Sri Lakshmi Narayana Institute of Medical Sciences

Date: 02.05.2018

From
Dr. Nithianandam
Professor and Head,
Department of Anaesthesia
Sri Lakshmi Narayana Institute of Medical Sciences
Bharath Institute of Higher Education and Research
Puducherry

To
The Dean,
Sri Lakshmi Narayana Institute of Medical Sciences
Puducherry

Sub: Request for Permission to conduct value-added course: Comprehensive Pain Care

Dear Sir,

With reference to the subject mentioned above, the department proposes to conduct a value-added course titled: Comprehensive Pain Care for undergraduates from July -Dec 2018. We solicit your kind permission for the same.

Kind Regards

Dr. NITHIANANDAM. S

FOR THE USE OF DEANS OFFICE

Names of Committee members for evaluating the course:

The Dean: Dr A.SUGUMARAN

The HOD: Dr.NITHIANANDAM. S

The Expert: Dr M KALASREE

The committee has discussed about the course and is approved.

Dean Subject Expert HOD

DEAN
SRI LAKSHMI NARAYANA INSTITUTE OF MEDICAL SCIENCES
OSUDU, AGARAM VILLAGE,
KOODAPAKKAM POST,
PUDUCHERRY - 605 502

DEPARTMENT OF ANAESTHESIA
SRI LAKSHMI NARAYANA INSTITUTE OF MEDICAL SCIENCES
OSUDU, KOODAPAKKAM, PUDUCHERRY-605 502

OFFICE OF THE DEAN

Sri Lakshmi Narayana Institute of Medical Sciences

OSUDU, AGARAM VILLAGE, VILLIANUR COMMUNE, KUDAPAKKAM POST,
PUDUCHERRY - 605 502.
[Recognised by Medical Council of India, Ministry of Health letter No. U/12012/249/2005-ME (P -II) dt. 11/07/2011]
[Affliated to Bharath University, Chennai - TN]

Circular

08.06.2018

Sub: Organizing Value-added Courses: Comprehensive Pain Care- reg

With reference to the above mentioned subject, it is to bring to your notice that Sri Lakshmi Narayana Institute of Medical Sciences, **Bharath Institute of Higher Education and Research**, is organizing **"Comprehensive Pain Care"** course in July-Dec 2018. The course content is enclosed below."

The application must reach the institution along with all the necessary documents as mentioned. The hard copy of the application should be sent to the institution by registered/ speed post only so as to reach on or before 15/06/2018. Applications received after the mentioned date shall not be entertained under any circumstances.

Dean

DEAN
SRI LAKSHMI NARAYANA INSTITUTE OF MEDICAL SCIENCES
OSUDU, AGARAM VILLAGE,
KUDAPAKKAM POST,
PUDUCHERRY - 605 502

Encl: Copy of Course content.

COURSE PROPOSAL

Course Title: COMPREHENSIVE PAIN CARE

Course Objective:

1. To enable the students to learn about definition of pain and the pain pathway. It will also focus on different types of pain and to treat them both pharmacologically and using other methods.

2. To learn about newer modalities of pain management

Course Outcome:

On successful completion of the course the students will have skill in understanding the different pain mechanisms, causes and management modalities for pain.

Course Audience: II year MBBS students

Course Coordinator: Dr Sugumaran

Course Faculties with Qualification and Designation:

1. Dr Kalasree- Associate Professor
2. Dr. Thirilogasundari-Associate Professor

Course Curriculum/Topics with schedule (Min of 30 hours)

S.No	Date	Topic	Time	Hours	Faculty
1	14.07.2018	Introduction to course and definition	2-4PM	2	Dr Kalasree
2	21.07.2018	Anatomy, pathology and pharmacology of pain	2-4PM	2	Dr. Thirilogasundari
3	28.07.2018	Clinical methods and history taking	2-4PM	2	Dr Kalasree
4	04.08.2018	Evaluation of patients with pain	2-4PM	2	Dr. Thirilogasundari
5	11.08.2018	investigations	2-4PM	2	Dr Kalasree
6	18.08.2018	Drug therapy- WHO ladder	2-4PM	2	Dr. Thirilogasundari
7	25.08.2018	opioids- cornerstone of pain control	2-4PM	2	Dr Kalasree
8	01.09.2018	Nutritional physiotherpy	2-4PM	2	Dr. Thirilogasundari
9	08.09.2018	Interventional pain management	2-4PM	2	Dr Kalasree
10	15.09.2018	Headache and their management	2-4PM	2	Dr. Thirilogasundari
11	22.09.2018	Low back pain	2-4PM	2	Dr Kalasree
12	29.09.2018	Physiotherapy modalities	2-4PM	2	Dr. Thirilogasundari
13	06.10.2018	Ozone therapy	2-4PM	2	Dr Kalasree
14	13.10.2018	Steroids in management of pain	2-4PM	2	Dr. Thirilogasundari
15	20.10.2018	Non pharmacological methods in management of pain	2-4PM	2	Dr Kalasree

REFERENCES

1) Howe L, Peppercorn J. Early palliative care in cancer treatment: rationale, evidence and clinical implications. There Adv Med Oncol 2013.

2) WHO Definition of Palliative Care. Available online, www.who.int/cancer/palliative/definition/en

3) Sternward J, Clark D. Palliative medicine-a global perspective. In: Doyle D, Hanks G, Cherny N, et al, editors. Oxford textbook of palliative medicine, 3rd ed. Oxford: Oxford University Press, 2004

VALUE ADDED COURSE

1. Name of the program & Code

COMPREHENSIVE PAIN CARE, ANAES 07

2. Duration & Period

30 hrs: July 2018- December 2018

3. Information Brochure and Course Content of Value Added Courses

Enclosed as Annexure- I

4. List of students enrolled:

Enclosed as Annexure- II

5. Assessment procedures:

Multiple choice questions- *Enclosed as Annexure- III*

6. Certificate of Participation:

Enclosed as Annexure- IV

7. No. of times offered during the same year:

1 Time JULY 2018-DEC 2018

8. Year of discontinuation: 2018

9. Summary report of each program year-wise

Value Added Course- JULY 2018-DEC 2018					
Sl. No	**Course Code**	**Course Name**	**Resource Persons**	**Target Students**	**Strength & Year**
1	ANAES 07	COMPREHENSIVE PAIN CARE	DR. KALASREE	II MBBS	20

10. Course Feed Back

Enclosed as Annexure- V

RESOURCE PERSON

DR. KALASREE

COORDINATOR

Dr S NITHIANANDAM

COMPREHENSIVE PAIN CARE

INTRODUCTION

Pain is defined by the InternationalAssociation for the Study of Pain as “an unpleasant sensoryand emotional experience associated with actual orpotential tissue damage, or described in terms of suchdamage”.

Pain can be divided into 2 categories: physiological (acute) and pathological (chronic). Physiological pain is transient and necessary for alarm system that warns the individual and helps to protect the body from tissue damage. While pathological pain is usually persistent and unnecessary. In many pathological conditions pain has lost its protective role and mayinstead cause substantial suffering. Disorders resulting in persistent pain are among the most prevalent forms of chronic illnesses like cancer, arthritis, diabetes, migraine, AIDS etc. To develop novel therapeutic strategies for pathological pain, a better understanding of the molecular and cellular mechanisms underlying is required to fundamentally inhibit its induction and maintenance.

Pain is a subjective experience with two complementary aspects: one is a localized sensation in a particular body part; the other is an unpleasant quality of varying severity commonly associated with behaviors directed at relieving or terminating the experience.

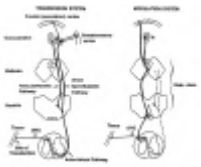
Pain has much in common with other sensory modalities (National Academy of Sciences, 1985). First, there are specific pain receptors. These are nerve endings, present in most body tissues, that only respond to damaging or potentially damaging stimuli. Second, the messages initiated by these noxious stimuli are transmitted by specific, identified nerves to the spinal cord. The sensitive nerve ending in the tissue and the nerve attached to it together form a unit called the primary afferent nociceptor. The primary afferent nociceptor contacts second-order pain-transmission neurons in the spinal cord. The second-order cells relay the message through well-defined pathways to higher centers, including the brain stem reticular formation, thalamus, somatosensory cortex, and limbic system. It is thought that the processes underlying pain perception involve primarily the thalamus and cortex.

In this chapter we review the anatomy and physiology of pain pathways. We also discuss some of the physiological processes that modify the pain experience and that may contribute to the development of chronicity. For obvious reasons, most of this information comes from animal experiments. However, in recent years, experimental studies of human subjects using physiological, pharmacological, and psychophysical methods indicate that much of what has been learned in animals is applicable to humans (National Academy of Sciences, 1985). Research into basic mechanisms underlying pain is an increasingly exciting and promising area. However, most of what is known about the anatomy and physiology of pain is from studies of experimentally induced cutaneous (skin) pain, while most clinical pain arises from deep tissues. Thus, while experimental studies provide fairly good models for acute pain, they are poor models for clinical syndromes of chronic pain. Not only do they provide little information about the muscles, joints, and tendons that are most often affected by chronically painful conditions, but they do not address the vast array of psychosocial factors that influence the pain experience profoundly. To improve our understanding and treatment of pain we will need better animal models of human pain and better tools for studying clinical pain.

Pain Processes

Figure 7-1 illustrates the major components of the brain systems involved in processing pain-related information. There are four major processes: transduction, transmission, modulation, and perception. Transduction refers to the processes by which tissue-damaging stimuli activate nerve endings. Transmission refers to the relay functions by which the message is carried from the site of tissue injury to the brain regions underlying perception. Modulation is a recently discovered neural process that acts specifically to reduce activity in the transmission system. Perception is the subjective awareness produced by sensory signals; it involves the integration of many sensory messages into a coherent and meaningful whole. Perception is a complex function of several processes, including attention, expectation, and interpretation.

Figure 7-1



Diagrammatic outline of the major neural structures relevant to pain. The sequence of events leading to pain perception begins in the transmission system with transduction (lower left), in which a noxious stimulus produces nerve impulses in the primary (more...)

Transduction, transmission, and modulation are neural processes that can be studied objectively using methods that involve direct observation. In contrast, although there is unquestionably a neural basis for it, the awareness of pain is a perception and, therefore, subjective, so it cannot be directly and objectively measured. Even if we could measure the activity of pain-transmission neurons in another person, concluding that that person feels pain would require an inference based on indirect evidence.

Transduction

Three types of stimuli can activate pain receptors in peripheral tissues: mechanical (pressure, pinch), heat, and chemical. Mechanical and heat stimuli are usually brief, whereas chemical stimuli are usually long lasting. Nothing is known about how these stimuli activate nociceptors. The nociceptive nerve endings are so small and scattered that they are difficult to find, let alone study. Nonetheless, there have been some studies of the effects of chemicals on the firing frequency of identified primary afferent nociceptors.

A variety of pain-producing chemicals activate or sensitize primary afferent nociceptors (Bisgaard and Kristensen, 1985; Juan and Lembeck, 1974; Keele, 1966). Some of them, such as potassium, histamine, and serotonin, may be released by damaged tissue cells or by the circulating blood cells that migrate out of blood vessels into the area of tissue damage. Other chemicals, such as bradykinin, prostaglandins, and leukotrienes, are synthesized by enzymes activated by tissue damage (Armstrong, 1970; Ferreira, 1972; Moncada et al., 1985; Vane, 1971). All of these pain-producing chemicals are found in increased concentrations in regions of inflammation as well as pain. Obviously, the process of transduction involves a host of chemical processes that probably act together to activate the primary afferent nociceptor. In theory, any of these substances could be measured to give an estimate of the peripheral stimulus for pain. In practice, such assays are not available to clinicians.

It should be pointed out that most of our knowledge of primary afferent nociceptors is derived from studies of cutaneous nerves. Although this work is of general importance, the bulk of

clinically significant pain is generated by processes in deep musculoskeletal or visceral tissues. Scientists are beginning to study the stimuli that activate nociceptors in these deep tissues (Cervero, 1982, 1985; Coggeshall et al., 1983; National Academy of Sciences, 1985). In muscle, there are primary afferent nociceptors that respond to pressure, muscle contraction, and irritating chemicals (Kumazawa and Mizumura, 1977; Mense and Meyer, 1985; Mense and Stahnke, 1983). Muscle contraction under conditions of ischemia is an especially potent stimulus for some of these nociceptors.

Despite progress in our understanding of the physiology of musculoskeletal nociceptors, we still know very little about the mechanisms underlying common clinical problems such as low back pain. Even when there is degeneration of the spine and compression of a nerve root—a condition generally acknowledged to be extremely painful—we do not know which nociceptors are activated or how they are activated. Neither do we know what it is about the process that leads to pain.

Transmission

Peripheral Nervous System

The nociceptive message is transmitted from the periphery to the central nervous system by the axon of the primary afferent nociceptor. This neuron has its cell body in the dorsal root ganglion and a long process, the axon, that divides and sends one branch out to the periphery and one into the spinal cord (Figure 7-2). The axons of primary afferent nociceptors are relatively thin and conduct impulses slowly.

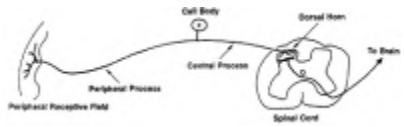


Figure 7-2

The primary afferent nociceptor. This is the route by which the central nervous system is informed of impending or actual tissue damage. Its peripheral process runs in peripheral nerves, and its peripheral terminals are present in most body structures (more...)

It is possible to place an electrode into a human peripheral nerve and record the activity of primary afferent nociceptors (Fitzgerald and Lynn, 1977; Torebjork and Hallin, 1973). The nociceptor is characterized by its response to noxious heat, pressure, or chemical stimuli. The "pain" message is coded in the pattern and frequency of impulses in the axons of the primary afferent nociceptors. There is a direct relation between the intensity of the stimulus and the frequency of nociceptor discharge (Figure 7-3). Furthermore, combined neurophysiological and psychophysical studies in humans have shown a direct relation between discharge frequency in a primary afferent nociceptor and the reported intensity of pain (Fitzgerald and Lynn, 1977; LaMotte et al., 1983). Blocking transmission in the small-diameter axons of the nociceptors blocks pain, whereas blocking activity of the larger-diameter axons in a peripheral nerve does not. These identified primary afferent nociceptors are thus necessary for detecting noxious stimuli.

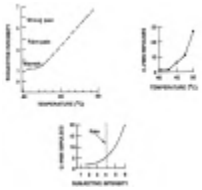


Figure 7-3

The relation of discharge frequency in primary afferent nociceptors to subjective pain intensity in human subjects. Top left: The skin of human subjects was subjected to brief, calibrated temperature increases. Subjects began to identify the temperature (more...)

Monitoring activity in identified primary afferent nociceptors is a potential tool for the evaluation of certain types of clinical pain. In fact, this method has been used clinically to demonstrate pain-producing neural activity arising from a damaged nerve (Nystrom and Hagbarth, 1981). At present, this method should be considered just a research tool; however, it is technically feasible and is of great potential value for evaluating pain patients. It raises the possibility of actually demonstrating nociceptor activity coming from a painful area. This method could be an advance over other correlative techniques for assessing pain because it measures the presumed noxious input, that is, the neural activity that ordinarily causes pain. Most of the other measures assess responses that could be, but are not necessarily, caused by noxious stimuli.

It is important to point out that (1) there can be pain without activity in primary afferent nociceptors, and (2) there can be activity in primary afferent nociceptors without pain. These phenomena occur when there has been damage to the central or peripheral nervous systems. In addition, the modulating system can suppress central transmission of activity elicited by nociceptor input. Thus, there is a variable relation between nociceptor input and perceived pain intensity. For this reason the method of recording primary afferent nociceptors could be used to confirm the presence of an input, but it could not be used to prove that pain was not present.

Besides these theoretical limitations of trying to assess subjective pain intensity by recording primary afferent nociceptors, there are important practical problems in measuring either pain-producing substances or primary afferent nociceptor activity. One is that the largest group of patients disabled by pain localize it to musculoskeletal structures in the lower back. Because the nerves innervating these structures are not near the skin, they are difficult to find. Another problem is that pain arising from deep structures is often felt at sites distant from where the tissue damage occurs. In contrast to the pain produced by skin damage, which is sharp or burning and well localized to the site of injury, the pain that arises from deep tissue injury is generally aching, dull, and poorly localized (Lewis, 1942). When the damage to deep tissues is severe or long lasting, the sensation it produces may be misperceived as arising from a site that is distant from the actual site of damage (Head, 1893; Kellgren, 1938; Lewis, 1942; Sinclair et al., 1948). This phenomenon, known as *referred pain*, helps to explain the frequent discrepancy between physical findings and patient complaints. The mechanism of referred pain is unknown for any particular case.

Referred pain can be a major source of confusion in the examination of patients complaining primarily of pain. The fact that pain is referred from visceral internal organs to somatic body structures is well known and commonly used by physicians. For example, the pain of a heart attack is not always localized to the heart but commonly is felt diffusely in the chest, the left arm, and sometimes in the upper abdomen. Less widely recognized is the fact that irritable spots, such as myofascial trigger points, in skeletal muscles also cause feelings of pain in locations distant from the irritable spot. This was demonstrated experimentally in muscle and fascia by Kellgren in the late 1930s (Kellgren, 1938). Specific patterns of pain referred from particular muscles

have been described clinically (Travell and Rinzler, 1952; Travell and Simons, 1983). (See Chapter 10 and Appendix.)

At least four physiological mechanisms have been proposed to explain referred pain: (1) activity in sympathetic nerves, (2) peripheral branching of primary afferent nociceptors, (3) convergence projection, and (4) convergence facilitation. The latter two involve primarily central nervous system mechanisms.

1.Sympathetic nerves may cause referred pain by releasing substances that sensitize primary afferent nerve endings in the region of referred pain (Procacci and Zoppi, 1981), or possibly by restricting the flow of blood in the vessels that nourish the sensory nerve fiber itself.

2.Peripheral branching of a nerve to separate parts of the body causes the brain to misinterpret messages originating from nerve endings in one part of the body as coming from the nerve branch supplying the other part of the body.

3.According to the convergence-projection hypothesis, a single nerve cell in the spinal cord receives nociceptive input both from the internal organs and from nociceptors coming from the skin and muscles. The brain has no way of distinguishing whether the excitation arose from the somatic structures or from the visceral organs. It is proposed that the brain interprets any such messages as coming from skin and muscle nerves rather than from an internal organ. The convergence of visceral and somatic sensory inputs onto pain projection neurons in the spinal cord has been demonstrated (Milne et al., 1981; Foreman et al., 1979).

4.According to the convergence-facilitation hypothesis, the background (resting) activity of pain projection neurons in the spinal cord that receive input from one somatic region is amplified (facilitated) in the spinal cord by activity arising in nociceptors originating in another region of the body. In this model, nociceptors producing the background activity originate in the region of perceived pain and tenderness; the nerve activity producing the facilitation originates elsewhere, for example, at a myofascial trigger point. This convergence-facilitation mechanism is of clinical interest because one would expect that blocking sensory input in the reference zone with cold or a local anesthetic should provide temporary pain relief. One would not expect such relief according to the convergence-projection theory. Clinical experiments have demonstrated both kinds of responses.

