Compact Clinical Guide to Women’s Pain Management
An Evidence-Based Approach for Nurses

Yvonne D’Arcy, MS, CRNP, CNS

“Unfortunately, the care provided to women in pain often adds to the suffering rather than relieving it. This clinical resource describes the evidence-based approach to women’s pain that offers optimum relief as well as a compassionate response. . . . Congratulations to Yvonne for the creation of this resource, which will serve as an excellent tool for clinicians dedicated to pain relief for women.”

—Betty Ferrell, PhD, MA, FAAN, FPCN, CHPN
Professor and Research Scientist, City of Hope, Duarte, California

Concise and portable, this is the only clinical reference to address the management of all commonly presented pain conditions particular to women—both physiological and psychological. It is written by an NP pain management specialist for nurses in all settings, and provides evidence-based guidelines for treating women’s pain as a unique entity.

The guide provides quick access to nursing guidelines for treatment of fibromyalgia pain, TMJ pain, phantom breast pain, postmastectomy pain syndrome, menstrually related migraine headaches, irritable bowel syndrome pain, interstitial cystitis pain, and STD-related and pelvic pains. Pharmacologic and nonpharmacologic treatment options, current information from national guidelines (including using a combination of pain management scales for optimal pain assessment and management), along with regional anesthesia techniques, patient-controlled analgesia, and epidural pain management, are also included. Also addressed is the role of estrogen in female pain response.

Options for managing extreme pain situations, how to screen and treat potential substance abusers, and the physiologic bases of gender-different pain responses are additionally covered. Each chapter features a Questions to Consider section that focuses on interventions and techniques to improve outcomes. Of particular note is a section on managing pain in obese women who suffer from pelvic pain syndromes and fibromyalgia, among other types of pain.

KEY FEATURES:
- Discusses pharmacologic and complementary pain management
- Addresses physiologic bases of gender-different pain responses
- Provides cutting-edge information regarding pain in obese women and managing extreme pain situations
- Offers new information on opioid polymorphisms that helps explain why pain medication is sometimes less effective than expected
Compact Clinical Guide to
CHRONIC PAIN MANAGEMENT:
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Compact Clinical Guide to
ACUTE PAIN MANAGEMENT:
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Compact Clinical Guide to
CRITICAL CARE, TRAUMA, AND EMERGENCY PAIN MANAGEMENT:
An Evidence-Based Approach for Nurses
Liza Marmo, MSN, RN-BC, CCRN, and Yvonne D'Arcy, MS, CRNP, CNS

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Compact Clinical Guide to

WOMEN’S PAIN MANAGEMENT

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Compact Clinical Guide to

WOMEN’S PAIN MANAGEMENT

An Evidence-Based Approach for Nurses

Yvonne D’Arcy, MS, CRNP, CNS
I dedicate this book to all women who have experienced unrelieved pain. Women who looked for help and did not find any. Women who have been told their pain was in their heads, not real. Women whose pain has been minimalized and dismissed. Women who have been told they should stop talking about their pain. I hope this book will give you renewed confidence that there are answers about the causes of your pain and you deserve them.

I also dedicate this book to my mother, Mary D’Arcy, and my grandmother, Stephanie Hermanek, who came to this country with nothing but hope. These women are my roots from where I get my strength and perseverance. To my daughters, Lauren Burns and Leslee Cronin, and my granddaughters Jacqueline Cronin, Sophia Burns, and Gabriella Burns, who are the recipients of my legacy and who will, in turn, bloom and find their own mission in life.
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Foreword

The topic of women's pain is seriously neglected and women are an example of one of the most vulnerable patient groups experiencing pain. Women in pain often experience complex pain syndromes, struggle to be believed, and face issues of power imbalance, lack of understanding of women's health needs, and treatment approaches inadequate for the significant pain experienced. Pain syndromes in women such as fibromyalgia, migraines, interstitial cystitis, and irritable bowel syndrome are, unfortunately, often not believed, not thoroughly assessed, and systematically undertreated. Unfortunately, the care provided to women in pain often adds to the suffering rather than relieving it. This clinical resource describes the evidence-based approach to women's pain that offers optimum relief as well as a compassionate response.

