
  - Recognize the linguistic variation within a cultural group
  - Recognize the cultural variation within a language group
  - Recognize the variation in literacy levels in all language groups
  - Distinguish between translation, interpretation, and medical interpretation
  - Receive training to enhance linguistic capacities and increase knowledge of cultural practices
  - Contract with telephone interpreter services
  - Screen all materials for cultural and linguistic appropriateness
- Facilitate learning between providers and consumer communities
  - Regard individuals and communities as experts
  - Create and sustain "learning loops" between health care providers and consumer communities
  - Partner professionals and consumers when providing professional training
- Involve community in defining and assessing needs
  - Enlist community members in governing boards
  - Involve community members in community advisory boards, patient panels, task forces, or neighborhood meetings
  - Sponsor community-based research and integrate results into program design
  - Affirm that understanding gained from community-based research belongs to communities
- Professionalize staff hiring and training
  - Establish specific hiring qualifications and mandated training requirements in cultural and linguistic competence
  - Develop and provide comprehensive and replicable training curricula
  - Allocate funding and time for staff training
- Institutionalize cultural and linguistic competency
  - Integrate cultural/linguistic competence into all aspects of planning
  - Make funding for staffing and training for cultural/linguistic competence sustainable
  - Design cultural/linguistic competence activities that can be replicated and developed
  - Create procedures that help disclose cultural preferences
  - Apply knowledge of cultural beliefs to program areas

ical and administrative support, they will benefit the most by evidence-based direction. Scholarship must be encouraged to develop the methods and analytical tools necessary to best assess the structure and outcomes of cultural and linguistic competency, and must examine these in relationship to consumer, provider, treatment, and organizational characteristics. The development of curricula that emphasize the cultural influence on the pain experience and the examination of what training approaches work best will need continued support if quality and equity in our clinical responses to pain are to be achieved. Workers in relevant disciplines, particularly those who are underutilized in the treatment and palliation of pain, such as social workers, spiritual care providers, and music therapists, need to creatively and, at times, aggressively carve out their niche in research, clinical, and training contexts that aim for appropriate and effective pain care and equity

in clinical outcomes. Finally and perhaps most importantly, just and effective clinical responses to pain across cultures are more likely to occur if consumer communities exercise their strengths and power to advise and govern the institutions that serve them.

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6

Pain and the Family

Suzanne Young Bushfield, PhD, MSW

INTRODUCTION AND OVERVIEW OF CONCEPTUAL FRAMEWORK

Individuals construct their world of meaning in many ways and within many contexts. Pain is a powerful organizing force; living with pain becomes a central element in shaping the lives and stories of families. To be successful in mediating the experience of pain, practitioners must pay attention to the context in which the pain occurs. As Jerome Bruner (1990) argued, "interpretive meanings are very sensitive to context" (p. 24). Pain is essentially experienced subjectively, and despite attempts to address one's experience of pain objectively, the subjective reality expands beyond the individual's physical condition to include the psychological, sociocultural, and spiritual self. Helping, for the person experiencing pain, may also need to extend beyond the physical and most certainly to family and community. Pain, more than other symptoms, has a powerful potential for negatively affecting one's quality of life. The complexity of the pain experience may require a complex set of interventions and approaches that considers the knowledge, attitudes, beliefs, and practices present in the family, as well as in the larger sociopolitical context in which pain resides.

"Person, environment, and time interact dynamically" (Hutchison, 2003, p. 17). This multidimensional model for understanding human behavior recognizes that effective practice requires attention that is balanced between the uniqueness of the individual in his or her situation and the general knowledge of patterns, derived from theory and empirical research (Meyer, 1993). This tension between the objective reality and the subjective experience seems to characterize the "place" in which the person experiencing pain resides. Incorporating a multidimensional approach to understanding the person in pain demands that we acknowledge the paradox of the person as both free and constrained, and of family and social life as both cohesive and conflicted. This perspective accepts both consistencies and contradictions and will be used to examine the influence of theories of human behavior on direct interventions targeted at the management of pain. A critical review of the evidence of the effectiveness of diverse approaches is expected to yield a greater variety of options, some of which might "fit" the diverse and unique experiences of the person experiencing the common impacts of pain, within a family context.

THE FAMILY DEFINES PAIN

What Is the Family

The family, two or more people who love and care for each other, is essentially a system with attitudinal, behavioral, and communicational rules; reciprocal roles; and boundaries. "Every event within a family is multiply-determined by all the various forces operating within that system" (Andrae, 1996, p. 606). Families, whether intact or not, retain their primary influence in people's lives. Families revolve around themes and patterns that may be multigenerational, and horizontal as well as vertical (Bowen, 1978; Brown, 1991; Carter & McGoldrick, 1989). Family members must maintain both separateness from and connectedness to families. Major disruptions in the family life cycle always have an impact on its members. These basic principles related to families are important in understanding the role of the family when one of its members is experiencing pain. Early experiences, family traditions and beliefs, ascribed roles, and reciprocal encounters are all essential features of the pain experience within families.

While medicine may categorize pain according to biological, psychological, or idiopathic sources, most pain sufferers become focused on a quest for relief from the pain. Organizing one's life around pain restructures families so pervasively that often, by the time patients present for comprehensive pain management, new patterns of communication, roles, and structures have replaced the family environment that existed before pain became the central organizing feature. The relationships and transactions within the family are shaped by the pain, which becomes the proximal, contingent, and immediate environment (Saleeby, 2004). Acknowledging the importance of family, as well as the reciprocity within family systems, Northen (1994) indicated that "an illness or disability seriously influences the functioning of the family and the functioning of the family seriously influences the course of the patient's rehabilitation" (p. 168). The pervasiveness of family influences on pain is demonstrated in a variety of ways. There is evidence that family support is an important factor in the rehabilitation of chronic pain (Jamison & Virts, 1990), while family enmeshment and rigidity (Liebman, Honig, & Berger, 1976) have been associated with intractable pain. Pain has been called a "metaphor for family dysfunction" (Wynn, Shields, & Sirkin, 1992, p. 3), and chronic pain results in significant structural, communication, role and rule changes within the family system (Marcus, 1986).

What Is Pain

Webster defines pain as "**a**: usually localized physical suffering associated with bodily disorder (as a disease or injury); *also*: a basic bodily sensation induced by a noxious stimulus, received by naked nerve endings, characterized by physical discomfort (as pricking, throbbing, or aching), and typically leading to evasive action; and **b**: acute mental or emotional distress or suffering" (Merriam-Webster, 1991, p. 846). Pain becomes "chronic" when it has been in existence for 6 months and is recognized for its debilitating psychological and social effects (Snelling, 1990). Pain sufferers have very concrete needs, but their lives have been characterized by "a sense of loss of self" (Kelley & Clifford, 1997, p. 276). Just as pain becomes primary in its sufferer's world, it also becomes central in the family's world. There are significant personal and social costs associated with pain: loneliness, isolation, withdrawal and avoidance, anxiety, depression, fear, lack of trust, impaired sexual relationships, loss of productivity, strained marital and family relationships, overuse or misuse of medical care, addiction, and the development of a pain identity (Kelley & Clifford, 1997).

What Is Suffering

The distinction between pain and its companion, suffering, has been explored (Van Hooft, 1998). Mirriam-Webster (1991) describes *suffering* as: "Deep and poignant distress; a profound and disturbing crisis and threat to one's sense of being that exceeds the bodily sensation is characteristic of suffering" (p. 1179). Recognizing the reality of suffering as larger, more systemic, and more profound than pain allows the practitioner to understand the need for a comprehensive approach to the larger family system, in order to relieve suffering. The practitioner would be well advised to approach the patient and family with competency regarding the diverse cultural and linguistic constructs of pain and suffering. Cultural competence carries requirements of both organizations and personnel to value diversity and manage and adapt to the cultural contexts of the individuals and communities served (Goode, Jones, & Mason, 2002).

INFLUENCE OF THEORETICAL MODELS AND IMPLIED TREATMENT STRATEGIES

There is a rich range of theories found to have significant utility in contemporary practice (Andrae, 1996). This "theoretical plurality" can be both an asset and a hindrance to the practitioner. In the absence of practice-based evidence, theories may prevent us from recognizing alternative explanations. This overview of theoretical models and the treatment strategies for pain that they imply assumes that individuals, families, dyads, groups, and communities turn to professionals for treatment that is ethical, accountable, value sensitive, and effective (Andrae, 1996). Therefore, interventions for which there is a strong theoretical basis, and for which there is sufficient evidence of efficacy, are the primary focus.

Ego Psychology

Ego psychology is built around concepts of ego functions, defenses, ego mastery and adaptation, and object relations (Goldstein, 1996). Pain research based on principles from ego psychology has identified a number of significant contributing factors to the perception and experience of chronic pain, including a history of childhood abuse and family dysfunction (Mersky & Boyd, 1978), physical and emotional abuse (Engel, 1959; Violon, 1980), and increased dependency and the resulting attitudes of caregivers (Berry & Ward, 1995). Effective interventions focus on helping the patient to understand the pain experience and providing short term, ego supportive counseling (Roy, 1981).

While this perspective may imply a focus on the family in terms of reworking family-of-origin issues and addressing current family functioning, its focus is primarily the inner life. There are limitations of the strategies derived from ego psychology due to the reliance on insight for change, and the impact from pathologizing of the person in pain. In addition, negative attitudes toward the patient may further contribute systemically to the patient's

existing damaged sense of self and ability of the patient to feel empowered to control or manage his or her pain. There is further evidence that these negative attitudes are disproportionately experienced by women, minorities, and those for whom power and access to medical care are further limited by societal power structures (Lee, 1994).

Behavioral Approaches

Pain is normally viewed as a warning signal that something is not right; when it persists as chronic pain, it may be influenced by operant mechanisms (Skinner, 1988). The behavioral approach assumes that when pain responses, such as grimacing, complaining, sighing, and moaning, are systematically followed by favorable consequences, such as sympathy, attention, and avoidance of unpleasant tasks, the pain behavior is reinforced and maintained (Hudgens, 1977; Marcus, 1986). The negative role of the spouse in maintaining and perpetuating chronic pain receives considerable focus in this model.

The contingency management approach (Bonica, 1990; Fordyce, 1990) to pain management is widely accepted, and many distinguished pain management programs are derived from this model. Approaches address the patient's self-talk, reframing the situation to promote cognitive restructuring, changing contingencies (reinforcers) within the family, and enlisting family as part of the treatment strategy. The goal of treatment is to help the patient return to normal functioning without pain medications, or with reduced reliance on medication. Pain behaviors are ignored; appropriate activity and interactions are reinforced with attention and praise. The approach may result in the patient learning to live a normal life by ignoring the pain. Changing family interactions and responses to pain is reframed as constructive caring, and the role of the worker in this model is to teach patients with pain and their families to eliminate the subject of chronic pain from their family system interactions (Hudgens, 1977).

Success in this model is highly dependent on several factors: (1) a supportive family amenable to retraining, (2) a patient able to learn new skills, and (3) available community supports to maintain changes (Hudgens, 1977; Marcus, 1986). The behavioral model acknowledges the impact of knowledge and attitudes on pain (Brockopp, Warden, Colclough, & Brockopp, 1996) and may include effective nonpharmacological strategies such as relaxation, imagery, and distraction (Korcz, 2003).

"Family oriented" treatment in this model places a significant focus on modifying the family response behaviors to pain, as an aspect of contingency management. However, manipulation of the environment sometimes requires collusion on the part of the family and may certainly interrupt or change the delicate balance of reciprocity within families. Acknowledging the interconnectedness of systems, it is important to recognize that the unintended consequences of behavioral manipulation may precipitate other, equally intractable problems within the family. The behavioral approach may further fail to recognize the significant attitudinal barriers from health care professionals and others regarding pain, addiction, and the harmful effects of pain medication (Korcz, 2003).

Strengths and Empowerment Perspectives

The empowerment approach makes connections between social and economic justice and individual pain and suffering (Lee, 1996). Drawing from theories on strengths (Saleeby, 1997), empowerment (Gutierrez, Parsons, & Cox, 1998), resilience (Fraser, 1997), hardiness (Kobasa, 1979), and solution-focused philosophies (De Jong & Miller, 1995), these models suggest how people overcome and resist the effects of adversity (McMillen, 1999). While there may be benefits from adversity (McMillen, 1999; Tedeschi & Calhoun, 1995), people with few coping skills, children, and those with low socioeconomic status may be less able to benefit from adversity. Pain management, in this paradigm, will address the strengths of the patient and family through a comprehensive assessment and holistic approach that acknowledges the interdependence and transactional nature of the person in his or her environment (Germain, 1991).

A strengths and empowerment perspective acknowledges the powerlessness that comes from the pathologizing of pain (either physical or psychological), versus the empowerment that derives from a validation of the experience of suffering and its impact on the individual and family. The empowerment process resides in the person, not the helper (Lee, 1996). This model assumes a biopsychosociocultural-spiritual approach to understanding the pain experience and may incorporate a variety of both active and passive techniques for pain management, including relaxation, imagery, distraction, reframing, cognitive reappraisal, patient education, patient involvement, psychotherapy, peer support, and pastoral counseling. Incorporating a humanistic perspective, this model recognizes that living with pain is a life course that calls into question meaning and suffering. People often cope with suffering and pain by seeking and finding meaning (Frankl, 1962). For many people, spirituality is a source of hope in the midst of despair (Puchalski, 2002).

The strengths and empowerment paradigm suggests a holistic approach to pain management and the family, and may include providing additional support and attention to the suffering, in order to assist the sufferer in making sense of his or her world. In contrast to behavioral approaches, exploring the person's historical experiences of pain, the sick role, and care giving and care receiving within the context of the family is both welcomed and advised. There is evidence that the patient experiencing chronic pain needs validation and understanding, both from the health care team and from family and friends (Kelley & Clifford,

1997). This need exists concurrently with concrete needs and the need for very specific coping skills. The REEP model proposed by McMillen (1999) recommends a process of reflecting, encouraging, exploring, and planning benefit, which may assist pain sufferers in constructing changes needed to facilitate recovery and growth.

Professionals addressing pain using the strengths perspective may need to focus on the experience of vulnerable populations and the need for empowerment and advocacy in the processes of accessing resources for pain management (Mendenhall, 2003), recognizing the losses experienced with chronic pain, validating the patient's struggles for survival, and formulating a plan of action to enhance a sense of control over pain, relationships, and lives (Macdonald, 2000). The practice focus in this model may include individual and family empowerment counseling, advocacy, and organization of sufferers into viable advocacy groups to influence research, policy and program construction (Glajchen & Blum, 1995).

INTERLOCKING, INTERCONNECTING, INTERINFLUENCING ASPECTS OF PAIN

A multidisciplinary team approach is necessary to maximize the potential for effectively addressing the biological components of pain both pharmaceutically and with other medical aspects; the psychological components of pain, taking multidimensional perspectives into account; the sociocultural context of pain for the person in his or her family and environment; and the spiritual components of pain, especially the meaning of pain and suffering to the individual and family. Evidence of health system inflexibility, lack of role definitions in health care, cultural and attitudinal barriers, and knowledge deficits in pain management among health care professionals all suggest that approaches must be interlocking and interconnecting with respect to direct service, education, advocacy, and research (Glajchen & Blum, 1995).

FUTURE DIRECTIONS FOR PAIN AND THE FAMILY

As the field of pain management undergoes rapid changes and development of new techniques, drugs, and intervention strategies, it is necessary for practitioners who focus on pain relief to stay current. In addition, understanding the rapid social changes affecting the family and roles within families may suggest successful approaches to pain management in the context of family. Research trials in recent years have included attention to the efficacy of alternative medicine and complementary approaches. As evidence is established for new resources, practitioners will need to disseminate this information and knowledge so that patients and families are better able to make use of new discoveries. The study of alternative approaches, including acupuncture, massage, touch, meditation, and prayer, combined with new developments in genetics, scanning, and understanding of the neurobiology of pain and addiction, may yield entirely new approaches to pain management. In addition, greater recognition of the role of the larger community and social supports for the family may offer additional resources in managing chronic pain (Subramanian, 1991).

Policies that recognize the unique needs of women, children, minorities, and disadvantaged groups may address some of the contextual issues in which pain resides. How society responds to pain and those seeking relief is closely tied with ethical and policy issues. Continued research will need to incorporate an understanding of how social justice influences care for those experiencing pain.

The power of expectation, meaning, possibility, and intentionality may be one of the "next frontiers" in pain management. Support and acceptance of alternative resources, "what works," and the sharing and validating of these personal experiences and stories often provides pain sufferers and their families with necessary relief.

Recognizing the true anatomy of pain and suffering may need to include hope. "Cross cultural practitioners consistently report that hope is an important curative factor in all cultures and societies. The more one has hope about the power or potential for help in the healing relationship or healing process, the greater the chance that the healing process will be effective" (Harper & Lantz, 1996, p. 10).

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7

Sex, Gender, and Pain: Clinical and Experimental Findings

Roger B. Fillingim, PhD, and Barbara A. Hastie, PhD

INTRODUCTION

Definition of Sex and Gender

In recent years, burgeoning evidence indicates sex and gender differences in pain in both clinical and experimental settings. In order to discuss these findings, it is helpful to understand the distinction between "sex" and "gender." Specifically, *sex* refers to biological substrates that clearly distinguish an organism as "male" or "female" in terms of their genetic composition including chromosomes (XX for females and XY for males), hormones, anatomy, and the subsequent development of secondary physical characteristics, which place the organisms in the category "female" or "male" (Frable, 1997; Hughes, 2003; Pollad & Hyatt, 1999; Wizemann & Pardue, 2001). Gender refers to the way in which an individual is defined based on socioculturally shaped behaviors and traits (such as femininity and masculinity) that are an amalgam of the psychological, social, and cultural factors that influence it (Pollard & Hyatt, 1999; Robinson et al., 2000; Wizemann & Pardue, 2001). Other theorists define gender as "the structured set of gendered personal identities that results when the individual takes the social construction of gender and the biological 'facts' of sex and incorporates them into an overall self-concept." (Ashmore, 1990; Pollard & Hyatt, 1999; Robinson et al., 2000; Wizemann & Pardue, 2001). It is important to recognize that gender roles are sculpted by both biological and social factors. Indeed, the relevance of social learning and its effect on sex differences in pain modulation have been presented from a neurobiological perspective (Choleris & Kavaliers, 1999).

Historically, before the 1970s, the term *gender* was glaringly absent from biomedical research literature (Ashmore, 1990; Choleris & Kavaliers, 1999; Greenberger, 2001; Pollard & Hyatt, 1999; Robinson et al., 2000; Wizemann & Pardue, 2001). In the 1970s, the movement toward equality of genders downplayed any differences either inadvertently or, in some cases, by conducting research in strictly uni-gender samples. Noting the grave inequalities in treatment as well as overrepresentation of one gender with certain pain conditions, there has been a movement in the past decade not only to study sex and gender differences but also to create models of testing and understanding the nature and origins of such differences.

Thus, in contrast to gender, it is important to highlight that the term "sex" is used exclusively for nonhuman animal investigation, as it is practically impossible to operationalize gender roles in nonhumans. Conversely, in human pain research, it is entirely possible for both sex and gender to contribute to the individual's experience of pain. Fillingim and Maixner (1995) previously proposed an interactive model of pain that encapsulated neurobiological, physiologic, hormonal, and genetic factors that dynamically and interchangeably influenced and were affected by psychological (affective), cognitive, and sociocultural factors (e.g., social learning, gender role, etc).

Thus, whereas the study of sex differences in pain may be more straightforward in nonhumans, it is extraordinarily complex in humans because it seems to be a dynamic and fluid interplay of both sex and gender. Thus, it is critical to make the distinction between sex and gender and to study their mutual, yet varying, influences

on a person experiencing pain. The influence of sex versus gender is not a philosophical principle, but an empirical question, particularly with regard to health outcomes. Moreover, it is important to note the distinctions since not only can gender aspects affect expression of pain as well as the interpretation of biological traits, and the experience of pain, but also sex-related biological characteristics can contribute to, diminish, or amplify gender differences in pain.

Interest in Sex, Gender, and Pain

Interest in sex, gender, and pain has proliferated in the past decade. This amplified interest has been accompanied (and perhaps driven) by increased federal funding for research on this topic. This proliferation of research likely reflects the growing attention to the issue of gender in the laypublic (e.g., Mars and Venus), but also is fueled by novel findings documenting important sex differences in the neurobiology of pain in preclinical investigations. This has sparked concerted efforts to conduct translational research to the human dimension (e.g., Mogil et al. (175)). These efforts have been coupled with resurgence in clinical attention to sex and gender differences, such that clinical scientists have applied the preclinical and experimental findings to gender and sex differences in clinical treatment and outcome. Yet, despite this remarkable growth in the spectrum of research on sex and gender differences in pain, it is still a relatively nascent field of exploration.

The purpose of this chapter is to review the literature regarding sex, gender, and pain. This includes results of community surveys, epidemiological investigations, and clinical research in specific pain conditions that have addressed the issue of gender-related differences in pain. In addition, findings from human laboratory research and nonhuman animal studies are also presented. Potential mechanisms underlying sex and gender differences in pain are discussed, and important future directions for research on sex, gender, and pain are proposed.

SEX, GENDER, AND CLINICAL PAIN

Community Surveys

As early as 1985, one of the first community surveys on pain in the United States was conducted. The Nuprin Pain Report was a national survey conducted on a random sample of 1254 adults. It was the first nationwide survey to provide quantitative data on pain prevalence and severity, demographic characteristics of pain sufferers; how people cope with pain; the relationship between pain and stress; the relationship between pain and health locus of control scales; use of medical and other professionals in the treatment of pain; the relationship between pain and different lifestyles and behavior patterns; and the impact of pain on work and other activities (Sternbach, 1986; Taylor & Curran, 1985). Gender was essentially a demographic variable (50.2% male; 49.8% female) and women were divided into "homemakers" and "working mothers" and men had the designation of executives, floor trader, professional/managerial/proprietor, sales/service, skilled and unskilled labor (Taylor & Curran, 1985).

Results from the survey showed that compared with men, women reported more headaches and were more affected than men in their daily activities by headache-related pain. The Nuprin Report also found that women experienced backaches, joint pains, and stomach pains slightly more than men (Taylor & Curran, 1985). Subsequently, the American Pain Foundation conducted surveys in various states to determine the extent to which pain affects the average citizen. Their findings revealed that more than 55% of the general population in different states experienced pain in the moderate to severe range and more than 40% face some kind of chronic pain condition and women seemed to outnumber men in each of the types of pain (American Pain Foundation, 2002). Other community surveys have revealed similar findings such that in general U.S. populations, women tended to report higher prevalence of several types of pain (Riley et al., 1998; Scudds & Robertson, 1998; Verhaak et al., 1998; Von Korff et al. 1988), and additional data suggest that these sex differences are most robust in middle age (LeResche, 1997; Riley & Gilbert, 2001; Verhaak et al., 1998; Von Korff et al. 1988). Specifically, women are more likely than men to experience recurrent headache disorders in each type except cluster headache (Holroyd & Lipchik, 2000; Lipton et al., 2001; Schwarts et al., 1998; Stewart et al., 1992). Women are also reported to have greater frequency than men in experiencing joint pain, abdominal pain, including irritable bowel syndrome, fibromyalgia, oral pain, specifically temporomandibular disorder (TMD), and low back pain (Barsky et al., 2001; Buckwalter & Lappin, 2000; Chang & Heitkemper, 2002; Drangsholt & LeResche, 1999; Wolfe et al.,. 1995; Wolfe et al., 1995).

In other population-based surveys, compared to men, women reported greater frequency of pain-related symptoms across multiple age groups (Buckwalter & Lappin, 2000; Croft et al., 2001; LeResche, 1999; Unruh, 1996). Furthermore, compared to men in the general population, women experienced more disruption, distress, and disability from pain (Affleck et al., 1999; Keefe et al., 2000; Leveille et al., 2000; Sandanger et al., 2000; Soares & Jablonska, 2004). In addition, other investigators found women to report more frequent use of analgesics (Eggen, 1993; Isacson & Bingefors, 2002). However, some researchers have reported increased disability among men compared to women with conditions such as low back pain in middle adulthood (Kostova & Koleva, 2001; Walsh et al., 1992).

Cultural influences on sex differences in pain are only beginning to be addressed. Thus, community surveys in cultures other than those represented in American and Western European countries are few in number. Consequently, it is acknowledged that pain experiences and expression may vary by cultures and gender-related issues such as social roles may play a part in differences displayed (Costa et al., 2001). The notion of cultural factors influencing responses to accident-related pain and subsequent development of chronic pain conditions has been briefly explored. Accident victims from Eastern European countries do not appear to report the chronic pain-related symptoms to the extent that are reported in many Western societies, including the United States (Ferrari et al., 1999; Obelieniene et al., 1999). There is evidence that coping styles, environment and other psychosocial factors across and within countries may influence recovery and pain conditions (Buitenhuis et al., 2003; Ferrari et al., 2003; Maraste et al., 2003; Miettinen et al., 2002); whether gender contributes to these sociocultural differences in pain expression has not been determined. Thus, in epidemiological studies, sex differences in pain report emerge across multiple countries and in various pain conditions; however, the extent to which these differences are due to sex differences in pain reporting versus sex differences in the experience of pain is not known (Vallerand, 1995).

Epidemiological Findings

Considerable data on sex differences in pain prevalence and incidence arose inadvertently from population studies that were focused on specific diseases and pain as a secondary aspect of such health conditions (Gordis, 1988; LeResche, 1999; Unruh, 1996). When discussing gender-related differences, it is important to consider the three salient theoretical perspectives from an epidemiological perspective that include population, developmental, and ecological views (LeResche, 1999). Briefly, the population view espouses that to understand pain conditions fully, they must be examined from general populations and not just from those in treatment centers (e.g., with preexisting pain conditions). The second view, the developmental approach, asserts that it is critical to investigate pain across the lifespan since factors that influence risk may change with age and the prevalence may vary between genders at different points in the life cycle. The ecological perspective of epidemiological research promotes that any disease is a product of a combination of disease agents (e.g., genetics/biological), characteristics of the host (e.g., psychological), and the environment (e.g., social), which is highly consistent with the biopsychosocial model of pain (LeResche, 2000).

Epidemiological findings related to pain have identified several common recurrent pain conditions that differ in frequency among women and men. These include headache, migraine, facial/oral pain, musculoskeletal pain, back pain, and abdominal pain (Crombie et al., 1999; LeResche, 2000; Unruh, 1996). It should be noted that the findings discussed below come predominantly from investigations conducted in North America or Western Europe. These results must be interpreted in light of the possibility that the sex differences in the prevalence of pain may vary depending on geographic region as well as sociocultural and ethnic factors.