This phenomenon of referred pain can present a serious problem to both patients and physicians when it goes unrecognized. Because the source of the pain lies overlooked at a distant location, the lack of any demonstrable lesion at the site of pain and tenderness often leads to the suspicion that the pain has a strong psychological component. When health professionals insist that there is no reason for the pain, patients sometimes begin to wonder whether the pain is "all in their head." As is discussed in later chapters, this can exacerbate anxiety and other psychological reactions to the pain, is likely to frustrate both the doctor and the patient, and may lead to "doctor shopping" and inappropriate treatment.

Pain Pathways In the Central Nervous System

Primary afferent nociceptors transmit impulses into the spinal cord (or if they arise from the head, into the medulla oblongata of the brain stem). In the spinal cord, the primary afferent nociceptors terminate near second-order nerve cells in the dorsal horn of the gray matter (Willis, 1985). The primary afferent nociceptors release chemical transmitter substances from their spinal terminals. These transmitters activate the second-order pain-transmission cells. The identity of these transmitters has not been established, but candidates include small polypeptides such as substance P and somatostatin, as well as amino acids such as glutamic or aspartic acid.

The axons of some of these second-order cells cross over to the opposite side of the spinal cord and project for long distances to the brain stem and thalamus. The pathway for pain transmission lies in the anterolateral quadrant of the spinal cord. Most of our information about the anatomy and physiology of pain-transmission pathways in the central nervous system is derived from animal studies. However, it is known that in humans, lesions of this anterolateral pathway permanently impairs pain sensation and that electrical stimulation of it produces pain (Cassinari and Pagni, 1969; White et al., 1950; Willis, 1985).

There are two major targets for ascending nociceptive axons in the anterolateral quadrant of the spinal cord: the thalamus and the medial reticular formation of the brain stem. Our knowledge is most extensive for the spinal cells whose axons project directly to the thalamus, that is, the spinothalamic tract cells. The spinothalamic pathway is implicated in human pain perception because lesions of it, at any level, produce lasting impairments of pain sensation.

Studies of the properties of spinothalamic tract cells have been carried out in several species. In all these species, a major proportion of spinothalamic neurons respond maximally to noxious stimulation. Furthermore, there is a direct relationship in spinothalamic tract cells of firing frequency to stimulus intensities in the noxious range for human subjects (Kenshalo et al., 1980; Willis, 1985). These observations, coupled with decades of careful clinical studies, strongly implicate the spinothalamic tract as a major pathway for pain in humans.

The other major ascending nociceptive pathway in the anterolateral quadrant is the spinoreticular tract. The medullary reticular formation receives a major direct projection from the spinal cord as well as from branches of some of the spinal neurons that project to the thalamus (Kevetter and Willis, 1984; Mehler, 1962).

At the thalamic level, pain pathways have two major sites of termination: ventrocaudal and medial. The ventrocaudal thalamus receives nociceptive input directly from projecting spinal neurons. Neurons in the ventrocaudal thalamus project directly to the somatosensory cortex (Willis, 1985). The medial thalamus receives some indirect input from the spinal cord, but in addition, it receives a major input from the region of the brain stem reticular formation to which the nociceptive spinoreticular neurons project. The medial thalamus projects to widespread areas of the forebrain, including the somatosensory cortex (Jones and Leavitt, 1974). Thus there are two major ascending pathways for pain: a direct lateral spinothalamic pathway and an indirect medial spinoreticulothalamic pathway. It is thought that the lateral pathway from the spinal cord to the ventrocaudal thalamus and to the cortex is responsible primarily for sharp, well-localized pains that arise near the body surface. In contrast, the medial spinoreticulothalamic pathway responds more to stimuli of deep somatic and visceral structures.

There is some evidence for further functional differences between medial and lateral thalamic pathways. Lesions of the ventrocaudal thalamus and somatosensory cortex produce long-lasting deficits in the sensory aspects of pain that are very similar to those produced by lesions of the anterolateral spinal cord pathway. Lesions of the medial thalamus have very little effect on pain sensation per se; pain threshold is unaffected, as are the other sensory aspects of the pain experience. In contrast, the emotional or reactive aspects may be totally abolished (Barber, 1959).

Sensory Versus Affective Aspects of Pain

The processes set in motion by noxious stimuli can be divided into two broad categories. On one hand, there are the sensory processes that lead to the detection and identification of the stimulus. On the other hand, presumably because of the tissue-damaging potential of the noxious stimulus, aversive behavioralsequelae such as withdrawal and escape can terminate the stimulus and protect the organism. Correlated with these two categories of response are two subjective aspects of pain: sensory and affective.

The sensory aspects concern detecting, localizing, assessing the intensity of, and identifying the stimulus. Focusing on the sensory aspects, a person might describe his or her pain as a mild burning pain located on the back of the hand. In contrast, the affective or unpleasantness aspect of pain correlates with the aversive drive to terminate the noxious stimulus and is described by terms that are not specifically tied to a sensory experience, for example, nagging, uncomfortable, or excruciating. The affective aspects would also be accompanied by mood changes such as anxiety and depression, which are usually considered psychological rather than sensory.

The difference between the sensory and affective aspects of pain can be illustrated further by distinguishing between pain threshold and pain tolerance. For example, if one delivers calibrated thermal stimuli to the skin, most people will report that the sensation becomes painful over a narrow range of skin temperatures (43-46ºC) (LaMotte et al., 1983; Willis, 1985). The temperature that is called painful 50 percent of the time would be the pain detection or sensory threshold.

In contrast to this relatively reproducible pain-detection threshold, *tolerance* for pain differs widely among individuals. For example, subjects immersing their hands in ice water fall into distinct groups those who keep their hands in for over 5 minutes and those who pull them out after less than 90 seconds (Turk and Kerns, 1983-1984). The tolerance for pain is a complex function that may be modified by personality traits, attitudes, previous experience, economic factors, gender, and the particular circumstance under which the pain is experienced. Tolerance may be thought of as a response threshold. Pain of a certain intensity and duration may be ignored, whereas a somewhat more intense pain might induce some people to take painkillers, stay home from work, or consult a physician. The particular behavior elicited by pain of a given intensity is highly individual and greatly influenced by what the patient believes will be helpful

and how serious he or she thinks the situation is. For example, most people with headaches do not seek medical attention because headaches are not considered indicative of serious disease (and usually are not). In contrast, a person whose father died recently from a brain tumor might be very frightened by even a mild headache and seek medical attention (see Chapter 8).

Tolerance is also tied to the cognitive and affective aspects of pain. For patients with cancer, pain may be a sign that the tumor has recurred or spread and that death is near. For such patients, the suffering is due not only to the pain's intensity but also to its meaning. Anguish, suffering, and anxiety commonly accompany pain.

In the 1950s many patients with severe pain due to malignancy were given frontal lobotomies (Barber, 1959). These operations disrupt the projections to the frontal lobe from the medial spinoreticulothalamic pathway. In such patients, pain intensity and threshold were unaffected, but the emotional aspects (suffering and anguish) were abolished. Unfortunately, the severe personality changes that accompanied the elimination of suffering made this an unacceptable approach to the treatment of pain. However, these clinical observations show that the affective component of pain has a separate anatomical substrate from the sensory component.

Modulation

The abovementioned processes were discussed in terms of a highly reliable pain-transmission system, the assumption being that pain intensity is a direct function of nociceptor activity. In fact, the excellent correlation among stimulus intensity, impulses in primary afferent nociceptors, and reported pain intensity demonstrated in human subjects under experimental conditions often does not apply to the clinical situation. The most remarkable observations are those in which patients subjected to injuries that ought to be very painful report no significant pain (Beecher, 1959).

An hypothesis for spontaneous analgesia emerged when it was discovered that electrical stimulation of certain brain regions blocks responses to noxious stimulation in laboratory animals (Basbaum and Fields, 1978). This phenomenon, stimulation-produced analgesia (SPA), became more than a laboratory curiosity when it was shown that stimulating homologous brain regions provided relief for patients suffering from chronic pain (Hosobuchi et al., 1977; Richardson and

Akil, 1977). SPA has been demonstrated in a variety of animal species and in hundreds of patients.

SPA can be elicited from well-defined brain stem sites. A body of evidence now indicates that SPA is mediated by a discrete neuronal network running from the midbrain to the medulla and then to the spinal cord (Figure 7-1) (Basbaum and Fields, 1978, 1984). This descending, pain-modulating pathway projects to regions of the spinal cord that contain pain-transmission neurons. Stimulation at brain stem sites that produce behavioral analgesia also selectively inhibits identified nociceptive spinothalamic tract neurons. This inhibition may underly the behavioral and clinical analgesia produced by brain stem stimulation.

In addition to electrical stimulation, the analgesia network can be activated by morphine and other opiate analgesic drugs (Yaksh, 1978). The brain stem sites for SPA and the spinal cord are both sensitive to directly applied opiates. The weight of evidence indicates that opiates produce analgesia in part by activating these pain-modulating networks.

One of the most important discoveries in pain research was that the brain contains substances that have the same pharmacological properties as plant-derived opiates and synthetic opioid drugs. These substances, called endogenous opioid peptides, axe present within nerve cells of the peripheral and central nervous systems (Palkovits, 1984). Of particular importance for our discussion is the presence in high concentrations of these peptides in those brain stem sites implicated in pain suppression (Basbaum and Fields, 1984). As discussed in Chapter 9, these findings have led to some promising new psychopharmacological applications.

Studies of this endorphin-mediated analgesia system in laboratory animals have shown that it can be activated by a variety of stressful manipulations, including painful stimuli (Basbaum and Fields, 1984). Clinical studies indicate that it is activated after surgery and can have a significant analgesic effect (Fields and Levine, 1984; Levine et al., 1979). The important point is that there is a well-defined network for controlling pain transmission. Current evidence indicates that this network accounts for some of the striking variability of reported pain intensity in different patients who have had apparently similar noxious stimuli.

It has been suggested that failure of the pain-suppression system accounts for certain types of chronic pain states (Sicuteri et al., 1984; Terenius, 1985), but most pain experts consider this

conclusion premature. Much more work is needed to determine the extent to which this pain-modulating network operates on chronic pain.

Go to:

Physiological Processes That Enhance Pain and May Lead to Chronicity

One of the most troublesome issues for patients, clinicians, and disability examiners is how to account for pain experiences that seem disproportionate to physical findings or objectively verifiable disease or injury. Although it is well known and well accepted that various psychosocial factors may enhance pain, the role of several physiological processes in amplifying and maintaining pain is perhaps not adequately taken into account when assessing patients' complaints.

Sensitization

Tissue damage initiates a variety of processes that sustain and amplify pain. With repeated stimuli, the thresholds of primary afferent nociceptors progressively decrease, so that normally innocuous stimuli become painful (Campbell et al., 1979; Gybels et al., 1979; LaMotte et al., 1983). For some primary afferent nociceptors, repeated noxious stimuli may induce continuous activity lasting for hours (National Academy of Sciences, 1985). The most familiar example of this is sunburn, in which the skin becomes a source of pain; hot water applied to the skin is perceived as unbearably painful and a friendly slap on the back is excruciating. Other examples are the tenderness of a sprained ankle or an arthritic joint. In these situations it is painful to bear weight or even move the affected joint. Sensitization is a major feature of many and perhaps most clinically significant pains, but its cellular mechanism is unknown.

Hyperactivity of the Sympathetic Nervous System: Reflex Sympathetic Dystrophy

Patients with relatively minor injuries occasionally develop pain disproportionate to their injuries. Such pain often becomes progressively worse rather than following the usual course of lessening with time. It is important to stress that the pain persists well beyond the time when the original tissue-damaging process has ended. Furthermore, the location of the pain may be quite different from the site of the precipitating pathology.

In some of these patients hyperactivity of the sympathetic nervous system clearly plays a major role in sustaining the pain because selective blockade of the sympathetic outflow produces immediate and dramatic relief. The pain is usually accompanied by signs of sympathetic hyperactivity, such as a cold (vasoconstricted), sweaty limb. In addition, the skin may be hypersensitive to touch, as if the nociceptors were sensitized. With time, osteoporosis, arthritis, and muscle atrophy may set in and a permanent impairment of function may ensue. This condition, called *reflex sympathetic dystrophy*, usually responds to sympathetic blocks and physical therapy (De Takats, 1937; Livingston, 1943; Procacci et al., 1975). Physiological studies in animals indicate that the sympathetic outflow can induce discharge of primary afferent nociceptors. This is most prominent in damaged and regenerating afferents (Devor, 1984) but also occurs in undamaged, sensitized afferents (Roberts, 1986) (Figure 7-4).

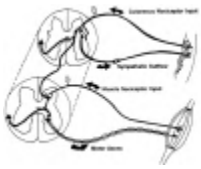


Figure 7-4

Reflex activation of nociceptors in self-sustaining pain. There are two important reflex pathways for pain. The top loop illustrates the sympathetic component. Nociceptor input activates sympathetic reflexes, which activate or sensitize nociceptor terminals. (more...)

The reflex sympathetic dystrophy syndrome is relatively uncommon in its full-blown form, but sympathetic activity could be a common factor in sustaining or amplifying pain that would ordinarily fade as the injured tissues heal. If this were the ease, local signs of increased sympathetic activity could help provide objective evidence that a pain-producing pathological process is present.

Muscle Contraction

Nociceptor activity results in sustained contraction in muscles. In limbs, this muscle contraction produces flexion, a form of primitive withdrawal that is presumably a protective movement. Disease in the abdominal viscera (e.g., gut, liver) produces tension in the muscles of the abdominal wall. Pain arising from musculoskeletal structures also produces contraction and

tenderness in other muscles innervated by the same spinal segment (Head, 1893; Kellgren, 1938).

There is some evidence that this spreading muscle contraction plays an important role in clinically significant pains. In patients with persistent pain it is common to find small areas in muscles that are quite tender. Pressure over these myofascial trigger points can reproduce the patient's pain, and locally anesthetizing the points (or other manipulations of them) can give relief lasting days to months (Simons and Travell, 1983). The physiological basis of these trigger points is unknown, but the clinical evidence suggests that they are often involved in sustaining pain in the absence of ongoing tissue damage.

Self-Sustaining Painful Processes: Livingston's ''Vicious Circle''

From the material just discussed, clinical observations clearly indicate that several processes are set in motion by tissue-damaging stimuli that activate nociceptors. In the peripheral tissues, pain-producing substances are released that sensitize the nociceptors so that normally innocuous stimuli can activate them. In addition, nociceptors themselves release factors such as substance P that in turn cause vasodilation, edema, and the release of sensitizing substances from nonneural cells (Lembeck, 1983). Presumably, these processes play a role in the activation of host defenses against infection or toxins. However, they do prolong and amplify pain.

For example, a noxious stimulus to the skin would activate nociceptors. These nociceptors then activate spinal reflexes that produce sustained muscle contraction with consequent activation of muscle nociceptors (Figure 7-4). In this case, the production of a second site of noxious input in muscle is due to a spinal reflex. In some cases (e.g., reflex sympathetic dystrophy), the nociceptive input also activates the sympathetic nervous system, which can feed back to the periphery to sensitize or even activate nociceptive primary afferents. Livingston (1943) was the first to emphasize the clinical importance of these positive feedback loops; that is, the pain produces muscle contraction and sympathetic outflow that in turn activate nociceptors, which produce more sympathetic outflow and muscle contraction, and so on (Figure 7-4). The point is that painful injuries set in motion secondary processes, not associated with tissue damage, that cause a prolongation and spread of nociceptive input and may contribute to chronicity. These

secondary processes set up foci of nociceptive input that are independent of the original site of injury. The pain acquires, so to speak, a life of its own.

Although there is no question that these factors contribute to the pain in some cases, it is not clear what proportion of patients with chronic pain have it because of these factors. This would obviously be an important area for future research on chronic pain.

Neuropathic Pain

Damage to the peripheral or central nervous systems can produce chronic pain. For example, in some diseases that affect peripheral nerves, such as diabetes mellitus or alcohol toxicity, pain is very common. Traumatic injury to a peripheral nerve is rarely painful, but when it is, it may be dramatically so. Causalgia (heat pain) is an example of pain induced by traumatic injury to a peripheral nerve. Causalgia is a syndrome characterized by severe burning pain and signs of sympathetic nervous system hyperactivity (Mitchell, 1965; Roberts, 1986). Similarly, lesions of the central nervous system are rarely painful, but when they are, the pain is severe and resistant to treatment (Cassinari and Pagni, 1969; Riddoch, 1938).

There are certain characteristics of neuropathic pain. It frequently begins several days to weeks after the injury that produces it and tends to worsen before stabilizing. It is usually accompanied by sensory abnormalities, including, paradoxically, deficits in pain sensation and painful hyperreactivity to ordinarily innocuous stimuli (Noordenbos, 1959; Ochoa, 1982).

The mechanisms of neuropathic pain are not completely understood, but there are several factors that could contribute to them (Ochoa, 1982). Damaged primary afferents, presumably including nociceptors, acquire certain properties when they begin to regenerate. These include spontaneous activity, mechanical sensitivity, and sensitivity to sympathetic nervous system activity (Ochoa, 1982; Scadding, 1981).

Note that under these circumstances there can be pain either without any stimulus or with a very gentle, non-tissue-damaging stimulus.

In addition to the peripheral sources of pain, damage to primary afferents produces changes in the pain-transmission neurons to which they project in the central nervous system. These cells

become spontaneously active and could be a source of pain, again in the absence of any noxious stimuli (Lombard and Larabi, 1983; Roberts, 1986).

Trigeminal neuralgia and post-herpetic neuralgia are among the most common types of neuropathic pains. These conditions tend to strike older individuals, many of whom are retired. This may be why patients with pains that are obviously neuropathic account for only a small proportion of those who seek disability benefits. On the other hand, some patients with low back pain might have an element of nerve damage that adds to the painfulness of their problem as well as to its chronicity and resistance to conventional treatment. Further research on this issue is clearly needed, as are better methods for detecting injuries to nerves that innervate deep structures.

Acute Versus Chronic Pain

Is there any physiological basis for differentiating between acute and chronic pain? Little is known about the effects of prolonged pain on the central nervous system. There is some evidence that the transition from acute pain to chronic pain alters patients' neurophysiology in a way that makes them somewhat different from people with acute pain. In arthritic rats, for example, there are changes in the peripheral nerves that alter their range of response to applied stimuli, and there may be changes in the central pathways for pain transmission as well (Guilbaud et al., 1985; Kayser and Guilbaud, 1984). Experiments with rats in which nerves have been injured and observed over time have shown changes in the central nervous system, but it is not known how these changes relate to pain (Markus et al., 1984).

People with recurrent headaches, arthritis, low back pain, angina, or low-grade malignancies may have had pain for years. The complaints, treatment, and patients' reactions may be different for each of these conditions. In some cases, psychological factors loom large. These factors are particularly prominent in patients with low back pain, facial pain, and headaches and seem to be more prominent the longer the pain persists.

Psychological and somatic factors are not completely separate in maintaining pain. For example, stress and anxiety increase both muscle contraction and sympathetic outflow and would be expected to exacerbate any ongoing pain problem to which they contribute. Conversely, any treatment that induces relaxation will reduce these factors and lessen pain. This may be one

important connection between the psychosocial and the somatic factors that influence pain tolerance.