This book is written by Yvonne D'Arcy, a true leader, educator, clinician, and advocate for pain relief for all vulnerable populations. I met Yvonne in 1991 and was, and remain, very impressed by her passionate commitment to pain relief. For Yvonne, pain management is not just a clinical area of practice; it is a calling. I have witnessed her passion and compassion and her excellence in education and practice.

Only once over these 20-plus years did I witness a slight break in Yvonne's passion and commitment. It occurred when Yvonne, a nurse from the northern United States, attended our pain resource nurse training in California and had the unfortunate timing of being here for an earthquake. I still recall Yvonne's change in enthusiasm as the earth shook beneath her. A few years later Yvonne invited Margo McCaffery and me to the launch of her long-planned Pain Resource Nurse Training Course in upper Wisconsin. We arrived in the midst of a horrendous blizzard. After what truly was a travel nightmare, we were able to arrive in the early morning, just hours before the course began. Waiting at the hotel desk was a note for us from Yvonne that read, “Got you back. Welcome to Wisconsin.”
Foreword

Congratulations to Yvonne for creation of this resource, which will serve as an excellent tool for clinicians dedicated to pain relief for women. Women deserve respectful, evidence-based care and relief from pain that destroys quality of life, if undetected by the clinician and left untreated. That care begins with educated and empowered clinicians who can advocate for such care.

Betty Ferrell, PhD, MA, FAAN, FPCN, CHPN
Professor and Research Scientist
City of Hope, Duarte, California
Preface

This book is something that I dreamed of writing for many years. Some might say, “Why write a book about women’s pain, isn’t all pain the same?” My answer would have to be no, there are differences that make women’s pain unique and therein lies the crux of the problem. Only someone who has experienced pain as a woman would be able to see that the differences are there. These very real differences affect outcomes and quality of life and reach down to the basic essentials of everyday life, such as being able to support yourself or care for children. It’s been my mission to provide information about why pain is different in women, which makes treating it more complex; differences that I knew were there but could not always convey or explain.

My own experience with women’s pain began in December of 1991 when I fell on my driveway in 30-below wind-chill temperature on a cold and snowy day in Wisconsin. When I looked down I could see that there was something dramatically wrong with my left leg. My knee was pointing up and my lower leg was pointing sideways. Being a good neurosurgery nurse, I flexed my toes and could still feel everything. That falsely reassured me that all was well. Still, being a little shocked to be in this situation, as I was loaded into the ambulance I deferred getting any pain medication until I was in the emergency department, where the pain of the multiple fractures began to make itself an entity that was going to be a part of my life from that day forward. I could never have anticipated how that simple misstep would change the quality of my life.

Over the weeks, months, and years, I have had surgery and physical therapy, and been told by well-meaning health care providers who really did not understand what I was trying to tell them, that I should stop looking for a way to treat my pain and “just live with it.” They just could not seem to get their heads around the idea that I really wanted to have good pain control and go back to work. They felt that if I could work, my pain was well controlled. Little did they understand how much it took for me to get to work and be able to work a shift. My physician colleagues would see
I was in pain and tell me to come see them, but they had no answers. Other coworkers could see I was in pain and became somewhat immune as time went by.

I remember the look on the physician’s face when he informed me that he did not treat chronic pain. Because it was now over 3 months and I still had pain, I needed to be seen by a physical medicine specialist. The specialist’s response was to take heavy nonsteroidals and get physical therapy, because since I was able to work I certainly “could not be having that much pain.”

I went looking for answers to “Why me?” “Why so much pain?” “What was causing the pain?” and no one had any answers that could help me. At a nursing conference, Margo McCaffery told me if no one could help me with my pain, then she could. It was the first time even a brief ray of hope existed. She empowered me to take control of my pain treatment; to look for doctors who believed that I had pain, who would not dismiss my complaints and needs, and would not condemn me to a life of heavy reliance on nonsteroidal anti-inflammatory drugs (NSAIDs).

They say that all things have a reason for being. I believe my experience led me to a new career in pain management. I have worked in the field for 20 years and have seen women have the same experience that I had; women whose pain was minimalized and dismissed as emotional or psychiatric, women who suffered from poorly understood conditions, such as fibromyalgia, where treatment options were limited.