One of the advantages of epidemiological studies in pain is that the findings can lend explanation to magnitude of differences observed as well as risk factors in gender-specific prevalence. This is especially useful because several recent reviews of gender-related differences in pain have revealed that women have higher prevalence of pain in many different conditions and across several settings (Barsky et al., 2001; Berkley, 1997; Fillingim & Maixner, 1995; Unruh, 1996). Epidemiological research adds specificity in that women are more likely than men to report temporary or chronic pain, and it tends to be more severe, more frequent, and of longer duration than men (Andersson et al., 1993; Blyth et al., 2001; Crombie et al., 1999; Taylor & Curran, 1985; Unruh, 1996). A brief description of the most prevalent pain conditions will ensue. For a more in-depth analysis of these issues, the reader is referred to the publication by the International Association for the Study of Pain, *Epidemiology of Pain* (Crombie et al., 1999).

Back Pain. Some evidence suggests that back pain is more common among females than males (Balague et al., 1999; Hartvigsen et al., 2003); however, other data suggest minimal sex differences in the prevalence of back pain (Croft et al., 1999; Leboeuf-Yde & Kyvik, 1998; LeResche, 2000; Wedderkopp et al., 2001). Nevertheless, what is conclusive is that back pain is variable across the lifespan with changing levels of debilitation depending on the etiology and other factors often not addressed in epidemiological studies. Moreover, factors other than gender, such as genetics, occupation, socioeconomic issues, and cultural influences, may represent more important predictors of back pain (Croft et al., 1999; Leboeuf-Yde, 2004; LeResche, 2000).

Headache and Migraine. Investigations predominantly in the United States and Western Europe have reported higher rates of headaches in women than men with the exception of cluster headache (Holroyd & Lipchik, 2000; Lipton et al., 2002; Schwartz et al., 1998; Stewart et al., 1992). However, studies from myriad worldwide populations have provided some conflicting evidence, depending on the population in question (Scher, Stewart, & Lipton, 1999). A comprehensive overview of national and international studies is addressed in-depth in the International Association for the Study of Pain's (IASP) Publication entitled *Epidemiology of Pain* (Scher et al., 1999). Despite some discrepancies between studies in prevalence, based on 29 epidemiological studies, inves-

tigators report that the prevalence of headache in men appears as a flat slope across the lifespan, while in women, it appears flat until reproductive age, where there is an increase, and then a significant drop after age 60 (Scher et al., 1999). LeResche (2000) reports that in a lifetime, 60% of males and 75 to 80% of females will report experiencing headache at some point, although in women it tends to decrease with age. Thus, what is typically not contested is that even when the prevalence curves take similar shape, women tend to experience headaches in much greater number, frequency, duration, they tend to be more debilitated by them, and the female:male ratio seems to be most marked in migraines (Celentano et al., 1992; LeResche, 2000).

Abdominal Pain. Population-based studies of gastrointestinal functional-related abdominal pain have revealed a higher frequency and severity in women than men across all ages (Adelman et al., 1995; Agreus et al., 1994; Chang & Heitkemper, 2002; LeResche, 2000; Mayer et al., 1999). Moreover, the prevalence in both genders seems to be steady until the age of 40, at which time, there is a trend to decline (Unruh, 1996). However, no gender differences in onset of abdominal pain were reported in one large prospective epidemiologic investigation (Halder et al., 2002).

Joint Pain/Fibromyalgia. Women are at greater risk for joint pain and fibromyalgia/chronic widespread pain compared to men. In accordance with diagnostic criteria from the American College of Rheumatology, population studies report that women are at greater risk and have higher prevalence for both joint pain and fibromyalgia (Buckwalter & Lappin, 2000; Gran, 2003; Wolfe et al., 1995). Women and girls also report more painful sites, more intense pain, and more frequent pain (Anderson et al., 1993; Hasvold & Johnsen, 1993; White, Speechley, Harth, & Ostbye, 1999). Interestingly, the prevalence curves for men and women are similar, with an increase until approximately age 65, then a slight decrease between 65 and 74 years of age, and a gradual increase after that (LeResche, 2000; Macfarlane, 1999).

Orofacial Pain/TMD. Most epidemiological studies on orofacial pain/TMD report that women have higher prevalence as well as more pain and tenderness in jaw muscles and temporomandibular joint, and other researchers have found increased sensitivity and decreased pain tolerance and threshold in women with such disorders (Sallfors et al., 2003; Wahlund, 2003). Notably, the prevalence seems to increase sharply for females during adolescence (Pilley et al., 1992; Sallfors et al., 2003). Peak prevalence for both sexes is typically between the ages of 40 and 50 years old, (Goulet et al., 1995; Macfarlane et al., 2001; Von Korff et al., 1988) and these findings seemed to be consistent in other Western countries (Sipila et al., 2001; Wahlund, 2003). There are limited studies addressing gender-related differences in adolescents although the same trend seems to emerge with girls reporting increased prevalence, and more pain and symptoms compared to boys (List et al., 1999; Wahlund, 2003).

These epidemiological findings offer strong evidence that in contrast to men, women are more likely to report pain at multiple body sites and they tend to be more at risk for developing certain chronic pain disorders such as TMD, fibromyalgia, irritable bowel syndrome, migraine headache, and other forms of musculoskeletal pain (LeResche, 1999; Unruh, 1996). It is important to highlight that most of these epidemiological data address adults, although a number of studies have found similar trends in children and adolescents with a higher prevalence and severity in girls compared to boys (Haugland et al., 2001; McGrath, 1999). Despite the absence of information regarding potential cultural influences, these data offer compelling evidence that women are at greater risk for developing several chronic pain conditions compared to men. Whether the *severity* of pain in clinical settings differs in women and men is now discussed.

Sex Differences in Clinical Pain Severity

Sex differences have been investigated in the acute clinical pain setting. For example, women reported greater pain than men following oral surgery as well as orthopedic and other surgical procedures (Averbuch & Katzper, 2000; Taenzer et al., 2000). Women have also reported higher pain ratings in acute cancer-related pain (Cepeda et al., 2003), procedural pain such as colonoscopy (Froehlich et al., 1997); and conditions presented in emergency rooms (Boccardi & Verde, 2003). A recent review article addressed the issue of gender-related risk in developing post-whiplash-related chronic pain condition(s) following acute injury and females were at increased risk given their initial presentation of more severe pain in the acute stage (Scholten-Peeters et al., 2003). These data highlight the importance of possible gender-correlated complications in the acute pain stage particularly that high initial pain intensity is often an important predictor for delayed functional recovery, which is consistent with the involvement of central centralization in the development of — or transition to — a chronic pain condition.

Additionally, research into gender-related differences in children's pain is a growing area of investigation. Despite the need for more empirical evidence, some studies have found that girls tended to report more pain than boys from venipuncture (Goodenough et al., 1997, 1999); although other investigators have found no sex differences among children undergoing certain medical procedures (Lander et al., 1989, 1990). To date, few investigators have examined any gender-related influences on pediatric procedural pain and more research is needed to identify such differences.

As reviewed above, there are clear gender differences in the prevalence of several chronic pain disorders; however, the evidence supporting differences in the severity of pain-related symptoms within chronic pain populations is less compelling. For example, among individuals with pain that limited their activity, women reported more frequent pain, greater pain-related affective symptoms, and higher pain-related disability compared to men (Mullersdorf & Soderback, 2000). Women reported higher levels of arthritis pain and disability than men (Affleck et al., 1999; Keefe et al., 2000), and at the time of total hip arthroplasty women reported higher levels of pain and disability than men (Holtzman et al., 2002). Similarly, pain among patients with multiple sclerosis was more frequent and severe among women (Warnell, 1991). Also, in a heterogeneous chronic pain population recruited from a multidisciplinary pain clinic, women had higher pain severity than men (Fillingim et al., 2003). However, other investigators have reported minimal sex differences in pain severity in heterogeneous chronic pain populations (Edwards et al., 2003; Robinson et al., 1998; Turk & Okifuji, 1999). Also, no sex differences in measures of clinical pain, experimental pain sensitivity, psychological/personality factors or illness behaviors were reported among patients with pain due to TMD (Bush et al., 1993). A recent study found that men had higher levels of pain and poorer pain-related adjustment in a sample of patients seeking treatment primarily for myofascial pain in a multidisciplinary clinic (Marcus, 2003). Taken together, these findings suggest that sex differences in the severity of pain-related symptoms are inconsistent among patients with chronic pain in clinical settings. This lack of differences could reflect the selection bias introduced by the decision to seek treatment.

SEX DIFFERENCES IN RESPONSES TO NOXIOUS EXPERIMENTAL STIMULI

Overall, the literature reviewed above indicates that women experience greater clinical pain than men. While multiple factors inevitably determine these sex differences in clinical pain, we have previously proposed that enhanced pain sensitivity among women may be an important contributor (Fillingim & Maixner, 1995). Before reviewing the experimental literature on sex differences in pain perception, a brief discussion of experimental pain methods will be provided. Multiple noxious stimuli are used in examining laboratory pain responses, and they differ along important dimensions, including temporal and spatial qualities, anatomical site stimulated, specificity of afferent fibers stimulated, and whether the evoked pain mimics clinical pain. Thermal and mechanical stimuli are the most commonly used methods, due to their ease of administration and convenience. It is important to recognize that when multiple pain assays are conducted in the same subjects, correlations across pain stimuli are generally low (Janal et al., 1994; Lautenbacher & Rollman, 1993). Thus, different stimulation method(s) can yield discrepant results; therefore, using multiple stimulation methods that differ along important dimensions often will be most informative.

In addition to the varieties of noxious stimuli available, the methods for assessing pain-related responses must also be considered. Pain threshold (i.e., the minimum amount of stimulation required to produce a pain) and pain tolerance (the maximum amount of stimulation an individual is willing to endure) are common measures. While these responses are intuitively appealing and quantitative, they are unidimensional in nature, which makes it difficult to disentangle the behavioral, affective/motivational, and sensory components of the responses. Numerous scaling methods are available for determining perceptual responses to noxious stimuli, such as numerical rating scales, visual analog scales, and multiple item scale (e.g., the McGill Pain Questionnaire). These methods offer the advantages of permitting assessment of multiple pain dimensions and determining responses to stimuli dispersed throughout the noxious range (e.g., stimulus–response functions). A complete discussion of pain assessment methods is beyond the scope of this chapter, but the interested reader can find more detailed information elsewhere (Arendt-Nielsen & Lautenbacher, 2004; Jensen Karoly, 2001).

Numerous studies have investigated sex differences in responses to experimentally-induced pain, and both qualitative (Berkley, 1997; Berkley & Holdcroft, 1999; Fillingim, 2000; Fillingim & Maixner, 1995) and quantitative (Riley et al., 1998) reviews of this literature are available. To summarize the findings of these reviews, women display lower pain threshold and tolerance and generally report higher ratings of experimental pain compared to men. A meta-analysis revealed that the effects sizes for sex differences in pain threshold and tolerance were moderate, and the magnitude of the sex difference varies across pain stimuli (Riley et al., 1998). The least consistent results emerged from measures of thermal pain sensitivity.

Since the publication of these reviews, additional data addressing sex differences in experimental pain responses have been reported. For example, we (Fillingim et al., 1998) previously reported that, relative to men, women displayed greater temporal summation of thermal pain, and these findings have since been replicated and extended. Specifically, Robinson et al. (2004) reported greater temporal summation of thermal pain among women and that psychological factors, including anxiety and willingness to report pain, partially mediated this sex difference. Also, Sarlani and Greenspan (2002) reported greater temporal summation of mechanical pain among women than men. Cairns and colleagues (Cairns et al.,

2001; Svensson et al., 2003) reported that injection of glutamate into the masseter muscle produced higher peak pain, longer lasting pain, and a greater area of pain among women compared to men, consistent with their finding that glutamate injection evoked significantly greater muscle afferent activity among female compared to male rats.

These findings from humans are supported to some degree by findings from nonhuman animals. Several investigators have reported greater behavioral responses to laboratory pain stimuli among female compared to male rodents (e.g., (Barrett et al., 2002, 2003; Terner et al., 2003); also for reviews see (Berkley, 1997; Bodnar et al., 1998)), while others report no such differences (Kayser et al., 1996; Mogil et al., 1993). In a particularly large study, which included 8000 observations of thermal nociceptive responses in mice, females exhibited enhanced sensitivity relative to males (Chesler et al., 2002). In contrast, studies of nonhuman primates suggest greater nociceptive responses in males than females. As a whole, nonhuman animal findings seem to show less-consistent and smaller-magnitude sex differences in basal nociceptive sensitivity compared to the human literature. This is likely related to multiple factors, such as genetics, differences between nociceptive assays used in nonhumans and humans, and greater involvement of psychological factors in humans, which are discussed in more detail below.

SEX DIFFERENCES IN RESPONSES TO ANALGESIC MEDICATIONS

In addition to basal pain sensitivity, sex-related influences on responses to analgesic drugs have been reported. The antinociceptive effects of several pharmacologic agents in animals have been found to be sex dependent. Specifically, male rats exhibit greater analgesic responses to both μ and opioid agonists (Bodnar et al., 1988; Cicero et al., 1996; Cicero et al., 1996, 1997; Craft, 2003a, 2003b; Islam et al., 1993; Kepler et al., 1989; Kepler et al., 1991; Kest et al., 2000; Kiefel et al., 1992). Sex differences in morphine-induced analgesia occur following either systemic or central intracerebroventricular administration (Berglund & Simpkins, 1988; Bodnar et al., 1988).

In contrast to these findings from rodents, Miaskowski and Levine (1999) reviewed studies of patient-controlled analgesia after surgery and found that in more than half of the studies women consumed significantly less opioid medication than men; however, analgesic responses were not directly assessed in most of these studies. Additional clinical investigations that assessed both pain and opioid consumption provide contradictory findings. For example, a large study recently demonstrated that women consumed substantially less opioid medication postoperatively and females had similar or lower postsurgical pain ratings than males (Chia et al., 2002). In contrast, Gordon and colleagues (1995) reported no sex differences in the analgesic effects of morphine administered after oral surgery. Likewise, Kaiko et al. (1983) reported no sex differences in morphine analgesia in a large sample of patients with chronic cancer pain. More recently, Cepeda and Carr (2003) found that women required 30% more morphine than men to achieve comparable levels of postoperative analgesia. In another series of studies examining analgesic responses to -agonist-antagonists using an oral surgery model, women showed greater analgesic responses to pentazocine and more prolonged analgesia to nalbuphine and butorphanol (Gear et al., 1996) compared to men. Also, low-dose nalbuphine (5 mg) increased pain ratings in men but not women, while higher doses (10 and 20 mg) produced analgesia of longer duration in women than men (Gear et al., 1999). More recently, among 94 patients (45 F, 49 M) presenting to the emergency department with trauma-related pain, butorphanol produced greater pain relief than morphine for women, and there was a trend toward greater morphine analgesia in men than in women (Miller & Ernst, 2004). Taken together, these clinical findings suggest more robust analgesic responses to -agonist-antagonist medications among women, but sex differences in μ-opioid analgesia are less consistent.

Sex differences in responses to opioids have also been investigated with experimental pain models. Sarton and colleagues (Sarton et al., 2000) examined morphine analgesia among 10 healthy women and 10 healthy men using an electrical pain model. Women showed greater analgesic potency but slower onset and offset of analgesia. These authors had previously reported greater morphine-induced respiratory depression among women than men (Dahan et al., 1998; Sarton et al., 1999). More recently, they reported no sex differences in analgesic responses to morphine-6-glucuronide, an active metabolite of morphine (Romberg et al., 2004). Zacny (2002) reported that the μ-opioid agonists morphine, meperidine, and hydromorphone produced greater analgesic responses among women than men using cold pressor pain, but no sex differences in analgesia emerged for pressure pain. Using a substantially larger sample size than previous investigators (41 F, 38 M), we recently reported that there were no sex differences in pentazocine analgesia for pressure, thermal, and ischemic pain (Fillingim et al., 2004). Thus, evidence from laboratory studies suggests that women may experience greater μ-opioid analgesia for some pain assays than men, and the only experimental study of a -agonist-antagonist found no sex difference in analgesic responses.

The evidence reviewed above presents an inconsistent picture of sex differences in pain and analgesic responses, since the presence, direction, and magnitude of the differences reported seem to vary across pain assays and patient populations. It is also important to note that these findings refer to quantitative sex differences; i.e., do women and men differ in the amount of pain or analgesia

that they display? Of potentially greater importance are qualitative sex differences in pain and analgesia; i.e., do certain factors (e.g., genetics) moderate pain and analgesic responses differently in women versus men? Such differences are particularly compelling as they may indicate sex-specific mechanisms underlying individual differences in pain and analgesia.

MECHANISMS UNDERLYING SEX DIFFERENCES IN PAIN

Before discussing the mechanisms underlying sex differences in pain responses, some general interpretive issues should be noted. First, an individual's sex (i.e., male vs. female) is not the cause of the observed group differences; rather, sex represents a convenient grouping variable that is a surrogate for potentially clinically and scientifically important biological and psychosocial factors. Second, there are two types of sex differences that should be considered, quantitative and qualitative differences. Quantitative sex differences refer to whether women and men differ in the amount of pain or analgesia that they display, and these are the most common conceptualization of sex differences. Of potentially greater importance are qualitative sex differences in pain and analgesia, which relates to whether certain factors (e.g., genetics, anxiety) influence pain-related responses differently in women versus men. Such differences are particularly compelling as they may indicate sex-specific mechanisms underlying individual differences in pain. Thus, the following discussion of mechanisms underlying sex differences in pain is relevant to both quantitative and qualitative differences.

It is important to recognize that sex differences in pain are inevitably mediated by multiple biopsychosocial factors, including basic biological mechanisms such as genetic and hormonal influences as well as sex differences in the functioning of pain modulatory systems. In addition, psychosocial factors represent important mediators of sex differences in pain responses. Examples include cognitive/affective variables (e.g., pain coping, mood, expectancies), gender role influences, and family history. While these mechanisms are frequently described as either psychosocial or biological, this conceptualization is artificial and is based more on the level of analysis than on the actual mechanism of action. For instance, sex differences in expression of pain are often attributed to the effects of stereotypic sex roles, which is typically viewed as a psychosocial issue. However, we must remember that there are neurophysiological correlates of masculine versus feminine sex roles, which may be related to differences in nociceptive processing. Thus, the "psychosocial" and "biological" mechanisms mediating sex differences in pain responses could refer to the same fundamental processes described at different levels of analysis.

Several "biological" processes have been proposed to explain sex differences in both clinical and experimental pain responses. Considerable evidence suggests that gonadal hormones are important. The clinical symptoms of several pain disorders vary across the menstrual cycle (Anderberg et al., 1999; Heitkemper & Jarrett, 1992; Keenan & Lindamer, 1992; LeResche et al., 2003), and exogenous hormone use has been associated with increased risk for or severity of clinical pain (Brynhildsen et al., 1998; LeResche et al., 1997; Musgrave et al., 2001; Wise et al., 2000). Similarly, responses to experimentally induced pain vary across the menstrual cycle in healthy women (Fillingim & Ness, 2000; Riley et al., 1999), and postmenopausal women taking hormone replacement show enhanced sensitivity to thermal pain compared to age-matched women not on hormone replacement (Fillingim & Edwards, 2001). Sex differences in analgesia may also be influenced by both organizational (i.e., long-term developmental influences) and activational (acute, receptor-mediated) effects of sex hormones (Cicero et al., 2002). A review by Fillingim and Ness (2000) concluded that, among female animals, high estrogen levels were associated with diminished opioid analgesia, which suggests activational effects of estrogen on antinociceptive responses. Cicero and colleagues (2002) found that neonatal but not adult castration significantly decreased morphine analgesia in male rats, and neonatal testosterone treatment enhanced morphine analgesia in females. Likewise, neonatal castration in males reduced the analgesia produced by morphine injected into the ventrolateral periaqueductal gray (vlPAG), while neonatal testosterone in females increased vlPAG morphine analgesia (Krzanowska et al., 2002). Thus, opioid antinociception is influenced by both activational and organizational effects of gonadal steroids. However, hormonal effects may depend on which opioid receptor subtype is activated, as it has been reported that estrogen-attenuated analgesia for μ- but not κ-opioid agonists (Sandner-Kiesling & Eisenanh, 2002). To date, limited information is available regarding hormonal effects on analgesic responses in humans.

In addition to the influence of sex hormones, endogenous pain inhibitory systems may function differently in females and males. Male rodents exhibit more robust stress-induced analgesia (SIA) than females (see Berkley, 1997; Sternberg & Liebeskind, 1995 for reviews), and SIA appears to be mediated by different neurochemical mechanisms in females and males (Kavaliers & Choleris, 1997; Mogil et al., 1993). Recent findings from humans demonstrated that tonic experimental muscle pain produced a greater decrease in μ-opioid receptor availability in several brain regions among men compared to women, apparently due to increased pain-induced binding of endogenous ligand to the receptor (Zubieta et al., 2002). This suggests that the μ-opioid system may differentially modulate pain in women and men.

Genetic factors may contribute to sex differences in pain. Indeed, substantial evidence from nonhuman animals suggests that both basal nociceptive sensitivity and antinociceptive responses to drugs show significant heritability (Lariviere et al., 2002; Mogil et al., 1999a, 1999b; Mogil, 1999). Of particular relevance to the current topic are findings that sex differences in basal nociceptive sensitivity and opioid analgesia are dependent on the strain of rodent tested (Barrett et al., 2002; Cook et al., 2000; Mogil et al., 2000; Mogil et al., 2003; Terner et al., 2003). However, there is limited evidence of genetic influences on pain sensitivity and analgesic responses in humans. Pressure pain threshold was assessed in monozygotic and dizygotic twins and showed a heritability of only 10% (Macgregor et al., 1997). In contrast, recent studies suggest significant associations between single nucleotide polymorphisms (SNPs) of specific genes and experimental pain responses. One group of investigators reported heritability estimates of 22 to 46% across three pain modalities and a SNP of the δ-opioid receptor gene (*OPRD1*) was associated with thermal pain responses among men but not women (Kim et al., 2003), consistent with the results of a previous linkage mapping study in mice (Mogil et al., 1997). Zubieta and colleagues (2003) reported that an SNP of the catechol-*O*-methyltransferase gene (COMT) was marginally associated with pain report and significantly associated with pain-induced brain μ-opioid receptor binding. It was recently demonstrated that genotype at the melacocortin-1-receptor gene was associated with analgesic responses to pentazocine among women but not men (Mogil et al., 2003). These findings from both rodents and humans indicate that genetic factors are associated with pain responses, and some of these associations are sex-dependent.

In addition to these multiple "biological" factors, numerous "psychosocial" variables also contribute to sex differences in pain responses. For example, the greater levels of depression and anxiety reported by women may be associated with increased clinical pain (Kroenke & Spitzer, 1998; Moldin et al., 1993; Rajala et al., 1995), as well as enhanced experimental pain sensitivity (Cornwall & Donderi, 1988; Graffenried et al., 1978). The association of negative affect to pain may be sex related, as several investigators have reported a stronger relationship between emotional distress and pain-related symptomatology among men than women (Edwards et al., 2003; Edwards et al., 2000; McCracken & Houle, 2000; Riley et al., 2001). Relatedly, we previously reported that anxiety was more strongly associated with experimental pain sensitivity among men than women (Fillingim et al., 1996). Taken together, this evidence indicates a stronger association between psychological distress and enhanced pain responses among men.

Cognitive variables may also contribute to sex differences in pain. For instance, numerous studies have reported sex differences in cognitive and behavioral coping strategies, with women reporting higher levels of many forms of pain coping (Affleck et al., 1999; Keefe et al., 2000; Mercado et al., 2000; Osman et al., 2000; Unruh et al., 1999). Keefe et al. (2000) reported that catastrophizing mediated the higher levels of pain and disability reported by women compared to men with osteoarthritis. Another potentially important cognitive factor is self-efficacy, which predicts improved adjustment to chronic pain (Jensen et al., 1999; Jensen & Karoly, 1991), decreased procedural pain (Kashikar-Zuck et al., 1997), and lower sensitivity to experimental pain (Keefe et al., 1997). Both women and men report that men are better able than women to tolerate pain (Robinson et al., 2001), and a greater perceived ability to tolerate and control pain has been related to lower pain sensitivity among women but not men (Fillingim et al., 1996).

Stereotypic gender roles may also contribute to sex differences in pain. Among men, masculinity has been associated with higher pain thresholds (Otto & Dougher, 1985), and one study found that men but not women reported less pain to an attractive opposite-sex experimenter than to a same-sex experimenter (Levine & De Simone, 1991). Importantly, while two studies have demonstrated that sex roles are associated with experimental pain responses, in neither study did sex role measures account for the gender difference in pain (Myers et al., 2001; Otto & Dougher, 1985). In an experiment that manipulated gender role expectations, Robinson, Gagnon, Riley, & Price (2003) found that sex differences in pain responses disappeared when subjects were given gender-specific expectations regarding pain tolerance. Thus, in the laboratory setting, gender role expectancies may contribute to sex differences in pain responses; however, little information is available regarding the association of gender roles to clinical pain.

Familial factors may contribute to sex differences in pain. Several chronic pain conditions are characterized by familial aggregation, including fibromyalgia (Buskila et al., 1996; Buskila & Neumann, 1997; Pellegrino et al., 1989), headache (Aromaa et al., 2000; Ehde et al., 1991; Messinger et al., 1991; Ottman et al., 1993; Schrader et al., 1996; Turkat et al., 1984), irritable bowel syndrome (Kalantar, Locke, Zinsmeister, Beighley, & Talley, 2003; Kalantar et al., 2003), and low back pain (Balague, Troussier, & Salminen, 1999). Moreover, in community studies, individuals reporting a family history of pain have increased pain complaints (Edwards et al., 1985; Koutantji et al., 1998; Lester et al., 1994; Sternbach, 1986). The association between family history and pain may differ across sexes, as reported that familial pain history predicted pain complaints more strongly among women than men (Edwards et al., 1985). Also, an association between family pain history and enhanced experimental pain sensitivity has been reported among women but not men

(Fillingim et al., 2000; Neumann & Buskila, 1997). Whether this stronger association between familial factors and pain responses among women is due to social learning or genetic factors has yet to be determined.

Thus, multiple biopsychosocial factors contribute to sex differences in clinical and experimental pain responses. The biospychosocial model of pain suggests that biological, psychological, and sociocultural factors interact to influence pain responses. Additional research is needed to elucidate these interactions in the context of sex differences in pain.