Go to:

Potential Methods of Physiological Monitoring

In this chapter we have briefly surveyed the anatomy, physiology, and pharmacology of nociceptive transduction, transmission, and modulation. These are objective and potentially observable phenomena initiated by stimuli that damage or threaten tissue.

As we learn more about the transduction process, it may be feasible to measure the concentration of substances in regions of ongoing tissue damage that activate or sensitize primary afferent nociceptors. This could give an estimate of the level of stimulation of chemically sensitive nociceptors. The most promising technique at present is direct recording of the electrical activity in primary afferents. This is technically feasible and has been used in research, but it is not presently available for general clinical use.

The monitoring of central pain transmission pathways is not practical with the technology available. Although it is theoretically possible, recording single units within the human nervous system requires a potentially dangerous surgical procedure. Multiunit, or evoked-potential, studies do not have the required specificity or spatial resolution to permit collecting meaningful data about clinical pain. It is technically possible to measure the chemicals released at spinal synapses by primary afferent nociceptors. If the concentration of such chemicals in the cerebrospinal fluid could be shown to correlate with either the activity of the primary afferent nociceptors or with the severity of clinical pain, this could provide evidence similar to that derived from recording the activity of the primary afferents. However, at the present time, the transmitter or transmitters for the primary afferent nociceptors are unknown.

Another approach is to use positron emission tomography (PET) to monitor metabolic activity in central nervous system pain pathways. PET is a noninvasive scanning technique that can provide evidence of focal brain activity and of the concentration of certain chemicals. This technique requires that enough neurons be active in a large enough region for a long enough period of time to be detected. Because of the topographical organization of the cortex, this technique might be

used to monitor the somatosensory cortex. A precise map of the body surface spreads over many millimeters of the cortex. Representation of the face and hand on this map is very large, so it might be possible to detect ongoing activity produced by nociceptive input from these regions. At present, there is no evidence that such measurements show anything in patients with chronic pain.

Indirect measures, such as those of sympathetic nervous system activity (skin temperature or skin resistance) or of muscle contraction in painful areas might be helpful in providing objective evidence of sustained nociceptive input. The measurement of skin temperature over extensive areas of the body surface, thermography, is being used clinically but is still not widely accepted as a reliable indicator of pain. Although they are simple, painless, and safe indicators of sympathetic function, indirect measures of painful input like thermography could be misleading. Sympathetic changes could be produced by nonspecific factors such as surprise or anxiety that do not involve pain. On the other hand, if the changes in sympathetic activity are highly localized, persistent, and consistent with the reported location of the patients' pain, routine evaluation of sympathetic function with techniques like thermography in patients with chronic pain might provide clues about the mechanisms sustaining the pain.

Ultimately, the presence of pain in another individual is always inferred. Even if we could measure pain directly, such a measure would not be adequate to describe the experience of pain, and it is the experience that affects functioning, including the ability to work.

Pain can be treated with invasive or non-invasive methods. Pharmacologic treatment, mostly systemic administration, uses non-invasive methods. Definite targeted invasive treatments, such as a percutaneous osteoplasty for metastasized bone fractures, or endoscopic discectomy for compressed nerves, have a definite advantage over broad-spectrum systemic analgesics in that they remove the source of the pain. If it is impossible to correct or remove the source of pain, non-invasive administration of systemic analgesics is the second choice.

First of all, recognition of the source of the pain is the first step in choosing analgesics. When the origin of the pain is classified, it is preferable to use the International Association for the Study of Pain definition of pain [1]. Therefore, it can be divided into the emotional component, caused by potential tissue damage, and the sensory component, caused by actual tissue damage. The sensory component of pain is also divided into nociceptive (somatic and visceral) and neuropathic pain (positive and negative) (**Table 1**).

Table 1

Classification of Pain and Recommendable Appropriate Analgesics

Emotional pain	Anxiolytics (minor tranquilizers)	Benzodiazepines	Clonazepam, diazepam, midazolam
		Etifoxine (etafenoxine)	
	Antidepressants	Typical	Nortriptyline, amitriptyline,
		Atypical	SSRIs, SSNRIs
	Antipsychotics (major tranquilizers)	First generation	Haloperidol, chlorpromazine
		Second generation	Quetiapine, risperidone, olanzapine
Sensory pain	Nociceptive pain	Somatic (Superficial and deep[a])	NSAIDs, APAP, ASA, and steroids
		Visceral[a]	Opioids: weak and strong
	Neuropathic pain	Positive symptoms	Anticonvulsants
		Negative symptoms	Antidepressants: nortriptyline, amitriptyline

SSRIs: selective serotonin reuptake inhibitors, SSNRIs: selective serotonin norepinephrine reuptake inhibitors, NSAIDs: non-steroidal anti-inflammatory drugs, APAP: N-acetyl-para-aminophenol, ASA: acetyl salicylic acid.

[a]Deep somatic and visceral pain may present referred pain or radiating pain including radicular pain.

Somatic nociceptive pain, which can be divided into superficial and deep categories, shows a good response to non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen (Paracetamol®, N-acetyl-para-aminophenol [APAP]), acetylsalicylic acid (ASA), and steroids. Visceral nociceptive pain usually responds to opioids. Deep nociceptive and visceral pain may sometimes present as referred pain and radiating pain, which create great confusion in deciding the origin of the pain.

Neuropathic pain can be divided into positive and negative symptom categories. Neuropathic pain with positive symptoms shows a good response to anticonvulsants, while neuropathic pain with negative symptoms responds well to antidepressants [2-5].

Most analgesics, except some which exhibit a therapeutic ceiling, such as NSAIDs, APAP, and ASA, need dose and dosage titration for seeking the appropriate analgesic blood level, which can control persistent pain, but not breakthrough pain.

The three steps for analgesic administration and pain management are pain relief at night, bed rest in the daytime, and active movement during daily life. In addition, the principle of polypharmacy is focused on increasing therapeutic effects (analgesia) while reducing adverse reactions (ADRs), based on the source of the pain.

This review provides appropriate choices of analgesics for the treatment of pain, based on the supposed origins of the pain.

Go to:

MAIN BODY

1. Sensory component of pain

Nociceptive pain arises from actual or threatened damage to non-neural tissue, due to the activation of nociceptors. On the other hand, neuropathic pain is caused by a lesion or disease of the somatosensory nervous system, which exhibits abnormal function [6].

1) Nociceptive pain

Superficial somatic nociceptive pain exhibits well-demarcated, sharp, aching pain, while deep somatic nociceptive pain presents ill-demarcated, dull pain. Visceral pain shows poorly-demarcated, heavy, dull pain. Deep somatic and visceral nociceptive pain may have referred pain or radiating pain characteristics (including radicular pain).

Basically, the borders of the somatic and visceral structures are the dura in the head, the pleura and pericardium in the chest, the peritoneum in the abdomen, and the (potential) retroperitoneum (retroperitoneal space) behind the abdominal cavity in the pelvis.

Well-known referred pain from the visceral structures includes left shoulder pain from myocardial infarctions, and right supraclavicular pain from hepatobiliary disorders. Examples of representative referred pain from the deep somatic structures can be found in spinal joint pain from the atlanto-occipital and atlanto-axial joints, classic cervical, thoracic, and lumbar facet joints, and sacroiliac joints.

It has already been demonstrated that substance P, calcitonin gene-related peptide, and protein gene product 9.5 containing nerve fibers, exist in the cervical facet joints in a cadaveric study [7]. This means that anti-inflammatory drugs may be effective through either systemic administration or local infiltration. Therefore, in the case of inflamed knee joints, as with the diarthrodial joints, it seems more effective to use direct intra-articular injections than innervating nerve branch blocks [8-10].

The medial branch also innervates bones, including the posterior lamina and spinous process, ligaments, including the supraspinous ligament, interspinous ligament, and ligament flavum, erect muscles, skin, and subcutaneous tissues, as well as the facet joints [11]. Therefore, the diagnostic value of medial branch blocks can be diluted, and the therapeutic effect may be lower than with facet joint injections.

(1) Non-steroidal systemic analgesics

① NSAIDs

The name NSAIDs includes analgesic drugs, which are not in the class of steroids and have an anti-inflammatory property. The NSAIDs reduce pain and inflammation, as well as fever. In addition, ASA also has the ability to reduce itching. However, APAP can only reduce pain and fever, not inflammation. Therefore, APAP is not an NSAID because it does not reduce inflammation. So, if there is inflammation, anti-inflammatory drugs which act by peripheral mechanisms are needed. Otherwise, if there is no inflammation, APAP, which acts on central mechanisms, can replace the NSAIDs.

The action mechanism of NSAIDs is usually explained by cyclo-oxygenase (COX). The COX is traditionally divided into the constitutive COX-1 isoform in the normal condition and the inducible COX-2 isoform in the inflammatory condition. However, controversially, the COX-1 and -2 isoforms are widely found in the human body, such as the central nervous system, peripheral nervous system, cardiovascular system, gastrointestinal system, endocrine system, and reproductive system under normal conditions. In addition, the COX-2 is especially found in the brain, kidney, and female reproductive system [12].

All currently available NSAIDs have 3 common representative therapeutic effects, namely, an analgesic, anti-inflammatory, and antipyretic effect, and also have 3 common representative ADRs, specifically gastric damage, renal damage, and an antiplatelet function. Therefore, it is better to choose and prescribe a familiar NSAID only for a short period of inflammation, while considering its half-life.

Common ADRs of NSAIDs in detail are (1) gastrointestinal problems related to gastrointestinal mucosa damage, due to decreased prostaglandin (PG) E_2 resulting from COX-1 inhibition, such as dyspepsia, and gastric erosion, ulceration, perforation, and bleeding, (2) renal problems related to sodium and water retention, hypertension, and hemodynamic acute renal injury due to

decreased PG E_2 and PGI_2, resulting from COX-1 and COX-2 inhibition, and (3) cardiovascular and platelet aggregation problems, such as stroke and myocardial infarction due to decreased PGI_2, resulting from greater COX-2 and lesser COX-1 inhibition, and increased bleeding tendency due to decreased thromboxane (TX) A_2, resulting from COX-1 inhibition.

Relative COX-1 and COX-2 selectivity (COX-1/COX-2 half maximal inhibitory concentration [IC_{50}] value) for commonly used NSAIDs and ASA in order of value would be ketorolac, ketoprofen, indomethacin, ASA, naproxen, ibuprofen, piroxicam, meloxicam, diclofenac, celecoxib, valdecoxib, etoricoxib, rofecoxib, and lumiracoxib [13].

NSAIDs, APAP, and ASA have a ceiling effect, in which the fixed maximal therapeutic effect is achieved, but ADRs continue to worsen, as their doses increase. Finally, they increase the risk to benefit ratio, developing a ceiling effect.

② *ASA*

ASA has been commercially available from 1899 under the name Aspirin® (Bayer AG, Leverkusen, Germany). In addition to the 4 representative therapeutic effects already mentioned, a low dose of ASA has been used for reducing the risk of heart attack and stroke [14]. Long-term medication for at least 10-20 years may be effective in cancer prevention, especially with colorectal cancer [15], but also with endometrial [16], breast [17], and prostate cancer [18].

After Vane's discovery of COX in 1971, the mechanisms of action of non-opioid analgesics, including ASA, NSAIDs, and steroids, have been apparent [19,20]. However, ASA, unlike other NSAIDs, is known to produce a unique, irreversible inactivation of COX, since it covalently modifies both COX-1 and COX-2 by acetylating serine residue within the COX active sites. This irreversible inactivation of COX-1 results in a representative ADR, gastrotoxicity, ranging from gastritis to peptic ulcers and gastrointestinal bleeding [21-23].

In addition, COX-1 is the main form in the mature platelets in the blood, where it transforms arachnoid acid via the intermediates PG G/H to TX A_2 (vasoconstrictor and platelet activator). This inhibition of TX A_2 explains the antithrombotic properties of ASA [14,21-23].

There is a theory related to a clinical benefit in which ASA turns off COX-2's production of PGs, but switches on COX-2's ability to produce novel protective lipid mediators (ASA-triggered lipoxins). In other words, ASA, in a different way from NSAIDs, converts COX-2 into a protective mediator-generating system with anti-inflammatory and pro-resolving properties [23].

③ *APAP*

APAP is used to treat pain and fever (but not inflammation or itching) after being synthetized in 1877 and being marketed as Tylenol® or Panadol® in 1955 [24,25]. Its weak anti-inflammatory property is probably due to its poor effectiveness in high peroxide concentrations at the inflammatory site [26,27].

As with ASA, which has a history of more than 100 years, the mechanism of action of APAP is still unclear. Potential analgesic mechanisms of APAP are (1) positive effects on the serotonergic descending inhibitory pain pathway, and (2) interactions with opioid systems, eicosanoid systems, and nitric oxide containing pathways [27,28].

(2) Steroids

Steroids have the ability to inhibit both COX and lipoxygenase, resulting in a reduction of PGs and leukotrienes (LTs).

LTs are inflammatory mediators, and include the di-hydroxy acid LT (LTB4) and the cysteinyl LTs (CysLTs; LTC4, LTD4, LTE4). The high-affinity LTB4 receptors are known as BLT1, the LTC4, and LTD4 receptors as CysLT1 and CysLT2, and the LTE4 receptors as GPR99. BLT1 signaling stimulates the degranulation, chemotaxis, and phagocytosis of neutrophils, and CysLT1 and CysLT2 signaling induces airway inflammation by bronchial smooth muscle contraction and increasing vascular permeability. Therefore, these LTs are involved in chronic inflammatory disorders, such as asthma, atopic dermatitis, psoriasis, atherosclerosis, arthritis, obesity, cancer, and age-related degeneration [29,30].

Steroids in palliative care are indicated for special conditions, such as spinal cord compression, increased intracranial pressure, and bowel obstruction, and for responding to general conditions, such as reducing pain, stimulating appetite, suppressing nausea, and alleviating fatigue. Generally, inhibition of PG and LT synthesis by steroids leads to reducing pain, inflammation, and vascular permeability (edema) [31].

(3) Opioids

Opioids for analgesia have been used for over 5,000 years. Opioids are substances that acts on the opioid receptors, such as the mu, kappa, and delta receptors. According to the action on the opioid receptors, opioids can be divided into agonists, antagonists, and partial agonists/antagonists. Opioid agonists bind to G-protein coupled receptors, and cause cellular hyperpolarization [32].

Opioid up-titration may be needed due to cancer progression from a visceral origin. However, in cases of newly-developed invasions into other structures, non-opioid analgesics are helpful to manage the somatic pain, and anticonvulsants and antidepressants are effective to control the neuropathic pain.

Opioids are effective for both somatic and visceral nociceptive pain; however, they should only be started in patients with chronic non-malignant disorders if physicians are confident, they can taper and then discontinue them. Extra caution should be used in giving immediate-release opioids to young patients with chronic non-malignant disorders, especially chronic pancreatitis (visceral pain), complex regional pain syndrome (neuropathic pain), or bony fracture (somatic pain). Thanks to the development of the diagnosis and treatment of cancer, patients who experience complete recovery from cancer may be candidates for opioid addiction.

Methadone was approved by the U.S. Food and Drug Administration in 1972 for the treatment of opioid addiction. It has 2 enantiomers found in equal amounts in a racemic mixture; the active R enantiomer has a half-life of 36-48 hours and the inactive S enantiomer has a half-life of approximately 16 hours. Therefore, it is rapidly absorbed by the oral route with a delayed onset of action (with peak level at 2-4 hr) and with sustained levels maintained over 24 hours. It also has N-methyl-D-aspartate (NMDA) receptor antagonist properties. The initial dose starts with 20-40 mg/day, then the dose is gradually increased by 10 mg every 4-7 days [33].

Conventional opioids activate 2 intracellular signaling pathways: the G protein pathway induces analgesia, while the beta-arrestin pathway is responsible for the opioid-related ADRs. An academically ideal oliceridine (TRV130) has been studied for its role in both activation of the G protein pathway for analgesia and deactivating the beta-arrestin pathway for reducing ADRs [34]. Clinicians await the launch of this novel opioid with lesser ADRs.

2) Neuropathic pain

Pharmacologic treatment of neuropathic pain begins from the translation of symptoms and signs in patients into the underlying mechanisms, and simply classifying them as positive or negative (**Table 2**) [2,5].

Table 2

Recognition of Neuropathic Pain: Sensory Symptoms and Signs of Neuropathic Pain, Clinical and Laboratory Tests, and Underlying Mechanisms

Sensory symptom and sign	Bedside examination	Laboratory examination	Mechanism
1. Negative sensory symptoms and signs			
1) Reduced touch	Touch skin with cotton wool	Graded von Frey hair	Aβ fibers
2) Reduced pin prick	Prick skin with a pin single stimulus	von Frey hair specific (e.g., 100-g)	Aδfibers
3) Reduced cold and warm	Thermal response to cold and warm objects (20℃ and 45℃)	Detection of pain threshold for warm and cold objects	Aδ/C fibers

Sensory symptom and sign	Bedside examination	Laboratory examination	Mechanism
4) Reduced vibration	Tuning fork on the medial malleolus	Vibrometer	Aβ fibers
2. Positive sensory symptoms and signs			
1) Spontaneous pain			
(1) Paresthesia	Grade (0-10)	Area in cm^2 grade (0-10)	Spontaneous activity in long-term Aβ afferent fibers
(2) Dysesthesia	Grade (0-10)	Area in cm^2 grade (0-10)	Spontaneous activity in Aδ/C afferent fibers
(3) Paroxysms	Grade (0-10)	Threshold for evocation	Spontaneous activity in C nociceptors
(4) Superficial	Grade (0-10)	Area in cm^2 grade (0-	Spontaneous activity in C

Sensory symptom and sign	Bedside examination	Laboratory examination	Mechanism
burning pain		10)	nociceptors
(5) Deep pain	Grade (0-10)	Area in cm^2 grade (0-10)	Spontaneous activity in joint/muscle nociceptors
2) Evoked pain			
(1) Touch evoked hyperalgesia	Stroking skin with brush	None	Central sensitization: C fiber input and loss of C fiber input
(2) Static hyperalgesia	Gentle mechanical pressure	Evoked pain to pressure	Peripheral sensitization
(3) Punctate hyperalgesia	Pricking skin with a pin	von Frey hair	Central sensitization: Aδ afferent fibers input

Sensory symptom and sign	Bedside examination	Laboratory examination	Mechanism
(4) Punctate repetitive hyperalgesia (windup-like pain)	Pricking skin with a pin 60 times/30 sec	von Frey hair	Central sensitization: Aδ afferent fibers input
(5) Aftersensation	Measurement of pain duration after stimulation	Measurement of pain duration after stimulation	Central sensitization
(6) Cold hyperalgesia	Stimulation skin with cool metal roller	Evoked pain to cold stimuli	Central sensitization and disinhibition
(7) Heat hyperalgesia	Stimulation skin with warm metal roller	Evoked pain to heat stimuli	Peripheral sensitization
(8) Chemical hyperalgesia	Topical capsaicin	Topical capsaicin	Peripheral sensitization

Sensory symptom and sign	Bedside examination	Laboratory examination	Mechanism
(9) Sympathetic maintained pain	Sympathetic blockade	Modulation of sympathetic outflow	Sympathetic afferent coupling

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Representative negative sensory symptoms and signs in neuropathic pain (with their underlying mechanisms) are a reduced sensation of (1) touch (Aβ fiber abnormalities), (2) vibration (Aβ fiber abnormalities), (3) pin prick (Aδfiber abnormalities), and (4) cold and heat (Aδ/C fibers abnormalities).