I remember the hopeful look on one patient’s face when I told her I believed she had pain. She had come into the hospital complaining of severe neck pain but had had no luck over the past 6 months in finding a cause or reason for her pain, leading those around her to think she did not have the pain she was describing. She was tearful and looked so defeated. After a comprehensive workup the doctors did discover a source of pain easily treated with a simple surgery that made her completely pain free. She thanked me profusely as she left the hospital with a new hopeful outlook. She told me she appreciated my belief in her pain and that my support helped her through the arduous diagnostic process.

I hope this book presents the helpful information that I wish I had been able to find when I first evaluated women’s pain and why it was different from that in men. I am so pleased that researchers are developing protocols to assess the basis for the sex and gender differences in pain and coming to some clinically applicable conclusions. I am always excited to attend lectures that these days have a base in the genetics and polymorphisms of pain, where differences in pain response are correctly attributed to variations in physiology. Women’s pain is different from men’s;
we have some disparate physiologic processes, and we respond differently to pain medications.

Sex and gender differences and genetic variations in pain are the new frontiers of pain management. In the future, I hope that pain treatments will be individualized to each person’s needs rather than a “one-size-fits-all” approach. I have strong faith that women will see great advances in how their pain is perceived and treated. To my readers, I hope you take this information into your practices and work to make adequate analgesia a reality for all women.

Yvonne D’Arcy, MS, CRNP, CNS
For many years the idea of differences in the pain of men and women was not a topic that was discussed in professional circles, let alone considered as a focus for research studies. It was assumed that pain was pain, and that women reacted to a pain stimulus differently with a more emotional response. It was commonly accepted that women had a higher prevalence of pain, but the mechanisms that created the difference were not well understood (Fillingim, 2010; LeResche, 2011). It was postulated that since women sought help from health care providers more frequently, they would naturally seem to have more pain complaints. No one even considered that women might respond to pain or pain medications differently than men.

When researchers looked at what might be different in sex-related response to pain, any differences in physiologic response were explained by the variation in monthly estrogen levels in women. As such, women were not considered to be good research subjects, and even in a condition typically affecting women such as breast cancer, many of the early studies were done using only men as study participants. After studying pain differences in women, findings indicated that women had a two- to six-fold higher prevalence of persistent painful conditions that produce higher intensities of pain (Greenspan et al., 2007).

In the mid-1990s, publications started appearing in reputable journals, highlighting the need to study the pain response of women and determine if there was a difference that made women’s pain a unique experience for them. In a review of studies published in PAIN, the journal of the International Association for the Study of Pain (IASP), between 1996 and 2005, 79% of the animal studies observed male subjects only, with only 4% reporting data from both sexes (Mogil, 2009). The findings of these male-exclusive studies began to call into question the validity and generalizability of the results. The scientific community began to
understand that using a narrow window for research, such as the use of all-male subjects, might have created bias and skewed the results of numerous research studies, making them less generalizable to the population as a whole.

At the same time, the National Institutes of Health (NIH) developed several initiatives on pain in women that generated significant interest in the topic. In 1994 the NIH mandated that all clinical trials with NIH support include a representative sample of female participants (Hurley & Adams, 2008). After this initiative, researchers began to explore the various areas of pain in women. They tried to determine if there was an overall difference in pain in women, or if there was only a difference in some of the pain syndromes that were more common in women than in men, such as fibromyalgia and osteoarthritis pain.

In 2006 the IASP Sex, Gender, and Pain Special Interest Group (SIG) developed a consensus document on the differences between sexes in pain and analgesia (Greenspan et al., 2007). This document presents best practice data that can be used to develop and expand the role of research using female participants. One of the basic recommendations to researchers was that they include both sexes in their research. If limited by practical considerations, then using only female subjects was recommended (Greenspan et al., 2007). Additionally, the consensus document indicates that sex-related differences in pain change over time as female subjects mature and estrogen levels fall.