CONCLUSIONS AND FUTURE DIRECTIONS

The literature reviewed above clearly demonstrates that pain is characterized by both quantitative and qualitative sex differences. Multiple factors contribute to sex differences in pain responses, including those traditionally referred to as "biological" (e.g., genetics, hormones, pain modulatory systems) and "psychological" (e.g., cognitive/affective variables, social roles, family history). A major challenge for the future will be translating these findings into clinical practice. An example of this might be sex-related treatment tailoring. It seems plausible that sex differences in analgesic responses may ultimately lead to the development of sex-specific medications and/or dosing regimens. Similarly, some evidence indicates sex differences in the outcomes of nonpharmacologic treatment for pain. For example, women but not men showed significant benefit following multidisciplinary treatment for back pain (Jensen et al., 2001) and pain due to TMD (Krogstad et al., 1996). Moreover, the predictors of treatment outcomes have differed for women and men in some studies (Burns et al., 1998; Edwards et al., 2003). Therefore, in the future it may be possible to tailor interdisciplinary pain treatment by sex to optimize treatment outcomes.

Another important issue is that clinicians and scientists should be educated regarding the existence and nature of sex differences in pain. Increasing our awareness of these differences should help reduce gender-related biases, which can adversely influence treatment decisions. Indeed, some findings indicate that women presenting with chest pain were less likely than men to receive both invasive and non-invasive cardiac procedures (Roger et al., 2000). Although multiple reasons could produce these differences in medical decisions, we must avoid minimizing women's pain reports based on the assumption that women are overreporting or exaggerating symptoms, since it could just as well be true that men are underreporting (Barsky et al., 2001).

In summary, based on considerable basic and clinical pain research, we can now state the obvious with confidence, women and men are different. Women report more frequent and/or more severe clinical pain and display enhanced perceptual responses to experimentally-induced pain. In addition, responses to analgesic medications have shown sex differences, although the results are somewhat inconsistent across studies. Multiple biopsychosocial factors contribute to sex differences in pain, and continued research to further characterize the nature of sex differences in pain will inform pain treatment for patients of both sexes.

ACKNOWLEDGMENTS

This material is the result of work supported with resources and the use of facilities at the Malcom Randall VA Medical Center, Gainesville, FL. This work was supported by NIH Grants NS41670 and NS42754 and the NIH/NCMHD Loan Repayment Program.

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Racial and Ethnic Issues in Chronic Pain Management: Challenges and Perspectives

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INTRODUCTION

One of the greatest obstacles to the effective treatment of chronic pain is the temptation of clinicians to explain it solely in terms of physiological mechanisms. Without recognizing the complex interaction between pathophysiology and psychosocial factors, chronic pain cannot be adequately understood and, accordingly, cannot be adequately treated. Since the pioneering work of Chapman and Jones, (1944) and Zborowski (1952), numerous researchers have examined racial and ethnic influences on patients' perceptions and responses to acute and chronic pain experience. The findings of a myriad of studies on group differences in pain experience and response are mixed, which may be due, to a certain extent, to methodological issues. While additional research on racial and ethnic differences in the experience and meaning of pain may be useful, the possibility exists that findings will only marginally affect the quality of treatment minorities with chronic pain receive. Of greater importance, perhaps, is how diverse racial and ethnic groups' views of pain, health care providers, medications, and the medical system as a whole along with physician and medical system variables affect their access to the treatment that is likely to meet their specific needs.

A review of the literature suggests that some of the disparity in findings on racial and ethnic issues in chronic pain management relates to inconsistencies in operational definitions of race and ethnicity. *Race* refers to differences in major groups of people based on ancestry and physical characteristics, while *ethnicity* refers to distinctions based on behavior and culture as well as on biological and physical differences (Edwards et al., 2001).

It is also important to specify an operational definition of "chronic pain," as this is another issue regarding which considerable disagreement exists. While certain clinicians and investigators view chronicity as based on the duration of symptoms, others consider chronic pain to be defined by the amount of dysfunction it causes across a wide range of dimensions of one's life. For purposes of consistency, the International Association for the Study of Pain (IASP) definition of chronic pain as that persisting "beyond normal tissue healing time, which is assumed to be 3 months" (IASP, 1986) is used in this chapter. Both malignant and nonmalignant chronic pain are discussed.

PAIN PERCEPTION

Most of the research on racial and ethnic differences in pain experience has focused on acute pain, with much of this research involving experimental rather than clinical pain. However, a number of investigators have examined intergroup variance in the perception of chronic pain severity (Ang et al., 2003; Bates & Edwards, 1992; Bates et al., 1993; Bates et al., 1995; Garron & Leavitt, 1979; Gaston-Johansson et al., 1990; Green et al., 2003a; Greenwald, 1991; Jordon et al., 1998; Kramer et al., 2002a, b; Kramer et al., 2002; Lawlis et al., 1984; Lipton & Marbach, 1984; McCracken et al., 2001; Plesh et al., 2002; Riley et al., 2002) with mixed results. For example, while Edwards et al. (2001), Green et al. (2003a), and McCracken et al. (2001) each found that African American patients seeking treatment for chronic pain reported higher pain severity than did their Caucasian counterparts,

Ang et al. (2003), Jordan et al. (1998), and Riley et al. (2002) found no interracial differences in pain intensity in their studies, and Plesh et al. (2002) found interracial differences in pain intensity only at certain body locations. While several studies (Bates & Edwards, 1992; Bates et al., 1995; Lawlis et al., 1984) have indicated that Hispanics suffering from chronic pain report higher levels of pain severity than non-Hispanic Caucasians, it has been suggested that problems with relatively simple conceptual models and the use of univariate statistical approaches limit the meaning of these findings (Edwards & Keefe, 2000; Lipton & Marbach,1984).

Medical research often considers Hispanics a homogeneous group, with insufficient attention paid to the considerable differences between various Hispanic cultures. Keefe (1982) noted, for example, large differences between foreign-born versus American-born Mexican Americans in terms of help-seeking behavior. Similar differences are likely to exist between Puerto Rican patients with chronic pain who were born in Puerto Rico versus those born in the mainland United States, based on levels of acculturation. Comparing Puerto Ricans with Mexican Americans in their experiences of chronic pain, to take the issue yet further, should be done only with extreme caution. These same issues are likely to exist in considering the literature examining chronic pain experience among African Americans. In an excellent editorial, Edwards and Keefe (2000) noted that the meaning of pain for an individual who has recently emigrated from the Caribbean may differ greatly from that of an African American whose fourth-generation status has resulted in a different experience of acculturation. Bates and Edwards (1992) noted that "ethnic stereotyping is as dangerous as inattention to cultural variables." As the tendency for researchers of differences between races in chronic pain experience has clearly been toward ethnic stereotyping, the meaning and value of the body of existing literature in this area are questionable. More sophisticated and thoughtful research on racial and ethnic differences in the chronic pain experience would potentially be beneficial.

RESPONSE TO CHRONIC PAIN

A related area of investigation that has received considerable attention has been differences between racial and ethnic groups in terms of emotional and behavioral responses to chronic pain. Again, studies examining emotional and behavioral adaptation to chronic pain have yielded mixed results (Ang et al., 2002; Bates & Edwards, 1992; Bates et al., 1995; Brena et al., 1990; Gatchel et al., 1995; Green et al., 2003a; Greenwald, 1991; Ibrahim et al., 2003; Jordon et al., 1998; Li & Moore, 1998; McCracken et al., 2001; Riley et al., 2002; Sanders et al., 1992). However, a review of the literature suggests that the findings on racial and ethnic differences in response to pain are more consistent than are those on intergroup differences in pain perception. For example, African American patients with chronic pain were found to display less adaptive coping strategies (Ang et al., 2002; Jordon et al., 1998), to demonstrate higher levels of physical and psychological disability (Green et al., 2003a, b; McCracken et al., 2001), and to be more avoidant of physical activity (McCracken et al., 2001) than were Caucasian patients with chronic pain. Non-Caucasians were found to be more likely to be classified as "disabled" 6 months following acute back injuries than were Caucasians (Gatchel et al., 1995). Two studies (Bates & Edwards, 1992; Bates & Rankin-Hill, 1994) have suggested that Puerto Rican patients with chronic pain reported more psychological distress and higher degrees of interference with physical activities than non-Hispanic Caucasians, with these findings attributed to differences in locus of control. While the studies implicating locus of control as responsible for differences in behavioral and emotional responses to chronic pain have compared Puerto Ricans with Anglo-Americans, external locus of control has been related to maladaptive responses to illness among African Americans as well (Bell et al., 1995; Wilson et al., 1994). Issues of locus of control are addressed later in this chapter. It should be noted, however, that the studies that suggest that Caucasians' emotional and behavioral adjustment to chronic pain is superior to those of racial and ethnic minority patients with pain may have been reliant on independent variables that were not necessarily culturally sensitive.

Two studies on cross-cultural differences in response to chronic pain should be mentioned by virtue of their blatant problems with ethnic stereotyping. Brena et al. (1990) determined that Japanese patients with chronic low back pain were less impaired psychologically, socially, vocationally, and avocationally than were American patients with low back pain. In a study of "Chronic Low Back Pain Patients Around the World," Sanders et al. (1992) compared levels of chronic low back pain–related self-perceived dysfunction in samples of American, Japanese, Mexican, Colombian, Italian, and New Zealander sufferers of chronic low back pain. The authors concluded that "there were important cross-cultural differences in chronic low back pain patients' self-perceived level of dysfunction, with the American patients clearly the most dysfunctional." They attributed the differences that they found to potential explanations including a number of sociocultural factors and differences in emotional and cognitive functioning. Unfortunately, the authors of both of these studies failed to state what constitutes being an American. Given that the American population is likely the most heterogeneous in the world, the findings of these studies tell us little of meaning regarding differences between groups in pain-related self-perception of chronic low back pain disability. Brena et al. (1990) noted that

their findings may have been due to the stoicism and ethnic homogeneity of Japanese culture, making pain-related impairment less acceptable than it is in the "liberal, permissive, and pluralistic American society." However, the validity of this statement is limited due to a lack of information regarding the specific composition of the American sample.

DIFFERENCES IN THE TREATMENT OF MINORITIES VERSUS NONMINORITIES WITH CHRONIC PAIN

In general, racial and ethnic minorities have been determined not to have the same access to medical treatment and other health services as do the non-Hispanic Caucasian population, with African Americans at particular risk for underservice (Mayberry et al., 2000). As discussed above, the mixed results of research on racial and ethnic differences in pain perception do not support drawing particularly meaningful conclusions, and investigations of intergroup differences in emotional and behavioral response to pain suggest that African American and Hispanic patients may respond less favorably to chronic pain than do non-Hispanic Caucasians. However, these bodies of literature provide little insight into the disparity in treatment of chronic pain that is received by minorities as opposed to nonminority groups in the United States. The existence of this disparity is well documented in the literature, in which numerous studies on racial and ethnic differences in both acute and chronic pain treatment can be found. It appears likely that the results of many of the investigations that suggest that minorities are at higher risk for the ineffective treatment of acute pain may generalize to the treatment of chronic pain as well.

While results of several studies (Ducharme & Barber, 1995; Selbst & Clark, 1990; Wilson & Pendleton, 1989) have indicated that the inadequate prescribing of analgesics for patients in pain in emergency rooms is common, it appears that racial and ethnic minorities who present at emergency departments are at even greater risk for oligoanalgesia, despite similar levels of pain complaints (Todd et al., 1993; Todd et al., 2000). Todd and his colleagues (1993) found that 55% of Hispanics received no analgesic for long bone fractures, while no analgesic was provided for only 26% of non-Hispanic Caucasians with identical diagnoses. Of note are the results of a 1994 companion study (Todd, Lee, & Hoffman, 1994) to Todd et al.'s original work, in which no difference between physicians' assessments of pain between Caucasian and Hispanic patients was identified. Accordingly, physician error in assessment of pain levels could not account for the identified disparity in the administration of analgesics between Hispanics and non-Hispanic Caucasians. Similarly, African American patients with extremity fractures were at 66% greater risk for receiving no analgesic from an emergency medicine department than were Caucasians (Todd et al., 2000).

Ng and colleagues (1996a, b) published results of two studies that examined differences in the treatment of postoperative pain between Caucasians and racial/ethnic minorities. These investigations were conducted to assess whether the findings of Todd and colleagues (1993, 1994) would generalize from the emergency room to the postoperative setting. In both studies, Caucasian patients were provided with higher doses of analgesics than were racial or ethnic minority patients. Ng et al. (Ng et al., 1996a) acknowledged that their results could not determine whether this disparity was due to the attitudes and behaviors of the patients, of the medical staff, or some combination of the two. As is the case with the aforementioned studies on racial and ethnic differences in emergency room treatment of fractures, the results of the studies by Ng and colleagues (1996a, b) become more striking in light of a study that indicated that white patients reported *less* postoperative pain than did African Americans or Hispanics (Faucett et al., 1994).

Although the body of literature on racial and ethnic differences in the treatment of acute pain is limited, studies on such differences in the treatment of cancer pain are somewhat more abundant. Overall, the literature suggests that minority patients with cancer are more likely to be faced with oligoanalgesia than are Caucasian cancer patients. In an early study of racial and ethnic disparities in the treatment of cancer pain, Cleeland et al. (1997) compared medication practices of oncology clinics that treated primarily African Americans and Hispanics with those treating more heterogeneous patient populations. The authors determined that while 42% of all recurrent or metastatic cancer patients were undermedicated, those seen in centers that treated predominantly minorities were three times more likely than were patients treated elsewhere to report inadequate pain management. In a follow-up study, Cleeland and his colleagues (1997) determined that 65% of minority patients suffering from recurrent or metatstatic cancer did not receive Pain Management Index–recommended analgesic prescriptions, as compared with only 50% of nonminority patients. Hispanic cancer patients in this study were found to be more inadequately medicated for their pain than were African American patients, which is particularly intriguing given the results of an investigation that determined that Hispanic cancer patients reported higher levels of pain and lower quality of life than did non-Hispanic Caucasian or African American cancer patients (Juarez et al., 1999). Consistent with these results are findings that elderly minority cancer patients were statistically more likely to receive no analgesia than were elderly nonminority patients, with African Americans being 63% more likely to be untreated for their

cancer pain than were non-Hispanic Caucasians (Bernabei et al., 1998).

Although a number of studies of racial and ethic disparities in the treatment of acute pain and cancer pain have been published, there are relatively few studies examining disparities in treatment between racial/ethnic minorities and nonminorities who suffer from benign chronic pain conditions. In an extensive review of racial and ethnic disparities in access to medical care, Mayberry et al. (2000) concluded, "the literature shows that racial and ethnic minorities frequently do not have the same access to medical treatment and other health services as the majority white population," and that this difference is particularly true for African Americans. While Mayberry and his colleagues reviewed the literature on racial disparities in the treatment of cancer, they did not include benign pain conditions in their review.

Among the published studies of racial and ethnic disparities in the treatment of chronic pain, the majority appear to relate to issues of *access* to services. Access to services appears to be related to a combination of patient variables, communication issues, physician issues, and social system variables, all of which contribute to suboptimal outcomes for too many minority patients with chronic pain. These variables and their impact on access to appropriate medical care for chronic pain conditions are the focus of the remainder of this chapter.

PATIENT VARIABLES

As mentioned earlier in this chapter, the findings of studies of differences between racial and ethnic groups in their perceptions of chronic pain have been mixed and therefore nonconclusive. Accordingly, these differences, if they do exist, are unlikely to adequately explain racial and ethnic disparities in access to chronic pain management services. However, as the research appears to suggest the existence of racial and ethnic group differences in emotional and behavioral responses to chronic pain, these differences merit investigation as a possible explanation for disparities in access to appropriate services.

The literature suggests that differences between racial and ethnic minorities' patterns of seeking medical assistance in dealing with chronic pain are rooted deeply within their cultures. This appears to be particularly true of Hispanic sufferers of chronic pain, although intraethnic differences may exist. Perhaps the most prolific investigators of Hispanic/Caucasian differences in chronic pain experience and response have been Bates and her colleagues (Bates & Edwards, 1992; Bates, Edwards, & Anderson, 1993; Bates & Rankin-Hill, 1994; Bates et al., 1995; Bates, Rank-Hill, & Sanchez-Ayendez, 1997). Bates and Edwards (1992), Bates, Edwards, & Anderson (1993), and Bates and Rankin-Hill (1994) determined that locus of control style is an important predictor of chronic pain experience, affecting not only the subjective experience of pain severity, but also behavioral, psychological, and attitudinal responses. The Latino cultural tradition is one that emphasizes external locus of control, viewing reality as something that cannot be manipulated or transformed by the individual. This worldview, suggest Bates and Edwards (1992), is one that is accepted as realistic by Hispanic researchers, despite the tendency of Caucasian researchers to see external locus of control as reflective of a passive and pessimistic attitude. Bates and Rankin-Hill (1994) determined that patients with external locus of control were more likely to have sought immediate medical care upon the onset of their pain symptoms. However, their study did not indicate that locus of control style affected patients' likelihood of seeking and/or continuing to pursue medical care once a pain condition had become chronic. A review of the literature suggests that the relationship between a patient's locus of control style and willingness to seek treatment for *chronic* pain has yet to be investigated. This topic certainly merits exploration, particularly given the identified tendency of Hispanics to manifest external health locus of control (Sugarek et al., 1988; Aruffo et al., 1993; Spaulding, 1995).

Bates and Rankin-Hill (1994) suggest that among patients with chronic pain, an internal locus of control is beneficial in that it helps patients regain the perception of control over their lives and their pain. However, if an external locus of control is actually associated with seeking medical attention upon the onset of pain symptoms, is an external locus of control style necessarily maladaptive? A study by Gatchel and colleagues (2003) identified patients with acute low back pain determined to be at risk for developing chronic low back pain. Those who received early medical intervention fared better on a wide range of work, heath care utilization, medication use, and self-report of pain variables at 1-year follow-up than did those patients who did *not* receive early medical treatment. Their results were consistent with those of earlier studies (Epker et al., 1999; Gatchel et al., 1995; Jordon et al., 1998; Linton et al., 1993; Schultz et al., 2002). While Hispanics' tendencies toward external locus of control may indeed result in suboptimal emotional and behavioral responses to chronic pain, in terms of access to medical services, this culturally ingrained tendency may actually serve the function of helping avoid the development of chronicity. Further investigation is required to determine whether Hispanics' external locus of control styles actually do result in passivity and pessimism, as such attitudes could theoretically result in hopelessness and thereby serve to prevent Hispanic chronic pain sufferers from seeking access to potentially beneficial medical treatment.

It should be noted that intracultural variation in help-seeking behavior may relate to differences in access to treatment for chronic pain among Hispanics, although no such specific study appears in the literature. Keefe (1982),

however, noted that foreign-born Mexican Americans are less likely to seek help from doctors than are native-born Mexican Americans. The author suggested that this distinction is likely to relate to socioeconomic status, level of acculturation, intensity of religious affiliation, the presence of a strong social support network, and familiarity with available services. While Keefe's study pertained specifically to mental health issues, it seems plausible that her results may be generalized to the seeking of treatment of other conditions, including chronic pain.

Without regard to locus of control style, Hispanics may choose to seek medical treatment for their chronic pain less frequently than do non-Hispanic Caucasians because of their tendency to rely on family and friends for assistance prior to or rather than seeking outside help. Bates and Edwards (1992) found that Hispanic sufferers of chronic pain were significantly more likely to consult friends and family for advice regarding their pain than were other ethnic groups in their study. Additionally, there exists a tradition in Hispanic culture to rely on *espiritismo* (faith healing), which may serve as a substitute for seeking mainstream medical care for chronic pain. While this possibility has not been formally investigated, Ruiz and Langrod (1976) identified a culturally accepted belief system in faith healing in a Hispanic urban ghetto. However, Lipton and Marbach (1984) noted that the levels to which pain sufferers rely on home remedies and spiritist healers are likely to be subject to intra-ethnic variation based on degree of assimilation into American society and acculturation of medical norms.

Hispanics in the United States are not the only racial or ethnic group likely to demonstrate lower levels of formal help-seeking for their chronic pain, choosing to rely on spiritual approaches instead. Jordan et al. (1998) determined that African American women were more likely to engage in "praying and hoping" as a primary strategy for dealing with chronic pain than were Caucasian women in their study. The authors noted that African Americans' greater use of praying/hoping was consistent with their emphases on church, prayer, and religion within their community, which has been supported elsewhere in the literature (Arcury, 1996; Bill-Harvey et al., 1989; Coulton et al., 1990; Cronan et al., 1993; Jacobson, 1987; Mutran, 1985). Ang et al. (2002) determined that African Americans were less than half as likely as Caucasians to consider arthroplasty as a treatment option for their severe arthritis, identifying African Americans' belief in the "helpfulness of prayer" as an important explanatory variable for this disparity.

Another patient variable that may explain, to some degree, undertreatment of chronic pain among African Americans is the relationship between their pain experience and perceived quality of life. In two studies by Ibrahim and colleagues (Ibrahim et al., 2002, 2003), negative correlations between pain quality variables and global quality of life ratings were identified among Caucasians suffering from osteoarthritis, but not among their African American counterparts. While neither of these studies directly examined the relationship between race and the perceived overall impact of chronic pain on seeking medical intervention, the possibility exists that African Americans are more likely to consider their pain as less meaningful than are Caucasians within the frequently unfortunate socioeconomic context of their lives. A number of studies (Fiscella & Franks, 1997; Fuhrer et al., 1993; Myers et al., 2002; Vermom et al., 1982) have suggested that African Americans are more likely than Caucasians to experience hopelessness in general, and it is plausible that this phenomenon can explain their decision to be reticent to seek aggressive treatment for their chronic pain. Studies have suggested that Hispanics in the United States are also more likely to evidence hopelessness than are Caucasians, and may actually manifest greater hopelessness than do African Americans (Fuhrer et al., 1993; Garcia & Marks, 1989; Kemp et al., 1999; Myers et al., 2002; Vermom et al., 1982). Accordingly, generalized hopelessness may serve as an explanation for Hispanics' reticence to seek chronic pain treatment as well. Research in this area could be useful in terms of designing psychosocial interventions for racial and ethnic minority chronic pain sufferers manifesting high levels of hopelessness.

The involvement of psychologists in interdisciplinary (and some multidisciplinary) treatment programs for chronic pain may provide yet another explanation for racial and ethnic minorities' reduced likelihood of seeking chronic pain management services. The literature suggests that African Americans are less likely to seek mental health services than are Caucasians (Alvidrez, 1999; Bristow & Patten, 2002; Diala et al., 2000; Padgett et al., 1994; Snowden, 1999; Wells et al., 2001), that African Americans view mental health services as not being particularly useful (Snell & Thomas, 1998), and that African Americans have more negative expectations of mental health services than Caucasians (Richardson, 2001). Hispanics have been found to be less likely to seek mental health services than non-Hispanic Caucasians (Alegria et al., 2002; Alvidrez, 1999; Greenberg & Rosenheck, 2003; Padgett et al., 1994; Pumariega et al., 1998; Starrett et al., 1992; Wells et al., 2001) and to be more likely to drop out of counseling prematurely (Cheung & Snowden, 1990). Some of the Hispanics' discomfort with mental health services is certainly likely to relate to issues of communication secondary to language barriers, which will be addressed later in this chapter. The possibility that racial and ethnic minorities suffering from chronic pain avoid appropriate treatment due to an aversion toward mental health services is particularly distressing given the findings that suggest that African Americans with chronic pain demonstrate less adaptive coping strategies, evidence higher levels of psychological disability, and are more

avoidant of physical activity than Caucasian patients with chronic pain (Ang et al., 2002; Edwards et al., 2001; Green et al., 2003a; Jordon et al., 1998; McCracken et al., 2001;). Similarly, the strong need for psychological services in the treatment of Hispanic patients with chronic pain is supported by research that suggests that they reported higher levels of psychological distress and interference with physical activities than did non-Hispanic Caucasians with chronic pain (Bates & Edwards, 1992; Bates & Rankin-Hill, 1994). If the proponents of the aforementioned theory that Hispanics' external locus of control is detrimental to coping with chronic pain are accurate, psychologists may be particularly important in their treatment in terms of providing them with cognitive behavioral intervention, including biofeedback training. Such treatment has been found to be effective in increasing internal health locus of control among patients suffering from chronic pain and illness (Gruber et al., 1988; Mizner et al., 1988; Rybarczyk et al., 2001).

Another patient-related factor that may have an impact on access to appropriate treatment for chronic pain among racial and ethnic minorities is trust of medical professionals and the medical system in general. This factor, however, is likely to be influenced by communication issues as well as medical and social system variables, which are addressed in greater detail later in this chapter. Despite the existence of a body of literature indicating that racial and ethnic minorities trust physicians and the medical system less than do Caucasians (Doescher et al., 2000; Corbie-Smith et al., 2002; Boulware et al., 2003), there is a paucity of research on issues of trust of the medical establishment among minorities suffering from chronic pain. Lipton and Marbach (1984) determined that African American patients presenting for treatment at a facial pain clinic were significantly more skeptical regarding what they believed their physicians could do to help them as compared with Caucasian patients. Otherwise, no investigations of this type appear in the literature, and additional research is merited.

COMMUNICATION ISSUES

Related to trust issues is communication between minority patients with chronic pain and the providers of pain management services. This is obviously a physician/medical staff issue as well as a patient variable. Language barriers can certainly exist in the treatment of chronic pain, as is the case with all medical treatment. Hispanic patients who are not conversant in English are at risk of simply not understanding physicians who are non-Spanish speaking, and they are similarly likely to have problems conveying the physical, emotional, and behavioral aspects of their pain conditions to their physicians. The hope is that the rapidly growing Hispanic population and the increasing number of Spanish-speaking health care providers in the United States will progressively reduce the magnitude of this issue. The importance of physician–patient communication in cases of chronic pain can be evidenced through the results of a study by Lacroix et al. (1990), who determined that patients with chronic low back pain who had a strong understanding of their condition were statistically more likely to return to work during the course of the study than were patients with a poor understanding of their condition.

Bates et al. (1997) suggest that due to a lack of understanding of the views and values of ethnic minority patients with chronic pain by clinicians, these patients are likely to experience higher levels of treatment-related distress. Accordingly, minority patients with chronic pain are more likely to avoid medical services and are at greater risk for dropping out of treatment. Goldberg and Remy-St. Louis (1998) emphasize the importance of nonminority clinicians making a conceptual shift to understand the meaning of pain to the minority patient, as failing to do so adversely affects the credibility of the health care professional, thereby rendering treatment ineffective.