On the other hand, positive symptoms and signs can be divided into spontaneous or evoked pain according to the absence or presence of stimuli. Spontaneous pain (and its underlying spontaneous activity) includes (1) paresthesia (low threshold Aβ afferents), (2) dysesthesia (Aδ/C afferents), (3) paroxysms (C-nociceptors), (4) superficial burning pain (C-nociceptors), and (5) deep pain (joint/muscle nociceptors). Evoked pain includes (1) touch evoked hyperalgesia (central sensitization related to C fiber input), (2) static hyperalgesia (peripheral sensitization), (3) punctate hyperalgesia (central sensitization related to Aδfiber input), (4) punctate repetitive hyperalgesia (windup-like pain, central sensitization related to Aδfiber input), (5) aftersensation (central sensitization), (6) cold hyperalgesia (central sensitization and disinhibition), (7) heat hyperalgesia (peripheral sensitization), (8) chemical hyperalgesia (peripheral sensitization), and (9) sympathetic maintained pain (sympathetic afferent coupling). In summarizing positive neuropathic pain, spontaneous pain includes paresthesia, dysesthesia, paroxysms, superficial burning pain, and deep pain; evoked pain includes various kinds of hyperalgesia, aftersensation, and sympathetic maintained pain [5].

The representative evoked positive symptoms of neuropathic pain are mechanical (dynamic, punctate, and superficial or deep static) and thermal (cold and heat) hyperalgesia and allodynia [5].

Several available clinical assessment tools for neuropathic pain have been developed for evaluation of the neuropathic pain component ratio among patients' whole pain, and for comparison of neuropathic pain scores before and after non-invasive or invasive treatment. Common screening tools for neuropathic pain are (1) the neuropathic pain questionnaire (NPQ), (2) douleurneuropathique en 4 (DN4), (3) Leeds assessment of neuropathic symptoms and signs (LANSS), (4) ID pain, (5) painDETECT (**Table 3**), as well as (6) the neuropathic pain symptom inventory (NPSI) questionnaire (**Table 4**) [4,5,35-42].

Table 3

Summary of Various Neuropathic Pain Questionnaires

NPQ [38]	DN4 [39]	LANSS [40]	ID pain [41]	painDETECT [42]
1. Burning × 0.006	Question 1[a]	Pain questionnaires	1. Pins and needles (Yes: 1, No: 0)	1. Grading of pain (0: never, 1: hardly, 2: slightly, 3: moderately, 4: strongly, or 5: very strongly noticed)
2. Overly sensitive to touch × 0.005	1. Burning	1. Dysesthesia (Yes: 5, No: 0)	2. Hot/burning sensation (Yes: 1, No: 0)	2. The pain course pattern (0: persistent pain with slight fluctuations, –1: persistent pain with pain attacks, +1: persistent pain without pain between attacks, or +1: persistent pain with pain between attacks)
3. Shooting pain × 0.005	2. Painful cold	2. Color change of the skin in the painful area (Yes: 5, No: 0)	3. Numbness (Yes: 1, No: 0)	3. Radiating pain (+2: yes, or 0: no)
4. Numbness ×	3. Electric	3. Abnormal	Electric	The total score varies

NPQ [38]	DN4 [39]	LANSS [40]	ID pain [41]	painDETECT [42]
0.020	shocks	sensitivity to touch in the affected skin (Yes: 3, No: 0)	shocks (Yes: 1, No: 0)	from 0 to 8.
5. Electric pain × – 0.008	Question 2[a]	4. Abnormal skin temperature change in the painful area (Yes: 2, No: 0)	Worsening with touch (Yes: 1, No: 0)	
6. Tingling × 0.010	4. Tingling	5. Abnormal skin temperature change (Yes: 1, No: 0)	Limited to the joints (Yes: –1, No: 0)	
7. Squeezing × – 0.004	5. Pins and needles	The sensory testing	The total score varies from –1 to 5.	
8. Freezing × 0.004	6. Numbness	1. Allodynia (Yes: 5, No: 0)		
9. Unpleasant ×	7. Itching	2. An altered pin-prick threshold		

NPQ [38]	DN4 [39]	LANSS [40]	ID pain [41]	painDETECT [42]
0.006		(Yes: 3, No: 0)		
10. Overwhelming × –0.003		The total score varies from 0 to 24.		
11. Tactile hyperalgesia × 0.006	Question 3[b]	If the score < 12, neuropathic mechanisms are unlikely to be contributing to the patient's pain.		
12. Increased pain due to weather changes × –0.005	8. Hypoesthesia to touch	If the score ≥ 12, neuropathic mechanisms are likely to be contributing to the patient's pain.		
If the total score minus 1.408 is below 0, it predicts non-neuropathic	9. Hypoesthesia to pinprick			

NPQ [38]	DN4 [39]	LANSS [40]	ID pain [41]	painDETECT [42]
pain.				
On the contrary, if the total score minus 1.408 is at or above 0, it predicts neuropathic pain.	Question 4[b]			
	10. Pain caused by or increased by brushing			
	Yes = 1, No = 0			
	Patient's score = □/10			

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NPQ: neuropathic pain questionnaire, DN4: douleurneuropathique en 4, LANSS: Leeds assessment of neuropathic symptoms and signs.

[a]From interview of the patient. [b]From examination of the patient.

Table 4

Neuropathic Pain Symptom Inventory Questionnaire

Neuropathic pain symptom inventory	Interpretation of pain	Score

Neuropathic pain symptom inventory	Interpretation of pain	Score
Q1. Burning	Superficial spontaneous pain	0-10
Q2. Squeezing	Deep spontaneous pain	0-10
Q3. Pressure		0-10
Q4. Spontaneous pain during the past 24 hr		Permanently
		8-12 hr
		4-7 hr
		1-3 hr
		< 1 hr
Q5. Electric shocks	Paroxysmal pain	0-10

Neuropathic pain symptom inventory	Interpretation of pain	Score
Q6. Stabbing		0-10
Q7. Pain attacks during the past 24 hr		> 20 times/day
		11-20 times/day
		6-10 times/day
		1-5 times/day
		0 times/day
Q8. Pain provoked by or increased by brushing on the painful area	Evoked pain	0-10
Q9. Pain provoked by or increased by pressure on the painful area		0-10

Neuropathic pain symptom inventory	Interpretation of pain	Score
Q10. Pain provoked by or increased by contact with something cold on the painful area		0-10
Q11. Pins and needles	Paresthesia/Dysesthesia	0-10
Q12. Tingling		0-10

Results

Total intensity score	Sub-scores	0-100
Q1 = Superficial spontaneous pain	/1 = 0-10 × 2	0-20
Q2 + Q3 = Deep spontaneous pain	/2 = 0-10 × 2	0-20
Q5 + Q6 = Paroxysmal pain	/2 = 0-10 × 2	0-20
Q8 + Q9 + Q10 = Evoked pain	/3 = 0-10 × 2	0-20

Neuropathic pain symptom inventory	Interpretation of pain	Score
Q11 + Q12 = Paresthesia/Dysesthesia	/2 = 0-10 × 2	0-20

Open in a separate window

0 means no pain, but 10 means maximal pain imaginable.

Modified from the article of Bouhassira et al. (Pain 2004; 108: 248-57) [5].

The NPQ includes 12 items scored from 0 to 100 and its coefficient: (1) burning × 0.006, (2) overly sensitive to touch × 0.005, (3) shooting pain × 0.005, (4) numbness × 0.020, (5) electric pain × –0.008, (6) tingling × 0.010, (7) squeezing × –0.004, (8) freezing × 0.004, (9) unpleasant × 0.006, (10) overwhelming × –0.003, (11) tactile hyperalgesia × 0.006, and (12) increased pain due to weather changes × –0.005. If the total score minus 1.408 is below 0, it predicts non-neuropathic pain. On the contrary, if the total score minus 1.408 is at or above 0, it predicts neuropathic pain [37].

The DN4 is composed of 10 question items (yes: 1, no: 0) with 2 categories. First, from the interview of the patient, question 1 includes pain characteristics: (1) burning, (2) painful cold, and (3) electric shocks. Question 2 includes the presence of these combined symptoms: (4) tingling, (5) pins and needles, (6) numbness, and (7) itching. From the examination of the patient, question 3 includes the presence of hypoesthesia: (8) hypoesthesia to touch, and (9) hypoesthesia to pinprick. Question 4 is whether (10) the pain can be caused by or increased by brushing the painful area [39].

The LANSS pain scale includes a pain questionnaire and sensory testing. The pain questionnaire includes (1) unpleasant sensations such as pricking, tingling, or pins and needles (yes: 5, no: 0), (2) different appearance of the skin in the painful area, such as mottled or a red/pink appearance (yes: 5, no: 0), (3) abnormal sensitivity to touch (yes: 3, no: 0), (4) pain appearing suddenly and in bursts for no apparent reason, such as electric shocks, jumping, and bursting (yes: 2, no: 0), and (5) abnormal skin temperature change, such as feeling hot or a burning sensation (yes: 1, no: 0). The sensory testing for the presence of allodynia and an altered pinprick threshold includes (6) allodynia (yes: 5, no: 0) and (7) an altered pinprick threshold (yes: 3, no: 0). The total score varies from 0 to 24. If the score < 12, neuropathic mechanisms are unlikely to be contributing to the patient's pain. If the score ≥ 12, neuropathic mechanisms are likely to be contributing to the patient's pain [40].

The ID pain score includes 6 items scoring from –1 to 5: (1) pain feeling like pins and needles (1/0), (2) hot/burning sensation (1/0), (3) numbness (1/0), (4) electric shocks (1/0), (5) worsening with touch (1/0), and (6) pain limited to the joints (–1/0) [41].

The painDETECT was developed to assess the neuropathic pain component in low back pain. It includes 3 items with (1) grading of pain (0: never, 1: hardly, 2: slightly, 3: moderately, 4: strongly, or 5: very strongly noticed), (2) the pain course pattern (0: persistent pain with slight

fluctuations, –1: persistent pain with pain attacks, +1: persistent pain without pain between attacks, or +1: persistent pain with pain between attacks), and (3) radiating pain (+2: yes, or 0: no). The total score varies from 0 to 8 [42].

The NPSI is recommendable for evaluating the change of intensity of neuropathic pain before and after treatment. It includes positive symptoms and signs of neuropathic pain, including spontaneous pain (superficial burning and deep pain [squeezing and pressure], paresthesia or dysesthesia [pins/needles and tingling], as well as paroxysmal pain [electric shocks and stabbing]) and evoked pain (by brushing, pressure, and contact) (**Table 4**) [5].

(1) Carbamazepine

Carbamazepine (Tegretol®) is still considered the first-line drug for the treatment of trigeminal neuralgia [43,44]. According to the White and Sweet diagnostic criteria of trigeminal neuralgia, the pain should be (1) paroxysmal, (2) provoked by light touch to the face, (3) confined to the trigeminal zone, and (4) unilateral, with (5) showing a normal clinical sensory test in the painful area [45].

In addition, according to the diagnostic criteria for classical and symptomatic trigeminal neuralgia of the International Classification of Headache Disorders (second edition) by the International Headache Society, classical trigeminal neuralgia shows (1) a paroxysmal attack of facial pain which last a few seconds to less than 2 minutes, affecting one or more divisions of the trigeminal nerve, (2) intense, sharp, superficial, or stabbing pain, or pain precipitated from trigger areas or by trigger factors, (3) stereotyped attacks in the individual patient, (4) no abnormal neurologic deficit, and (5) that it is not attributed to another disorder [46].

The metabolite of carbamazepine, carbamazepine-10,11-epoxide, plays an important role for ADRs of carbamazepine. For the safer use of carbamazepine, (1) a monotherapy prescription (if possible), (2) adequate dose titration with monitoring plasma concentration, and (3) routine laboratory check-up, such as complete blood count and liver function test, are recommended [47].

(2) Oxcarbazepine

Oxcarbazepine (Trileptal®) has been developed from carbamazepine through structural variation to avoid metabolites causing ADRs. However, oxcarbazepine is different from carbamazepine; (1) The mode of action of both drugs consists mainly of a blockade of sodium currents. However, in comparison to calcium channel blockade, oxcarbazepine or monohydroxy derivate expresses its effect *via* N-, P-, and/or R-type calcium currents, instead of the L-type calcium currents in carbamazepine. (2) It increases neither 5-hydroxytriptamine (HT) release nor acetylcholine receptor blockade. (3) It does not inhibit the cytochrome P 450 enzymes, and it reduces the concentration of gamma-glutamyltransferase in the serum [48].

Oxcarbazepine and its metabolites are mostly excreted in the urine; an ability of renal clearance is important to determine the dose of administration. In patients with an impaired glomerular filtration rate below 30 mL/mo, (1) the daily dose should be halved to 4-5 mg/kg (almost 300 mg/day), (2) slower dose increases should be made, and (3) the dosing interval should be prolonged [48].

There is no evidence that oxcarbazepine is more effective than other medications in the treatment of diabetic neuropathy, radiculopathy, or postherpetic neuralgia [49]. First-line therapy for trigeminal neuralgia is still considered to be carbamazepine (600-1,200 mg/day), or if not, oxcarbazepine (600-1,800 mg/day) [4].

(3) Gabapentin

When we think of neuropathic pain, except trigeminal neuralgia, gabapentin and pregabalin are the first-line medications. Pain physicians consider these drugs to be neuropathic medications rather than anticonvulsants. Most medications are effective for specific symptoms and signs, not specific disorders or diseases. Gabapentin and/or pregabalin are effective for positive symptoms of neuropathic pain in various disorders or diseases. The current consensus for pain management includes not only opioid and non-opioid analgesics, as major analgesics, but also anticonvulsants and antidepressants, as adjuvants. Chronic pain results from subacute pain followed by acute pain, due to extensive tissue damage or the presence of neuropathic pain. Therefore, evaluation of pain characteristics is essential at the beginning of pain treatment.

Gabapentinoids $\alpha_2\delta$ ligands, are derived from gamma aminobutyric acid (GABA) which blocks $\alpha_2\delta$ subunit-containing voltage-dependent calcium channels. Currently available gabapentinoids include gabapentin (Neurontin®), pregabalin (Lyrica®), mirogabalin (Tarlige®, DS-5565) used in Japan since 2019 [50], and gabapentin enacarbil (Horizant®, Regnite®) [51].

(4) Pregabalin

The next generation anticonvulsant for neuropathic pain, which followed gabapentin, is pregabalin. Pregabalin shows a stronger and longer action duration than gabapentin. However, it is necessary to change from gabapentin to pregabalin in patients with intractable neuropathic pain who are taking a high single dose of gabapentin (over 900 mg), which causes lower bioavailability (a high dose administration of oral gabapentin excretes directly into the stool). An increased frequency of oral intake with a different dose may be needed in prescriptions for both gabapentin and pregabalin for reducing pain and ADRs in initial titration (**Table 5**) [52].

Table 5

Different Titration Methods and Conversion of Gabapentin and Pregabalin for Patients with Intractable Pain Requiring a Rapid Dose Increase

Day	Gabapentin	Pregabalin

	TID				QID					BID			TID	
	7A	1P	7P	Total daily dose	7A	1P	7P	11P	7A	7P	7A	Total daily dose	3P	11P
1	-	-	300	300	-	-	-	300	50	50	100	25	25	50
2	300	-	300	600	100	100	100	300	75	75	150	50	50	50
3	300	300	300	900	200	200	200	300	100	100	200	50	50	100
4-6	400	400	400	1,200	300	300	300	300	150	150	300	75	75	150
7-10	500	500	500	1,500	300	300	300	600	200	200	400	100	100	200
11-	60	60	60	1,80	40	40	40	600	25	250	500	125	125	250

	Gabapentin								Pregabalin					
Day	TID			Total daily dose	QID				BID		Total daily dose	TID		
	7A	1P	7P		7A	1P	7P	11P	7A	7P	7A		3P	11P
14	0	0	0	0	0	0	0		0					
15	800	800	800	2,400	600	600	600	600	300	300	600	150	150	300

TID: ter in die; three times a day, QID: quarter in die; four times in a day, BID: bis in die; twice in a day, -: not available.

Modified from the article of Yang et al. (Korean J Anesthesiol 2013; 65: 48-54) [52].

The maximal dose recommended by the manufacture is 600 mg/day; however, many patients with intractable neuropathic pain during the period of up-titration may need a higher dose to achieve adequate pain relief with tolerable ADRs [53].

(5) Mirogabalin

Both gabapentin and pregabalin have been known to act non-specifically on the $\alpha_2\delta$-1 and -2. Binding to the $\alpha_2\delta$-1 may produce analgesic effects, whereas binding to the $\alpha_2\delta$-2 may be related to ADRs of the central nervous system, such as somnolence. Mirogabalin has been known to show more selective binding and slower dissociation to the $\alpha_2\delta$-1. Maximal plasma concertation

after oral intake is achieved at around 1 hour. The plasma protein binding of mirogabalin is relatively low at 25%. It is largely excreted in the urine [54,55].

The equianalgesic dose of 30 mg/day mirogabalin, for achieving over 50% pain relief (when the number needed to treat is around 5) in the treatment of diabetic peripheral neuropathy, is considered to be roughly 600 mg/day of pregabalin, over 1,200 mg/day of gabapentin, and 60 mg/day of duloxetine. However, the ADRs of mirogabalin are lower than the other 3 drugs [55,56].

(6) Nefopam

Nefopam (fenazocine, Acupan®) is a non-opioid, non-steroidal, centrally acting analgesic drug. The mechanism of analgesic action is similar to those of the triple neurotransmitters (serotonin, dopamine, and norepinephrine), uptake inhibitors (antipsychotics or antidepressants), and anticonvulsants. Therefore, it is suitable to use for neuropathic pain intravenously (continuous infusion), intramuscularly, or orally. It should be given intravenously, slowly, over 15-20 minutes, or intramuscularly, due to preventing known ADRs, such as cold sweating, dizziness, tachycardia, and drowsiness. It is also convenient to convert from intravenous medication during hospitalization into oral medication after discharge. The recommended dose of intravenous administration is 60-120 mg/day, and oral administration for 3 to 6 times totaling 90-180 mg/day [57].

(7) Antidepressants

Antidepressants have been used for the treatment of negative neuropathic pain, based on 6 mechanisms; (1) blockade of norepinephrine and serotonin, (2) blockade of sodium channels, (3) antagonism of NMDA glutamate receptors, (4) sympathetic blockade, (5) effects on visceral nerve fibers, and (6) effects on mood [58].

Antidepressants can be divided into first generation and second generation antidepressants. Nortriptyline has been chosen among the first generation antidepressants (tricyclic antidepressants, including amitriptyline, imipramine, and desipramine), due to the same strong analgesic effect with norepinephrine and serotonin reuptake inhibition, but lesser ADRs, such as anticholinergic effects (dry mouth), postural hypotension, and sedation. On the other hand, amitriptyline may be chosen due to its strong sedative effect in cases of insomnia (**Table 6**) [59].