The IASP also declared 2007 as the Global Year Against Pain in Women. Funded by the IASP, the entire year’s initiatives focused on the effect of pain in women. One of the most important findings of this new research was that women do, in fact, experience more pain than men (Collett & Berkley, 2007) and found that there are any number of physiologic and psychological differences in pain response in women. Pain in women not only affects individual families but also affects work productivity and health benefits and creates low incomes (Collett & Berkley, 2007). This is an area that truly deserves more research to fully understand the impact of pain in women; not only for women themselves, but for society as a whole as well.

The research and related guidelines for women’s pain are not as developed as those for patients with more common pain conditions such as chronic pain. However, with the support of the NIH initiatives and more national and international exposure, the focus on women’s pain has increased. There is also much more interest in determining the differences in the two sexes when pain is involved, and in learning about how women process pain and respond to medications.
GENDER AND SEX

There is a difference between the terms gender and sex. They are not interchangeable. Sex is defined as “the classification of living things, generally as male or female according to their reproductive organs and function assigned by the chromosomal complement” (Hurley & Adams, 2008). Gender is defined as “a person’s self-representation as male or female, or how society reacts to that person on the basis of the individual’s gender presentation” (Hurley & Adams, 2008).

Sex, by definition, is considered to be more related to the physical differences between men and women. Gender, on the other hand, has more psychological, environmental, and sociological effects, including society’s acceptance of a person presenting as a man or woman (Greenspan et al., 2007; Racine et al., 2012a).

PREVALENCE OF WOMEN’S PAIN SYNDROMES

There are some basic differences between pain in women versus pain in men, with some pain syndromes more prevalent in women.

In general, women:
- Report pain that is more severe in intensity
- Have more frequent episodes of pain
- Have pain that is more diffuse and longer lasting than males with the same condition
- Have pain that is more frequently visceral or musculoskeletal in origin
- Experience more pain related to autoimmune disorders (Hurley & Adams, 2008)
- Have a higher incidence of pain catastrophizing (Greenspan, Craft, & LeResche, 2007)

What types of painful conditions are more prevalent in women than men? Overall, women seem to have higher odds of developing chronic pain conditions (Fillingim & Gear, 2004). General findings from chronic pain studies indicate that women have higher intensities of pain, more frequent pain, higher levels of pain-related negative effects, and higher pain-related levels of disability than men (Fillingim, 2010). Although some conditions such as osteoarthritis affect both men and women, some conditions have more females than males in the patient groups. The conditions that affect more females than males include:
- Autoimmune diseases: rheumatoid arthritis, lupus erythematosus, and multiple sclerosis
- Diseases of visceral origin: chronic constipation, irritable bowel syndrome, proctalgia fugax, esophagitis pain, and postcholecystectomy pain
1. The Problem of Pain in Women

- Extremity pain: carpal tunnel syndrome, Raynaud's disease, complex regional pain syndrome (CRPS) type I, scleroderma, chronic venous insufficiency, peroneal muscle atrophy, and piriformis syndrome
- Types of head pain: chronic tension headache, migraine with aura, postdural puncture headache, cervicogenic headache, temporal arteritis, occipital neuralgia, odontalgia, burning mouth, trigeminal neuralgia, temporomandibular disorder (TMJ) (Hurley & Adams, 2007)

OTHER PHYSIOLOGIC DIFFERENCES IN PAIN BETWEEN MEN AND WOMEN

Is there a difference in pain threshold, tolerance, and response to experimental versus clinical pain between men and women? The preliminary data on sex-related differences in the pain experience were first generated by experimental rodent studies and later moved to human research. It is very difficult to export findings to clinical pain management when using animal- and laboratory-invoked pain stimuli. Many of the early studies used experimental pain stimuli such as thermal or pressure pain rather than clinical presentations.

In the rodent studies, findings indicated that female rodents had a lower pain threshold when the research involved hot thermal, chemical, inflammatory, and mechanical pain stimuli (Hurley & Adams, 2008). The results for response to type of pain, neuropathic or visceral, had inconsistent findings. Overall, a review study indicated that female rodents were more sensitive to noxious stimuli than male rodents, and females had lower levels of endogenous analgesia (Mogil & Chanda, 2005). These rodent studies also eliminate the confounding variables of societal, environmental, and psychological influences that humans experience.