Davidhizar et al. (1997) postulate that ethnically and culturally diverse patients with pain demonstrate their pain either stoically or emotively. These two divergent response styles are determined, to a great extent, by the cultural traditions which specify the rules of conduct and conformity regarding the expression of pain. When dealing with nonminority health care professionals, both of these response styles can be problematic, as nonminority providers have the expectation that pain will be expressed neither in an overly stoic nor in an overly emotive fashion, but rather in a manner consistent with their own styles of communication. Bates et al. (1995) state that Puerto Ricans and Anglo-Americans appear to perceive and experience chronic pain differently, and that the difference is neither positive nor negative in itself. While the emotive expression of chronic pain among Puerto Ricans is considered normal and acceptable to Puerto Rican patients and medical professionals, non-Hispanic clinicians are likely to interpret the Puerto Ricans' emotive style as indicative of their inability to cope appropriately with chronic pain. The authors noted that Puerto Rican health care providers considered the patients' open display of what Anglo providers would consider excessive pain behavior to be normal and appropriate. Despite significant differences in style of expression of pain, Bates et al. (1995) did not find any differences between their Puerto Rican and non-Hispanic Caucasian groups in terms of interference with work, social, or family activities. In a study of 372 patients with chronic pain from six different ethnic groups that was conducted in New England, Bates and Edwards (1992) found that the Hispanic group's self-reported expression of pain was higher than that of the non-Hispanic Caucasian groups. While the authors did not mention the response to the Hispanics' emotive

expression of pain by the clinicians who were involved in this study, it is unlikely that they considered the Hispanics' pain behavior "normal and acceptable" as had the Puerto Rican medical professionals in the Bates et al. study (1995). As Anglo health care providers are likely either directly or indirectly to express their expectations regarding "appropriate" expression of pain to Hispanic patients (and may do so in a perceivably judgmental manner), Hispanics suffering from chronic pain may feel misunderstood and alienated and, accordingly, may choose not to seek or to withdraw from treatment that could potentially benefit them.

Although a number of investigators have addressed the impact of the emotive style of Hispanic patients with chronic pain, less has been written regarding the impact of the stoic style. Kramer et al. (2002a, b) studied pain-related beliefs and the manner in which symptoms are communicated among Native Americans suffering from chronic arthritis joint pain. In both studies, the authors determined that Native Americans suffering from chronic pain tended to voice subtle pain complaints, used vague verbal descriptions for their pain, and accordingly, may have understated serious symptoms. The investigators reported that while most of these Native American pain sufferers eventually sought medical attention, the under-recognition of the severity of their symptoms resulted in suboptimal treatment as opposed to appropriate multidisciplinary care (Kramer et al., 2002b). A strength of both of these studies was the drawing of their samples from an urban area in which more than 200 different Native American tribes were represented, thereby enhancing the generalizability of their results.

A surprising paucity of research on chronic pain among Asians is evident, particularly given the rapid growth rate of the population within the United States. Salimbene (2000) emphasizes the importance of taking Asians' traditions of stoicism into consideration when providing medical services to these minority groups. The author notes the strong Buddhist and Taoist emphases in their teachings regarding stoicism, behavioral reserve, and suppression of negative thoughts and complaints. Lee et al. (1997) notes that Asians are more passive in their relationships with health care providers than are Caucasians and that they will rarely admit ignorance or ask questions regarding their care. While no literature on Asian-Americans' access to chronic pain management services has been published up to this point, Brown (1987) determined that higher levels of stoicism among Vietnamese Americans limited their utilization of the mental health care system. Stoicism among Asian Americans appears to be supported in the acute pain literature, as the results of a number of studies (Carnie & Perks, 1984; Carragee et al., 1999; Houghton et al., 1992; Houghton et al., 1993; Streltzer & Wade, 1981) have indicated that Asians require and/or request substantially lower dosages of opioids than Caucasians post-operatively.

In a review, Lee et al. (1997) noted that although ethnic differences in the pharmacokinetics of opioids may exist, results of such studies have been mixed and have not demonstrated clinical significance. Accordingly, it appears likely that differences in requests for narcotic analgesics between Caucasians and Asians relate to the Asians' stoicism. Based on these studies, the possibility that Asian Americans are at risk for not seeking appropriate treatment for chronic pain conditions certainly should be considered. However, once again it is important to avoid stereotyping. As the pain experiences and emotional and behavioral responses to chronic pain may differ drastically between Mexican Americans and Puerto Ricans, it cannot be assumed that all Asian Americans will evidence the same levels of stoicism in regard to their chronic pain. Despite certain cultural similarities, the meaning of pain to a third-generation Japanese American is likely to be very different from that of a Vietnamese refugee whose level of acculturation is still minimal and whose history of privation due to living in the midst of a war for many years has dramatically altered his or her view of life in general.

Peripherally related to stoicism as a variable that may be related to the undertreatment of chronic pain is fear of dependence on or addiction to narcotic analgesics. Anderson et al. (2002) found that more than 90% of African Americans and 76% of Hispanics in their sample of cancer patients expressed belief that they should not be reliant on pain medications. The majority of patients in both of these groups expressed concerns regarding addiction and developing tolerance to opioids. Of the Hispanic patients, 65% reported that they were concerned regarding their families' reactions to their use of pain medications. Hispanics have been found to be particularly concerned regarding their utilization of narcotic analgesics due to a fear of becoming addicted or developing tolerance (Cleeland et al., 1997; Juarez et al., 1999). Nemoto and colleagues (1999) identified an Asian cultural construct of fear of addiction. While Caucasians suffering from chronic pain also often fear that they will become addicted to or dependent on opioids, the limited literature available suggests that this fear may be more pronounced among certain racial and cultural groups, potentially resulting in their undertreatment. Several studies (Lin & Ward, 1995; Ward & Hernandez, 1994; Ward et al., 1993) that examined fear of addiction and tolerance to opioids among cancer patients of different ethnic backgrounds have suggested that these concerns are strongest among lower socioeconomic status patients. Given the strong negative correlation between racial/ethnic minority status and socioeconomic status (U.S. Bureau of the Census, 2001), however, minority chronic pain sufferers are at greater risk

for undermedication due to fears of addiction and tolerance to narcotic analgesics.

HEALTH CARE AND SOCIAL SYSTEM VARIABLES

Mayberry et al. (2000) provided a comprehensive review of racial and ethnic differences in access to medical care. Their conclusion that racial and ethnic minorities, particularly African Americans, do not have the same access to health services is consistent with their thesis of pervasive racism in the American health care system. In *any* society, *individual* health care providers are not immune to the risk of discriminatory behavior. Mayberry and colleagues (2000) wrote, "The history of medical care in the United States is replete with discriminatory practices that denied ethnic minorities access to services based on skin color. Thus, the medical system of the past is correctly described as a racist institution, and the legacy of racism should not be minimized. Clearly, the patient's race, but specifically skin color, influence decision making, whether it is overt prejudice or subconscious perceptions" (pp. 134–135). However, Mayberry and colleagues also wrote, "The lack of SES (socioeconomic status) indicators in the study of racial and ethnic differences in health care is a common refrain among researchers" (p. 117). The importance of taking socioeconomic status into account in studies of racial and ethnic differences in health care can be fully appreciated through Mayberry et al.'s finding, "In some cases, when important variables [among which they include SES, describing it as the "most important" explanatory variable] are controlled, racial and ethnic disparities are reduced and may even disappear under certain circumstances" (2000, p. 112). The authors reviewed evidence of racial and ethnic inequities in the treatment of a number of health conditions, including heart disease and stroke, cancer, diabetes, HIV/AIDS, mental disease, and children's health issues. Little was mentioned in the article regarding chronic pain. Mayberry and colleagues (2000) did not specify whether they believed that the racism in health care in the United States is consciously or unconsciously motivated.

Mayberry et al.'s (2000) findings suggest that despite the existence of a number of studies that indicate that racial and ethnic minority chronic pain sufferers are at greater risk than Caucasians for being undertreated, it is difficult to specifically attribute this disparity in treatment to health care providers themselves. Given the numerous variables that can contribute to unequal treatment, methodological problems are likely to result in confounded findings. Investigators have tended to rely on the use of medical vignettes as a research approach for determining whether medical professionals treat chronic pain differently based on race and ethnicity. Chibnall and Tait (1999) present vignettes to nonphysician medical center employees in which ethnicity, the presence of litigation, and the strength of medical evidence were varied. Each participant was asked to evaluate the "patient's" pain, disability, and emotional distress; to attribute causality for the patient's pain and disability; and to rate the patient's veracity and the extent to which the patient evoked sympathy from the participant. While interaction effects were identified, the study did not yield any main effects associated with ethnicity. The authors express surprise regarding the lack of a unique effect of patient ethnicity on either attributions or symptom evaluation, and suggest that their ethnicity manipulation may have been too obvious to the participants. Therein lies a significant weakness of this type of vignette study. In another vignette study, Weisse et al. (2001) found interaction effects but no main effects of race on primary care physicians' willingness to prescribe narcotic analgesics for pain associated with kidney stones or acute back pain. Weisse et al. (2003) also used vignette methodology in a study of internists' pain management practices in cases of renal colic and persistent back pain. Again, no main effects for patient race were found, despite the identification of interaction effects.

Given the aforementioned weaknesses of vignette studies, the results of the investigations by Chibnall and Tait (1999) and Weisse et al. (2001, 2003) should not be taken to suggest that health care provider bias against racial and ethnic minorities in their chronic pain management practices does not exist. As mentioned above, a lack of an appropriate methodology for assessing provider bias in treating patients with chronic pain limits the confidence with which one can attribute racial and ethnic differences in chronic pain management services to racism. Perhaps the strongest suggestion of health care providers discriminating in their chronic pain management practices relies on extrapolation from the companion studies by Todd et al. (1993, 2000) mentioned earlier in this chapter in which Hispanics received less analgesia than non-Hispanic Caucasians for acute long bone fracture pain, despite a lack of difference in assessments of pain severity between the two groups by physicians. Todd and colleagues (1994) suggest that this finding of discrepant treatment could be explained by a "straightforward bias by physicians who are equally aware of pain in both ethnic groups, but less interested in treating it when patients are Hispanic" (p. 928). However, the body of literature as a whole suggests that if health care providers are actually providing inferior levels of chronic pain management services to racially and ethnically diverse minorities due to actual prejudice, the empirical evidence for such a disparity is weak.

What, then, can potentially explain the findings of inferior access to chronic pain management services to which racial and ethnic minorities appear to be subjected? As mentioned earlier in this chapter, the negative relationship between racial/ethnic minority status and socioeco-

nomic status has been well established (U.S. Bureau of the Census, 2001). In addition to the numerous patient variables that were mentioned earlier in this chapter, it appears that the lower socioeconomic status of racial and ethnic minorities rather than minority status itself is responsible for much of the limited access to chronic pain management that underserved minorities experience.

There exists a substantial body of literature that suggests that low socioeconomic status, independent of race and ethnicity, is positively related to underservice in medicine in general (Becker & Newsom, 2003; Franks & Fiscella, 2002; Krzyzanowska et al., 2003; Merzel & Moon-Howard, 2002; Newacheck et al., 2003a, b; Omalley et al., 2001; Ozminkowski et al., 1998; Scarinci et al., 2001). A Norwegian study (Brekke et al., 2002) in which race was not considered determined that socioeconomic status related negatively to severity of musculoskeletal pain, higher levels of pain-related physical disability, mental distress, and low life satisfaction. Most recently, Portenoy and his colleagues (2004) utilized survey methodology to assess racial and ethnic differences in pain experience between Caucasians, African Americans, and Hispanics in the United States. They found that a composite variable identified as "disabling pain" was negatively associated with socioeconomic status, although not with racial and ethnic minority status once they had controlled for socioeconomic factors. While a review of the literature indicates a lack of investigations of the specific relationship between socioeconomic status and access to appropriate treatment for chronic pain, some of the studies that have examined the relationship between racial and ethnic minority status and access to services suggest that socioeconomic factors are heavily implicated in the identified disparities.

Escalante et al. (2000) determined that recipients of hip replacements for severe arthritis were less likely to be Hispanic than of other races and ethnicities. The authors cited low socioeconomic status as one of the reasons for this underrepresentation. Similarly, Ang et al. (2003) determined that despite similar self-reported degrees of pain and dysfunction secondary to joint involvement in cases of osteoarthritis, Caucasians were significantly more likely than African Americans to undergo hip and knee replacement surgery. The authors noted that the underlying reasons for this ethnic variation are likely to be "multifactorial" and may include issues of insurance coverage. Hootman et al. (2002) determined that African Americans and Caucasians had the same number of ambulatory medical care visits for arthritis and other rheumatic conditions, but that African Americans were more likely to be seen in emergency rooms and hospital outpatient centers as opposed to private physicians' offices. The authors included insurance coverage and level of socioeconomic resources among the reasons for this disparity. In a study of cancer pain in Puerto Rico, Ward and Hernandez (1994) attribute the use of inadequate analgesia to misconceptions regarding their utilization. The authors suggest, however, that these misconceptions were likely to relate to their subjects' low socioeconomic status rather than to their Hispanic ethnicity itself. Cleeland et al. (1994, 1997) determined that cancer patients treated in community clinical oncology programs that treated primarily minority patients were more likely to receive inadequate analgesia than were patients treated in centers that did not treat primarily minorities. The authors fail to mention the possibility that socioeconomic differences rather than racial and ethnic issues may have caused the identified disparity. Finally, a study by Payne et al. (2003) determined that African Americans suffering from breast cancer underuse hospices and palliative care relative to the general population. The authors note, however, that African Americans may find hospice care inaccessible for economic reasons.

One of the most intriguing studies of racial and ethnic minority difficulties with access to appropriate pain management services examined their relative lack of access to strong prescription narcotic analgesics. Morrison and colleagues (2000) determined that only 25% of pharmacies in minority neighborhoods in New York City carried supplies of narcotic analgesics sufficient to treat severe pain, as opposed to 72% of pharmacies in predominantly non-Hispanic Caucasian neighborhoods. Reasons for inadequate opioid supplies reported by surveyed pharmacists included a lack of demand for certain drugs, concern regarding disposal, fear of fraud and illicit narcotic use that could result in Drug Enforcement Administration investigations, fear of robbery, and problems with reimbursement by health plans and Medicaid. Surprisingly, Morrison and colleagues (2000) make no reference whatsoever to the socioeconomic status of the inhabitants of the "minority areas" in which pharmacies were surveyed. New York City's segregation is certainly as socioeconomically based as racially and ethnically based. Areas such as the South Bronx and Harlem, whose populations are composed almost entirely of racial and ethnic minorities, are among the most poverty-stricken urban areas in the nation. Studies of availability of narcotic analgesics in impoverished areas of the country which are inhabited by non-Hispanic Caucasians would help determine whether the issue of access to opioids is related to racial/ethnic or to socioeconomic factors.

While there have not been any studies published on the relationship among racial/ethnic minority status, access to chronic pain management services, and ability to pay for these services, a review of related literature may, in part, explain disparities in access. Minorities have been found to be significantly less likely to purchase health insurance, even after adjustments for income and wealth have been made (Saver & Doescher, 2000). Lillie-Blanton et al. (2000) determined that minority Americans were more concerned about health care's cost than about

other issues of access to medical services. Income has been determined to be a more significant predictor of lack of health insurance coverage than is race, although racial and ethnic minorities were found to be overrepresented in the low income group (Shi, 2001). Recently, Callahan and Cooper (2004) determined that the socioeconomic variable of lack of formal education was a substantially greater predictor of a lack of health care insurance than was racial/ethnic minority status. As a group, these studies suggest that racial and ethnic minorities are more likely than non-Hispanic Caucasians to be without health care insurance, but that this lack of coverage is related to socioeconomic status and the perceived value of health insurance rather than to racial and ethnic minority status per se.

Chronic pain management services can be costly, particularly when provided in a multidisciplinary or interdisciplinary fashion. A study by Marketdata Enterprises (1995) determined the average cost of pain rehabilitation programs to be $8,100.00. This type of treatment, however, has been found to be considerably more cost-effective than any other options (Turk, 1996). The average cost of multidisciplinary chronic pain management services at present has not been assessed in the literature, but is likely to be greater than the average cost of such services at the time of the Marketdata Enterprises study due to dramatic increases in the cost of health care services in general. Regardless, it is unlikely that many patients are able and willing to pay for multidisciplinary chronic pain management services out of pocket. Accordingly, the frequent lack of adequate health care insurance among racial and ethnic minorities is likely to result in limited access to appropriate treatment of their chronic pain. Racial and ethnic minorities are overrepresented on the Medicaid rolls (Mills & Bhandari 2003). As many practitioners and for-profit chronic pain treatment centers are unwilling to accept Medicaid for their services, racial and ethnic minorities are again at greater risk for lack of access to appropriate treatment. It should be noted, however, that the insurance-related lack of access to the best possible chronic pain management services is a *socioeconomic* rather than a racial/ethnic variable.

CONCLUSIONS

The question of why racially and ethnically diverse minorities suffering from chronic pain are underserved in the United States is certainly a complex one. However, in reviewing the literature on patient variables, communication issues, health care provider issues, and social system variables, it appears that deeply ingrained cultural patterns of seeking access to chronic pain management services and the dual health care system based primarily upon socioeconomic status are most strongly implicated in this disparity. While some of the identified racial and ethnic inequity in access to chronic pain management services may relate to issues within the medical and social systems independent of socioeconomic status, there exists no empirical evidence that would suggest that minorities are underserved due to overt prejudice. Nevertheless, specific instances in which racial and ethnic minorities suffering from chronic pain are undertreated based on prejudice certainly occur, as they do in other service areas within American society.

Because completely eradicating overt prejudice in medicine is unlikely, it is important that health care providers make an effort to do everything possible to overcome the impact of the patient variables that cause racial and ethnic disparities in access to chronic pain management services, as well as consciously monitoring themselves against inadvertent minority stereotyping. The key to providing more equitable access to chronic pain management services is appropriate education of both minority chronic pain sufferers and the pain management specialists who have the potential to ease their suffering. While revamping the American health care system to assure that socioeconomic factors do not affect access to quality care would be a noble undertaking, the complexities of doing so within a larger system characterized by such pervasive inequalities between social classes would be overwhelming.

Educating members of racial and ethnic minorities who suffer from chronic pain may represent a difficult undertaking, as issues of trust of the Caucasian majority-dominated medical establishment are likely to impede such efforts. Some of the patient variables (e.g., racial and ethnic minority reliance upon the family and prayer) discussed earlier in this chapter that may potentially limit access to chronic pain management services are so deeply and pervasively culturally ingrained that extreme caution would need to be taken not to risk further alienation of racial and ethnic minority members. Rather than making what are likely to be futile efforts to educate racial and ethnic minority patients with chronic pain regarding the "superiority" of the standard biomedical approaches, it would perhaps behoove health care providers to accept minorities' emphases on family and prayer. In addition to building trust, acceptance of complementary and alternative medicine *in conjunction with traditional biomedical approaches* appears to be clinically reasonable based on empirical support. Hunt et al. (2000) found that Mexican American patients with diabetes who very actively used alternative treatments such as prayer also tended to be very active using traditional biomedical methods. Ni et al. (2002) studied a sample of more than 30,000 U.S. adults, finding that people who used methods such as prayer, spiritual healing, and herbal medicine were more likely to have customary health care providers and to have visited a physician during the previous year than were those who did not use complementary and alternative medicine.

To deal with the sense of hopelessness that likely makes members of racial and ethnic minorities reluctant

to seek treatment for their chronic pain, psychoeducational counseling may be beneficial. As mentioned earlier in this study, racial and ethnic minorities are less likely to seek psychological counseling than are non-Hispanic Caucasians, likely due to issues of communication and perceived benefit as well as finances. As proportionally more racial and ethnic minorities are being trained in mental health service provision (National Science Foundation, 2003), the hope exists that communication issues will become less problematic, thereby enticing minority patients to accept counseling within the context of their chronic pain treatment. Additionally, studies suggest that nurses can be effective providers of counseling services in the comprehensive treatment of chronic pain (Wells-Federman et al., 2002; Olason, 2004).

In terms of educating health care providers regarding the treatment of racial and ethnic minorities suffering from chronic pain, an article by Bates and colleagues (1997) on the effects of the cultural context of health care on the treatment of chronic pain offers clinicians some excellent ideas for maximizing patient response. The authors noted that medical professionals in Puerto Rico maintained different norms for patients' pain behaviors than did health care providers in the mainland United States, who expected more stoicism by patients. Pain behavior, when observed by Anglo health care providers, was viewed not as indicative of severe pain but rather as a sign that the patient was "overly emotional." Accordingly, Hispanic patients who demonstrated pain behavior in the presence of Anglo health care providers were not given any consideration for prompt treatment. Thus, the Hispanic chronic pain patients being treated in the mainland United States were at risk for feeling alienated by health care practitioners likely to have been seen as uninvolved and incapable of empathy, with little chance of a working alliance developing.

Bates et al. (1997) noted that cultural differences in the doctor–patient relationship exist. The authors suggested that the relationships between patients with chronic pain and their physicians in Puerto Rico were less formal and more personal than in the mainland United States. In Puerto Rico, a greater emphasis is placed on spending significant amounts of time with patients and listening to them express their concerns, fears, anger, and frustrations. Visits to patients' homes by their physicians are not uncommon. Patient-centered medical practice emphasizing empathy has been linked to improved compliance and more positive medical outcomes (Comstock et al., 1982; Scopp, 2000; Sullivan et al., 2000; van Dulmen & Bensing, 2002). Based on the research of Bates and colleagues (1997), the importance of placing more emphasis on the practitioner–patient relationship when treating Puerto Ricans with chronic pain should not be understated. Research on the importance of empathetic, patient-centered approaches in the treatment of other racial and ethnic minorities suffering from chronic pain would also be useful.

A final difference between health care providers in Puerto Rico and those on the mainland who work with patients with chronic pain that should be mentioned is that providers in Puerto Rico function as patient advocates and counselors as well as biomedical pain practitioners (Bates et al., 1997). The authors reported that Puerto Rican physicians counseled patients with chronic pain on social and economic problems associated with their disabilities, served as patient advocates in medicolegal matters, and even served the role of vocational counselors. While no mention was made of treatment of chronic pain in Puerto Rico through a truly interdisciplinary team, the numerous roles that physicians played in patients' recoveries provided chronic pain sufferers with the benefits of interdisciplinary treatment. While multidisciplinary and interdisciplinary chronic pain management programs may include physicians, psychologists, social workers, and vocational counselors, Bates et al. (1997) described the pain physician in Puerto Rico as encompassing all of these roles. The practice of the pain physician in Puerto Rico is the antithesis of that of the pain physician in the mainland United States in terms of accessibility and scope of practice. It is accordingly not surprising that Puerto Rican patients in the mainland United States, along with other racial and ethnic minorities, do not possess the level of trust that Bates et al. (1997) described of patients with chronic pain in their article. The authors stated: "As long as the cultural backgrounds of both patients and providers are ignored in assessment and treatment programs, expensive treatments will remain primarily ineffective. Long-term investment in educating health care providers in personal cultural self-awareness, awareness of the culture of biomedicine, and in cultural relativity may lead to more effective care and treatment, and ultimately save money and reduce human suffering" (p. 1445).

THE FUTURE

Cultural awareness training is finally becoming a part of the training curricula for health care providers in the United States (Donini-Lenhoff & Hedrick, 2000). Nevertheless, racial and ethnic minorities are likely to continue to be underserved for many years to come, as changes in training, attitudes of practitioners and minority patients, and socioeconomically based issues of access to appropriate pain management are likely to occur only very gradually. A study by Anderson et al. in 2000 provided a modicum of optimism, as the authors found that only 30% of African American and Hispanic cancer patients in the study were receiving inadequate analgesics, as compared to 65% of minority patients with cancer in a study that the group had conducted only 3 years earlier (Cleeland et al., 1997). Anderson and colleagues (2000) identified a

change they hope will be perpetuated. However, if this is to occur, racial and ethnic minority patients, health care providers, and the medical and social systems will all need to contribute by demonstrating initiative and flexibility.

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Assuring the Quality of Pain Services: Assessing Outcomes

Michael E. Clark, PhD, Ronald J. Gironda, PhD, and Stacey Carter, PhD

INTRODUCTION

Quality assurance (QA) refers to the program of steps necessary to maximize customers' confidence in the reliability and utility of a product. Within health care systems, maintaining and improving quality typically involves a multitude of procedures, mechanisms, and interventions designed to evaluate health care services, identify and remove barriers to care, and enhance outcomes. QA is an *active* process that focuses on implementing change within organizations or systems within organizations. It is this focus on change that differentiates QA from other health care system structures that use more passive approaches in an attempt to change *responses* to the system, rather than changing the system itself.

Among the many components required for effective QA, whether applied to health care programs in general or specifically to pain services, assessing and monitoring outcomes is perhaps the most important. Outcomes assessment drives the QA process. It provides the means for identifying areas that need improvement, and directs efforts to change. It must be global enough to be sensitive to a range of potential service delivery problems, yet specific enough to suggest possible causes and solutions. Like QA, outcomes assessment is an ongoing process rather than a static event and requires constant maintenance, revision, and "fine tuning."

Within health care settings, outcomes assessment is a multipart process that involves "the systematic collection and analysis of information that is used to evaluate the efficacy of an intervention" (Clark & Gironda, 2002, p. 995). To be *systematic* data must be collected in a consistent and repetitive manner using identical or very similar outcomes measures or instruments. The resulting data then undergo *analysis,* which refers to the process of summarizing and interpreting the data to identify any meaningful trends. Although many settings excel in collecting data, the process of analysis often is neglected or underutilized. Data that are collected but not analyzed do not fulfill the spirit of outcomes measurement nor do they contribute to QA.

In the following sections we discuss the rationale underlying the use of outcomes measures in health care settings focusing on pain-related issues. Next we offer a brief review of instruments used to assess pain outcomes focusing first on the consumer of services and second on the service delivery system. We then talk about the processes of selecting appropriate outcomes domains and applying them in clinical practice. Last, we close with some impressions and general recommendations as applied to efforts to enhance the quality of pain services provided in health care settings.

IMPORTANCE OF OUTCOMES MEASUREMENT IN CLINICAL CARE SETTINGS

The emphasis on measuring the quality of pain treatment services has intensified in the past 15 years and is exemplified by the fact that Congress declared the first decade of the 21st century as the Decade of Pain Control and Research (Joint Commission on Accreditation of Healthcare Organizations [JCAHO], 2003). Improving pain management practices is a primary component of health

care's humanitarian mission, and interest in the application of QA processes to pain began following recognition that pain often is undertreated and managed inappropriately (American Pain Society Quality of Care Committee, 1995; JCAHO, 2003). This recognition spawned several movements to enhance the availability and quality of pain treatment, initially in medical settings and eventually in all patient populations. Subsequently, guidelines for pain treatment have been developed (Agency for Health Care Policy and Research, 1992, 1994; Clinical Practice Working Group [CPWG], 2003), which provide a consensus-based model of care against which health care settings can compare their own services.

Recent regulatory initiatives and legal precedents have increased the demand for quality pain care. Both health care organizations and physicians have been held financially liable for inadequate pain management (Lande & Loeser, 2001). Many states have codified statutes and regulations addressing multiple aspects of pain management (for a complete review of state pain policies see the Pain and Policies Study Group website, University of Wisconsin Comprehensive Cancer Center; http://www.medsch.wisc.edu/painpolicy/). Additionally, recommendations specific to certain treatment methods have been developed, such as the joint Department of Veterans Affairs/Department of Defense guidelines for the use of opioids for pain treatment (http://www.oqp.med.va.gov/cpg/cot/ot_base.htm; CPWG, 2003).