Table 6

Antidepressants Commonly Used to Treat Pain

Antidepressant	Analgesia	Reuptake inhibition	Adverse effects	Elimination of

								half-life of parent drug (hr)
		NE	**SE**	**Anticholinergic effects**	**Postural hypotension**	**Sedation**	**Cardiac arrhythmia**	
Nortriptyline	+++	++	++	++	+	+	+++	18-48
Amitriptyline	+++	++	++	+++	+++	+++	+++	9-46
Imipramine	+++	++	++	+++	+++	++	+++	6-28
Desipramine	++	+++	0	+	++	+	+++	12-28
Paroxetine	+	0	+++	0	0	0	0	21
Citalopram	+	0	+++	0	0	0	0	24
Venlafaxine	?	++	+++	0	0	0	0	4

NE: norepinephrine, SE: serotonin.

Modified from Max and Gilron (Antidepressants, muscle relaxants, and N-methyl-D-aspartate receptor antagonists. In: Bonica's Management of Pain. 3rd ed. Edited by Loeser JD; 2000, pp. 1710-26) [59].

2. Emotional component of pain

In addition to the sensory component of pain originating from actual tissue damage, the emotional component of pain from potential tissue damage should also be treated. While treating all sensory components of pain, including nociceptive and neuropathic pain, patients may complain of mysterious and vague generalized pain [59].

Available medications for the emotional component of pain are antipsychotics, anxiolytics, and antidepressants. There are 3 major neurotransmitters in the human brain: serotonin, norepinephrine, and dopamine. These neurotransmitters have their own functions: (1) serotonin is charged with the control of cognitive impulse and relaxation with memory, (2) norepinephrine has a relation to alertness, concentration, socialization, and energy, and (3) dopamine is deeply engaged in pleasure, motivation, reward, pain avoidance, and reality [59].

It is difficult to quantify each emotional item and to supply a deficit in the clinical field. However, not only the sensory component, but also the emotional component should be considered in the treatment of pain.

1) Antipsychotics

Antipsychotics are effective in pain patients with positive psychotic symptoms (related to the mesolimbic pathway), not negative, affective, and cognitive symptoms (related to the mesocortical pathway) [59].

The antipsychotics can be divided into typical and atypical categories. The typical antipsychotics act on the D_2 receptor; however, they produce extrapyramidal symptoms (dystonia, pseudo-parkinsonism, akathisia, and tardive dyskinesia) related to the nigrostriatal pathway and produce elevated serum prolactin levels.

In order to reduce the extrapyramidal symptoms and hyperprolactinemia, atypical antipsychotics have been developed through a decreased D_2 receptor binding affinity, but an increased 5-HT_{2A} receptor binding effect. Certain atypical antipsychotics, such as risperidone, ziprasidone, sertindole, clozapine, olanzapine, zotepine, aripiprazole, and quetiapine, produce somnolence effect related to the 5-HT_{2A} receptor binding. On the contrary, sulpiride and amisulpride, like the typical antipsychotic haloperidol, do not produce somnolence. In addition, they increase the risk of metabolic syndromes, such as weight gain, diabetes, or dyslipidemia.

Antipsychotic equivalent oral doses, based on a daily oral dose of 100 mg of chlorpromazine, are similar to 2 mg (1-5 mg) of haloperidol, 100 mg (30-150 mg) of clozapine, 2 mg (0.5-3 mg) of risperidone, 75 mg of quetiapine, 5 mg of olanzapine, and 7.5 mg of aripiprazole [59].

2) Anxiolytics

If antipsychotics are called as major tranquilizers (neuroleptics), anxiolytics are known as minor tranquilizers. Representative anxiolytic agents are GABAergics, such as benzodiazepines, barbiturates, and etifoxine.

The GABAA receptor consists of 5 subunits, two $\alpha_{(1-6)}$, two $\beta_{(1-3)}$, and one $\gamma_{(1-3)}$. Benzodiazepines are binding at the interfaces between the α_1 and γ_2 subunit, and barbiturates bind at the interfaces between the α_1 and β_2 subunit. Etifoxine directly acts on the β_2 or β_3 subunit, and indirectly activates the 18 kDatranslocator protein. It shows lesser ADRs of anterograde amnesia, sedation, impaired psychomotor performance, and withdrawal syndromes than those of benzodiazepines [58].

3. Transition from intravenous patient-controlled analgesia into oral medication inpatients with intractable pain

Patients with intractable pain need hospitalization for the investigation of the origin of the pain, the treatment of correctable causes, and the transition of analgesia from intravenous to oral medication for discharge. Available intravenous medications for analgesia are morphine, ketorolac, nefopam, dexmedetomidine, midazolam, steroids, and antiemetics (ramosetron, palonosetron, or ondansetron).

The first dose of each medication is determined by the origin and intensity of the pain. While escalating the daily dose of oral medication, the dose of intravenous medications with patient-controlled analgesia can be diluted with normal saline to half of the initial dose every 3 days.

After 4 cycles of dilution at 12 days, the transition to oral from intravenous medications is completed, using such medications as oral morphine, NSAIDs, nefopam, anxiolytics (antidepressant or antipsychotic), anticonvulsants, antidepressants, and steroids. Patients can be discharged from the hospital at 14 days after confirmation of having tolerable pain and ADRs.

Go to:

CONCLUSIONS

Most analgesics, except NSAIDs, ASA, or APAP, need the process of dose-up and -down titration. In order to achieve the 3 steps including reducing (1) night pain, (2) resting pain during the day, and (3) daily activity, the initial dose at night should be larger, even though the daily total dose is the same. Simultaneously, it is emphasized that the ADRs, such as orthostatic hypotension and dizziness, may develop at night. Dose-up titration is finished when both pain and ADRs are tolerable. When down-titration for discontinuing the analgesics begins, the dose at night should be the last to be reduced or discontinued.

According to the origin of the pain, an effective analgesic drug should be chosen. 1) For an unpleasant emotional experience, an antipsychotic, antidepressant, or anxiolytic is considered. 2) Various analgesics are needed for the control of an unpleasant sensory experience. (1) An NSAID, ASA, or APAP is effective for somatic nociceptive pain. (2) An opioid is helpful to relieve visceral nociceptive pain. (3) An anticonvulsant is used to control positive neuropathic

pain. (4) On the contrary, an antidepressant should be chosen to relieve negative neuropathic pain.

Chronic pain, which has 2 or more pain components, needs combined therapy using these analgesics. Chronification of pain comes from a greater intensity of tissue damage or an existence of neuropathic pain. Therefore, chronic pain may include sensory component (nociceptive and/or neuropathic pain), as well as, emotional component which has developed from the beginning and/or may develop during the chronification of pain. In summary, various combination of analgesics, such as NSAIDs for somatic pain, opioids for visceral pain, anticonvulsants and/or antidepressants for neuropathic pain, and antipsychotics and/or anti-anxiety drugs for emotional component, should be used properly and/or simultaneously. Polypharmacy is enhancing therapeutic analgesic effects while reducing ADRs. It is unreasonable to assume that opioids rather than NSAIDs are more effective or stronger for somatic pain.

When multiple analgesics are used for the treatment of pain (emotional and/or sensory components), the general and special condition of the patients and inter-analgesic medications should be considered.

Diagnosis is the most important part in any branch of clinical practice for management of patient's complaints. Similarly we cannot choose the correct treatment modality unless we identify the pain generator correctly and understand the pathophysiology behind it.

In modern medicine with the advent of sophisticated imaging, there are tendencies of ignoring history part in clinical examination. Many times we jump directly into the magnetic resonance imaging (MRI) or other scans ignoring the importance of proper history in diagnosis of pain. But we must remember that some abnormality in MRI may not be indicative of the source of pain.

In making a clinical diagnosis there are three essential steps: History taking, clinical examination, and investigations. In establishing diagnosis of painful conditions, there is another special subheading under investigation part, called diagnostic interventions or diagnostic nerve blocks, which help us in finding pain generators.

Proper targeted history taking may help us in avoiding unnecessary costly investigations. History taking is an art, which makes physician and patients to have a good rapport and helps us to find the pain generator. Sufficient time should be given to the patients who are anxious, depressed, or overtly frightened, feels hopeless from medical science that their pain can be treated and may not be able to express the present situation. Repeated history taking of more patients gives us

experience and teaches us to handle situation, which may confuse us at the beginning.

Analysis of history is also very important in making many other decisions such as history suggestive of red flags in back pain or headache prompt us to go for more invasive investigations or management. For example, history of bladder and bowel dysfunction, weakness of legs, increasing numbness, history of malignancy, and history of trauma in low back pain and leg pain, all point to the red flags of low back pain.

The history part of patient evaluation can be divided as follows:

Pain at different locations as chief presenting complaints.
Ruling out red flags or warning signals.
Past history.
Personal history, including sleep, bladder/bowel habit.
Treatment history.
Family history.

During history taking we must remember the following:

- Adequate time must be given to express their problems and the reasons for seeking advice from pain clinic care.
- We need to listen carefully without distractions in order to obtain and interpret the clinical information provided by the patient.
- Physician should be empathetic.
- Patient should believe that my physician is accepting my complaint.

Comprehensive history taking is usually done on first consultation. This will be more time consuming and laborious. Preconsultation questionnaire can help in overcoming this problem. This can be used as baseline reference about the patient in all aspects of pain. While taking history we should concentrate to get answers for two questions. First is to find out the source of

pain and other to find out the type of pain.

Pain History

The chief complaint can be dealt with in the following steps:

1. Quantity or severity of pain.
2. Quality or nature of pain.
3. Mode of onset and location.
4. Duration and chronicity.
5. Provocative and relieving factors.
6. Special character.
7. Timing of pain.
8. In relation to posture.
9. Associated complaints.

Quantity or Severity or Intensity of Pain

Pain is a subjective experience. Like many diseases, such as hypertension or diabetes, there is no objective measurement for a patient's pain intensity. Unfortunately we do not have thermometer-like device to measure pain so we need to rely on the patients' statements. Pain is a complex neurobehavioral problem affected by psychological, cultural, and environmental factors. The variables to be measured are current pain intensity and average pain intensity over a specified period of time, for example, last 1 week or 4 weeks. It is the average pain intensity, which is the usual target for pain treatment both by the clinician and the patient. The goal of treatment in chronic pain is to reduce pain intensity as much as possible while avoiding side effects. Numerous pain scales for practical assessment of pain intensity in clinical studies have been developed. The chosen one should be appropriate for patient's abilities and preferences. These

scales are more appropriate for detecting change within individuals rather than comparison between individuals.

Types of Pain Intensity Assessment

Pain can be assessed in two ways, by either unidimensional or multidimensional instruments. Pain should be assessed upon movement, not just like that when the patient is lying still to minimize discomfort.

Unidimensional instruments

1. *Verbal Rating Scales (VRS)*

In VRS, pain is described as none, mild, moderate, or severe. This is the usual way a patient express pain. This scale is short, easy to administer, and understand especially in elderly patients. Lack of reproducibility makes this one less suitable for research purposes. [1]

2. *The Binary Scale:*

The patient is asked to answer for the question like - is your pain 60% relieved? "Yes or No." This is short, easy to administer, and easy to understand. This can mislead the patient; along with lack of reproducibility make this less suitable for research purposes.

3. *The Numerical Rating Scale (NRS):*

It is the most commonly used. In this the two extremes of the pain experience is noted and has a numerical scale between "no pain" and "worst pain imaginable." "Zero" corresponds to no pain and "10" corresponds to the worst pain imaginable [Figure 1].

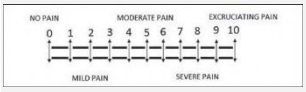


Figure 1: Numerical rating scale

	Click here to view

The advantage of this scale is that it easy for the patients to understand. The disadvantage is that the digital scale reduces the capacity to detect subtle changes as the digits act as anchoring points. A reduction of 30% or 2 points and more from baseline in patient on treatment indicates positive response for treatment.

4. *The Faces Rating Scale:*

It is commonly used. The patient is asked to point to various facial expressions ranging from a smiling face (no pain) to an extremely unhappy one (the worst possible pain). It can be used in patients with whom communication may be difficult.

5. *The Visual Analog Scale (VAS):*

It is similar to the numerical rating scale. There is a 10-cm horizontal line labeled "no pain" at one end and "worst pain imaginable" on the other end. The patient is asked to mark on this line where the intensity of the pain lies. The distance from "no pain" to the patient's mark numerically indicates the severity of the pain. Slide rule-like devices are also available that make measurement easier. The device has a line on the patient side and a numeric score on the clinician side. The VAS is a simple, efficient, valid, and minimally intrusive method that correlates well with other reliable methods.

The disadvantage is it is more time consuming than other instruments. There is some difficulty in using and understanding this scale in elderly patients.

Multidimensional Instruments

1. *The McGill Pain Questionnaire (MPQ)*[2],[3]

It was developed by Melzack and Torgerson. It is a checklist of words describing symptoms. Unlike other scales, it attempts to define the pain in three major dimensions by 20 sets of descriptive words divided as follows:

a. Ten sets describe sensory - discriminative (nociceptive pathway).
b. Five sets describe motivational - affective (reticular and limbic structures).
c. One set describes cognitive - evaluative (cerebral cortex).
d. Four sets describe miscellaneous dimensions.

The patient selects the sets that apply to his or her pain, and circles the words in each set that best describe the pain. The words in each class are given rank according to severity of pain. It is translated to multiple languages. The advantage is that it is reliable and can be completed in 5-15 min and it helps in the diagnosis as the choice of descriptive words that characterize the pain correlates well with pain syndromes. The disadvantage is that high levels of anxiety and psychological disturbance can obscure the MPQ's discriminative capacity.

2. *Brief Pain Inventory (BPI):*[4]

It measures both the intensity of pain (sensory dimension) and the interference of pain in the patient's life (reactive dimension).

It is translated to multiple languages.

Advantages:

a. It is a reliable and valid for the cancer pain and many pain syndromes and can be completed in 5-15 min.
b. It shows good sensitivity to treatment effects (mostly in pharmacological treatments).

3. *West Haven-Yale Multi-dimensional Pain Inventory (WHYMPI):*[5],[6]

Technique:

It is composed of 56 items with three parts:

a. Five dimensions covering the experience of pain and suffering, interference with family, social and work functions.
b. The patient's perception of the pain with determining the responses or significant other displays to pain.
c. The degree to which the patient engages in common daily activities.

Patients respond to the questions on a 7-point scale.

Advantages:

a. It is valid in many pain syndromes.
b. It shows good sensitivity to treatment effects.

4. *Medical Outcome Study 36-item Short-form Health Survey (SF-36):*[7],[8]

It consists of eight subscales including

1. Physical functioning.
2. Limitations due to physical problems.
3. Social functioning.
4. Bodily pain.

5. Role limitations due to emotional problems.
6. General mental health.
7. Vitality.
8. General health perceptions.

Advantages:

a. It is the most widely used instrument to measure multiple dimensions of quality of life.
b. It is used in almost every diseases or conditions imaginable.
c. It is easy to administer, taking about 10 min to complete.

Assessment of Quality or Nature of Pain

It is one of the most important components in making diagnosis, particularly if we want to diagnose the nature or character of pain whether it is nociceptive or neuropathic or a mixed variety. There are different validated questionnaire-based tools, which helps us in identifying neuropathic pain conditions. And most of these tools are based on analysis of history. Even when we are not using such tools, proper history can guide us in making diagnosis of neuropathic pain. Simple questions like whether there is burning sensation, tingling, numbness, sensations such as crawling of ants, cramping, electric shock-like pain, and so on, can guide us to understand whether there is neuropathic component in pain. Allodynia can also be assessed by history, when touching parts of body with clothes or simple touch with fingers is evoking the pain. Nociceptive pain is somewhat easy to manage. Neuropathic pain if it is not diagnosed and treated properly in time, then it can lead to catastrophic stage where no options are available to treat.

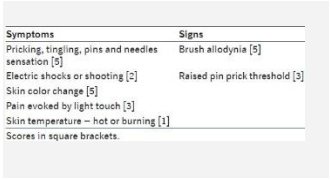
Neuropathic pain has been defined by the Special Interest Group on Neuropathic Pain (*NeuPSIG*) as "*pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.* " [9] It is a common type of pain associated with suffering, depression, anxiety, disturbed sleep, and impaired quality of life. Because these components require different pain management strategies, correct diagnosis is highly desirable. [10] The presence of validated

tools to diagnose neuropathic pain is therefore required as improper assessment is frequently associated with undertreatment, underdiagnosis, and increased cost to the patient and society as a whole. A number of screening tools in the form of questionnaires have been developed and validated in the past decade to address the above purpose.

Screening tools for neuropathic pain

1. Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)

LANSS, first described in 2001, [11] was the first screening test to identify pain of neuropathic origin. It is a simple tool consisting of five symptoms addressing pain quality and triggers and two signs [Table 1]. Each item is a binary response (yes or no) to the presence of symptoms (five items) or clinical signs (two items). It is easy to score in clinical settings and has been tested and validated in a number of neuropathic pain conditions since then with a sensitivity and specificity ranging from 82% to 91% and 80% to 94%, respectively. [12],[13],[14],[15]



Symptoms	Signs
Pricking, tingling, pins and needles sensation [5]	Brush allodynia [5]
Electric shocks or shooting [2]	Raised pin prick threshold [3]
Skin color change [5]	
Pain evoked by light touch [3]	
Skin temperature – hot or burning [1]	

Scores in square brackets.

Table 1: Leeds Assessment of neuropathic symptoms and signs[16]

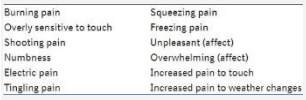
Click here to view

Score < 12/24 indicates that the pain is unlikely to be neuropathic in origin and *Score ≥ 12/24* indicates that the pain is likely to be neuropathic in origin. The need for clinical examination and pin prick testing limits its use in clinical setting. To overcome this drawback, a self-report tool, *S-LANSS* has been developed and validated to identify patients whose pain is dominated by neuropathic mechanisms. [17]

2. *Neuropathic Pain Questionnaire (NPQ)*

It was administered to 382 patients of whom 149 had neuropathic pain and 233 patients had nonneuropathic pain. [18] It is a *self-questionnaire* consisting of 12 items: 10 related to sensations and two related to affect [Table 2]. Each item is scored on a scale of *0 (no pain)* to *100 (worst*

possible pain). The sensitivity and specificity have been demonstrated to be 66% and 75%, respectively, compared with clinical diagnosis. A *short form* of NPQ has been described consisting of three items: numbness, tingling, and pain increase in response to touch. [19]



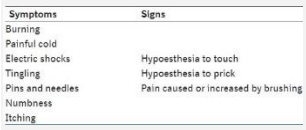
Burning pain	Squeezing pain
Overly sensitive to touch	Freezing pain
Shooting pain	Unpleasant (affect)
Numbness	Overwhelming (affect)
Electric pain	Increased pain to touch
Tingling pain	Increased pain to weather changes

Table 2: Neuropathic pain questionnaire

Click here to view

3. *DouleurNeuropathique en 4 questions (DN4)*

It consists of seven items related to symptoms and three items related to physical examination [Table 3]. [20] Each item is scored 1 (yes) or 0 (no) and sum of all 10 items is taken as total score with a score of ≥4 as neuropathic pain. It was developed in 160 patients: 89 with nerve lesions and 71 without nerve lesions. Sensitivity and specificity of 83% and 90%, respectively, has been demonstrated, respectively. The seven sensory descriptors can be used as a self-reported questionnaire with similar results.