Pain studies in humans present different challenges. The subjects are able to verbalize pain, but creating a pain stimulus for research purposes alone creates an ethical question. Additionally, the results of an experimental pain stimulus are not easy to transfer to a clinical practice.

In experimental studies using human subjects less than 60 years of age and deemed as healthy, female participants reported higher pain severity at

**Clinical Pearl**

- **Pain threshold**: Ability of the nervous system to first identify a sensation as pain.
- **Pain tolerance**: Amount of pain that the person will tolerate.
lower thresholds. Females also had less tolerance for noxious stimuli than males, with differences being seen when mechanical pain or pressure pain was used (Hurley & Adams, 2008). When observing patients with pain induced by immersion in a hot water bath, correlation of increased heart rate to pain was present in men but not women (Tousignant-Laflamme, Rainville, & Marchand, 2005). Conversely, when cold was used as a pain stimulus, females tolerated less pain than male subjects, while data indicated little difference in pain threshold (Racine et al., 2012a). In a review of 122 studies, results seem to indicate that females and males have comparable detection thresholds for cold and ischemic pain, while females tolerate less pressure and thermal pain (Racine et al., 2012a).

Since the research on male versus female pain is scant and based on experimental pain, it is hard to make firm conclusions. Most of the current research has been done in animal models or with healthy subjects, and some studies have very small sample sizes given the type of research being done. Hopefully, as the science progresses, clinical studies in patients with painful conditions can yield more applicable data that can be used for patient care.

**MEDICATION RESPONSE DIFFERENCES**

The potency of opioids varies according to sex affected by different types of opioid receptor agonists, mu or kappa, and gonadal hormone levels (Dahan, Kest, Waxman, et al., 2008). Overall, males tend to have a better analgesic response to mu binding opioids such as morphine. Women, on the other hand, tend to have a greater analgesic response to kappa receptor agonist drugs such as buprenorphine. This is especially true for a specific variant of melanocortin-1 receptor (MC1R), a protein linked to the traits of red hair and fair skin (Mogil et al., 2003). This indicator seems to predict that there are different pathways for some medications such as kappa agonist drugs where greater analgesia is produced in women but not in men (D’Arcy, 2011b; Fillingim & Gear, 2004; Gear et al., 1996).

Men had more activation of endogenous opioids when deep tissue stimulation was used as a pain stimulus (Zubieta et al., 2002) A comprehensive review of opioid differences between genders found that men reported less efficacy from analgesia than did women. In order to achieve analgesia, men required higher doses of analgesics, from 24% to 40% more (Miaskowski & Levine, 2004).

However, when patient-controlled analgesia (PCA) was used as the medication administration modality, the question was then reduced to opioid consumption and did not address analgesic effect (Mogil & Kest, 2011).
1. The Problem of Pain in Women

In a review of 18 studies where PCA was used to administer opioids to postoperative surgical patients, findings indicated that women used less opioid in 10 of the studies, and 8 of the studies found no difference in consumption by sex (Miaskowski, Gear, & Levine, 2000). These findings seem to provide conflicting data from other opioid studies, which further complicates the issue of which sex responds more fully to opioid analgesics.

Although these differences in analgesic effect are interesting, what holds more promise is the development of specific medications and methods to provide analgesia to both women and men. This area of research is new and novel and merits attention if we are to improve pain relief for both sexes.

More information on differences in opioid medication response can be found in Chapter 11, Effect of Opioid Polymorphisms.

THE ESTROGEN EFFECT

As previously noted, estrogen effect was felt to be a variable that most researchers did not want to deal with in pain research. However, excluding females from research studies did not completely control for the effect of hormones, since male subjects also have hormonal testosterone variations, especially over the life span as they age. Gender differences in pain tend to appear during adolescence when hormonal changes occur (Le Resche, 2011).

In one group of female patients undergoing in vitro fertilization, despite fluctuations in estrogen levels across the treatment session, there was little effect on pain perception. The control groups in a study that included men had similar positive findings for cold pain perception changes as did the study population. The indication was that variations in pain perception as a result of cold pain stimulus were more related to time across the treatment sessions rather than any hormonal effect from estrogen (Stening et al., 2012).