Changes in health care accreditation standards also are responsible for increased attention to assuring quality pain management services. For example, the Rehabilitation Accreditation Commission (CARF) has been a leader of these efforts by developing elaborate outcomes standards for pain treatment programs (1999). The American Academy of Pain Management (AAPM) began its voluntary pain program accreditation service in 1992, initially requiring participating programs to submit data to the National Pain Data Bank for benchmarking and quality assurance (AAPM, 2001). In 2001, the Joint Commission of Accreditation of Healthcare Organizations (JCAHO) incorporated pain management and assessment into its survey and accreditation process for all organizations providing direct care (Gordon et al., 2002; JCAHO, 2001). These standards build on earlier guidelines developed by the Agency for Healthcare Research and Quality (AHRQ) and the American Pain Society (APS) outlining responsibilities for improving outcomes in pain management. However, unlike these voluntary guidelines, JCAHO standards are required — health care institutions must demonstrate compliance by their pain management programs, including evidence of ongoing quality monitoring.

In addition to complying with regulatory issues and accreditation requirements, establishing routine assessment practices for the provision of pain services allows for the collection of research data to validate treatment efficacy and to establish evidence-based standards of care (Gordon & Dahl, 2004). Pain management guidelines have been developed for different patient populations (pediatric, adult, geriatric), types of pain (acute or chronic), and conditions or procedures (low back pain, postoperative pain, cancer pain; see JCAHO, 2003, for a list of pain management guidelines).

Not only is the measurement of pain services warranted to promote clinical effectiveness, it is also advantageous from a cost-effectiveness standpoint (Turk, Loeser, & Monarch, 2002). In the age of managed care, resources for health care are limited. The use of outcome data provides a managed care organization (MCO) an evaluative tool to assist in determining which products to make available to their patients. Indeed, MCO medical directors have indicated that the likelihood of a disease program's being funded is increased by providing evidence of clinical data supporting its effectiveness (Lande & Loeser, 2001).

Finally, and perhaps most importantly, outcomes data should be integrated into the clinical decision-making process in order to improve the quality of pain treatment services provided. This is true not only for day to day patient contact, but at a systemic level as well. While this may sound daunting, this is a routine component of practitioner care. At the most basic level, all revisions in patient care stem from evaluations of treatment outcome. As an example, consider an individual presenting to a provider with chronic noncancer pain. Initially, a trial of nonsteroidal anti-inflammatories (NSAIDs) may be initiated. At the next visit, effectiveness of the NSAIDs in relieving pain and improving function will be assessed. Depending on the results of that assessment of treatment outcome, the NSAIDs may be continued unchanged, revised, or discontinued. If they are discontinued, other pharmaceuticals (e.g., opioids) or interventions (e.g., physical therapy, nerve blocks) may be considered instead. In this example, the practitioner assessed the patient's pretreatment symptom report, administered an appropriate treatment, and then assessed post-treatment symptoms. These assessments guided the provider's decision-making process and allowed for treatment modifications as clinically necessary.

The same process can be incorporated into a larger pain treatment delivery system. For instance, in a multidisciplinary pain treatment program, pretreatment measures can be collected at the time of admission into the program. Review of the results of these same measures administered at the time of discharge provides information regarding the effectiveness of the program in changing targeted domains and suggests avenues for modifying the treatment regimen to enhance outcome. In other words, there exists a continuous feedback loop providing the health care provider with quantitative information to guide subsequent treatment decisions. Figure 9.1 depicts this

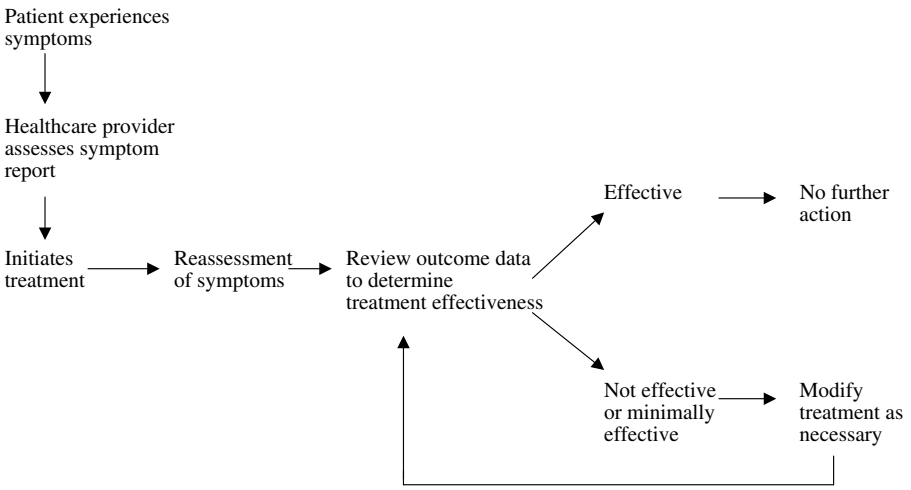

FIGURE 9.1 Clinical decision-making process.

decision-making process. With this said, however, it is important to note that assumptions regarding causation most often are based only on correlational data (i.e., changes in quality are correlated with the interventions for change employed) and, therefore, provide neither confirmation nor rejection of any hypothesized causative link. Other known or unknown factors also could account for the observed changes, particularly in settings where multiple interventions or events may have transpired between the initial assessment and the post-intervention assessment. Therefore, multiple episodes of data collection are preferred as they facilitate the identification of trends in the data that may be more reliable indicators of intervention-related change.

SELECTING RELEVANT OUTCOMES DOMAINS

Selecting appropriate outcomes measures is the key to developing a meaningful outcomes monitoring system. Two factors should be considered as part of the outcomes selection process (Clark & Gironda, 2002):

1. Pain outcomes focus (patient focused or process focused)
2. Practice setting

Pain Outcomes Focus

Patient-focused outcomes measures concentrate on changes in individuals' pain experience following interventions. To quantify change, measures must be administered at least twice (before and after treatment). For treatments spanning lengthy time intervals, repeated administrations (e.g., every month) may provide a more detailed picture of change.

Patient-focused measures often are used to evaluate a single patient's response to treatment. When they are used collectively to evaluate a specific treatment intervention or program of interventions, they serve as aggregate outcomes measures. The most common patient-focused outcome measure is pain intensity. Other measures might include pain-related interference, emotional distress, or physical capacities.

Process-focused measures concentrate on the pain service delivery system and usually are components of performance improvement activities. In some cases measures may be collected only once, but more often they will be collected repeatedly over time to evaluate trends in the measures or to assess the impact of a system intervention.

Results may be used to evaluate how well the pain service delivery system is meeting facility goals, regulatory statutes, or accreditation body (e.g., JCAHO) standards. Common measures include pain clinic waiting times, adequacy of pain assessment and treatment documentation, or compliance with patient pain education standards.

Practice Setting

Practice setting refers to attributes of the pain service delivery environment. Pain treatments may range from minimally complex (e.g., medication management) to highly technical (e.g., dorsal column stimulator implants).

In general, pain service settings that require minimal resources and use uncomplicated treatments may not warrant elaborate, expensive, and time-consuming outcomes measurement practices when less complex approaches would suffice. In contrast, more complex treatment settings requiring greater resource investment or patient risk may want to use broader, multidomain outcomes measures to assess change in a variety of pain experience areas.

The rationale underlying this variation in outcomes approach is twofold. First, from a cost–benefit perspective, when resource investment is greater, such as in complex

pain treatment settings, it is reasonable to expect that outcomes should be improved. Utilization of more comprehensive outcomes measures that assess function in a greater range of domains may provide evidence of a greater range of treatment-related improvements. Second, complex pain treatment settings are likely to treat individuals with more complicated and severe pain conditions and increased pain-related dysfunction that extends across multiple domains of function. Therefore, more elaborate measures of outcomes may be needed to accurately reflect both the extent of pain-related disability and the degree of improvement attained.

ASSESSING DOMAINS OF PAIN OUTCOMES

The assessment of pain treatment outcomes is multifaceted, and the selection of appropriate measures is dependent on the objectives of outcomes measurement. Patient-focused outcomes approaches are concerned primarily with treatment-related changes in patients' pain experience. Service delivery outcomes approaches focus on monitoring and enhancing pain service delivery systems. These two approaches should not be considered mutually exclusive; more elaborate outcomes systems may include aspects of each.

Patient Domains

Current standards for chronic pain treatment are based on biopsychosocial conceptualizations of chronic pain as a complex, multidimensional phenomenon with diverse etiologic and sustaining factors (Turk & Flor, 1999). Consistent across biopsychosocial perspectives is the underlying assumption that the chronic pain experience is a result of a dynamic interaction among biological, psychological, behavioral, and social factors that shape the individual's response to physical perturbations (Turk & Flor, 1999). Accordingly, recommendations for comprehensive treatment target multiple domains of patient functioning including the physical, perceptual, behavioral, and psychosocial status of the individual. Reflecting this multidimensional approach to conceptualization and treatment, current guidelines for pain outcomes assessment mandate the measurement of treatment-related change within each major domain of an individual's chronic pain experience (Rehabilitation Accreditation Commission, 2002).

The discussion that follows considers each of the domains of patient functioning that we believe to be an important aspect of the pain experience. While not all of these patient-centered domains are likely to be directly targeted by any single treatment approach, changes may be observed in any of these areas following even the most focused interventions due to the interrelationships among these domains. Where appropriate we have suggestions for measures that may be used to assess outcomes in each of these domains. However, it should be noted that only those measures that have been validated with pain patient samples and were judged by the authors to have some utility for outcomes assessment were included in this discussion. Criteria for inclusion in this review were (1) evidence of acceptable reliability, (2) data supporting instrument validity, (3) prior use as a pain outcomes instrument, and (4) high utility for pain outcomes assessment, as judged by the authors. If such measures are not available, suggestions for alternative assessment strategies are provided. The domains assessed by the instruments that are reviewed are presented in Table 9.1. Absent from this review are several well-validated measures, such as the Coping Strategies Questionnaire (CSQ; Rosensteil & Keefe, 1983), which tap important aspects of the pain experience and have been widely used in pain research, but lack significant evidence of utility for general pain outcomes assessment. For the reader who is interested in a wider range of pain measures, more comprehensive reviews may be found elsewhere (Bradely, Haile, & Jaworski, 1992; Jensen & Karoly, 2001; Tait, Pollard, Margolis, Duckro, & Krause, 1987).

Pain Intensity

While practitioners may not agree on the relative importance of pain reduction as a treatment objective, pain intensity is clearly an essential outcomes assessment domain from most perspectives. Fundamentally, the sensory experience of pain is a subjective aversive phenomenon that is unique to each individual, and as such, it is difficult to describe and quantify objectively. Fortunately, several easy-to-administer, psychometrically sound scales have been developed to assess this domain of the pain experience. There are three broad categories of commonly used pain intensity measures: the Visual Analog Scale (VAS), Numeric Rating Scale (NRS), and Verbal Rating Scale (VRS). The VAS and NRS typically consist of a single item requiring patients to quantify the intensity of their "current," "usual," "least," or "worst" pain. Empirical evidence suggests that the combination of "least" and "usual" pain ratings provides the best estimate of actual pain intensity, while "least" may be the single most accurate predictor (Jensen, Turner, Turner, & Romano, 1996). However, for practical purposes clinicians can have confidence in the choice of a single VAS or NRS rating of "usual" pain, which appears to provide a reasonably valid estimate of actual pain. Interestingly, "current" and "worst" pain ratings were found to have a weaker relationship with actual pain intensity (Jensen et al., 1996).

A reliable and well-validated form of the VAS is a 10-cm line anchored with the phrases "no pain" and "worst possible pain" or "excruciating pain." Patients are instructed to bisect the line at the point that best represents their level of pain, and the score is simply the length of

TABLE 9.1
Domains of Outcome Assessed by Self-Report Measures

Measure (Items)	Pain Intensity	Pain Interference	Emotional Distress	Fear	Employment	Utilization	Satisfaction
NRS/VAS (1)	X	—	—	—	—	—	—
MPQ (20)	X	—	—	—	—	—	—
PDI (7)	—	X	—	—	—	—	—
SIP (136)	—	X	—	—	—	—	—
ODQ (10)	—	X	—	—	—	—	—
BDI (21)	—	—	X	—	—	—	—
CES-D (20)	—	—	X	—	—	—	—
STAI (40)	—	—	X	—	—	—	—
PASS (40)	—	—	—	X	—	—	—
TS (17)	—	—	—	X	—	—	—
BPI (32)	X	X	X	—	—	—	—
POQ (45)	X	X	X	X	X	X	X
MPI (52)	X	X	X	—	—	—	—
POP (23)	X	X	X	X	—	—	—

Note: NRS/VAS = Numeric Rating Scale/Visual Analog Scale; MPQ = McGill Pain Questionnaire; PDI = Pain Disability Index; SIP = Sickness Impact Profile; ODQ = Oswestry Disability Questionnaire; BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies — Depression Scale; STAI = State-Trait Anxiety Inventory; PASS = Pain Anxiety Symptoms Scale; TS = Tampa Scale; BPI = Brief Pain Inventory; POQ = Pain Outcomes Questionnaire; MPI = Multidimensional Pain Inventory; POP = Pain Outcomes Profile.

the segment to that point. The VAS has been found to be valid and sensitive to changes in acute, cancer, and chronic pain (Breivik, Bjornsson, & Skovlund, 2000; De Conno et al., 1994; Hutten, Hermens, & Zilvold, 2001; Jensen & Linton, 1993; Ogon, Krismer, Soellner, Kantner-Rumplmair, & Lampe, 1996), and it yields ratio level data (Jensen, Turner, & Romano, 1992). Although comparisons of horizontal and vertical line orientations yield mixed results, using the VAS horizontally may provide slightly higher sensitivity (Jensen, Turner, Romano, & Fisher, 1999; Ogon et al., 1996; Stratford, Binkley, Riddle, & Guyatt, 1998).

The NRS consists of a numeric range from 0 to 10 or 100 with anchors similar to those of the VAS, which can be administered in oral or written form. Individuals are asked to quantify their pain levels by choosing a single number from the 11- or 101-point scale. The NRS has been found to have good psychometric characteristics (Jensen et al., 1999) and to be sensitive to changes in acute, cancer, and chronic pain (De Conno et al., 1994; Paice & Cohen, 1997). The data provided by the NRS can be treated as ratio level (Jensen & Karoly, 1992).

Verbal rating scales typically consist of a list or lists of pain descriptors that are rank-ordered along a continuum of severity. Patients are asked to select the most appropriate descriptor or set of descriptors, and a score is assigned based on the rank(s) of the chosen word(s) (Jensen & Karoly, 1992). The McGill Pain Questionnaire (MPQ; Melzack, 1975a) is a well-validated, widely used VRS that consists of 20 lists of descriptors of the sensory, affective, and evaluative dimensions of pain (Melzack, 1975b). The standard scoring procedure yields a Pain Rating Index (PRI) for each of the three subscales listed above, although in practice these subscales are often summed to create a single PRI. The PRI has been shown to be sensitive to change and valid for use among acute, cancer, and chronic populations (Davis, 1989; Lowe, Walker, & MacCallum, 1991; Sist, Florio, Miner, Lema, & Zevon, 1998). However, as is true of other verbal scales, it only yields ordinal level data as questions have been raised about the assumption of equidistance between ranked descriptors (Choiniere & Amsel, 1996). Additionally, support for the tripartite structure of the MPQ is mixed, and factor analyses generally reveal significant overlap between factors (Donaldson, 1995; Holroyd et al., 1992; Turk, Rudy, & Salovey, 1985).

Another verbal pain scale, often used in analgesic research, is a 0 to 3 categorical scale with 0 corresponding to "no pain," 1 to "mild pain," 2 to "moderate pain," and 3 to "severe pain." While there is evidence for the validity of this approach when used to differentiate between categories of pain intensity (Jensen & Karoly, 2001), this ranked-score approach often is treated as if it represented an interval scale where differences between any successive rankings are assumed to be equal. This may result in misleading estimates of changes in pain intensity and is therefore best reserved for use only as a descriptive scale.

Practical considerations suggest that the VAS or the NRS may be preferred to the MPQ or other verbal scales

for the clinical assessment of pain intensity as they provide psychometrically superior data that are relatively easy to collect and score. When ease of administration and scoring are of greatest concern, the 11-point NRS may be the best choice. In contrast, when greater measurement precision is desirable, the advantage goes to the VAS or to the 101-point NRS.

Pain Interference

A central goal of pain intervention is to reduce the extent to which pain impairs physical activity, emotional functioning, and psychosocial role fulfillment. The term *pain interference* has been used to define this broad construct, which taps patients' perceptions of the degree to which pain disrupts physical and emotional functioning. Measures of pain interference should not be confused with instruments that simply quantify functional status without attempting to account for the role of pain in the reported impairment. This difference is illustrated by the contrast between the Sickness Impart Profile (SIP) psychosocial scale, which measures the extent of emotional and social difficulties that are attributed to the pain condition, and the Beck Depression Inventory (BDI; Beck, 1987), which assesses depressive symptomatology without concern for etiology.

The Pain Disability Index (PDI; Pollard, 1984) is a seven-item measure of pain interference in physical and psychosocial role performance. The PDI has good internal consistency ($\alpha = 0.87$; Tait et al., 1987) and 1-week test–retest reliability (intraclass $r = 0.91$; Gronblad et al., 1993), and it has been shown to effectively discriminate groups of pain patients with varying levels of disability (Tait, Chibnall, & Krause, 1990). The measure appears to be sensitive to change (Strong, Ashton, & Large, 1994), and it is valid for use with patients with chronic and postoperative pain (Pollard, 1984). Factor analysis supports the classification of the PDI as a unidimensional measure of pain interference (Tait et al., 1990). The PDI has practical appeal as a brief, easy-to-use, and psychometrically sound measure of general pain interference when less comprehensive assessment of pain-related disability is adequate.

The SIP is a widely used, 136-item measure of perceived impairment (Brown, 1995; Williams, 1988) with high test–retest reliability (0.92) and internal consistency (0.94; Bergner, Bobbitt, Carter, et al., 1981). The SIP administration instructions were altered by Turner and Clancy (1988) to reflect pain-related impairment rather than general physical impairment. The 14 SIP subscales assess pain interference across a wide range of functioning, and they are combined to form the physical, psychosocial, and total scales. The SIP scales have been found to possess good concurrent validity in patients with chronic pain and cancer pain (Beckham, Burker, Lytle, Feldman, & Costakis, 1997; Watson & Graydon, 1989), and they are sensitive to change resulting from multidisciplinary inpatient treatment for chronic pain (Jensen, Strom, Turner, & Romano, 1992). From a practical standpoint, the main weaknesses of the SIP are its length and the relative difficulty of scoring the inventory. In addition, individuals with pain may find many SIP items to be less face valid and relevant to their condition than those of measures developed specifically to tap pain-related disability. Nevertheless, the SIP remains the "gold standard" for detailed assessment of self-reported pain interference.

The Oswestry Disability Questionnaire (ODQ) is a 10-item questionnaire assessing pain and pain-related limitations in daily activities (Fairbank, Couper, Davies, & O'Brien, 1980). Testees choose one of six response options for each item, and scores are summed across items. The ODQ has evidenced adequate stability (Davidson & Keating, 2002) and internal consistency (Hsieh, Phillips, Adams, & Pope, 1992), as well as discriminative validity (Leclaire, Blier, Fortin, & Proulx, 1997) and sensitivity to change (Davidson & Keating, 2002). ODQ item content suggests that it may be most useful for patients with more severe limitations or disability (Baker, Pynsent, & Fairbank, 1989).

Emotional Distress

Emotional distress is highly prevalent among individuals with pain, and it is a core feature of most chronic pain syndromes. Not only does emotional distress often exacerbate a pain condition, but it may also have a significant impact on treatment outcomes regardless of whether it is addressed clinically or not. Accordingly, treatment standards recognize the importance of incorporating the treatment of concurrent anxiety and depression into the intervention approach. Presented here are measures of emotional distress that, although not pain specific, are widely used in pain intervention outcomes assessment. These measures were selected based on their brevity, convenience, and general acceptance among pain researchers for outcomes assessment.

The BDI is a 21-item measure of depressive symptomatology (Beck, 1987). This widely used instrument has been shown to have adequate psychometric properties (Beck, Steer, & Garbin, 1988), and it is sensitive to change resulting from multidisciplinary pain clinic treatment (Kleinke, 1991). The BDI discriminates well between patients with chronic pain with and without depression (Geisser, Roth, & Robinson, 1997). However, researchers have raised questions about the appropriateness of using the BDI to detect depression among patients with pain (Williams & Richardson, 1993). Several BDI items contain somatic content (e.g., sleep disturbance, fatigability, and somatic preoccupation) that is confounded with commonly observed symptoms of chronic pain syndromes, and several studies have suggested that patients with pain

may produce higher scores on these items as a function of their pain-related physical symptomatology (Plumb & Holland, 1977; Wesley, Gatchel, Gorofalo, & Polatin, 1999). While this may limit total score comparisons with nonpain populations, removal of the somatic items has not been found to improve the accuracy of the measure for discriminating depressed from nondepressed patients with chronic pain (Geisser et al., 1997). Consequently, clinicians may choose to use the BDI for treatment outcomes, although accurate classification of depressive symptomatology may require higher cutoffs.

An alternative measure of depression favored by some researchers for pain outcomes is the 20-item Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). The CES-D has high internal reliability ($\alpha = 0.85$) in normal populations and good concurrent validity in chronic and cancer pain populations (Beckham et al., 1997; Radloff, 1977). The CES-D may be more sensitive to change than the BDI (Turk & Okifuji, 1994). Normed on a normal population, the CES-D suffers from many of the same limitations as the BDI, potentially producing a high number of false positives among patients with chronic pain and cancer pain. However, like the BDI, the CES-D has been shown to discriminate between patients with chronic pain with and without depression, and removal of somatic items did not appreciably improve accuracy (Geisser et al., 1997; Turk & Okifuji, 1994). Nonetheless, higher cutoffs should be used in pain populations.

The impact of anxiety on pain treatment outcome has not been studied as extensively as that of depression. However, the existing evidence suggests a high concordance between pain and anxiety (Polatin, Kinney, Gatchel, Lillo, & Mayer, 1993), and the need to address these symptoms in comprehensive pain intervention is well recognized. The State-Trait Anxiety Inventory (STAI) is a 40-item self-report inventory of state and trait anxiety that possesses adequate psychometric properties (Spielberger, 1983) and is widely used for pain outcomes measurement. The STAI is sensitive to change (Mongini, Defilippi, & Negro, 1997) and is an adequate choice for the clinician wishing to quantify levels of both acute anxiety and the more stable tendency to perceive one's environment as threatening.

Pain-Related Fear

Recently, researchers have begun to focus on the role of pain-specific emotional distress in the experience of pain. Emerging data indicate that pain-specific emotional distress, particularly pain-related fear, may play a more important role than general levels of affective disturbance in the development and maintenance of pain-related physical disability (McCracken, Faber, & Janeck, 1998). The construct of pain-related fear may be defined broadly as the fear of pain and the avoidance of behaviors that are anticipated to produce painful sensation or injury. Although no evidence currently exists linking levels of pain-related fear to treatment outcome, the available data suggest that pain-related fear may seriously compromise an individual's willingness to initiate and persist in the degree of physical reactivation and restoration that is essential to reversing the progression of pain-related disability. Accordingly, clinicians and researchers are beginning to pay more attention to the role of pain-related fear in pain treatment outcome.

Of the few available measures of pain-related fear, the Pain Anxiety Symptoms Scale (PASS; McCracken, Zayfert, & Gross, 1992) and the Tampa Scale (TS; Kori, Miller, & Todd, 1990) are the most promising. The PASS is the longer of the two measures, with 40 items assessing cognitive and pain-related physiological anxiety symptoms, escape and avoidance responses, and fearful appraisal of pain (McCracken et al., 1992). The four PASS subscales have good internal consistency (McCracken, Zayfert, & Gross, 1993), and the total score has good predictive validity and appears to be adequate for outcomes assessment (McCracken et al., 1998). Scores on the PASS have been found to predict self-reported pain severity, disability, pain behavior, and range of motion on straight leg raise (McCracken, Gross, Aikens, & Carnrike, 1996; McCracken, Gross, Sorg, & Edmands, 1993). In addition, pain patients classified as "dysfunctional" by the Multidimensional Pain Inventory (MPI; Kerns, Turk, & Rudy, 1985) were more likely to produce high scores on the PASS than those classified as "interpersonally distressed" or as "adaptive copers" (Asmundson, Norton, & Allerdings, 1997).

Perhaps a better measure of the pain-related anxiety is the TS, a 17-item instrument developed to assess kinesiophobia, or the fear of movement and activity due to concerns about injury or reinjury (Kori et al., 1990). Although limited, recent evidence suggests that the TS may possess greater predictive validity than the PASS and other measures of pain-related fear. The TS has been found to be a superior predictor of a range of pain symptoms and behaviors, even after controlling for known confounding factors such as pain intensity and duration, gender, and negative emotionality. For example, the TS was an incrementally valid predictor of self-reported disability and behavioral performance during a lifting task after controlling for pain onset, lower extremity radicular pain, and pain intensity, while the PASS was not (Crombez, Vlaeyen, Heuts, & Lysens, 1999). In addition, the TS has been found to be a superior predictor of disability as compared with pain intensity, biomedical signs and symptoms, and negative emotionality (Crombez et al., 1999; Vlaeyen et al., 1999). Although there are no data on the ability of either the TS or the PASS to capture treatment-related change, either measure may be appropriate. However, given its superior predictive validity and shorter length, the TS appears to be the instrument of choice for assessing treatment-induced changes in pain-related fear.

Activity Level

Individuals with pain conditions often exhibit a pattern of gradually declining physical activity. In many cases, activity is associated with the experience of discomfort or the potential for reinjury and, therefore, is generally avoided. The resulting deconditioning increases the probability that activity will be experienced as aversive or harmful. In this manner, inactivity is reinforced and becomes an entrenched behavioral pattern. Accordingly, physical reactivation is a central component of most multidisciplinary treatment approaches, and most outcomes batteries include a measure of activity level. Unfortunately, most measures of activity rely on patient self-report, which may be subject to considerable biases stemming from such factors as differences in self-perceived effort expenditure, secondary gain factors, or inaccuracy in retrospective reporting. In response to this measurement issue, some pain experts have begun to consider the potential utility of actigraphy as a means to capture treatment-related changes in physical activity. Currently, there are at least two commercially available actigraphs that promise to provide an objective measure of this important outcomes domain. Both devices are wrist-worn and provide an unobtrusive method of recording ongoing activity counts over a period of up to 30 days. While very little literature documenting the use of these devices for pain treatment outcomes currently exists, interest in the pain research community is growing and likely to produce support for this approach within the next few years.