Symptoms	Signs
Burning	
Painful cold	
Electric shocks	Hypoesthesia to touch
Tingling	Hypoesthesia to prick
Pins and needles	Pain caused or increased by brushing
Numbness	
Itching	

Table 3: Douleurneuropathique en 4 questions

Click here to view

4. *Pain DETECT*

It is a simple patient-based self-report questionnaire consisting of nine items: seven sensory descriptors and two related to spatial (radiating) and temporal characteristics [Table 4]. [21],[22] The sensory descriptors are scored on a scale of 0 (no) to 5 (very strongly) and radiating pain as 1 (yes) or 0 (no). A score of ≥19 indicate neuropathic pain likely and ≤12 neuropathic pain unlikely. It does not require a clinical examination. It was validated in 392 patients: 228 with predominantly neuropathic origin and 164 with nociceptive origin. [23] Sensitivity and specificity of 85% and 80%, respectively, has been demonstrated.

Symptoms	Pain course: four items
Burning (stinging nettles)	Persistent pain with slight fluctuations
Tingling or pricking	Persistent pain with slight attacks
Is light touching painful?	Pain attacks without pain between them
Sudden pain attacks such as electric shocks	Pain attacks with pain between them
Is cold or heat occasionally painful?	Radiation
Numbness	Radiating pain
Does slight pressure trigger pain?	

Table 4: PainDETECT

Click here to view

5. *ID-Pain*

It is a self-questionnaire consisting of five sensory descriptors and one item regarding pain located in the joints (to identify nociceptive pain) and does not require a clinical examination [Table 5]. [24] Scoring is from 1 to 5 with higher score indicating neuropathic pain. It was validated in 307 patients: 105 with neuropathic pain, 104 mixed, and 98 with nociceptive pain.

Pins and needles	Electric shocks
Hot/burning	Is the pain made worse with touch of clothing or bed sheets?
Numb	Is the pain limited to your joints? (−1)

Table 5: ID-Pain

Click here to view

Mode of Onset and Location

Mode of onset and location is very important for the etiology of pain. It may be sudden or gradual onset. Sudden onset of severe pain without any provocation, for example, severe intolerable headache may be due to subarachnoid hemorrhage and sudden severe pain on patients with pre-existing pain, for example, severe back pain in elderly patients with pre-existing back pain may be due to spinal carcinoma metastases. Both these conditions indicate red flag, considered. Site of onset gives better idea in finding out primary reason, for example, lumbar facet joint arthropathy patient gives history of pain on lower back, buttock, and thigh but on enquiry they will show onset on paramedial region and later distributed to other regions. It is not uncommon for patient to link pain to trauma in the past or present, which may not be relevant. Detailed enquiry may reveal pain-free period after trauma.

Chronicity (Duration and Frequency)

The duration is important to an extent, if patient is having chronic pain of 20 years duration; it is not risky, in other aspect if new symptoms or sudden increase of pain occurs in already existing problem warrant's exclusion of malignancy or metastasis. Duration and frequency history plays a vital role in the diagnosis, for example, in migraine, the unilateral pain is frequently throbbing and may last for hours to days. Cluster headaches, in contrast, are named for their periodicity. In short, duration and frequency history ease our diagnosis. Patient with long history of pain, physical provocative test may become negative, for example, straight leg raise test in lumbar radiculopathy may be negative on long course. In this case, history of pain in leg with neuropathic character, exaggerated on exertion and relieved by rest may be only clue for its diagnosis. Very important in chronic pain conditions, always remember that sympathetic system (central sensitization) will become the main pain mediator, which may explain diffuse the nature of pain in patient and failure to respond to conventional (interventional) treatment.

Provocative and Felieving Factors

Assessing what provokes or relieves the pain provides valuable clues to the diagnosis. Leg and back pain due to spinal stenosis has a characteristic pattern of worsening with walking or standing, with the pain being totally relieved with sitting or lying down for less than 10 min. Neuropathic pain can present with spontaneous pain or pain can be provoked by different stimuli such as cold, light touch, or the brushing of sheets. It is usually improved with heat, often the opposite of inflammatory pain. Patient with pain generator very near to each other, for example, lower lumbar facet and sacroiliac joint may have similar history but provocative and relieving factors will give good idea for diagnosis as sitting relieve pain in facet joint syndrome not in sacroiliac joint arthropathy in which sitting may provoke pain.

Special Character

Between pain character and severity, considerable overlap can be identified. For examples, in cluster headache the pain usually will be deep, boring, wrenching, and the pain is most severe

while vascular headache tends to be throbbing, pulsatile, and severe in intensity. For facial pain the character and severity tends to be different for different conditions, in idiopathic trigeminal neuralgia pain tends to be unilateral, paroxysmal, sharp, shooting, and lancinating along one or more branches of trigeminal nerve, whereas the pain of temporomandibular joint dysfunction tends to be unilateral, dull aching, and around the affected joint. It is exacerbated by bruxism, eating, and yawning. Postherpetic neuralgia pain may be burning and aching superimposed on paroxysms of shocks and jabs. It is associated with dysesthesias, and allodynia (unpleasant sensation even with the slightest touch over the skin).

Timing of Pain

Pain and stiffness felt in the morning hours persisting for more than hours may be inflammatory arthropathy, whereas pain after any inactivity persisting less than half an hour or after prolonged activity goes more in favor of degenerative arthropathy. Severe headache occurring regularly at a particular time, particular season may give clue for cluster headache. Neuropathic pain can be more severe in the night.

Relation with Posture

Pain on sitting on floor may be because of sacroiliac(SI) joint arthropathy, whereas cross-legged sitting may be painful in piriformis syndrome, and others. Pain on change of posture such as turning in bed, standing from sitting position goes more in favor facet joint syndrome. Prolonged sitting produces more pain in discogenic pain. Patients with spinal canal stenosis have more pain on standing and walking.

Associated Complaints

Associated complains such as weakness, numbness may indicate neurologic deficits. Fever may indicate infections, nausea/vomiting also have diagnostic value in migraine, space occupying lesion of brain, and so on.

Understanding Red Flags or Warning Signals

We must be very cautious in dealing certain painful conditions, which can be potentially dangerous. We must be having multidisciplinary approach to deal with these patients. These vary in different anatomical locations, but the following features (not limiting to the followings) in general can be serious.

- Pain with major trauma
- Suspecting tumor
- Suspecting infection with fever, rigor, vomiting, and so on
- Unconsciousness
- Motor weakness
- Progressive sensory deficit
- Loss of vision
- Loss of bladder control with retention and incontinence
- Loss of bowel control with inability to force to pass stool
- Sudden onset pain, which is progressing rapidly
- Not relieved by analgesic within few days.

Past History

Past history includes any pain events mimicking present, ask for progress, diagnosis, and any treatment taken and procedure/operation done. Past history help in making diagnosis, for example, history of rash, vesicles in the same dermatome as of present

neuropathic pain can confirm postherpetic neuralgia. Some diseases have periodic occurrence and they can have multiple same type of previous episodes before presenting to us at present, for example, cluster headache. Patient with multiple episodes of pain can have associated significant cognitive disturbance. Patient can have some disease, which can influence the manifestation of pain (eg, dementia) or it can interfere with treatment (organ damage). History targeted on finding etiology of pain can help in finding other pain manifestations of a disease (eg, multiple sclerosis). Diabetes, hypertension, thyroid disorder, dementia, *Parkinsonism* More Details, liver and kidney compromise, inflammatory disorders should be given more importance on its presence.

Personal History Including Sleep, Bladder/Bowel Habit

Patient with pain can have some psychological disorders, such as anxiety and depression, which occurs primarily because of pain, leads to patient's less tolerance to pain and decreased coping capacity and some disorders, such as dementia, bipolar disorder, Post Traumatic Stress Disorder (PTSD) and Attention Deficit Hyperactivity Disorder (ADHD). A lot of tools are available for mental status assessment, which includes

- PHQ-9
- Beck Depression Inventory [25]
- Hamilton Depression Scale [25],[26]
- Zung Self-Rating Depression Score [25]
- Hospital Anxiety and Depression Scale (HADS) [27]
- Pain Catastrophizing Scale (PCS) [28]
- The Tampa Scale of Kinesophobia. [29]

1. *PHQ-9*

	Not at all	Several days, but less than half a month	Several days, more than half a month	Nearly everyday
A. Little interest or pleasure in doing things	0	1	2	3
B. Feeling down, depressed, or hopeless	0	1	2	3
C. Trouble falling or staying asleep or sleeping too much	0	1	2	3
D. Feeling tired or having little energy	0	1	2	3
E. Poor appetite or overeating	0	1	2	3
F. Feeling bad about yourself or that you are a failure or have let yourself or your family down	0	1	2	3
G. Trouble concentrating on things such as reading the newspaper or watching television	0	1	2	3
H. Moving or speaking so slowly or so restlessly that other people could have noticed	0	1	2	3
I. Thoughts that you would be better off dead, or thoughts of hurting yourself in some way	0	1	2	3

Maximum score is 27. Score 1-4/27 indicates minimal depression, 5-9/27 indicates mild depression, 10-14/27 indicate moderate depression, 15-19/27 indicate moderately severe depression, and 20-27/27 indicate severe depression.

2. *Beck Depression Inventory*[25]

This have 21 parameters and each are graded from 0 to 3 thus have total score of 63. Result will be inferred as below

- 1-10 - Ups and downs are considered normal.
- 11-16 - Mild mood disturbance.
- 17-20 - Borderline clinical depression.
- 21-30 - Moderate depression.
- 31-40 - Severe depression.
- >40-Extreme depression

3. Hamilton Depression Scale.[25],[26]

It includes 17 parameters with score grade of 4 items (symptom is absent, mild, moderate, severe and very severe), 2 items (symptom is absent, mild and definite). Total score of 0-7, 8-13, 14-18, 19-22, ≥ 23 indicates normal, mild, moderate, severe and very severe depression accordingly.

4. Zung Self-Rating Depression Score.[25]

It includes 20 parameters with grading ranging from 1 to 4, thus a total score of 20-80. Some parameters are given score from 1 to 4 for symptoms increasing in time duration and some are given in reverse.

5. *Hospital Anxiety and Depression Scale (HADS).*[27]

It includes 14 parameters with 2, 4, 6, 8, 11, 12, 14 for anxiety and 1, 3, 5, 7, 9, 10, 13 for depression.

Scoring is done as 3, 2, 1, 0 (for item 7 and 10 scoring is reversed). Score of 0-7 indicates noncase; 8-10 indicate borderline case; and 11 or above indicate case.

Pain Catastrophizing Scale (PCS) [28] **and The Tampa Scale of Kinesophobia** [29] helps in assessing personality disorder.

Sleep disorder and pain is highly interlinked together. Pain can cause sleep disorder in over 70% of patient. Pain may be interrupted, for example, posttraumatic stress disorder or patient can feel inadequate sleep on waking up, for example, in fibromyalgia. Some disorders associated with sleep such as obstructive sleep apnea can interfere with treatment and result, for example, treatment with opioids. Effective treatment of sleep disturbance will involve assessing and treating all of the contributing factors. Chance of pregnancy should be ruled out in women of child-bearing age. Bladder and bowel disturbance may be an associated component or etiology for present pain complaint. For example, history of inflammatory bowel disease may be a reason for seronegative inflammatory arthropathy, and irritable bowel disease may be an associated disease of fibromyalgia.

Treatment History

The initial questionnaire should allow the patient to list all the therapeutic modalities they are currently using or have used in the past. Chances of drug addiction should be ruled out before prescribing any drugs. Any drug allergy, any side effect/complication to past treatment or comorbid condition (renal, hepatic compromise) should be taken into consideration before prescribing medicine.

Family History

History of pain and diseases in family members can support in getting diagnosis as some diseases run among families, for example, rheumatoid arthritis, fibromyalgia, and others. History of family dispute should be ruled out in patients having disproportionate, irrelevant, and unusual manifestations.

Imaging Tests

Imaging tests are also called radiological tests. With these tests, the doctor uses different technologies to get a better picture of what's going on in the body—with the bones, soft tissues, and organs.
Here are the most common imaging tests:

- **X-ray:** These show the doctor your bony structures so that he or she can look for any abnormalities. For example, if the doctor suspects you have osteoarthritis in the knee, he or she may use x-ray to take a closer look at your joint.
- **CT scan:** A CT scan (which stands for computed tomography scan) is used to look at the soft tissues, as well as the bones. On a CT scan, the doctor can see ligaments, for example. For example, a CT scan can show a spinal herniated disc, which is a soft tissue. Looking the CT, the doctor can see if the herniated disc is pushing on a spinal nerve or the spinal cord.
- **MRI:** Similar to a CT scan, an MRI (which stands for magnetic resonance imaging) shows the relationship between soft tissues and the bones. Unlike CT scans, it doesn't use radiation (x-rays) to do this; instead an MRI uses magnetic fields and computers to produce high-resolution images of your bones and soft tissues.

Other imaging tests are myelograms, bone scans, and ultrasounds.

Remember, the doctor may not be able to see anything as a cause of your pain on imaging tests. Your structures may look completely normal—but that doesn't mean you aren't experiencing pain.

Nerve Tests

Nerve tests, which are part of the neurological exam process, can help your doctor see how well your nerves are working. Especially in neuropathic pain—such as diabetic peripheral neuropathy—nerve tests can provide important information about your nerves.
Here are the most common nerve tests:

- **Electromyography test:** This test, frequently abbreviated as EMG, tests how well your muscles respond to signals from the nerves, helping your doctor understand if those nerves going to the muscles are damaged. If they are damaged, then they won't send clear messages to the muscles, and the muscles won't respond well.
- **Nerve conduction velocity test:** This is abbreviated to NCV, and as suggested by the word *velocity* in the name, this nerve test measure how fast messages travel along the nerves. Since damaged nerves don't send signals as quickly, the doctor will be looking for messages that are slowed down.
- **Quantitative sensory testing:** That's a very big phrase for a few very basic tests. You have different nerves that transmit different messages—some transmit temperature messages and some send touch messages, for example. The doctor may assess how well you can feel temperature changes; if you can't feel the change from warm to cold, you may have a problem with your smaller peripheral nerves.

  Another test determines how much pressure you can feel, which tells the doctor how well your touch nerves are working.

  Also, the doctor may test your ability to feel vibrations. The nerves that send the vibration message are larger peripheral nerves, and they are especially important for balance.

Blood Tests

Complete blood count

ESR

In some cases, the doctor may want to have blood tests run on you. For example, if he or she suspects that you have rheumatoid arthritis (RA), you may have blood work done to see if you have the rheumatoid factor in your blood. That's an antibody often produced in people who have RA, so a doctor may order a blood test to check for it as part of the diagnostic process.

Blood tests can also be used to check for levels of inflammation in the body—important if the doctor thinks you may have some type of arthritis.

Labs and Diagnostic Tests Conclusion

The two most important things to keep in mind as you have tests done are that most likely, no one test will be able to diagnose the exact cause of your pain, and that you should fully understand the labs and diagnostic tests you're having. Ask questions, especially about the results of the tests so that you understand how it impacts your care.

Treatment of acute pain

The WHO pain relief ladder recommends a nonopioid such as acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) for the initial management of pain. Acute pain characteristics and patient risk factors should be considered when choosing

between acetaminophen and an NSAID (e.g., aspirin, other nonselective NSAIDs, cyclooxygenase-2 [COX-2] selective NSAIDs).

ACETAMINOPHEN

Acetaminophen, called paracetamol outside of the United States, is the first-line treatment for most mild to moderate acute pain.[8] The effectiveness of acetaminophen is similar to that of NSAIDs such as celecoxib (Celebrex), 200 mg; aspirin, 600 to 650 mg; and naproxen (Naprosyn), 200 to 220 mg.[8] It is generally well-tolerated, has few drug-drug interactions, is not associated with increased blood pressure (as with NSAIDs), can be used during pregnancy (U.S. Food and Drug Administration [FDA] pregnancy category B), and is the analgesic of choice for episodic use in patients with impaired renal function.[17] Although acetaminophen is less effective for acute low back pain than some NSAIDs, it is a reasonable first-line option because of its favorable safety and cost profiles.[18]

ASPIRIN

Aspirin effectively relieves mild to moderate acute pain. It is similar to the same dose of acetaminophen and is comparable to celecoxib, 200 mg.[9] Over a dose range of 500 to 1,200 mg, aspirin exhibits a dose-response relationship (i.e., a 1,200-mg dose of aspirin provides better pain relief than 600- to 650-mg doses).[9] Like NSAIDs, aspirin can cause gastrointestinal hemorrhage and ulcer.[19] Patients with chronic urticaria and asthma have a greater likelihood of salicylate hypersensitivity, which can manifest as bronchospasm (20% and 4%, respectively, compared with 1% in the general population).[6]

Aspirin, 900 to 1,000 mg, is as effective for acute migraine pain as oral sumatriptan (Imitrex), 50 mg.[10] Adverse events with aspirin use are generally mild and less common than with the use of sumatriptan, 100 mg.[9,10]

OTHER NONSELECTIVE NSAIDS

Nonselective NSAIDs inhibit both COX-1 and COX-2, whereas COX-2 selective NSAIDs have greater COX-2 selectivity. Inhibition of COX-2 is thought to mediate the analgesic properties of NSAIDs, whereas inhibition of COX-1 appears to be associated with gastrointestinal adverse effects. NSAIDs possess anti-inflammatory effects that are lacking with acetaminophen, and they can be especially useful for the treatment of acute pain associated with prostaglandin-mediated activity, such as dysmenorrhea or osteoarthritis.[11,12]

Because most NSAIDs have nearly identical analgesic effects, the choice is based on cost, dosing schedule, and the frequency or severity of adverse effects. Some NSAIDs (e.g., indomethacin [Indocin], mefenamic acid [Ponstel]) are now rarely used because of adverse effects. Ibuprofen and naproxen are among the most commonly used NSAIDs

in the United States because of their effectiveness, adverse effect profile, cost, and over-the-counter availability.[12,13]

There is a ceiling to the analgesic effects of NSAIDs but not to their anti-inflammatory effects, although adverse effects may limit upward dosing titration. NSAIDs are more effective than placebo or acetaminophen for primary dysmenorrhea, but they are associated with a higher incidence of adverse effects such as headache, drowsiness, nausea, and indigestion.[12] In general, there are no differences among NSAIDs in terms of effectiveness or adverse effects.