On the cellular level there are mechanisms that indicate estrogen does have more of a role in creating pain. Estrogen is found in nociceptors and estrogen receptors are located in areas of the central and peripheral nervous system that modulate nociception (Chaban, 2012). Estrogen has been found to affect the function of the primary afferent neurons, modulation of voltage gated channels, and purinoreceptor function (Chaban, 2012).

Estrogen can also have a very potent preinflammatory effect with women noted to have a more intense inflammatory response when compared to males (Manson, 2011). Estrogen levels tend to fluctuate over the
women’s life span. High levels of estrogen tend to inhibit inflammation such as during the early adult years while lower levels have no effect or a pro-inflammatory presentation in the perimenopausal years (Manson, 2011).

Although not usually studied, the male hormone testosterone can also have an effect on pain in male patients, and research should be developed to further advance the knowledge base of hormonal effect on pain.

**TYPES OF PAIN**

There are several different types of pain that can be experienced by both females and males.

**Acute pain** can be the result of surgery, tissue injury, or treatment. It is a type of pain that occurs suddenly and reflects tissue injury. The patient can expect that this type of pain will not last long. It serves the purpose of letting the body know it has been injured (APS, 2008).

**Chronic pain** is pain that lasts for more than 3 months. This type of pain really is a result of tumor growth or treatment-related pain, such as chemotherapy-related neuropathy (APS, 2008). It is a type of pain that can cause anxiety and depression as time goes on, and if relief is not adequate the patient becomes less certain that relief can be achieved.

**Neuropathic pain** is pain that is the result of damage to the nervous system. Nerve damage can result in physiologic changes that activate higher levels of pain facilitation such as neuronal plasticity and wind-up, activation of N-methyl-D-aspartate (NMDA) receptors that heighten pain response, and allodynia and hyperalgesia. More in-depth information on neuropathic pain will be provided in the chapter on neuropathic syndromes.

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**Clinical Pearl**

**Allodynia** is the production of a painful response to a normally nonpainful stimulus or sensation, such as a hug.

**Hyperalgesia** is a heightened painful response to a stimulus that is painful; for example, extreme pain with an intravenous catheter insertion.

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Determining any sex-related difference between neuropathic and nociceptive pain has been difficult to achieve. There is no evidence to support a higher rate of allodynia or hyperalgesia in female patients.
1. The Problem of Pain in Women

TRANSMISSION OF PAIN

1. Injury occurs in the body.

2. Nerves pick up the injury and send the message to the brain.
   - Dashed line shows message flow from pain site to brain.
   - Dotted line shows message going from brain to pain site.

3. Brain processes the message and alerts the body of pain.

Figure 1.1  ■ Pain transmission.

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The Concept of Nociception

How is pain really felt? The concept of nociception can help us determine just how pain moves through the nervous system and it can also provide us with ideas about how we can interfere with pain facilitation and inhibition. Nociception is defined as the perception of pain by sensory pain receptors called nociceptors, located in the periphery (Sorkin, 2005). In the theory of nociception there are four stages of pain transmission.

1. Transduction—A noxious stimulus converts energy into a nerve impulse, which is detected by sensory receptors called nociceptors.
2. Transmission—The neural pain signal moves from the periphery to the spinal cord and brain.
3. Perception—The pain impulse is transmitted to the higher areas of the brain, where it is identified as pain.
4. Modulation—Facilitating and inhibitory input from the brain modulates or influences the sensory transmission at the level of the spinal cord (Berry, Covington, Dahl, Katz, & Miaskowski, 2006; D’Arcy, 2011a).

The transmission of pain is basically the passing along of a pain stimulus from the peripheral nervous system into the central nervous system, where it is translated and recognized as pain (Figure 1.1). The afferent nerve fibers are the means of moving the stimulus along the neuronal pathways.