Physical Capacities

In contrast to functional capacities, little empirical or theoretical attention has been devoted to consideration of the role of physical capacities in pain-related disability. However, the importance of this construct, which refers to an individual's theoretical peak physical capabilities, is evident in the focus of many treatment programs on improving physical status variables such as strength, endurance, and range of motion. Unfortunately, the lack of agreement between self-report and actual physical capacities (Clark, 1996; Deyo, 1988) has complicated outcomes measurement leading many pain practitioners and researchers to suggest that objective physical capacity measures may serve as better indicators of treatment-related changes in this domain. At present there are no "gold standard" objective outcomes measures of pain-related physical capacity, although a variety of methods have been employed in attempts to quantify changes in the physical abilities of individuals with pain. Standardization of assessment methods is lacking, and practitioner ratings of function remain very popular despite numerous studies demonstrating their poor reliability. Although there are a few commercial systems that may eventually provide adequate validation data, they are very expensive and time intensive, limiting their utility for clinical settings. The best-supported performance measures, which tend to be less resource intensive, are the dual inclinometer method of assessing changes in trunk range of motion (Engelberg, 1993; Keeley et al., 1986; Mayer, Kishino, Keeley, Mayer, & Mooney, 1985) and the use of hand dynameters to evaluate upper extremity strength (Mathiowetz, Rennells, & Donahoe, 1985; Mathiowetz, Weber, Volland, & Kashman, 1984). In settings where rapid assessment is necessary, current alternatives appear limited to goniometer measures or practitioner ratings until alternative approaches are developed and validated.

Employment Status

Employment status is a key functional outcomes variable that is commonly used to evaluate the global success of chronic noncancer pain treatment programs. In fact, many treatment outcomes guidelines, such as those promulgated by CARF (Rehabilitation Accreditation Commission, 2002), mandate the use of work status as an outcomes indicator. Similarly, changes in disability status may be an important measure of the overall clinical impact of the intervention approach. Unlike most other outcomes domains discussed here, standardized measures are not required to assess changes in employment status. Current employment and disability status can be collected as part of pre- and post-treatment interviews, most commonly as a categorical variable in which the participant is characterized as being employed full-time, part-time, or not at all. An alternative approach may be to quantify the extent to which a person was gainfully employed and at work during a given period of time. Also important are changes in disability status that affect an individual's eligibility for employment, coded categorically as having a claim pending or not. Finally, for retirees or persons already established as being disabled, an increase in avocational activities may be an appropriate measure of pain treatment success as measured by volunteer work, increases in household chores or activities around the home, initiation of hobbies, or other changes consistent with general productiveness.

Relationship Outcomes

Central to current biopsychosocial conceptualizations of pain is the role of interpersonal relationships, particularly those with immediate family members. Interpersonal relationships may promote the development and maintenance of chronic pain conditions, and family involvement in the treatment process has long been recognized as an important predictor of outcome. Current treatment standards call for active significant other participation in treatment through activities such as family education, shared goal setting, and compliance support. Measurement of the effectiveness of these intervention components will

depend in part on the specific aspects of the social context that are addressed clinically. Although providers may want to include general measures of family functioning such as the Dyadic Adjustment Scale (Spanier, 1976), pain-specific and behaviorally focused measures may be most useful. One option is the Significant Others Response scale of the West Haven-Yale Multidimensional Pain Inventory (Kerns et al., 1985). Also important to assess may be satisfaction with sexual intimacy in the dyadic relationship. Unfortunately, there are few standardized measures of many aspects of relationship functioning (such as sexual intimacy) that are posited to have an impact on chronic pain disability, and therefore, providers must rely on nonspecific measures validated in other populations. Interested readers are referred to Jacob and Kerns (2001) for a comprehensive review of the available measures in this area.

Health Care Utilization

Individuals with chronic pain utilize health care resources at higher rates than those without pain (Gironda, Clark, Neugaard, & Nelson, 2004). From a patient-focused outcomes perspective, excessive use of health care resources may be conceptualized as reflecting sick role behavior, and therefore, utilization variables may serve as useful indices of functional status. Reduced reliance on provider intervention may indicate a reduction of symptomatology or a shift on the part of the patient to a more self-reliant proactive role in pain management. Patient-focused health care outcomes variables may range from simple counts of medical contacts for pain over a given period of time to quantification of the socioeconomic costs to the patient for the identified visits.

Patient Satisfaction

Satisfaction with treatment is a key outcome domain that may have significant implications for patient behavior and treatment success. Treatments that meet patients' expectations are more likely to facilitate a working therapeutic relationship and engender compliance (Aharony & Strasser, 1993; Carr-Hill, 1992). However, measurement of treatment satisfaction is hindered by widely varying conceptualization and by patients' difficulty in separating their satisfaction with pain management from their satisfaction with other aspects of care (e.g., relationships with the health care providers). One of the only treatment satisfaction measures to be developed specifically for use with patients with chronic pain is the Pain Treatment Satisfaction scale (PTS). This five-item scale, which consists of items from the National Pain Data Bank comprehensive outcomes measurement system (AAPM, 2000), is included in the post-treatment version of the Pain Outcomes Questionnaire (POQ) and can also be used as a stand-alone measure. The PTS scale has been demonstrated to have good internal consistency ($\alpha = 0.83$ to 0.90) and good concurrent and predictive validity (Clark, Gironda, & Young, 2003). As such, the PTS offers an easy-to-administer, pain-specific, and effective alternative to the generic satisfaction measures commonly relied upon by pain providers.

Drug-Related Problems

A drug related problem (DRP) is any undesirable event that involves some aspect of the patient's drug therapy and has the potential to negatively affect outcome. DRPs may include not taking or receiving the needed drug, taking or receiving the wrong drug, taking or receiving too little or too much of the correct drug, or experiencing an adverse drug reaction including drug–drug or drug–food interactions. Unfortunately, there are no widely available tools or standards for monitoring of DRPs. Providers who are interested in tracking DRPs should develop a coding and recording system that captures the types of problems described above and can be incorporated into standard assessment and documentation practices. Aggregate counts of DRPs may be tracked over time to provide a measure of the safety of prescribing practices. A root cause analysis or similar technique should be employed to refine, correct, or discontinue provider practices if the number of DRPs exceeds a predetermined threshold for a given period of time. DRP thresholds should vary according to the severity of the associated consequences (e.g., a brief medication-induced hypertensive episode vs. a medication-related death).

Multidimensional Measures

The preceding discussion has focused on unidimensional instruments, each of which measures a single pain outcomes domain. Unidimensional pain outcomes instruments generally are readily available, inexpensive, and necessitate minimal administration training time. Additionally, they are an efficient means of collecting data when only a limited number of outcomes domains are to be assessed. However, to assess multidomain pain treatment outcomes using unidimensional measures, it is necessary to assemble a battery of individual instruments. Because instrument selection is likely to vary across settings, the idiosyncratic nature of these batteries often restricts or prevents comparisons between local outcomes data and community benchmarked data. In addition, some of these instruments are quite lengthy and may include items that are not directly relevant to pain. Thus, while unidimensional measures may be the most efficient means of collecting pain data for one or two selected pain outcomes domains, the use of many unidimensional measures to cover all key chronic pain outcomes domains may

decrease the utility of the obtained data while increasing staff and patient burden. In response to the limitations associated with batteries of unidimensional instruments, a few *multidimensional* pain outcomes tools have been developed. Three of these are discussed below.

Brief Pain Inventory

The Brief Pain Inventory (BPI; Cleeland & Ryan, 1994) is a 32-item instrument developed to assess pain history, pain intensity, perceived recent response to medication/treatment, and pain interference. The BPI is well validated among patients with cancer and chronic disease (e.g., osteoarthritis) pain (Clark & Gironda, 2002), and it has been translated into several languages. Factor analytic studies consistently have revealed the two-factors of pain severity and pain interference in physical functioning across samples and language versions (Caraceni et al., 1996; Radbruch et al., 1999; Saxena, Mendoza, & Cleeland, 1999; Wang, Mendoza, Gao, & Cleeland, 1996). However, empirical data are limited mostly to cancer and chronic disease samples, and little is known about the sensitivity to change or psychometric properties of the instrument when used with chronic pain populations.

Multidimensional Pain Inventory

The MPI, formerly the West Haven-Yale Multidimensional Pain Inventory, is a popular pain measure that was developed to facilitate the comprehensive assessment of patients with chronic pain (Kerns et al., 1985). Designed to be used in conjunction with behavioral and psychophysiological measures, the 52 items comprise 12 subscales that are dispersed across three sections: (1) pain intensity, pain interference, dissatisfaction with current functioning, appraisal of support form others, perceived life control, and affective distress; (2) punishing, solicitous, and distracting responses from significant others to displays of pain behaviors; and (3) frequency of the performance of household chores, outdoor work, activities away from home, and social activities (Kerns et al., 1985). Kerns and colleagues (1985) showed that the 12 subscales possess good internal consistency ($\alpha = 0.70$ to 0.90) and acceptable 2-week test–retest reliability ($r = 0.62$ to 0.91). Adequate levels of unique variance and concurrent validity have been demonstrated for most scales (Kerns et al., 1985). The MPI appears to be sensitive to change, but the utility of specific subscales may vary across levels of adaptation and functioning (Strategier, Chwalisz, Altmaier, Russell, & Lehmann, 1997).

In addition to the measurement of treatment outcomes, the MPI has been used to classify patients with chronic pain to identify major treatment needs. Cluster analyses have yielded a three-group typology of patients with chronic pain consisting of dysfunctional, interpersonally distressed, and adaptive copers or minimizers categories (Turk & Rudy, 1990). Clinicians may find this typology useful for purposes such as planning pain treatment or testing the effectiveness of different interventions or intervention components across MPI groups of patients.

Pain Outcomes Questionnaire

The POQ is a pain outcomes package consisting of intake, post-treatment, and follow-up questionnaires. The POQ, which was originally based on the National Pain Data Bank questionnaires (AAPM, 2000), was developed specifically to assess treatment outcomes and therefore encompasses the key domains of functioning for comprehensive outcomes measurement. The outcomes package allows the clinician to track changes in pain intensity, pain interference, emotional distress, activity impairment, pain-related fear, vocational functioning, treatment satisfaction, perceived improvement, and medical resource utilization from intake through follow-up, obviating the need to use more than one measure (Clark et al., 2003). The POQ contains six core subscales which assess pain intensity, pain-interference in activities of daily living (ADLs) and mobility, negative affect, vitality impairment, and pain-related fear. The subscales possess excellent generalizability ($r = 0.78$ to 0.93) and acceptable 7- to 14-day test–retest reliability ($r = 0.63$ to 0.89). In addition, the subscales have good convergent and discriminant validity, and they are sensitive to change. Finally, confirmatory factor analyses have verified the multidimensional structure of the subscales (Clark et al., 2003). A similar but less comprehensive outcomes tool is the Pain Outcomes Profile (AAPM, 2003), which is published by the American Academy of Pain Management. It contains all of the POQ core scale items but does not assess employment status, medical utilization, or treatment satisfaction.

Advantages and Disadvantages of Multidimensional Measures

Multidimensional pain outcomes measures have several advantages relative to unidimensional measures. Because these instruments were specifically designed for pain populations, they often contain fewer total items than combinations of corresponding unidimensional measures and tend to be better integrated. Additionally, as the instruments are uniform, results can be compared across treatment settings or geographic regions, which may assist in the eventual development of universal pain outcomes benchmarks. Disadvantages of the multidimensional measures are that they may be more difficult to obtain, may require additional administration or scoring training as well as more data entry and management time, are more costly in some cases, and may not cover all of the key chronic pain outcomes domains. Nevertheless, when assessing multiple domains of outcomes in clinical settings, multidimensional measures generally are more practical.

Health Care System Domains

The preceding discussion provides an overview of the key domains of *patient* functioning that may be incorporated into an outcomes assessment system. While patient-focused assessment is critical to selecting, delivering, and refining intervention practices that produce improved patient functioning, measurement of health care system outcomes domains also provides important indices of the utility and effectiveness of pain treatment. Also called process outcomes dimensions or "service delivery outcomes" (Clark & Gironda, 2002, p. 998), these domains are the focus of efforts to monitor and improve pain service delivery systems. Typically, health care system outcomes procedures are part of facility performance improvement and accreditation activities. Unlike most patient-focused domains, health care system outcomes are not tracked using standardized measures, but rather involve monitoring aspects of service delivery or patient documentation by reviewing medical and facility records. The following discussion outlines important domains of health care system outcomes, including pain care delivery, pain care costs, and staff competency.

Pain Care Delivery

Pain care delivery outcomes encompass a range of service provision variables including pain screening and assessment procedures, clinic waiting times, patient education, the occurrence of pain-related events, and treatment effectiveness.

Pain Screening and Assessment

The foundation of effective pain treatment is thorough and reliable assessment of pain. Unfortunately, despite JCAHO standards mandating that pain be assessed in all patients, routine pain assessment is not consistently practiced across general health care settings, an omission that often results in the undertreatment of pain (American Pain Society, 1999). Evaluation of pain assessment practices is only possible when the medical records fully document the completed assessment process. It is important to note that pain intensity scores alone do not constitute a comprehensive assessment. Pain assessment should include documentation of the effects of pain on a broad range of life functions (Clark et al., 2003). Measures of pain assessment compliance may simply be the percentage of cases that evidence appropriate pain assessment documentation.

Waiting Times

Prompt access to pain treatment is an implicit corollary of current pain treatment standards. Assessment of waiting time may assess the period between the following sets of events: clinic referral and first available appointment, scheduled clinic appointment time and the time the patient actually is seen, initiation of a pain medication order and the administration of the pain medication (inpatient setting), and the patient's pain medication request and the time the medication is dispensed (inpatient setting). In some settings at least a portion of these data will be available in computerized medical record systems. However, it is likely that most facilities will need to develop specific monitors to record the relevant waiting periods.

Patient Education

Active patient and family participation in the treatment process is perhaps most successfully promoted through education regarding the experience of pain and the importance of effective pain management. Accordingly, patient and family education is considered an essential component of successful pain management programs. As with other health care systems outcomes domains, documentation of patient education should be available in the medical record. Another strategy may be to survey patients and their families regarding the nature and extent of pain education that they received.

Pain-Related Adverse Events

A pain-related adverse event may be defined as any event associated with the pain experience that negatively affects or has the potential to negatively affect the patient's well-being or probability of benefiting from treatment. Examples of common pain-related adverse events include (1) falls that result in injury, reinjury, or the reinforcement of pain-related fear of activity and (2) misuse of an opioid analgesic. Once again, careful documentation of all occurrences of pain-related adverse events is essential to evaluate clinical practices. Systematic tracking of these adverse event episodes over time may facilitate the identification of risk factors that exist within the pain service delivery system.

Treatment Effectiveness

From a health care systems outcomes perspective, treatment effectiveness evaluation differs from the patient-focused approach presented above in that the unit of measurement is not the individual patient but rather the system of clinical service provision. Appropriate units of measurement may include a provider, a group of providers, a group of clinics, etc., while the common goal is to assess the general effectiveness of the defined clinical delivery system for a group of patients treated during a given period of time. This type of evaluation is at the heart of PI efforts and may be as simple as reporting aggregate data collected as a component of the patient-focused outcomes process. An example of this approach is the evaluation of treatment-related pain intensity changes for all patients treated in a multiprovider clinic during a three-month period.

Pain Care Costs

It is estimated that direct and indirect costs associated with chronic noncancer pain exceed $125 billion yearly (Okifuji, Turk, & Kalauokalani, 1999). As mentioned previously, in this environment of soaring health care expenditures, treatment practices that do not demonstrate cost-effectiveness will no longer be economically viable as third-party payers and policy makers shift limited resources to proven intervention strategies. In a general sense, cost-effectiveness is based on a comparison of the benefits derived from receiving pain management services in relation to costs associated with those services. Important but often neglected in this discussion is the issue of cost-offset, which refers to the delayed benefits of an intervention that can be operationalized as reductions in health care costs that are reasonably believed to be attributable to the pain treatment. To conduct a cost-effectiveness evaluation, a system for capturing health care utilization and patient benefits must be developed. Monetary values must be assigned to the various types of services and patient outcomes within each category to allow estimation of the relative economic impact of patient benefits and health care expenses. If a common criterion of success is defined (e.g., return to work), costs associated with a variety of interventions can be compared (see Straus, 2002, and Turk et al., 2002, for specific examples).

Staff Competency

Staff competency in pain treatments maximizes the probability of the appropriate selection and delivery of effective interventions and minimizes the likelihood of the occurrence of pain-related adverse events. Ongoing training and education in both general and discipline-specific pain management are essential to cultivating staff competency. Routine testing of staff following completion of education or training experiences may be used to demonstrate that team members possess a criterion level of pain knowledge relevant the patient population being served. An example of this approach can be found in the work of McCaffery and Pasero (1999) who have developed and validated a test of nurses' pain knowledge and attitudes. Alternatively, changes in pain treatment approaches following focused educational experiences may be used as measures of increased pain competency.

IMPLEMENTING AN OUTCOMES-DRIVEN MODEL OF PAIN CARE

The process of designing a pain outcomes methodology consists of a series of discrete steps and requires that factors relevant to the outcomes system development process, such as those described above, be considered carefully. In the following we provide an outline of our suggested approach to this endeavor in the hope that it will assist the reader through this process.

Identify Outcomes Objectives

The first step in developing a pain outcomes measurement system consists of identifying the goals, objectives, and scope of the outcomes program.

- Identify the basis for establishing the pain outcomes strategy. It may be a new hospital policy, legal opinion, or accreditation standard. Familiarity with the underlying rationale may make it easier to enlist administrative and staff support.
- Determine whether the outcomes objectives primarily focus on pain treatment issues or on the efficiency of pain service delivery. This distinction will have important implications for the eventual selection of outcomes measures.
- Define the scope of the outcomes plan. Are all available pain treatments to be included, or will only selected treatments be monitored? Does the plan cover every type of pain (acute, cancer, and chronic), or is it limited to only one or two?
- Choose which types of service settings will be included. Is it limited to outpatient areas, inpatient units, or specialty pain clinics? Are all providers working in the defined areas participating, or only some?
- Decide whether the outcomes data collection will be ongoing or limited to a preselected time interval.

Identify Administrative Supports and Limitations

Without sufficient administrative support, efforts to develop a pain outcomes system will fail. Staff will resent the added responsibilities in the absence of increased staff or concrete rewards. Presumably the basis for developing the pain outcomes system (JCAHO standards, insurer recommendations) will enhance administrative interest in the effort.

- Meet with the appropriate administrative representative to discuss anticipated costs and needed resources, citing any relevant local policies, local or national regulations, professional practice guidelines, or local competitors' outcomes practices and marketing data.
- Define the administrative limits (funds, positions) that are operative.

- Negotiate an agreement regarding support for the necessary resources.

Select the Relevant Outcomes Domains

Decisions regarding which pain outcomes domains to include often involve compromises between available resources and outcomes objectives. Resources may be limited, and outcomes efforts may be too ambitious. Collecting data for outcomes domains that are not central to the outcomes program objectives is a waste of staff resources and patient time.

- Select the relevant outcomes domains according to the focus of the outcomes program (treatment effects or service delivery), type of pain population involved (acute, cancer, or chronic), and setting.
- Avoid adding outcomes domains that are not directly relevant to the outcomes objectives. Additional domains may be added later if objectives change.
- Review any applicable guidelines, standards, or policies to ensure that all needed domains are included.

Select or Design the Needed Outcomes Measures

Selecting Patient Outcomes Measures

If the objectives of the outcomes program involve evaluating the effects of pain treatment, it is likely that suitable pain outcomes instruments will be available for use. This will avoid the difficulties associated with designing and validating a new instrument and will minimize delays in implementing the outcomes programs.

- Identify potential instruments that assess the outcomes domains of interest (Table 9.1 may be helpful when matching outcomes instruments to outcomes domains).
- Investigate the reported reliabilities and review the validation data available for the identified instruments.
- Review any available data concerning reading level requirements, and determine whether those requirements are consistent with the target population's reading abilities.
- Attend to instrument length, administration and scoring requirements, and costs so as to maximize value and minimize resource demands.
- Determine whether the instruments are available in other languages if this is desirable given the characteristics of the target population.
- Choose the instrument or battery of instruments to use based on the above information.

Designing Service Delivery Outcomes Measures

As indicated previously, service delivery outcomes measures generally are not available in the form of validated outcomes instruments. In fact, with the exception of generic customer satisfaction measures, pain service delivery measures typically need to be designed locally. Fortunately, these measures are relatively simplistic. Usually they involve tracking whether required pain documentation is present or whether designated pain services were provided in an efficient and timely fashion. Thus, designing appropriate service measures may involve no more than developing pain-specific chart review forms or simple customer feedback tools.

- Identify the specific service delivery outcomes questions of interest.
- Design the necessary outcomes tools (e.g., chart review forms, customer satisfaction surveys).
- If patient surveys or questionnaires are involved, evaluate item wording, specificity, and reading level to meet the target population's abilities.

Develop Procedures Needed for Implementation

Once the scope of the outcomes project has been defined and the outcomes measures have been selected, specific procedures for implementing the outcomes system must be developed.

- Determine how the pain patients targeted for the study will be identified.
- Identify the roles, responsibilities, and training needs of all involved staff.
- Develop a timeframe for implementing all aspects of the outcomes system.
- Decide on a sampling strategy (i.e., randomly sample from among all possible data sources or attempt to collect data from every source during the data collection phase) depending on the sample size desired and the projected timeframe.

Design and Prepare the Outcomes Database

Preparation of the outcomes database prior to implementation of data collection requires the review of every outcomes item or measure as well as all data entry and organization issues. Often this process yields valuable information that may streamline data collection and data management procedures.

- Decide what database and data analysis tools will be used.
- Design the necessary records storage and retrieval tools and conduct a "dry run" of data entry to identify any data collection problems.

- Make certain that the confidentiality of any patient information is maintained by discarding identifying information or by using elaborate coding or encryption strategies.
- Develop a data analysis plan in advance of data collection efforts.

Collect the Outcomes

- Provide training in outcomes measure administration and data collection routines to relevant staff.
- Test the data collection procedures using only a few patients (treatment outcomes project) or records (service delivery project) prior to full-scale implementation.
- Arrange for backup coverage for the individuals collecting the data in the event of unexpected absences.
- Periodically review the workflow and data collection procedures to identify and troubleshoot any problem areas.

Analyze, Trend, and Report the Data

Unfortunately, it is common to find that elaborate outcomes data have been collected at significant expense but then have been virtually ignored! Outcomes data analysis and trending is the cornerstone of an effective outcomes program. Analysis involves more than "eyeballing" the data. Although the level of statistical analysis will vary depending on the objectives of the outcomes plan and the psychometric sophistication of the staff involved, at the very least, it will be necessary to statistically summarize the data in a way that directly addresses the outcomes questions of interest. Ongoing review of the results by key personnel is critical and is mandated by some regulatory or accrediting bodies.

- For an ongoing outcomes program, establish a timeframe for systematically reviewing and reporting on the obtained data (monthly, quarterly, semiannually, or annually).
- Develop a report "template" that provides summary data regarding the outcomes questions and use that same template for each reporting period in order to allow comparisons over time.
- If performance improvement actions are instituted prior to or during a data collection period, note the nature of the changes implemented, along with the date, in the database so that the effects of the changes can be evaluated.
- After each reporting period, review data from all prior periods in concert with the current results in order to identify trends of change in the data.
- Provide each staff person involved in the project with copies of the analysis report and schedule a meeting after each data collection period for review and discussion of the data and any identified trends.
- Design and complete a brief version of the analysis report for distribution to key administrators to help maintain their support for the project.
- Use the obtained data to explore any additional outcomes questions or to investigate observed trends in the data.
- Implement treatment protocol changes based on the identified trends. Changes should be introduced sequentially in order to allow the effects of each change to be evaluated separately.
- Review the outcomes data following each change in treatment protocol and decide whether to accept or reject the change.

CONCLUSIONS

The assessment of treatment outcomes is a necessary component of health care delivery and a key indicator of the quality of care delivered. In past years, evaluations of the effectiveness of pain interventions typically were based on providers' queries regarding treatment-related changes collected at patients' follow-up visits. Today, as a result of the demands of regulatory, accreditation, and advisory bodies, this informal outcomes assessment process no longer suffices. Instead, the focus is turning to the systematic collection and analysis of reliable data using validated measures. Indeed, the recent development of JCAHO pain standards and the growing national interest in pain issues have already had a profound effect on outcomes assessment within the pain management field. Outcomes measures now have become a standard component of pain treatment practices both for an individual practitioner and for health care systems. Given today's trends, it appears as if the importance of consistently monitoring, analyzing, and documenting the effects of pain treatment will continue to increase.

In this chapter we have attempted to summarize and briefly explore some of the key issues related to pain outcomes measurement endeavors. We also discussed the rationale underlying the use of outcomes measures in health care settings, focusing on pain-related issues, and provided a brief review of instruments and methods used to assess pain outcomes focusing first on the consumer of services and second on the health care delivery system. Last, we offered a method for designing and implementing appropriate outcomes measures in clinical practice settings. In recognition of the wide variety of pain practitioner settings and outcomes objectives, we tried to maintain a generalist's approach to the topic. In this

regard, we may have sacrificed precision to enhance utility. Nevertheless, it is our hope that the information we have provided will be of value to clinicians seeking to implement procedures to evaluate the effectiveness of their pain treatment interventions.

AUTHOR NOTE

This work was supported in part by the James A. Haley Veterans Affairs Hospital and the Department of Veterans' Affairs Rehabilitation Research & Development Grant O3283R awarded to the first author and Department of Veterans' Affairs Rehabilitation Research & Development Career Development Award/Eastern Paralyzed Veterans Association Scholar Award B2744V awarded to the second author. The views expressed herein are solely the authors' and do not represent those of the Department of Veterans Affairs, the University of South Florida, or the Eastern Paralyzed Veterans Association.

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10

Chronic Pain and Addiction

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INTRODUCTION

There are a number of reasons pain clinicians have been historically interested in the area of addiction. At first, chronic pain clinicians had the clinical impression that pain treatment outcome was influenced by addiction issues (Fishbain et al., 1992b). As such, the mantra in the 1980s and the early 1990s was that chronic pain patients (CPPs) should be detoxified from opioids and that placement on opioids leads to addiction. This position radically changed in the late 1980s when publications began to appear claiming success in treating intractable CPPs with chronic opioid analgesic treatment (COAT) without the development of significant addiction (Portenoy, 1989; Portenoy & Foley, 1986). The COAT literature has increased and now contains a significant number of randomized controlled trials. They have recently been the subjects of a meta-analysis (Graven et al., 2000). Findings of this meta-analysis were that patients with nociceptive and neuropathic chronic pain may benefit from COAT, while this positive effect was less clear for patients with chronic idiopathic pain. Thus, because of the clinical interest in COAT as a way of helping intractable CPPs, addiction has become a hot topic within the pain literature.