For osteoarthritis, NSAIDs provide significantly better pain relief than acetaminophen, but with more gastrointestinal adverse events.[11] Some evidence suggests that NSAIDs and acetaminophen may be comparable for mild osteoarthritis pain, whereas NSAIDs may be better for moderate to severe osteoarthritis pain.[11]

Acetaminophen and NSAIDs are equally effective for acute low back pain, although NSAIDs are associated with a higher incidence of adverse effects.[13,18] There is no difference in effectiveness among NSAIDs, narcotic analgesics, and muscle relaxants for acute low back pain.[13] Adding a muscle relaxant to an NSAID regimen does not provide further relief for acute low back pain and is associated with more adverse effects.[13]

Topical NSAIDs are more effective than placebo for treating acute pain (e.g., from strains, sprains, contusions, or overuse injuries) in superficial locations, and the incidence of local and systemic adverse events is similar to placebo.[20] Based on the number needed to treat, topical indomethacin is not as effective as topical diclofenac (Solaraze), ibuprofen, ketoprofen, or piroxicam (not available in the United States), which are similarly effective.[20]

COX-2 Selective NSAIDs. Celecoxib is the only COX-2 selective NSAID still available in the United States, where it is approved for bone or dental pain, dysmenorrhea, headache, osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Meloxicam (Mobic) is sometimes referred to as a COX-2 selective NSAID but is classified as a nonselective NSAID. COX-2 selective NSAIDs are considered second-line medications for mild to moderate pain because they have similar effectiveness to nonselective NSAIDs but with a greater cost.[13] COX-2 selective NSAIDs and traditional NSAIDs are similarly effective for acute low back pain, but COX-2 selective NSAIDs have fewer adverse effects.[13]

NSAID Complications. NSAIDs should be used cautiously in several patient populations. Risk factors for gastrointestinal bleeding and peptic ulcer disease associated with NSAID use include a history of gastrointestinal bleeding, peptic ulcer, older age, smoking or alcohol use, and longer duration of NSAID use. Indomethacin and ketorolac should not be used in older adults because of the increased risk of these

gastrointestinal adverse effects.[21] Concomitant use of NSAIDs and low-dose aspirin is associated with an increased risk of upper gastrointestinal bleeding.[22]

Studies of patients with rheumatoid arthritis or osteoarthritis, who were not taking low-dose aspirin and who did not have risk factors for gastrointestinal bleeding or peptic ulcers, have shown that celecoxib, NSAIDs, and acetaminophen have similar analgesic effects.[23–25] Althoughcelecoxib was associated with fewer gastrointestinal effects, the researchers concluded that this relatively small reduction does not justify the extra cost of celecoxib.[24] Celecoxib alone and an NSAID plus a proton pump inhibitor (e.g., diclofenac plus omeprazole [Prilosec], naproxen plus lansoprazole [Prevacid]) have the same probability of causing recurrent ulcer bleeding or recurrent gastric or duodenal ulcer complications in those at high risk of these complications.[26,27] However, a cost analysis suggests that in patients 75 years or older with a history of gastrointestinal bleeding or peptic ulcers, celecoxib treatment is less expensive than treatment with an NSAID plus misoprostol (Cytotec) or a proton pump inhibitor.[24]

In recent years, the concern about COX-2 selective NSAIDs and, to a lesser extent, nonselective NSAIDs has centered on their cardiovascular adverse effects (i.e., stroke, myocardial infarction, and thrombus formation),[13] and these drugs include an FDA boxed warning regarding these risks. An analysis of six randomized, placebo-controlled trials evaluating the cardiovascular risk associated with celecoxib use showed that the risk increases with dose and that patients with higher baseline cardiovascular risk are more likely to experience a cardiovascular event while taking celecoxib.[28] The cardiovascular risk is also thought to be greater with greater COX-2 selectivity (celecoxib>diclofenac> ibuprofen > naproxen).[29]

Renal insufficiency associated with NSAID use is related to inhibition of renal prostaglandin synthesis, which can present as azotemia and hyperkalemia. Use of NSAIDs in patients with impaired renal function, decreased creatinine clearance, or azotemia can result in acute renal failure.

Additional Pharmacotherapy

OPIOID COMBINATIONS

If nonopioid medications such as acetaminophen or NSAIDs do not adequately control pain, the next step of the WHO pain relief ladder includes considering an opioid, with or without a nonopioid.[5] Opioids such as hydrocodone and oxycodone are typically combined with acetaminophen or an NSAID. In 2010, hydrocodone/acetaminophen was the most commonly dispensed medication in the United States.[30] Opioid combinations are more effective than any one opioid for postoperative pain.[14,15] In a meta-analysis of double-blind randomized controlled trials, patients who received an opioid, such as morphine, with an NSAID had significantly lower pain scores and needed significantly less of the opioid for pain control.[31] Adding codeine, 60 mg, to acetaminophen, 600 to

1,000 mg, resulted in only 10% to 15% more patients achieving at least 50% pain relief compared with the same dose of acetaminophen alone.[15]

The FDA has been concerned about the potential for acetaminophen-induced hepatic injury,[32] and in 2011 requested that manufacturers of prescription products limit the amount of acetaminophen in each dosage unit to no more than 325 mg and to include a boxed warning about the risk of severe hepatic injury.[33] This does not affect over-the-counter products, although patients should not exceed 4,000 mg per day and should be cautioned about using prescription and over-the-counter products containing acetaminophen.

FULL OPIOID AGONISTS

Full opioid agonists, such as morphine, are potent analgesics that may be used if opioids combined with acetaminophen or NSAIDs are insufficient to control moderate to severe pain.[14,15,31] There is a lack of good evidence to suggest any one opioid is more effective or has a better adverse effect profile than morphine.[34] The exception is codeine. There is good evidence that codeine is less effective than morphine and other opioid agonists because of its low affinity for opioid receptors.[35] Some opioids commonly used in the past are now unavailable (e.g., propoxyphene [Darvon]) or no longer widely used (e.g., meperidine [Demerol], pentazocine [Talwin]).

Adverse effects of opioids include nausea, vomiting, constipation, sedation, pruritus, urinary retention, and respiratory depression. Opioid-induced emesis is mediated by histamine release and can be treated with antihistamines or selective serotonin antagonists (e.g., ondansetron [Zofran]), if needed. Opioids rarely cause gastroparesis, which can present as persistent vomiting. If the opioid cannot be discontinued, opioid-induced gastroparesis can be treated with a gastric motility agent, such as metoclopramide (Reglan). However, caution should be used because metoclopramide can cause extrapyramidal adverse effects. There is no good evidence that adverse effects vary among the different opioids given at equianalgesic doses.[36] If the initial opioid does not provide adequate pain relief or the patient experiences intolerable adverse effects, trying an alternative opioid may be reasonable. However, this has not been well studied in acute noncancer pain.[37]

Recent clinical guidelines recommend that the duration of opioid agonist therapy be limited if used to relieve low back pain.[18] Reassessment, other treatment options, or specialist referral should be considered if the patient's pain does not improve.[18]

DUAL-ACTION MEDICATIONS

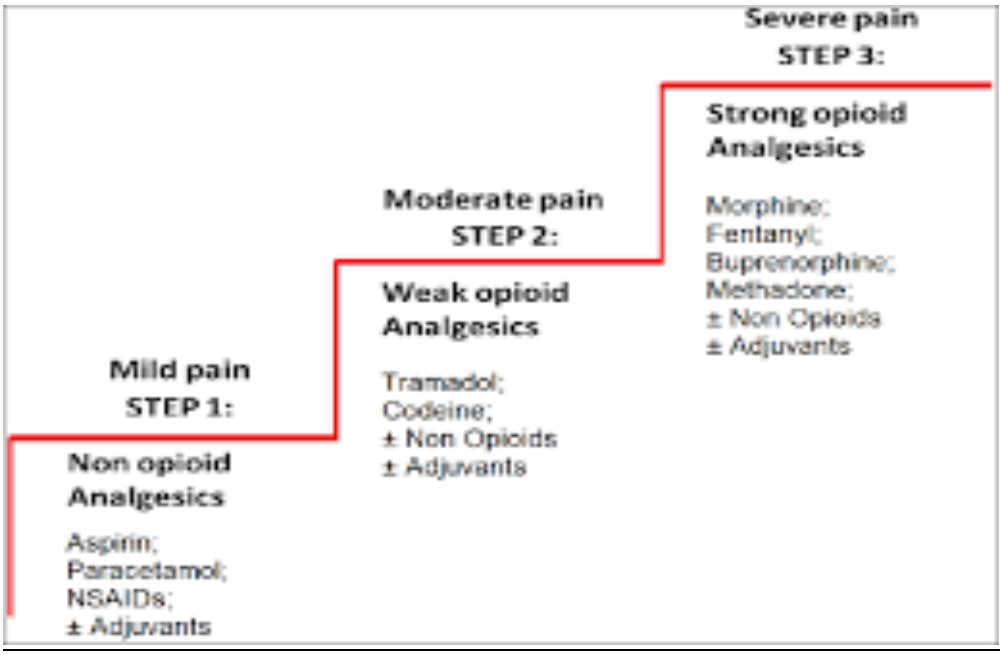
Tapentadol (Nucynta), a Schedule II controlled substance, is a muopioid receptor agonist and norepinephrine reuptake inhibitor that can be used orally for relief of moderate to severe acute pain. It has similar effectiveness as oxycodone for acute pain, with a significantly lower incidence of nausea, vomiting, and constipation.[38] Tapentadol

should be used cautiously with serotonergic medications because of the risk of serotonin syndrome.

Tramadol (Ultram) is not federally controlled but is a Schedule IV controlled substance in some states; its designation is currently being reviewed. It is a weak muopioid receptor agonist and a weak inhibitor of norepinephrine and serotonin reuptake in the central nervous system. It is effective for acute pain (e.g., osteoarthritis) in clinical trials, but the benefits are small and it is considered a second-tier medication.[16,39] Among patients presenting to the emergency department with acute musculoskeletal pain, hydrocodone/acetaminophen, 5 mg/500 mg, provided statistically and clinically significant reductions in pain at all time points compared with tramadol, 100 mg.[39] Tramadol should be used cautiously, if at all, in patients at risk of seizures.

Diversion and Addiction Risks

Opioids should be used cautiously because of the risk of diversion and addiction, even with short-term use. A study showed that in 2010, 2 million persons used prescription pain relievers nonmedically in the prior year; this was second only to marijuana.[40] Among individuals who reported the nonmedical use of a prescription analgesic, 55% obtained the drug from a friend or relative, 79% of whom obtained the prescription from a physician, and another 17% obtained the prescription directly from a physician.[40] Among patients hospitalized for opioid dependence, 51% first started using the drug to treat pain (e.g., after a surgery, dental procedure, or injury).[41] Patients should be counseled to safely dispose of any unused medication.[42]



WHO ladder

Treatment of chronic pain

There are several categories of medications that are used for the treatment of chronic pain. In general, your primary physician, patient management specialist, or pharmacist may be to answer any questions about the dosage and side effects from these medications. The most commonly used medications can be divided into the following broad categories:

1. **Nonsteroidal Anti-inflammatory Drugs and Acetaminophen**: There are many different types of nonsteroidal anti-inflammatory medications (NSAIDs), some of them (such as ibuprofen) may be obtained over-the-counter. NSAIDs can be very effective for acute muscular and bone pain as well as some types of chronic pain syndromes. When taken for an extended period of time or in large quantities, they may have negative effects on the kidneys, clotting of blood, and gastrointestinal system. Bleeding ulcers is a risk of these medications. Long-term use of cyclooxygenase II (COX II) inhibitors may be associated with an increase in cardiovascular (heart) risks. Acetaminophen is easily obtained over-the-counter, however, care should be taken not to take more than 4000 mg in 24 hours; otherwise, several liver failure may occur. There are some opioid medications that combine acetaminophen within the medication. You should be aware that many over-the-counter medications have acetaminophen as one of their ingredients and when taken in combination with prescribed medication, this may result in an overdose of acetaminophen.
2. **Antidepresssants**: Some of the older categories of antidepressants may be very helpful in controlling pain; specifically the tricyclic antidepressants. The pain relieving properties of these medications are such that they can relieve pain in doses that are lower than the doses needed to treat depression. These medications are not meant to be taken on an "as needed" basis but must be taken every day whether or not you have pain. Your physician may

attempt to lessen some of the side effects, particularly sedation, by having you take these medications at night. There are some other side effects like dry mouth that can be treated with drinking water or fluids. These medications may not be given to patients with certain types of glaucoma. In addition, these medications should never be taken in larger doses than are prescribed.

3. **Anticonvulsants (Anti-seizure) Medications**: These medications can be very helpful for some kinds of nerve type pain (such as burning, shooting pain). These medications also are not meant to be taken on an "as needed" basis. They should be taken every day whether or not you feel pain. Some of them may have the side effect of drowsiness which often improves with time. Some have the side effect of weight gain. If you have kidney stones or glaucoma, be sure to tell your doctor as there are some anticonvulsants that are not recommended to be given under those conditions. The newer anticonvulsants do not need liver monitoring but required caution if given to patients with kidney disease.
4. **Muscle Relaxants**: These medications are most often used in the acute setting of muscle spasm. The most common side effect seen with these medications is drowsiness.
5. **Opioids**: When used appropriately, opioids may be very effective in controlling certain types of chronic pain. They tend to be less effective or require higher doses in nerve type pain. For pain is present all day and night, a long acting opioid is usually recommended. One of the most frequent side effects is constipation, which if mild may be treated by drinking lots of liquids, but may need to be treated with medications. Drowsiness is another side effect which often gets better over time as you get used to the medication. Excessive drowsiness should be discussed with your physician. Nausea is another side effect which may be difficult to treat and may require changing to another opioid.

Opioids play a unique role in society. They are widely feared compounds, which are associated with abuse, addiction and the dire consequences of diversion; they are also essential medications, the most effective drugs for the relief of pain and suffering (Portenoy et al, 2004). Historically, concerns about addiction have apparently contributed to the undertreatment of disorders widely considered to be appropriate for opioid therapy, including cancer pain, pain at the end-of-life, and acute pain (Field and Cassel, 1997; Schnoll& Weaver, 2003; Portenoy& Lesage, 1999; Breitbart et al. 1998; Smith et al., 2008). The use of opioids for chronic non-malignant pain (CNMP) remains controversial (Manchikanti, 2008; McQuay, 1999). Following publication of reports on the safety and efficacy of opioids prescribed to small numbers of patients with CNMP (e.g., Portenoy and Foley, 1986; Nyswander and Dole, 1986) and the publication of a seminal article entitled “The Tragedy of Needless Pain”, (Melzack, 1990), the use of opioids to treat CNMP began to be more widely practiced and incorporated into clinical guidelines. Nevertheless, despite the advances in pain medicine and the wider use of opioids for various chronic pain conditions, there is still

considerable controversy surrounding the type of conditions that should be treated, whether the treatment can be generally safe and effective in selected patients, and what the clinical goals should be (Ballantyne& Forge, 2007; Streltzer& Johansen, 2006; Stretzler&Kosten 2003).

Go to:

History of Opioids

The Sumerians in Mesopotamia were among the first people identified to have cultivated the poppy plant around 3400 BC. They named it *Hul Gil*, the “joy plant” (Booth, 1986). It eventually spread throughout the ancient world to every major civilization in Europe and Asia and was used to treat pain and many other ailments (Schiff, 2002; Askitopoulou, Ramoutsaki, &Konsolaki, 2002; Booth, 1986; Dikotter, Laaman, &Xun, 2004).

Developments in the 19th century transformed the practice of medicine and initiated the tension between the desire to make available the medicinal benefits of these drugs and recognition that the development of abuse and addiction can lead to devastating consequences for individuals and for society at large (Booth, 1986; Musto, 1999):

- In 1803 morphine, an opioid analgesic, was extracted from opium by Friedrich Serturner of Germany;
- Dr. Charles Wood, a Scottish physician, invented the hyperdermic needle and used it to inject morphine to relieve pain from neuralgia;
- Dr. Eduard Livenstein, a German physician, produced the first accurate and comprehensive description of addiction to morphine, including the withdrawal syndrome and relapse, and argued that craving for morphine was a physiological response.
- Diacetylmorphine (brand name heroin) was synthesized and briefly promoted as more effective and less addictive than morphine. In the early 20th century, when heroin was legally marketed in pill form, it was used by young Americans to elicit

intense euphoria by crushing the heroin pills into powder for inhalation or injection (Katz et al., 2007, c.f. Meldrum, 2003; Hosztafi, 2001).

Beginning in the twentieth century, there were many research advances and major changes in the way opioids were used for the treatment of pain and addiction (Ballantyne, 2006; Corbett et al., 2006). These included attempts among several nations and international organizations to control the distribution and use of opioids (Musto, 1999); the introduction of opioid maintenance therapy for the treatment of opioid addiction (first with morphine and later with methadone, LAAM (levo-alpha acetyl methadol) and sublingual buprenorphine) (Courtwright, Joseph & Des Jarlais, 1989; Strain &Stitzer, 2006); the discovery of the endogenous opioids (Hughes, Smith, Kosterlitz, Fothergill, Morgan & Morris, 1975); and the recognition that pain is a debilitating and destructive disease and that opioids are essential for the treatment of many forms of acute and chronic pain.

During most of the twentieth century, the widely held perception among professionals in the United States was that the long-term use of opioid therapy to treat chronic pain was contraindicated by the risk of addiction, increased disability and lack of efficacy over time. During the 1990's, a major change occurred, driven by a variety of medical and nonmedical factors (see below). The use of opioids for chronic pain began to increase, showing a substantial year-to-year rise that continues today. This increased use of opioids for legitimate medical purposes has been accompanied by a substantial increase in the prevalence of nonmedical use of prescription opioids (Zacny, et al., 2003). The National Survey on Drug Use and Health reported that the number of first time abusers of prescription opioids increased from 628,000 in 1990 to 2.4 million in 2004, that emergency room visits involving prescription opioid abuse increased by 45% from 2000 to 2002, and that treatment admissions for primary abuse of prescription opioids increased by 186% between 1997 and 2002 (SAMHSA, 2004a, 2004b). Opioid abuse indices rose most for two frequently prescribed opioids, hydrocodone and controlled-release (CR) oxycodone (Cicero, Inciardi, Munoz, 2005). Although the increase in prescription drug abuse is likely to be multifactorial, it is likely to reflect, in part, changes in available drug formulations and prescribing practices of opioid

medication (Compton and Volkow, 2006). This link between increased medical use and increased abuse has driven some of the re-examination of the medical role of these drugs. The challenge, of course, is to reduce the likelihood of opioid misuse while not imposing barriers on the legitimate use of opioid medications, acknowledging both that increased abuse is probably inevitable when a psychoactive drug becomes more accessible and that attempts to control abuse can have the unintentional effects of discouraging treatment and placing severe restrictions on the medical profession.

Go to:

Brief Overview of Opioids: Neurobiology and Mechanism of Action

The term *opioid* refers to all compounds that bind to opiate receptors. Conventionally, the term *opiate* can be used to describe those opioids that are alkaloids, derived from the opium poppy; these include morphine and codeine. Opioids include semi-synthetic opiates, i.e., drugs that are synthesized from naturally occurring opiates (such as heroin from morphine and oxycodone from thebaine), as well as synthetic opioids such as methadone, fentanyl, and propoxyphene. The term *narcotic* is a legal designation and should not be used in the clinical setting; it refers to opioids and a few other drugs that are grouped with the opioids by law enforcement.

In the United States, numerous opioids have been commercialized for oral, transdermal and intravenous administration. Oral and transdermal formulations are usually administered for pain in the ambulatory setting. These include combination products, such as those containing hydrocodone and acetaminophen (Vicodin®, Lorset®) or ibuprofen (Vicoprofen®), tramadol and acetaminophen (Ultracet®), oxycodone and acetaminophen or aspirin (Percocet® or Percodan®), and those containing codeine and acetaminophen or aspirin. The single entity formulations on the market include those containing morphine (Avinza®, Kadian®, MS Contin®, MSIR®), oxycodone (OxyContin®), fentanyl (Duragesic®, Actiq®, Fentora®), hydromorphone (Dilaudid®), oxymorphone (Opana®), and methadone.