Nociception can come from various locations: visceral organs where pain is identified as crampy or gnawing pain; or somatic, pain from skin, muscles, bones, and joints identified by patients as sharp pain (Berry et al., 2006). There are several different types of receptors that can trigger a pain response:

- **Mechanoreceptors**—activated by pressure
- **Thermal receptors**—activated by heat or cold
- **Chemoreceptors**—activated by chemicals, such as inflammatory substances (ASPMN, 2010)

Peripheral Pain Transmission

Pain can be first experienced by free nerve endings or nociceptors located in the periphery of the body. When a person cuts a hand or fractures an extremity, the pain stimulus is first perceived in the nerves closest to the injury. In order for a pain stimulus to be created, the sodium ions on the nerve fiber must depolarize, causing the pain stimulus to be produced and passed along the neural circuitry. There are two main types of nerves that transmit pain impulses or stimuli:

- A-delta fibers are medium-sized, thinly myelinated nerve fibers that can transmit a nerve impulse rapidly, creating the so-called “first pain.” The
pain transmitted on an A-delta fiber is easily localized and the patient may describe the pain as sharp or stabbing.

- C fibers are small and unmyelinated, therefore the pain impulse is conducted at a much slower rate, creating “second pain.” Pain that is produced by C fibers is identified by patients as achy or burning in nature (ASPMN, 2010; Sorkin, 2005).

Two primary substances can help facilitate the transmission of pain from the periphery. Substance P is a neurotransmitter secreted by the free nerve endings of C fibers, which work to speed the transmission of the pain impulse. Bradykinin is a second type of neurotransmitter, which participates in the inflammatory response and hyperalgesia (ASPMN, 2010). Nociception can stimulate both A-delta and C fibers for pain transmission.

Other substances that participate in the facilitation of pain include:

- Histamine—a substance released from mast cells, produced in response to tissue trauma
- Serotonin—released from platelets, and produced in response to tissue trauma, causing pain in the periphery
- COX products—prostaglandins E₂ and thromboxane E₂ act to sensitize and excite C fibers, causing hyperexcitability
- Cytokines—interleukins and tumor necrosis factor (TNF) can sensitize C fiber terminals and participate in the inflammatory and infection process involving mast cells
- Calcitonin gene-related peptides (CGRP)—located at C-fiber nerve endings and produce local cutaneous vasodilatation, plasma extravasation, and skin sanitation in collaboration with substance P production (ASPMN, 2010; Berry et al., 2006; Sorkin, 2005).

Once transduction takes place, the nerve impulse is passed from the peripheral nervous system to the central nervous system through a synaptic junction. This synaptic junction has a variety of functions and substances being secreted. Some medications, for example, pregabalin, act at the synaptic junction by blocking calcium channels. This in turn can reduce the amount of neuronal firing and decrease the passage of pain stimuli to the second-order neuron. The synapse is between the first-order (peripheral) neuron and the second-order neuron in the central nervous system.

Central Nervous System Pain Transmission

As the pain stimulus is passed from the peripheral nervous system into the central nervous system, the signal passes through the dorsal root ganglion to a synaptic junction in the substantia gelatinosa located in the dorsal horn of the spinal cord. As the stimulus pushing the pain impulse forward overcomes any opposing or inhibiting forces, the “gate” is opened,
allowing the pain impulse to proceed up the spinal cord to the brainstem, thalamus, limbic system, and cerebral cortex.

The opening of the “gate” in the central nervous system is controlled by a summing of all the forces involved in the conduction of the pain impulse. If the facilitating forces, neural excitability, and pain-facilitating substances such as Substance P predominate, the pain impulse is passed on. If pain-inhibiting forces predominate, the signal is blocked and the gate does not open. If by chance the pain impulse is perceived as potentially life-threatening, a reflex arc across the spinal cord will fire, causing an immediate response to protect the affected area. For example, touching a hot surface causes the body to retract and remove the hand from the hot surface. This event can take place before any central processing (awareness) of the neural signal (Cervaro, 2005).