This interest in COAT and the associated addiction issue has also been influenced by a number of other developments, which have occurred at the same time. First, a significant literature developed that spoke to the chronic undertreatment of pain by health care professionals (Bendtsen et al., 1999). Second, research studies reported that some physicians were prejudiced against the use of opioids (opiophobia) because of fears of iatrogenic addiction (Bendtsen et al., 1999; Weinstein et al, 2000). Third, in the late 1990s, because of the chronic undertreatment of pain, state licensing boards began to develop policies that supported appropriate opioid prescribing rather than policies that hindered opioid prescribing. Fourth, in the early 2000s, Joint Commission on Accreditation of Health Organizations (JCAHO) incorporated the adequate treatment of pain as a patient right. Fifth, in the early 1990s, drug technology developed a number of controlled-release opioids, which were touted as controlling pain in a more effective manner than the immediate-acting opioids.

At the present time, COAT is mired in controversy. Clinicians who do not accept the current evidence for COAT efficacy still use the addiction issue as an argument against COAT. At the same time, clinicians who use COAT note that there appear to be addiction difficulties with some patients. Thus, at the present time, the issue of addiction is of intense interest to the pain clinician.

As the reader is aware, there are numerous books on the subject of addiction and its treatment. As such, the purpose of this chapter is not to review this literature, but to familiarize the pain clinician with addiction problems and issues that would be relevant to his or her pain practice. Thus, this chapter reviews the most recent research in reference to the following: substance abuse terminology definitions, identification of psychoactive substance use–related disorders or addiction, prevalence of addiction within CPPs, methods for diagnosing addiction in CPPs, risk of addiction in CPPs on opioid exposure, risk of re-addiction in addicts with chronic pain on opioid exposure, diversion, aberrant drug-taking behaviors as indicators of addiction, pseudo-addiction, psychiatric comorbidities in CPPs with addiction, use of short-acting opioids versus long-acting opioids for COAT, opioid treatment agreements, opioids and driving, legal issues in addiction and chronic pain, and opioid detoxification methods in addicts

and non-addicts. As can be seen, this chapter deals mainly with opioids and addresses other drugs of abuse, such as cocaine and cannabinoids, only peripherally. The reader is referred to addiction textbooks for in-depth discussion of the addiction issues relating to these drugs.

SUBSTANCE ABUSE TERMINOLOGY DEFINITIONS

Unfortunately, before we proceed to the addiction research relevant to chronic pain treatment, we need to address a major problem that has served as a confounder to much of this work. This is the confusion over substance abuse terminology (Fishbain et al., 1992b). Historically, there was little agreement between researchers on terms such as drug abuse, psychological dependence, drug dependence, and drug addiction (Rinaldi et al., 1988). Addiction initially meant a habit; however, in 1957 the World Health Organization (WHO) defined addiction as follows: a state or period of chronic intoxication characterized by (1) an overpowering desire or need or compulsion to continue taking the drug and to obtain it by any means; (2) tendency to increase dose; (3) a psychic (psychological) and generally physical dependence on the effects of the drug; and (4) detrimental effect on the individual and/or society (Fishbain et al., 1992b).

Because it was noted that some individuals could be physically dependent on a drug without compulsive use, and vice versa, the WHO then decided to use "dependence" as its crucial variable. Therefore, in 1964 the WHO defined drug dependence as "a state of psychic or physical dependence, or both, on a drug arising in a person following administration of that drug on a periodic or continuous basis." Around that time Rinaldi et al. (1988) performed a four-state Delphi survey of substance abuse experts to "achieve greater clarity and uniformity" for substance abuse definitions. These experts reached the consensus on 50 substance abuse terms. Seven definitions important to this article are taken from this list and presented in Table 10.3: Drug abuse, tolerance, physical dependence, psychological dependence, drug addiction, drug dependence, and drug withdrawal syndrome. It is to be noted that in the definition of drug addiction (Table 10.3), compulsive drug use is a central concept agreed upon by the experts. In addition, the following important concepts are to be noted in reference to the seven definitions in Table 10.3: they are distinct concepts in themselves and they should not be used interchangeably, physical and psychological dependence are encompassed within drug dependence, psychological dependence is distinct from tolerance and physical dependence, and tolerance and physical dependence develop on parallel time courses, but the rate of development of tolerance varies greatly between individuals (Rinaldi et al., 1988).

Psychological dependence is a behavior pattern characterized by continued craving for the substance and does not occur in every patient exposed to the substance. Compulsive drug-seeking behavior leading to overwhelming involvement in drug use and obtaining drugs is a manifestation of this craving. It is interesting to note that in some individuals compulsive drug-seeking behavior can occur before true physical dependence develops (Portenoy, 1989). These other points also apply to the interrelationship between these various concepts: one can be physically dependent without being drug addicted; one can be drug addicted without being physically dependent or drug tolerant; those who are drug addicted are likely to be physically dependent; not all drugs produce physical dependence, psychological dependence, and tolerance, with some drugs producing one manifestation only; and drug-addicted patients who are physically dependent are usually drug tolerant (Ludwig, 1980). Newman (1983) has therefore proposed that addiction needs to be redefined. He has concluded that narcotic addiction can be viewed as an "atypical response to exposure to opioids characterized by a tendency toward progressively greater consumption of the drug and a persistent disposition to relapse to drug use when abstinence has been achieved and physical dependence reversed." He then defined addiction as an "atypical behavioral pattern of drug use characterized by overwhelming involvement with the use of the drug (compulsive use), the securing of its supply, tendency toward progressive drug intake (loss of control) and the high tendency to relapse after drug withdrawal, and reversal of physical dependence."

The American Psychiatric Association (2000) incorporates some of these concepts into its diagnosis of substance dependence (Table 10.1). Unfortunately, there is difficulty in applying these criteria to CPPs for a diagnosis of addiction. For example, of seven criteria (of which three are required to fulfill this diagnosis), one relates to tolerance (criterion 1) and one to withdrawal (criterion 2). If patients with chronic pain are on significant opioids, they are invariably tolerant to opioids and manifest withdrawal when removed from opioids. Thus, these two criteria could lead to over-inclusiveness for this diagnosis in CPPs. In addition, criteria 3 and 4 (Table 10.1) can simply relate to the need to control pain. Thus, four of seven criteria may lead to over-inclusiveness in the application of this diagnosis to the patient with chronic pain.

Because of this confusion over the addiction concept and difficulties with its diagnostic application in CPPs, the American Academy of Pain Medicine, the American Pain Society, and the American Society for Addiction Medicine approved the following definition for addiction (American Academy of Pain Medicine, 2001). "Addiction is a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include

TABLE 10.1
Criteria for a Diagnosis of Substance Dependence (DSM-IV)

Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by the occurrence of three (or more) of the following during the same 12-month period:

1. Tolerance, as defined by either of the following:
   a. A need for markedly increased amounts of a substance to achieve intoxication or a desired effect
   b. Markedly diminished effect with continued use of the same amount of a substance
2. Withdrawal, as manifested by either of the following:
   a. Symptoms characteristic of withdrawal from a substance
   b. The ability to take a substance or one closely related to it, to relieve or avoid withdrawal symptoms
3. A need to take a substance in larger amounts or over a longer period than intended
4. A persistent desire to take a substance in larger amounts or over a longer period than intended
5. A great deal of time spent in activities necessary to obtain a substance (e.g., visits to multiple doctors or driving long distances), to use a substance (e.g., chain-smoking), or to recover from its effects
6. Abandonment of or absence from important social, occupational, or recreational activities because of substance use
7. Continued substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., continued cocaine use despite recognition of cocaine-induced depression or continued drinking despite recognition that an ulcer is made worse by alcohol consumption)

Source: Adapted from American Psychiatric Association (2000).

one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving." No diagnostic criteria, however, were proposed. As such, the pain clinician has the option of diagnosing addiction, using the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) criteria (Table 10.1), keeping in mind the criteria confounders described above, or using the above American Pain Society definition. This definition is defined by five Cs: *chronicity*, impaired *control*, *compulsive* use, *continued* use despite harm, and *craving*. Of these, chronicity, impaired control, and continued use despite harm could also be a manifestation of seeking pain relief. As such, this definition does not shed light on the issue of the difficulty of making an addiction diagnosis in the context of chronic pain. Support for the above comes from a recent study (Elander et al., 2003) with patients with sickle cell disease. Here researchers assessed DSM-IV symptoms of substance dependence and abuse and applied the DSM-IV criteria to differentiate between pain-related symptoms and nonpain-related symptoms. Pain-related symptoms were more frequent, accounting for 88% of all symptoms reported. When pain-related symptoms were included in arriving at a diagnosis, 31% of the sample met DSM-IV criteria for substance dependence versus only 2% when only the nonpain-related symptoms were used to meet criteria.

IDENTIFICATION OF PSYCHOACTIVE SUBSTANCE USE–RELATED DISORDERS OR ADDICTION IN CPPs

Because of the above discussion, the identification of addiction is a complex problem. Complicating this problem is the fact that some patients inaccurately report the use of prescribed medications or fail to report the use of nonprescribed medications or medication prescribed by other physicians, or fail to report the use of illicit drugs (Berndt et al., 1993; Fishbain et al., 1998a; Katz & Fanciullo, 2002). Thus, the use of external sources of information can be helpful. This can include an interview with the spouse, a review of medical records, and the input of prescription monitoring programs. In addition, testing of biological materials (urine) can be extremely helpful. This will be dealt with in its own section below. Because of the problem of inaccurate patient reports, the detection of addiction begins with a high index of suspicion, first trying to identify addiction risk factors (Table 10.2) and then

TABLE 10.2
Addiction Risk Factors

- Biological parent who abuses drugs
- Biological parent who has an antisocial personality
- Lower socioeconomic status
- Child of a divorce home and/or single-parent home
- Behavioral problems as a child
- Comorbid depression, alcohol abuse, antisocial personality disorder, anxiety disorder
- Current dysfunctional or enabling family system (drug abuse in a family)
- Regular contact with high risk people (drug-using friends) or involvement with high-risk activities (regular time spent in a bar)
- Smoking
- Gambling
- Impulsivity
- Multiple physical traumas
- Behaviors with compulsive, addictive quality
- High neuroticism, high extraversion
- Antisocial behaviors (arrests, fighting, early drunkenness, truancy, difficulty with school)
- Use of illicit drugs
- Belief of needing some substance to feel "normal"
- Positive response if asked if use of drugs/alcohol contributed to a problem for them

Source: Adapted from Nedejkovic, Wasan, & Jamison (2002); Robinson, Gatchel, Polatin et al. (2001).

TABLE 10.3
Substance Abuse Terminology Definitions

Term	Definition
(Drug) addiction	A chronic disorder characterized by the compulsive use of a substance resulting in physical, psychological, or social harm to the user and continued use despite that harm
(Drug) dependence	A generic term that relates to physical or psychological dependence, or both; it is characteristic for each pharmacological class of psychoactive drugs; impaired control over drug-taking behavior is implied
Drug abuse	Any use of drugs that causes physical, psychological, economic, legal, or social harm to the individual user or to others affected by the drug user's behavior
Physical dependence	A physiological state of adaptation to a drug or alcohol, usually characterized by the development of tolerance to drug effects and the emergence of a withdrawal syndrome during prolonged abstinence
Psychological dependence	The emotional state of craving a drug either for its positive effect or to avoid negative effects associated with its absence
Tolerance	Physiological adaptation to the effect of drugs, so as to diminish effects with constant dosages or to maintain the intensity and duration of effects through increased dosage
Drug withdrawal syndrome	The onset of a predictable constellation of signs and symptoms involving altered activity of the central nervous system after the abrupt discontinuation of or rapid decrease in dosage of a drug

Source: Adapted from Rinaldi, R. C. et al., 1988

looking for suggestive behavioral patterns (Table 10.4). This is then followed by a search for suggestive physical findings (Table 10.5). In addition, certain laboratory tests (Table 10.6) can provide clues. There are also a number of pencil and paper tests designed to identify drug/alcohol abuse/dependence: the Michigan Alcoholism Screening Test (MAST; Katz & Fanciullo, 2002; Pokornyet al., 1972), CAGE (Steinweg & Worth, 1993), Alcohol Use Disorders Identification Consumption Test (AUDIT-C; Bush et al., 1998), Benzodiazepine Dependence questionnaire (Baillie & Mattick, 1996), the Drug Abuse Screening Test (DAST; Skinner, 1982), the Self-Administered Alcohol Screen Test (Bailey et al., 2002), and the Addiction Severity Index (Savage, 2002). However, to the author's knowledge, none of these tests taps the concept of addiction described above and will not arrive at such a diagnosis. These tests will define the patient at risk for addiction if that patient answers the questions honestly. In addition, these tools have been developed for use with alcoholics

TABLE 10.4
Suggestive Behavioral Patterns for Suspicion for Drug Abuse

- Cigarette smoking
- Absenteeism
- Marital discord
- Driving problems
- Financial difficulties
- Suicide attempt history
- Child abuse history
- Use of stimulants
- Frequent accidents and falls
- Blackouts
- Memory loss

TABLE 10.5
Suggestive Physical Findings for Suspicion for Drug Abuse

- Evidence of current intoxication (sleepiness, nodding)
- Spider angiomata
- Hepatomegaly
- Red facies
- Liver palms
- Salivary gland enlargement
- Cigarette burns
- Unexplained bruises/frequent falls
- Diabetes/blood pressure/ulcers not responsive to treatment
- Inflamed/eroded nasal septum
- Dilated pupils
- Track marks/injection sites
- Gunshot/knife wounds
- Poor hygiene
- Nutritional deficits
- Frequent hospitalizations
- Alcohol withdrawal signs (flushing/hyperreflexia, elevated blood pressure and pulse, tremors)
- Opioid withdrawal signs (mydriasis, sweating/irritability/rhinorrhea)

TABLE 10.6
Suggestive Laboratory Findings for Suspicion for Drug Abuse

- Abnormal liver function tests
- Elevated MCV over 95
- Hypophosphatemia
- Hyperlipidemia.
- High carbohydrate-deficient transferrin
- MCH high
- Anemia
- Positive urinalysis for illicit drugs
- Positive for HIV
- Positive for hepatitis B or C

MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin.

and/or street addicts. There have been no large clinical trials confirming the validity of these tests with patients given opioids for pain (Nedejkovic et al., 2002). For details and descriptions of these tests, the reader is referred to addiction textbooks.

There are a number of addiction tools that are in the process of development specifically designed for use in medical patients. The first of these is the Screening Instrument for Substance Abuse Potential (SISAP). This five-item screen helps the clinician categorize patients for lower or higher risk of abusing prescribed opioids. The five SISAP questions are as follows:

1. If you drink alcohol, how many drinks do you have on a typical day?
2. How many drinks do you have in a typical week?
3. Have you used marijuana or hashish in the past year?
4. Have you ever smoked cigarettes?
5. What is your age?

The SISAP has been shown to have a low clinical false-negative rate when tested against the database of a large (N = 11,634) Canadian epidemiological survey of alcohol and drug abuse (Coambs & Jarry, 1996). It has not been prospectively tested in a chronic pain population. The SISAP is designed to pick up a high percentage of alcohol or polydrug abusers. As such, it has a high false-positive rate (18%). According to the SISAP, caution should be used in prescribing opioids for the following patients:

1. Men who exceed four drinks per day or 16 drinks per week
2. Women who exceed three drinks per day or 12 drinks per week
3. A patient who admits to marijuana or hashish use in the past year. (It is recreational use of cannabis for euphoric effect that is of concern. The use of tetrahydrocannabinol, THC, derivatives to treat pain is still very controversial. Clinicians should exercise caution in recommending opioid therapy to a patient who is using cannabinoids regularly.)
4. A patient under 40 who smokes.

The second tool in development that may be relevant to CPPs is called the Screening Tool for Addiction Risk (STAR; Li et al., 2001). This is a 14-item tool that has been shown to differentiate CPPs from CPPs with a history of drug addiction on three items: prior treatment in a drug rehabilitation facility, nicotine use, and feelings of excessive nicotine use. Prior treatment in a drug facility had a 93% positive prediction value for addiction. However, it is to be noted that predictive validity was not tested here. What is interesting here is that both the SISAP and STAR associate nicotine use with addiction risk.

If the above tools have not been developed specifically for CPPs, should the pain clinician utilize these tools in evaluating CPPs? It is the author's opinion for medicolegal reasons that the use of such tests is indicated if a clinician wishes to enlist a CPP into COAT treatment. The reasons for this are discussed below. Two other issues are important to COAT: addiction fear and detoxification fear. Recently, a number of authors have tapped the concept of addiction fear as a reason for noncompliance with COAT. Greer et al. (2001) noted addiction fear in 10.8% of patients undergoing orthopedic procedures. Patients with neuropathic pain have also been noted to voice this fear; 31.8% (Bailey et al., 2002) have expressed such a fear. Outside of potential noncompliance issues to COAT emanating from such a fear, it is likely that this group of patients would not be at risk for addiction unless it contained patients who had previous addiction and were now abstinent. To date, there has not been a questionnaire developed to tap this fear. There has, however, been a tool developed to tap the fear of detoxification. The Detoxification Fear Survey Schedule (DFSS; Ling et al., 1987) is a tool designed to quantify fear of detoxification. As pain patients are often detoxified from narcotics, such a tool could be a useful instrument to target a problem seen in some pain patients.

THE PREVALENCE OF ADDICTION WITHIN CHRONIC PAIN PATIENTS

In an early structured review, Fishbain et al. (1992b), reviewed studies relating to the prevalence of addiction within CPPs. They reported that different authors used different addiction definitions and criteria, making the data suspect. However, overall the prevalence percentages for drug abuse/drug dependence/drug addiction for patients with chronic pain were in the range of 3.2 to 18.9%. They caution that the results did not tap the concept of addiction and that the prevalence of addiction was likely to be at the middle of this range (Fishbain et al., 1992b). Since this review there have been a significant number of other studies that have directly or indirectly explored this issue. Hoffman et al. (1995a) found an addiction rate of 23.4%. Chabal et al. (1997) found an addiction rate of 34%, and Kouyanau et al., (1997) found a rate of 12%. There has also been one report of a chronic pain population at a Veterans Administration (VA) facility and a primary care setting. Here Reid et al., (2002) reported that prescription opioid abuse behavior was recorded for 24% of the VA patients and 31% of the primary care patients. As "opioid abusive behavior" does not necessarily translate into addiction (discussed below), one does not know how to interprete these results.

TABLE 10.7
Prevalence of Various Psychoactive Substance-Related Disorders within CPPs

Psychoactive Substance-Related Disorders	Prevalence within CPPs, %	More Common than General Population	Discrepancies between Authors
Current alcohol abuse/dependence	2–10.6 (Fishbain, Goldberg, Meager, & Rosomoff, 1986; Hoffmann, Olofsson, Salen et al., 1995; Katon, Egan, & Millder, 1985; Rafil, Haller, & Poklis, 1990)	No	Yes
Current drug dependence (opioids, barbiturates, sedative, cannabinoids)	5.2–34 (Skinner, 1982; Evans, 1981; Fishbain, Goldberg, Meager, & Rosomoff, 1986; Hoffmann, Olofsson, Salen et al., 1995; Katon, Egan, & Millder, 1985; Medina & Diamond, 1997; Rafil, Haller, & Poklis, 1990; Portenoy & Foley, 1986)	Probably	Yes
Current illicit drug abuse (cocaine cannabinoids, speed)	6.41–12.5 (Fishbain et al., 1998a; Evans, 1981; Rafil, Haller, & Poklis, 1990)	Probably	Yes
Total current alcohol and other drug dependence	14.9–23.4 (Fishbain, Goldberg, Meager, & Rosomoff, 1986; Hoffman, Olofsson, Salen et al., 1995; Magni, Caldieron, & Regatti-Luchini, 1990)	Probably	Yes

In addition, there have been two studies using urine toxicologies for prevalence of illicit drug use in patients with chronic pain. In the first study Fishbain et al. (1998a) reported that 8.4% of the patients had illicit drugs in their urine, while Raffi et al. (1990) reported a rate of 12.5%. Because illicit drug use has a high correlation with a predisposition to addiction in patients with chronic pain (Sees & Clark, 1993), these figures probably represent the lower end in the range for prevalence of addiction. Table 10.7 summarizes these studies in reference to various subcategories of drug abuse/dependence.

Although the above studies attempted to develop prevalence percentages for substance use disorders, none of them used control groups. A study by Brown et al.(1996) compared rates for substance use among patients with chronic pain attending a family medicine clinic with patients attending for other reasons. There was no statistical difference in prevalence between the two groups. Thus, it is possible that prevalence for drug addiction in patients with chronic pain is no greater than in other settings. This statement is even more relevant if one considers that the above drug addiction data were reported from tertiary facilities where patients with chronic pain have more significant problems. Overall, these data indicate that the prevalence of addiction may not be too much different from the general population. However, these data are limited by the problems with the definition and diagnosis of addiction.

These figures should also be viewed in the context of the prevalence rate for addiction in the United States. This has been estimated to be from 3 to 16% for alcoholism (Savage, 1993) and from 5 to 6% for other forms of substance abuse (Portenoy, 1993). Prevalence rates for alcoholism are much greater in hospitals. Here the rates have been reported to be 25% for medical services, 19% for neurology, and 23% for general surgery (Savage, 1993). Comparison of these prevalence rates to CPP reported prevalence rates indicates that CPP addiction prevalence rates are not necessarily greater than would be expected from general population data.

Another indirect line of evidence for/against addiction in CPPs is that of opioid use related to the presence of pain. Theoretically, opioid users with chronic pain should have higher levels of pain versus non-opioid users with chronic pain. If they do not, then they are using these drugs for addiction reasons. There have been two studies that have addressed this issue. In the first study, Ciccone et al. (2000) compared chronic pain opioid users and non-opioid users about to enter a pain management clinic for predictor variables. Opioid users were more likely to be physically disabled, be depressed, and report higher levels of pain and in more locations (Ciccone et al., 2000). Conversely, comparison of CPPs utilizing opioids long term versus only anti-inflammatories found that age, depression, personality disorder, and a history of substance abuse predicted opioid use with 79% being correctly classified (Breckenridge & Clark, 2003). Pain intensity did not predict opioid use (Breckenridge & Clark, 2003). It is to be noted that these two studies are not exactly comparable, as the second study used CPPs already selected for COAT. However, the latter study indicates that within this population, there were patients who had a history of substance abuse and that this predicted being on opioids.

The above section can then be summarized as follows: (1) addiction is found within CPPs; (2) at the present time prevalence percentages can be presented only as ranges due to disagreements between researchers; (3) at the present time it is unclear if these ranges are greater than

TABLE 10.8
Development of Craving on Exposure to Opioids in Volunteers (Non-drug Abusing)

Author, Year	Type of Population	No. of Patients Exposed	Percent with Craving
Zacny, 2003	Non-drug-abusing volunteer	18, acutely exposed to 6 sessions (oxycodone, morphine, lorazepam [placebo active])	Liking and wanting ratings no different from placebo after 24 h

that of the general population; and (4) some of the evidence indicates that these ranges may not be greater than for the general population.

ADDICTION GENETICS, RISK OF ADDICTION ON OPIOID EXPOSURE AND RISK OF RE-ADDICTION ON OPIOID EXPOSURE IN PATIENTS WITH A HISTORY OF ADDICTIVE DISEASE

Researchers working in the area of addiction have for years noted that many individuals are self-exposed to alcohol and drugs of abuse and many continue to use alcohol or illicit drugs on occasional or even on a regular basis yet only some individuals go on to develop specific addictions. This indicates that there may be a genetic predisposition in some individuals to developing addiction. Further evidence comes from family, twin, and adoption studies, which establishes the heritability of alcoholism with heterogeneity of inheritance patterns in alcohol abuse disorders and in part for other substance abuse disorders (Anthenelli et al., 1997; Kreek, 2002; Nurnberger et al., 2001). Recently, it has been postulated that an inherited neurotransmitter deficiency in the D_2 receptor makes people vulnerable to addictions and compulsions, such as alcoholism, smoking, cocaine addiction, and attention deficit hyperactivity disorder (Goldman, 1996). This has been called "the reward deficiency syndrome"(Goldman, 1996). Thus, it is likely that, on a biogenetic basis, some individuals have a greater risk than others of developing addiction on exposure to intoxicating substances (Anthenelli & Schuckett, 1997). As such, exposure of individuals with this predisposition to opioids could precipitate addiction. Similar exposure to opioids of those recovering from addictive disease could also precipitate the reemergence of addictive disease. In addition, cross-vulnerability to developing addiction to a variety of substances has been documented (Regier et al., 1984). This suggests that individuals with one addiction, for example, nicotine or alcoholism, may be at higher risk than the general public for developing addiction to other substances, for example, therapeutically prescribed opioids. Because of the above genetic vulnerability to addiction in some patients, there has been significant concern in the medical and pain literature on the development of addiction on exposure to opioids. Studies addressing this issue have been summarized in Table 10.8, Table 10.9, and Table 10.10. Table 10.8 presents a unique study performed with non-drug-abusing volunteers acutely exposed to opioids. Here, liking/wanting ratings, a measure of craving, were no different from placebo. The results of this study would then be in accord with the genetics of addiction discussed above.

The second table (Table 10.9) is divided into three sections: studies addressing general medical patients; studies addressing patients with chronic noncancer pain; and one study addressing epidemiological opioid exposure evidence. The following observations can be made from the data in Table 10.9: (1) In medical populations, the frequency of addiction on opioid exposure is almost nil. (2) In patients with chronic noncancer pain exposed to opioids, researchers report a range of addiction development from 0 to 17.3%. The studies reporting higher percentages (17.3%, Tennant et al., 1988; 9.2%, Lu et al., 1988) used aberrant drug-related behaviors (discussed below) as a means of diagnosing addiction. This may create many false positive cases. (3) A major epidemiological study (Joranson et al., 2000) demonstrated that although nationally opioid use increased, abuse cases decreased.

Overall, these data indicate that some clinicians do see addiction development with opioid exposure in patients with chronic noncancer pain, but most clinicians report low percentages for this problem.

The benzodiazepine drugs are also routinely used with CPPs. As such, there has also been concern over addiction development on exposure to these drugs. Table 10.10 highlights the one available study that has addressed this issue in a medical population. The frequency of addiction was low at 1.6%.

Use of illicit drugs is a good measure of potential addiction. Table 10.11 addresses this issue. Here CPPs exposed to opioids in a COAT treatment were subjected to urine toxicology screens. The range of urine positive for illicit drugs was from a low of 7.5% to a high of 23.1%. These data indicate that a significant percentage of CPPs *with* substance abuse problems are being placed on COAT. These substance abuse problems are likely preexistent to the COAT treatment.

TABLE 10.9
Development of Alleged Addiction on Exposure to Opioids in Medical Populations

Author, Year	Type of Population	No. of Patients Exposed	Percent with Abuse/Addiction Exposure
	Studies Addressing General Medical Patients		
Porter & Jick, 1980	Hospital General	11,882	0.03%
Perry & Heidrich, 1982	Burns	?	0%
Medina & Diamond, 1977	Headaches	2,369	0.13%
Chapman & Hill, 1989	Cancer	?	Insignificant
Cicero et al., 1999	Medical population exposed to Tramadol, a very weak opioid	757,558	0.001 to 0.002% (975 of the abuse cases had previous history of substance abuse)
	Studies of Patients with Chronic Noncancer Pain		
Moulin et al., 1996	Chronic noncancer pain	46	8.7%
Milligan et al., 2001	Chronic noncancer pain	301	1%
Dellemijn et al., 1998	Neuropathic pain	30	0%
Broaughton et al., 1999	Cancer and chronic noncancer pain	101	2%
Cowan et al., 2001	Chronic noncancer pain	36	0%
Burchman & Pagel, 1995	Chronic noncancer pain patients maintained on opioids	81	2.5% developed aberrant drug-related behavior (tried to fill prescriptions at other pharmacies)
Schaffer-Vargas et al., 1999	Chronic noncancer pain	30	0%
Doguong-Cantagrel et al., 1991	Chronic noncancer pain	91	1.1%
Cowan, 2003	Chronic noncancer pain	104	2.8%
Taub, 1982	Chronic noncancer pain	313	4.1% (presented management problems of which 61.5% had previous substance abuse)
Tennant & Uelman, 1983	Chronic noncancer pain	22	0%
France et al., 1984	Chronic noncancer pain	16	0%
Urban et al., 1986	Neuropathic pain	5	0%
Tennant et al., 1988	Chronic noncancer pain	52	17% (abuse behaviors)
Portenoy & Foley, 1986	Chronic noncancer pain	38	5.3%
Portenoy, 1989	Chronic noncancer pain	20	0%
Zenz, 1992	Chronic noncancer pain including neuropathic	100	9%
Lu et al., 1988	Chronic noncancer pain	76	9.2% (escalated their dosages)
Jamison, 1998	Chronic noncancer pain	36	2.7%
Kell, 1992	Chronic noncancer pain	16	0%
	Study of Epidemiological Opioid Exposure Evidence		
Joranson et al., 2000	Nationally representative sample of hospital emergency department admissions resulting from drug abuse	Medical use in grams per 1,000,000 population and mentions of drug abuse as percent of population	From 1990 to 1996 there was a 59% increase in use of morphine and a 6.6% increase in mentions per year of opioid abuse, but the proportion of mentions of opioid abuse relative to total drug abuse mentions decreased from 5.1 to 3.8%

A number of researchers (Collins & Streltzer, 2003; Nedejkovic et al., 2002; Sees & Clark, 1993; Weaver & Schnoll, 2002) have indicated that a previous history of addiction should not be an exclusion criteria for opioid treatment for pain. These patients with a history of addiction should be treated the same for their pain as other pain patients. At issue, however, is whether these patients develop re-addiction when exposed to opioids. Only two studies have addressed this issue and they are presented in Table 10.12. These studies report 0 to 45% and speak to a completely different experience. Both studies have low patient numbers. As such, it can only be concluded that re-addiction can occur on opioid exposure, but this issue requires much research.

TABLE 10.10
Development of Alleged Addiction on Exposure to Benzodiazepines in Medicaid Populations

Author, Year	Type of Population	No. of Patients Exposed	Percent with Escalation (as a measure of abuse/addiction exposure)
Soumerai, 2003	New Jersey Medicaid beneficiaries who received benzodiazepines for at least 2 years (low-income women with children, elderly, those receiving aid for permanently and totally disabled)	2,440	1.6% (occurred in those receiving lorazepam, on antidepressants, pharmacy hoppers [filling a prescription for the same benzodiazepine at two different pharmacies within 7 days])

TABLE 10.11
Development of Alleged Addiction on Exposure to Opioid as Identified by Drug Toxicology

Author, Year	Type of Population	No. of Patients Exposed	Percent with Abuse/Addiction Exposure
Vaglienti, 2003	Chronic noncancer pain maintained on opioids	186	23.1% had (+) urine for illicit drugs (4.8% cocaine, 18.2% THC)
Katz et al., 2003	Chronic noncancer pain maintained on opioids	122	21.3% had (+) urine for illicit drugs 13.9% had (+) urine for nonprescribed controlled drugs 13.9% had an aberrant drug-related behavior
Passik, Schreiber, Kirsch et al., 2000	Combined cancer, HIV, and chronic noncancer patients maintained on opioids	111	50% had evidence of illicit drug, a prescription medication not ordered or alcohol; note that this was a patient sample
Belgrade, 2001	Chronic noncancer patients	93	30% had some pain on noncompliant urine screen 6.5% refused urine toxicology 7.5% had illicit drugs 12.9% had unauthorized opioids 7.5% did not have expected opioid (no opioids)
Fishbain et al., 0000	Chronic non-cancer pain patients	226	11.8% did not have expected opioid
Fancullo et al., 0000	Chronic non-cancer pain patients maintained on opioids	78 of which 15 had a history of substance abuse.	3.9% positive for cocaine 20% positive for cannabinoids 7.7% positive for alcohol Approximately 33% negative for prescribed drug.

TABLE 10.12
Development of Alleged Re-Addiction on Exposure to Opioids in Addicts

Author, Year	Type of Population	No. of Patients Exposed	Percent with Abuse/Addiction Exposure
Dunbar & Katz, 1996	Substance abusers with chronic noncancer pain	20	45%
Collins & Stretzler, 2003	Substance abusers with chronic noncancer pain	4	0%

Collins & Streltzer (2003) have presented possible protective factors for re-addiction on opioid exposure, and a number of authors (Collins & Streltzer, 2003; Nedejkovic et al., 2002; Weaver & Schnoll, 2002) have attempted to develop measures to be taken to reduce re-addiction in addicts on opioid exposure. These concepts are outlined in Table 10.13 and Table 10.14. Close attention should be paid to Table 10.14, as it is the opinion of these authors that CPPs with a history of addiction can be offered COAT, but that the informed consent of these patients and monitoring should be extra stringent versus COAT patients.

TABLE 10.13
Protective Factors for Re-Addiction for Substance Abusers Exposed to Opioids for Chronic Noncancer Pain

- Prior history of alcohol dependence *alone*
- Active participation in alcoholics anonymous
- Presence of family support
- Absence of opioid treatment at entry

Source: Adapted from Dunbar, S. A. & Katz, N. P. (1996).

TABLE 10.14
Measures to Be Taken to Reduce the Risk of Relapse to Addiction in Addicts with Chronic Noncancer Pain Exposed to Opioids

- Obtain and document informed consent for risk of addiction with opioid exposure
- Consult with addiction specialist before beginning opioid exposure
- Document appropriateness/need for opioid treatment
- Encourage patient to participate in 12-step program
- Involve social support for patient (e.g., significant other) in the treatment
- Avoid rapidly peaking medications (Gardner, 1997; Kreek & Koob, 1998)
- Require frequent visits with weekly prescription
- Require one physician
- Require one pharmacy
- Ask patients to bring medications left over each visit
- Require random urines for toxicology
- Require treatment agreement
- Include measures/ways of medication compliance, e.g., written medication schedules

Source: Adapted from Collins & Stretzler, 2003; Nedejkovic, Wasan, & Jamison, 2002; Weaver & Schnoll, 2002.

The above discussion indicates that some pain researchers believe that at this time addiction or a history of addictive disease should not be considered an absolute contraindication to COAT. However, some authors have indicated that some patient characteristics may be predictive of poor response to COAT (Table 10.15). In addition, some authors have tried to develop exclusion/inclusion criteria for COAT (Table 10.16). Note that in Table 10.16, to be a candidate for COAT, a CPP should have intractable chronic pain and be a failure in other treatment. A history of addiction is a relatively exclusionary criterion.

ABERRANT DRUG-RELATED BEHAVIORS

In 1992, Jaffee described a group of drug-related behaviors, which he thought could be operationally used to diagnose/define addiction. These behaviors are presented

TABLE 10.15
Red Flags or Potential Contraindications to Chronic Opioid Analgesic Therapy

- Excessive pain intensity (10/10)
- Extreme ratings of emotional distress
- Poor coping
- Use of multiple pain descriptions
- Poor perceived social support
- Multiple pain sites
- Poor employment history
- Long-term reliance on health professionals

Source: Adapted from Nedejkovic, Wasan, & Jamison, 2002.

TABLE 10.16
Guidelines for Chronic Opioid Analgesic Therapy in Patients with Chronic Noncancer Pain

A. Inclusion Criteria (both required)
   - Chronic pain (intractable)
   - Failure of all other reasonable attempts at analgesia

B. Potential Exclusion Criteria (relative)
   - History of substance abuse
   - Chaotic home environment
   - Severe character pathology

Source: Adapted from Portenoy, 1990.

in Table 10.17 and appear to represent behaviors that are sociopathic/antisocial in reference to drug use. The short list of eight behaviors developed by Jaffee (1992) was expanded to 18 behaviors by Portenoy (1994) from his own clinical experience with CPPs maintained on opioids (Table 10.17). Since then, these behaviors have been ranked by pain clinicians in order of severity (Passik, Kirsh et al., 2002). In addition, the frequency of some of these behaviors within CPPs on COAT has also been recorded (Table 10.17). A number of observations can be made from Table 10.17: (1) Clinicians consider sociopathic behavior, such as selling prescription drugs, stealing/borrowing drugs from others, injecting oral formulations, as very serious. (2) In general the more sociopathic behaviors are not frequently found in COAT patients. (3) The most frequent behaviors are aggressive complaining about need for more drug (18.2%) and requesting specific drugs (10.2%). These frequencies fall in range of those reported by Katz et al. (2003). It is to be noted that these figures may not represent or be indicative of addiction, as indicated below. (4) However, it is to be noted that 1.9% of the COAT patients admitted to concurrent use of alcohol or illicit drugs. This again indicates that within this population there may be a CPP subpopulation with significant addiction problems. Based on another study

TABLE 10.17
Representative Aberrant Drug-Related Behaviors

Probably More Predictive

- Selling prescription drugs (**1**)*
- Prescription forgery (**2**)*
- Stealing or "borrowing" drugs from others (**5**)*
- Injecting oral formulations (**3**) (1.5%)*
- Obtaining prescription drugs from nonmedical sources (**6**)*
- Concurrent abuse of alcohol or illicit drugs (**4**) (1.9%)*
- Multiple dose escalations or other noncompliance with therapy despite warnings (**8**) (13.3%)*
- Multiple episodes of prescription "loss"*
- Repeatedly seeking prescriptions from other clinicians or from emergency rooms without informing prescriber, or after warnings to desist (**7**) (5.6%)
- Evidence of deterioration in the ability to function at work, in the family, or socially that appears to be related to drug use (1.8%)
- Repeated resistance to changes in therapy despite clear evidence of adverse physical or psychological effects from the drug

Probably Less Predictive

- Aggressive complaining about the need for more drug (**9**) (18.2%)
- Drug hoarding during periods of reduced symptoms (**11**) (1.1%)
- Requesting specific drugs (10.2%)
- Openly acquiring similar drugs from other medical sources
- Unsanctioned dose escalation or other noncompliance with therapy on one or two occasions (**12**)
- Unapproved use of the drug to treat another symptom (**10**)
- Reporting psychic effects not intended by the clinician
- Resistance to a change in therapy associated with "tolerable" adverse effects with expressions of anxiety related to the return of severe symptoms

Notes: Percentages represent the frequencies of these aberrant behaviors found in 388 CPPs treated with chronic opioid analgesic therapy (Passik et al., 2002b). Numbers 1–12 represent the relative ranking of these 52 aberrant behaviors by clinicians.

* Aberrant drug related behaviors identified by Jaffe (1992) as predictive of addiction.

(Kirsh et al., 2002) these results would need to be put into appropriate context. Kirsh et al. (2002) found that current aberrant drug-related behaviors were seldom reported by CPPs, but attitude items revealed that patients would consider engaging in aberrant drug-related behaviors or would possibly excuse them in others if pain or symptom management were inadequate (Passik et al., 2000). Thus, in interpreting the presence of aberrant drug-related behaviors, the clinician needs to keep in mind that these behaviors are indicative of the differential diagnosis presented in Table 10.18.

What, then, do aberrant drug-related behaviors represent and what is their clinical utility? At the present time it is unclear whether these behaviors are indicative of or represent addiction. It is also unclear which of these behaviors are more closely related to addiction, although

TABLE 10.18
Differential Diagnosis of Aberrant Drug-Taking Behaviors

Addiction
Pseudo-addiction
Other psychiatric diagnoses as a reason for inability to comply with treatment

- Encephalopathy
- Borderline personality disorder
- Depression
- Anxiety

Criminal intent (diversion)
Self-medication of mood, sleep, trauma (flashbacks), and other distress

Source: Adapted from Kirsh et al., 2002; Savage, 2002.

TABLE 10.19
Hints for the Possibility That an Established CPP on COAT Is Addicted[97]

- Unwillingness to taper opioids when other treatments are offered
- No relief from any other modality except opioids
- Preference for short-acting versus long-acting opioids

Source: Adapted from Goldman, 1993.

the more sociopathic behaviors may be more closely aligned with addiction. Finally, aberrant drug-related behaviors can best be used as a red flag during COAT treatment. Once noted by the clinician, they should trigger a search for a reason for the behavior noted according to the differential diagnosis described in Table 10.18.

If the clinician eliminates all other possibilities besides that of addiction as the reason for the aberrant drug-related behaviors, then he or she may wish to search for other hints for addiction in the patient in question (Table 10.19). There is one item in Table 10.19 that requires comment: preference for short-acting opioids versus long-acting opioids. There is some research on this issue that could potentially be clinically useful. Because short-acting opioids are thought to be associated with euphoria, transition to long-acting opioids could be a test for addiction. Some authors have therefore suggested that patients resistant to moving to long-acting opioids from short-acting opioids could have addiction issues. Raggi (2001) reported on 100 CPPs whom they attempted to switch to long-acting opioids from short-acting opioids. They reported that 28% resisted leaving the short-acting opioids and suggested that these patients could have been seeking the euphoria associated with this drug group. However, it is to be noted that there are a number of potential differential diagnoses besides that of addiction that could be the reason(s) for the resistance/refusal to move to long-acting opioids. This differential list is presented in Table 10.20.

TABLE 10.20
Differential Diagnosis for Those Chronic Pain Patients Who Resist/Refuse Transfer to Long-Acting Opioids

- Fear of increased pain
- Actual poor pain relief (i.e., breakthrough pain)
- Fear of loss of control over pain
- Fear of a loss of a coping strategy for pain
- Addiction

TABLE 10.21
Procedures to Follow if and when the Pain Clinician Suspects Addiction in a COAT CPP

- Obtain collateral information
- Reduce prescription interval
- Use pill counts
- Review patient agreement (discussed below) with patient and invoke relevant sanctions
- Do blood/urine toxicology
- Consider referring patient to addiction medicine and/or facility
- Document actions taken

Source: Adapted from Goldman, 1993.

A final issue here relates to what the pain clinician should do if he or she continues to harbor a significant suspicion that the patient is becoming addicted. Table 10.21 outlines the necessary options.

PSEUDO-ADDICTION

As noted above, pseudo-addiction is within the differential diagnosis of aberrant drug-related behaviors. As such, this concept can be understood only within the context of aberrant drug-related behaviors. Pseudo-addiction is operationally defined as aberrant drug-related behaviors that make the patient with chronic pain look like an addict. However, these behaviors stop if opioid doses are increased and pain improves (Weissman & Haddox, 1989). This indicates that the aberrant drug-related behaviors were actually a search for relief, i.e., pseudo-addiction. However, it is to be noted that there is little specific evidence for the concept of pseudo-addiction. This concept originated from one case report (Weissman & Haddox, 1989). Outside of one large-scale study reported as an abstract (McCarberg & Laskin, 2001), no studies of pseudo-addiction exist. In this last study of 500,000 patients, 316 were identified as problem opioid patients. Most of these patients, however, appeared to be pseudo-addicts. There is also some collateral evidence for the pseudo-addiction concept. Arthritic rats appeared to self-administer opioids at rates required to control their pain, rather than for the rewarding effects of the drug (Colpaert et al., 2001). This indicates that the two behaviors may also be separated in humans.

TABLE 10.22
Alleged Distinctions between Pseudo-Addiction and Addiction in Patients with Chronic Pain

Variable	Pseudo-Addicted	Addicted
Escalation of dose	Will stop escalating dose when pain controlled and may even decrease dose	Will continue escalating
Euphoria	Will not try to achieve euphoria	Will try to reach euphoria
Signs of intoxication (e.g., sedation, confusion)	No	Yes
Focus on side effects	Yes	No
Focus on consequences of side effects	Yes	No
Follow recommendations for other forms of treatment	Yes	No

It is almost impossible to differentiate a patient with chronic pain with addiction who escalates the dose of mediation to obtain euphoria from a non-addicted patient with undertreated pain because both will exhibit aberrant drug-related behaviors (Weaver & Schnoll, 2002). The best approach for the physician is to provide more pain medications and to observe the patient for aberrant drug-related behaviors (Weaver & Schnoll, 2002) and some of the characteristics listed in Table 10.22. Although the pseudo-addiction concept lacks significant scientific support and it is unclear how clinically relevant in is, it has nevertheless become widely accepted within the pain physician community. As such, this concept has now become a focus in some medicolegal cases. Thus, pain clinicians who do COAT treatment, or who are planning to, should be aware of this concept and address it in their patient notes.

Finally, it is to be noted that there is also a differential diagnosis for pseudo-addiction that relates to inadequate pain management. This differential diagnosis is presented in Table 10.23.

COAT TREATMENT AGREEMENTS

The concept of a Treatment Agreement for COAT was first developed by Burchman and Pagel (1995). The alleged benefits of such an agreement have now been outlined in the literature (Biller & Caudill, 1999; Bolen,

TABLE 10.23
Differential Diagnosis of Pseudo-Addiction

Inadequate pain management secondary to

- Progressive pathology
- Tolerance development
- Stable conditions, but suboptimal analgesia
- Development of opioid-induced hyperalgesia (discussed below)

2003; Burchman and Pagel, 1995; Doleys & Rickman, 2003; Fishman & Kreis, 2002) and are now thought to be the following: a constructive element for a physician–patient partnership; a motivational tool for both sides to reflect on their expectations and responsibilities; a demonstration that the decision to use opioids was seriously considered by all parties involved; an informed consent tool; a tool that allows the physician to break confidentiality to call a pharmacy, etc.; indirect protection of the physician from the fear of inappropriate investigation by regulatory authorities by establishing strict guidelines under which opioids will be administered; protection of the physician against subsequent medicolegal problems because of the informed consent aspects. Because most of the state licensing boards require written treatment plans for patients on COAT, the COAT treatment agreement can substitute for the treatment plan. It is to be noted that the COAT treatment agreements have been recommended for use by legal experts in the field (Bolen, 2003). Bolen pointed out that the Federation of State Medical Boards Model Guidelines in the use of controlled substances to treat pain contemplate the use of written treatment agreements with patients with pain who have a history of or present a problem with substance abuse. These experts suggest that the COAT treatment agreement should contain the elements outlined in Table 10.24. Finally, it is to be noted that the ability of COAT treatment agreements to prevent prescription abuse has not been established in the literature (Biller & Caudill, 1999). As such, the physician using these agreements should not expect to be free of patients who may abuse opioids.

TABLE 10.24
Elements to Be Included in a COAT Treatment Agreement

- Details of what the service physician will provide
- The condition or diagnosis necessitating the use of controlled substances (COAT)
- Goal of COAT, e.g., pain relief, increased function
- Risks of COAT (informed consent)
- Risks of off-label drugs, if those are to be prescribed
- Alternatives to COAT or that there are no alternatives (what reason) or that patient refused alternatives
- A list of compliance measures to be used (one pharmacy, one doctor for prescribing, pill counts, urine/serum random toxicologies, calling other pharmacists, etc.)
- Circumstances under which the agreement would be terminated and patient tapered off COAT (e.g., no decrease in pain, tolerance, no increase in function, escalation)
- An explanation of what would be considered noncompliance leading to agreement termination and referral to an addiction specialist and/or addiction program

TABLE 10.25
Sources of Diversion

- Health care professional, self-use (State Licensing Board)
- Illegitimate prescriptions:
  - Nonpatient prescription forgeries (police)
  - Patient-modified prescriptions (police)
  - Prescription obtained by illegitimate patients via doctor shopping (police)
- Drug burglary/robbery (FBI)
- Employee theft of drugs or scripts (police)
- Sale of drugs to addicts by legitimate patients (police)
- Illegal sales of prescriptions or drugs by health care professionals or pharmacies (DEA)

DIVERSION AND THE DRUG ENFORCEMENT AGENCY

Diversion is the use of a controlled substance for other than its intended medical use. Commonly, industry drugs are diverted to street use because their quality control makes them desirable and safe. Sources of diversion (and the legal agency responsible for that diversion) are presented in Table 10.25. A number of observations are to be noted in reference to this table. At the present time, the largest sources are patient-modified prescriptions and sale of drugs to addicts by patients. This table also confronts a general misconception of physicians who believe that the Drug Enforcement Agency (DEA) monitors any and all types of diversions. As noted in this table, the DEA is interested only in illegal sales of prescriptions of drugs by health care professionals. Thus, unless the physician is participating in such an activity, he or she is unlikely to come in contact with the DEA.

The DEA is governed by the Controlled Substance Act. As such, "it is the position of the DEA that controlled substances should be prescribed, dispensed or administered when there is a legitimate medical use" (*Physician Manual,* 1990). Therefore, the DEA cannot hold a physician criminally responsible for prescribing in the "usual course of medical practice." The DEA will send its agents into the offices of physicians whom it suspects are working outside of the "usual course of medical practice" in order to obtain controlled substances (buys). Here, the agent will look for physician–patient contact, an examination, a diag-

TABLE 10.26
Red Flags for Identifying Illegitimate Patients

Be suspicious of anyone who presents with characteristics below

- Without a family member
- Wanting appointment at end of office hours/arriving end of office hours (presents when regular physicians cannot be reached)
- As a cash-paying patient
- Insisting on being seen immediately (in a hurry)
- Not interested in having a physical examination or tests
- Unwilling to give permission for old medical records
- No physician referral
- Claims old medical records are lost
- Unwilling/unable to give names of past health care professionals
- Claims out of town and lost prescription, forgotten to pack medication, or claims it was stolen
- Has no interest in referral, wants prescription now
- Shows unusual knowledge of controlled substances
- Requests specific drug or unwilling to try any other
- Claims allergies to non-opioid analgesics
- No visible means of support except welfare/disability
- Frequent address change

Source: Adapted from Goldman, 1993; Tennant, Herman, Silliman, & Reinking, 2002.

nosis, and a prescription to meet the needs of that diagnosis. Physicians not fulfilling these criteria in the "buy" may be charged.

There are ways for physicians to protect themselves against diversion that relates to illegitimate prescriptions: always designate number of refills, even if none; use serialized, duplicate copy–resistant prescriptions; and write alpha and numeric quantity, dosage, and strength. There are also a number of signs (red flags) that may signal an illegitimate patient. These are designated in Table 10.26.

The final type of diversion that relates to physicians is that of the sale of drugs to addicts by legitimate patients. Little is known about this type of diversion except that it is claimed to be common. This type of diversion is extremely difficult to identify. To the author's knowledge, there are currently only two red flags for the possibility of this type of diversion: (1) the urine/blood toxicology screen does not contain the expected opioid or (2) the serum value of the opioids is much below what would be expected according to the patient's current dosage. As discussed under blood/urine toxicology procedures (below), a negative urine/blood toxicology does represent a differential diagnosis. As such, the patient with this type of result cannot be automatically considered to be diverting. In reference to serum values being below expected, patients do differ genetically in their opioid metabolism (Heiskanen et al., 2000). Thus, this result is also not an absolute proof of diversion.

URINE TOXICOLOGY MONITORING IN COAT AS A MEANS FOR MONITORING FOR ADDICTION

Previous research (Belgrade et al., 2001; Fishbain et al., 1998a; Joranson et al., 2000; Katz et al., 2003; Passik et al., 2000; Rafil et al., 1990; Vaglienti et al., 2003) has shown that urine toxicology studies can provide valuable information in CPPs as to their opioid and illicit drug use status. Thus, urine toxicology studies can play an important role in determining suitability for COAT and COAT adherence monitoring. However, before trying to interpret urine toxicology results, the pain clinician should understand the limits (Fishman et al., 2000) of the information provided by urine toxicology. These are outlined below.

Urine assays yield qualitative results only (positive or negative). Testing of opioid in urine is generally of two types: a screening method and a confirmatory test. Confirmatory testing may provide specific identification of individual opioid agents. Morphine, codeine, oxycodone, oxymorphone, hydrocodone, hydromorphone, heroin, methadone, and meperidine are routinely tested for in these screens. Limitations of the urine toxicology screen are the following: (1) A negative screen can rule out only opioids that are detectable. For example, it will not rule out fentanyl, buprenorphine, butorphanol, nalbuphine, and pentazocine, which are not routinely tested for in opioid screens. (2) An opioid may be present in the urine, but the detection limit of that screen may be set above the concentration of the drug in urine, thus resulting in a false-negative result. (3) Poppy seed ingestion may lead to a false-positive opioid screen. (4) Some opioids, such as oxycodone, may be less detectable than others (morphine, codeine) at therapeutic dosages, resulting in a false-negative screen. (5) Because confirmatory tests are usually limited to a certain number of opioids, not all positive determinations on a screening method will go on to be recorded as a positive test, thus leading to a false-negative result. (6) The period of detection for opioids in urine is 1 to 3 days after ingestion; however, this time period is dependent on the physiology of the individual and his or her current physiological status, e.g., hydration. Thus, there is significant individual variation in opioid clearance, which can lead to either a false-positive or false-negative result.

In general, the pain clinician can expect two types of urine toxicology results. The first of these is the unexpected substance (Table 10.27). In this situation, one would see either an illicit drug or unexpected opioid. The differential diagnosis for each of these situations is then presented in Table 10.27. The second type of urine toxicology result is that of the expected substance not being present in urine (Table 10.28). This situation was first noted by Fishbain et al. (1998a) who reported that 11.8% of the patients claiming to be taking a drug did not have evidence of that drug by urine toxicology. Since then, two