Centrally active pain-facilitating and -inhibitory substances include:

Facilitating substances

- Substance P
- Glutamate—responsible for communication between the peripheral and central nervous systems (Rowbotham, Kidd, & Porreca, 2006). Also plays a role in activating the NMDA receptors (Mersky, Loeser, & Dubner, 2005)
- Aspartate
- Cholecystokinin
- CGRP
- Nitric oxide

Inhibitory substances

- Dynorphin, an endogenous opioid
- Enkephalin
- Norepinephrine
- Serotonin (note: serotonin is facilitative in the peripheral nervous system, but inhibitive in the central nervous system)
- B-endorphin—an endogenous opioid
- Gamma-aminobutyric acid (GABA) (ASPMN, 2010; Sorkin, 2005)

Also performing an inhibitory role are the opioid receptors located both presynaptically and postsynaptically, which are available for binding opioid substances such as morphine and producing analgesia. Although there are opioid receptors located at other sites in the body, those that are located inside the spinal cord have the most information available about how they function.

As the pain impulse passes through the dorsal horn of the spinal cord, it passes across the spine to the lateral spinothalamic tracts, which then allow the pain impulse to proceed up to the thalamus and limbic system, activating the emotions and memories associated with pain.
The pain impulse then travels on to the cerebral cortex, where the pain impulse or stimulus is recognized as pain. Although this process seems complicated, the body can conduct a pain impulse in only milliseconds.

Within the limbic system two pain substances, norepinephrine and serotonin, are active. Current drug therapies such as tricyclic antidepressants (TCAs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are aimed at this process and use the substances to reduce the amount of norepinephrine available to activate neuronal firing at synaptic junctions. The synaptic junctions have such a variety of functions that they are important not only for passing on the pain impulse, but also for serving as critical sites for modulating pain by controlling the production of pain-facilitating substances and actions.

Once the pain stimulus reaches the cerebral cortex, the afferent pathway is completed. At that time, the efferent nerve fibers are used to pass the neuronal response identified as pain back to the periphery or affected area. Descending nerve fiber from the locus coeruleus and periaqueductal gray matter are activated. Interpretation of the pain stimulus is then passed back down the efferent pathway where a response to the pain stimulus is produced, such as moving the affected area away from the pain stimulus.

It is important to remember that pain transmission not only takes place when a stimulus is created and ascends the spinal cord, but that the descending neural pathways can also function to inhibit or limit the pain stimulus. This is called descending modulation of pain. In the case of neuropathic pain, the descending pathways do not inhibit the pain response and the pain is more difficult to control. An example of this phenomenon is fibromyalgia, where the descending pathways do not stop the pain stimulus in the descending pathways, allowing for high levels of pain to be created.

**BARRIERS TO TREATING PAIN IN WOMEN**

Although women have been noted to seek help for pain more frequently than men, there is still not enough information to make definitive statements about the sex and gender differences in pain and analgesic response. It is difficult to correlate research findings to clinical settings. Research is also trying to differentiate ethnic and genetic difference in pain response and analgesic efficacy. Given the wide range of topics for research studies and the limited ability of researchers to provide answers to the questions of sex and gender differences in pain response to both stimulus and analgesics, it will be some time before we can say with certainty that there is an identifiable difference in the sexes with the experience of pain.
Case Study

Amanda, 48 years of age, is being admitted for an abdominal hysterectomy. She has had surgery in the past and reports difficulty with anesthesia and prolonged nausea and vomiting after surgery. She also has a history of fibromyalgia. She tells the anesthesiologist that the surgical drugs just don’t agree with her. When you speak to Amanda she reports that she has had problems with her postoperative pain as well. She had orthopedic surgery not too long ago and reports that her pain was very severe and that the medications just “didn’t work too well.” You ask what types of medications she was given and she responds that she had a morphine PCA, and Percocet as oral medication when the PCA was discontinued. You note that Amanda is slightly overweight, is red-headed, and has a very fair complexion. You reassure Amanda that you will work with her to provide better analgesia than during her last surgery.

Questions to Consider

1. Does the fact that Amanda is female, red-headed, and fair make it more difficult to control her pain postoperatively?
2. What type of medication would you consider for Amanda after her surgery, considering that morphine was not effective during her last hospitalization?
3. Does the fact that Amanda has fibromyalgia make a difference in how she will respond to her surgical pain?
4. Would Amanda be a patient who could experience hyperalgesia or allodynia?

REFERENCES

1. The Problem of Pain in Women


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ADDITIONAL RESOURCES