Opioids act by binding to specific proteins, called opioid receptors. Receptors are widely distributed. Those involved in pain modulation are situated in both the central nervous

system and the peripheral nervous system. These receptors also bind endogenous opioid peptides (endorphins), which are involved in pain modulation and numerous other functions in the body. Among these functions are those mediated by deep structures of the brain, which are involved in the modulation of reinforcement and reward mechanisms, mood and stress. Opioid receptors are also found on cells from the immune system (Bidlack, 2000). In studies with rats, activation of these receptors with morphine is associated with varied effects, including sensitization of afferent nerves to noxious stimuli (Raghavendra, Rutkowski, &DeLeo, 2002).

When an opioid given for pain binds to receptors, analgesia may be accompanied by any of a diverse array of side effects related to the activation of receptors involved in other functions. These may include effects mediated by peripheral or by peripheral and central mechanisms, such as reduced peristalsis (leading to constipation) and itch, or primary central nervous system effects, such as miosis, (pupillary constriction) somnolence, mental clouding, and respiratory depression (Jaffe & Jaffe, 2004; Jaffe & Martin, 1990). Central mechanisms also lead to changes associated with hyperalgesia and decreased responsiveness to opioids (tolerance) and it has been speculated that opioid-induced hyperalgesiamay be a clinically-relevant phenomenon leading to increased pain in some situations (Deleo, Tanga, &Tawfik, 2004). Activation of other central nervous system pathways by opioids also may produce mood effects, either dysphoria or euphoria.

Presumably, binding to those receptors involved in reinforcement and reward also occurs whenever an opioid is taken. In most individuals, when opioids are taken to treat pain, there appears to be no overt effect from change in these systems. In some cases, however, powerful reinforcement occurs, expressed as efforts to repeat the administration and these reinforcing outcomes may be associated with craving and with positive mood effects such as euphorigenic or pleasurable effects (Di Chiara, 2002; Koob& Bloom, 1988). These outcomes, which are uncommon but potentially serious when they occur (driving the development of an addictive pattern of use), can occur in the presence or absence of pain. Although these effects could be associated with iatrogenic addiction, they appear to be rare in patients who do not have risk factors

suggesting the existence of the biological substrate for opioid-induced craving (see below).

Although several types of opioid receptors exist (e.g., mu, kappa and delta), opioid drugs largely produce their analgesic and reinforcing effects via activation of the mu opioid receptor; thus, opioids used for pain are often described as, “mu agonists”. Mu drugs that have the ability to fully activate opioid receptors (e.g., higher doses produce greater receptor activation in a dose-dependent manner) are referred to as opioid agonists or full mu agonists (such as morphine, oxycodone and methadone). Those opioids that occupy, but do not activate, receptors are referred to as opioid antagonists (e.g., naltrexone, naloxone); they can reverse the effects of mu opioid agonists. Those opioids that either have a low intrinsic activity at the mu receptor, or are agonists at another receptor and antagonists at the mu receptor are called agonist-antagonist drugs. Those with a low intrinsic activity are called partial opioid agonists and are characterized by a ceiling on most agonist activity, such that increases in dose will increase the drug’s physiological and subjective effects only to a certain level and further dose increases produce no additional effects (Jaffe & Martin, 1990).

These differences in mu receptor interactions are clearly related to the clinical use of opioid drugs and their abuse liability. Agonist-antagonist drugs are less attractive than pure mu agonists to individuals with addiction and no pain. Although other biochemical and molecular processes are presumably relevant to variation in these effects, relatively little is known about the interactions among these processes in humans.

The clinical use of opioid drugs is influenced by a variety of other characteristics, including pharmacokinetics. With the notable exception of methadone and buprenorphine, most opioids have relatively short half-lives and this has necessitated the development of new delivery systems designed to provide prolonged effects and a longer dosing interval.

Clinically-relevant physical dependence and tolerance (see below) may occur with short-term or long-term use of an opioid compound, particularly a pure mu agonist. These phenomena, which vary greatly in the clinical setting, represent neuroadaptational processes. The neurophysiology of physical dependence and

tolerance are closely related to each other and to the phenomenon of opioid-induced hyperalgesia (Mao, 2002). The possibility that opioid administration, particularly at relatively high doses, may lead to increased pain has contributed to the controversy about opioid therapy for non-cancer pain, notwithstanding the limited evidence that this phenomenon occurs in clinical settings.

Go to:

Brief Overview of Chronic Pain

Chronic pain has been described as pain that has persisted for at least 1 month following the usual healing time of an acute injury, pain that occurs in association with a nonhealing lesion, or pain that recurs frequently over a period of months. In most clinical and research reports, chronic pain is typically defined as pain that has persisted for at least 3 months (Verhaak, Kerssens, Dekker, Sorbi, & Sensing, 1998).

The prevalence of chronic pain in the general population is believed to be quite high, although published reports have varied greatly. Cautious cross-national estimates of chronic pain range from 10% (Verhaak et al., 1998) to close to 20% (Gureje, Simon, & Von Korff, 2001), which would represent 30 to 60 million Americans. A national survey of 35,000 households in the US, conducted in 1998, estimated that the prevalence among adults of moderate to severe non-cancer chronic pain was 9% (American Pain Society, 1999). A large survey (N=18,980) of general populations across several European countries reported that the prevalence for chronic painful physical conditions was 17.1% (Ohayon&Schatzberg, 2003).

Chronic pain is a highly complex phenomenon, which may or may not be primarily driven by tissue injury. Conventionally, the most common forms of chronic pain are divided into those labeled “nociceptive”, or pain caused by ongoing stimulation of pain receptors by tissue damage, and those labeled “neuropathic”, or pain presumed to be related to damage to or dysfunction of the peripheral or central nervous system. These categories of pain simplify a complex reality in which both acute and chronic pain are induced by multiple peripheral and central mechanisms, which continually interact with each other and with numerous pain modulating systems. The perturbations that

ultimately results in pain perception are caused by neurophysiological processes and other related systems. For example, recent evidence has begun to highlight the role of neuroimmune activation following a tissue injury as an important mechanism in the development of chronic pain (DeLeo, 2006). The role of cytokines and other inflammatory mediators is obvious in inflammatory nociceptive pains, such as some types of arthritis, but new data suggest an equally salient role in the development of chronic neuropathic pain associated with central sensitization of neural pathways following peripheral injury (Deleo, 2006).

All chronic pain is profoundly influenced by psychological processing and responses (Turk &Melzack, 2001). Pain severity and pain-related functional impairment are often found to be associated with psychological and social factors, and patients with identical diseases associated with pain, such as degenerative disk disease, may vary greatly in their reports of pain severity and pain behaviors (Aronoff, 1999). There is an extensive literature documenting the importance of operant conditioning factors (Fordyce, 1976) and cognitive-behavioral factors (Turk, Meichenbaum, &Genest, 1983) in the maintenance of chronic pain behaviors.

Chronic pain also is influenced by psychosocial and psychiatric disturbances, such as cultural influences, social support, comorbid mood disorder, and drug abuse (Gatchel, Peng, Peters, Fuchs & Turk, 2007). Classic studies of pain behavior indicate that cultural differences in the beliefs and attitudes towards pain (e.g., Zbrowski, 1969) and the social/environmental context of the pain (e.g., Beecher, 1959) have a significant impact on pain behaviors.

The contribution of psychological, social and psychiatric factors should not lead to the conclusion that a pain syndrome is primarily psychogenic. Pain related exclusively or primarily to psychological factors occurs, but is far less prevalent than pain associated with organic processes that are powerfully influenced by psychosocial mediators and psychiatric comorbidities (Portenoy, Payne, &Passik, 2004).

The “pattern of suffering” or the pain-related disability that often occurs in concert with persistent pain commonly touches on all domains of function. Patients with chronic pain may demonstrate pain-related interference with ability to perform usual activities at

home, work, or school; maladaptive or dysfunctional behaviors, social isolation, and poor sleep patterns; and frequent health care utilization (Dworkin& Sherman, 2001). The recognition that acute pain can compromises health has led major medical associations and accreditation committees to designate pain severity as a “fifth vital sign”, along with blood pressure, temperature, heart rate, and respiration (Fishman, 2005). Further recognition of the increased interest in the assessment and management of pain is underscored by the U.S. Federal Law (Pain Relief Promotion Act of 2000) that declared the first decade of the 21st century as the Decade of Pain Control and Research (Gatchel et al., 2007).

Chronic pain is a major public health problem, which is associated with devastating consequences to patients and families, a high rate of health care utilization, and huge society costs related to lost work productivity. The existing treatments for chronic pain are unable to address the problem and better therapies are urgently needed. The need for these therapies is the backdrop for the expanding use of opioid drugs. An extensive clinical experience indicates that long-term opioid therapy is able to help selected patients have a better quality of life, less use of health care, and improved productivity. The medical community is no longer debating the reality of these outcomes, but rather, is now focused on a more fruitful debate about patient selection and the benefits and burdens of these drugs in varied subpopulations. Whether the frame of reference is the individual patient and family, or society-at-large, the issue is about balancing the potential benefits of these drugs in the large and diverse population with chronic pain with its potential risks.

Go to:

Terminology of Opioid Abuse: Dependence, Tolerance, Addiction

Concerns that addiction is a frequent iatrogenic consequence of the medical use of opioids may partially be attributed to confusion over terminology, as a well as failure to recognize that both addiction and chronic pain have a multifactorial etiology. In an effort to develop universal agreement on terminology related to addiction, the American Academy of Pain Medicine (AAPM), the American Pain Society (APS), and the

American Society of Addiction Medicine (ASAM) approved a consensus document that clarified this terminology (ASAM, 2001; Savage, 2003).

According to the consensus document, *tolerance* is defined as a decreased subjective and objective effect of the same amount of opioids used over time, which concomitantly requires an increasing amount of the drug to achieve the same effect. Although tolerance to most of the side effects of opioids (e.g., respiratory depression, sedation, nausea) does appear to occur routinely, there is less evidence for clinically significant tolerance to opioids– analgesic effects (Collett, 1998; Portenoy et al., 2004). For example, there are numerous studies that have demonstrated stable opioid dosing for the treatment of chronic pain (e.g., Breitbart, et al., 1998; Portenoy et al., 2007) and methadone maintenance for the treatment of opioid dependence (addiction) for extended periods (Strain and Stitzer, 2006). However, despite the observation that tolerance to the analgesic effects of opioid drugs may be an uncommon primary cause of declining analgesic effects in the clinical setting, there are reports (based on experimental studies) that some patients will experience worsening of their pain in the face of dose escalation (Ballantyne, 2006). It has been speculated that some of these patients are not experiencing more pain because of changes related to nociception (e.g. progression of a tissue-injuring process), but rather, may be manifesting an increase in pain as a result of the opioid-induced neurophysiological changes associated with central sensitization of neurons that have been demonstrated in preclinical models and designated opioid-induced hyperalgesia (Mao, 2002; Angst & Clark, 2006). Analgesic tolerance and opioid-induced hyperalgesia are related phenomena, and just as the clinical impact of tolerance remains uncertain in most situations, the extent to which opioid-induced hyperalgesia is the cause of refractory or progressive pain remains to be more fully investigated. *Physical dependence* represents a characteristic set of signs and symptoms (opioid withdrawal) that occur with the abrupt cessation of an opioid (or rapid dose reduction and/or administration of an opioid antagonist). Physical dependence symptoms typically abate when an opioid is tapered under medical supervision. Unlike tolerance and physical dependence which appear to be predictable time-limited drug effects, *addiction* is a chronic disease that “represents an idiosyncratic

adverse reaction in biologically and psychosocially vulnerable individuals" (ASAM, 2001).

The distinction between physical dependence and addiction is not always made clear in the pain literature (Ferrell, McCaffery, Rhiner, 1992). Most patients who are administered opioids for chronic pain behave differently from patients who abuse opioids and do not ever demonstrate behaviors consistent with craving, loss of control or compulsive use (e.g., Cowan et al., 2001). Of course, pain and addiction are not mutually exclusive and some patients who are treated for pain do develop severe behavioral disturbances indicative of a comorbid addictive disorder.

Some patients who are treated with opioids for pain display problematic behaviors that, on careful assessment, do not reflect addiction, but rather, appear to relate to a different process. This may be another psychiatric disorder associated with impulsive drug-taking, an unresolved family issue, a disorder of cognition, or criminal intention. In addition, there appear to be some patients who engage in problematic behaviors related specifically to desperation about unrelieved pain. The term *pseudoaddiction* was coined to describe the latter phenomenon (Weissman&Haddox, 1989).

Behaviors that may represent pseudoaddiction and behaviors that reflect addiction or some other serious psychopathology can occur simultaneously, and presumably, one type of phenomenon may incite the others. The diagnosis of these and other conditions may be challenging and requires a careful assessment of clinical phenomenology, specifically a range of drug-related behaviors during treatment with a potentially abusable drug (Portenoy, 1994, Lue, Passik, &Portenoy, 1998).

The term *aberrant drug-related behaviors* has been used to indicate the broad array of problematic nonadherencebehaviors (Passik, Kirsh, Donaghy, &Portenoy, 2006), the nature of which is uncertain until a diagnosis can be developed based on astute clinical assessment. Some aberrant drug-related behavior strongly suggests the existence of addiction. These may include the use of alternative routes of administration of oral formulations (e.g., injection or sniffing), concurrent use of alcohol or illicit drugs, and repeated resistance to changes in therapy despite evidence of adverse effects; examples of aberrant behavior less suggestive of addiction are drug hoarding during

periods of reduced symptoms, occasional unsanctioned dose escalation, and aggressive complaining about the need for more drugs (Portenoy, 1994).

Go to:

Distinction between Withdrawal and Chronic Pain

Because addiction is associated with psychological distress and physical discomfort in the form of opioid withdrawal symptoms, it may be difficult to distinguish primary chronic pain complaints from withdrawal pain. Withdrawal also may have the potential to increase baseline pain related to other processes. For example, based on anecdotal evidence from chronic pain patients, withdrawal from opioids can greatly increase pain in the original pain site. These phenomena suggest the need to carefully assess the potential for withdrawal during long-term opioid therapy (e.g, at the end of a dosing interval or during periods of medically-indicated dose reduction).

These phenomena notwithstanding, there also is evidence that experienced drug abusers are able to distinguish withdrawal pain from chronic pain. For example in studies of methadone maintenance patients, both the phenomenology and correlates of chronic pain were different than for withdrawal pain (Karasz et al., 2004; Rosenblum et al., 2003). Chronic pain is typically localized (e.g., back pain, headache) and persists (although with varying degrees of severity) for long periods of time (Gureje, Von Korff, Simon &Gater, 1998). Although certain subjective experiences of withdrawal (e.g., muscle ache) are similar to some distinct pain syndromes, other withdrawal experiences such as yawning, sweating and hot and cold flashes are likely to be more commonly associated with subjective drug withdrawal than with primary pain conditions. Moreover, the constellation of words used to describe withdrawal pain is likely to be different than words used to describe other painful disorders. Qualitative studies of addicts going through withdrawal typically refer to the experience as “being sick” (similar to a moderate to severe flu-like illness) and not as representing a distinct pain (Farrell, 1994). The subjective experience of withdrawal can be validly measured with an instrument such as the Subjective Opiate Withdrawal Scale (SOWS; Handelsman, et al., 1987). Withdrawal from short-acting opioids, such as heroin, is typically short-lived;

physical symptoms are likely to reach their maximum intensity over a 36–72 hour period and to reduce in intensity after that (Farrell, 1994).

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Co-occuring Chronic Pain and Opioid Addiction

The prevalence of addictive disorders among chronic pain patients is difficult to determine (Covington and Kotz 2003). One 1992 literature review found only seven studies that utilized acceptable diagnostic criteria and reported that estimates of substance use disorders among chronic pain patients ranged from 3.2% – 18.9% (Fishbain, Rosomoff, &Rosomoff, 1992). A Swedish study of 414 chronic pain patients reported that 32.8% were diagnosed with a substance use disorder (Hoffmann, Olofsson, Salen, &Wickstrom, 1995). In two US studies, 43 to 45% of chronic pain patients reported aberrant drug-related behavior; the proportion with diagnosable substance use disorder is unknown (Katz et al., 2003; Passik et al., 2004). All these studies evaluated patients referred to pain clinics and may overstate the prevalence of substance abuse in the overall population with chronic pain.

A relatively high prevalence of substance abuse disorders among persons with chronic pain can also be inferred by the high co-occurrence of these two disorders. There have been several reports that the prevalence of chronic pain among persons with opioid and other substance use disorders is substantially higher than the pain prevalence found in the general population (Breitbart, et al., 1996; Brennan, Schutte, & Moos, 2005; Jamison, Kauffman, & Katz, 2000; Rosenblum et al., 2003; Sheu, et al., 2008).

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Opioid Treatment for Chronic Pain

Opioid therapy is the mainstay approach for the treatment of moderate to severe pain associated with cancer or other serious medical illnesses (Patt& Burton, 1998; World Health Organization, 1996). Although the use of opioid analgesics for the treatment of CNMP has been increasing in recent years (Joranson, Ryan, Gilson & Dahl, 2000) and has been endorsed by numerous professional societies (AAPM, APS, 1997; American

Geriatric Society, 1998; Pain Society, 2004), the use of opioids remains controversial due to concerns about side effects, long-term efficacy, functional outcomes, and the potential for drug abuse and addiction. The latter concerns are especially evident in the treatment of CNMP patients with substance use histories (Savage, 2003).

Other concerns that may contribute to the hesitancy to prescribe opioids may be related to perceived and real risks associated with regulatory and legal scrutiny during the prescribing of controlled substances (Office of Quality Performance, 2003). These concerns have propelled extensive work to develop predictors of problematic behaviors or frank substance abuse or addiction during opioid therapy. Questionnaires to assist in this prediction and monitoring have been developed and used in research and field trials. Examples include the Prescription Drug Use Questionnaire (PDUQ; Compton et al., 1998); the Pain Assessment and Documentation Tool (PADT; Passik et al., 2004) and the Current Opioid Misuse Measure (COMM; Butler et al., 2007). These instruments are not used in practice settings at this time.

Narrative reports on the use of opioids for CNMP have underscored the effectiveness of opioid therapy for selected populations of patients and there continues to be a consensus among pain specialists that some patients with CNMP can benefit greatly from long-term therapy (Ballantyne& Mao, 2003; Trescot et al., 2006). This consensus, however, has received little support in the literature. Systematic reviews on the use of opioids for diverse CNMP disorders report only modest evidence for the efficacy of this treatment (Trescot et al., 2006; 2008). For example, a review of 15 double-blind, randomized placebo-controlled trials reported a mean decrease in pain intensity of approximately 30% and a drop-out rate of 56% only three of eight studies that assessed functional disturbance found improvement (Kalso, Edwards, Moore, &McQuay, 2004). A meta-analysis of 41 randomized trials involving 6,019 patients found reductions in pain severity and improvement in functional outcomes when opioids were compared with placebo (Furlan, Sandoval, Mailis-Gagnon, &Tunks, 2006). Among the 8 studies that compared opioids with non-opioid pain medication, the six studies that included so-called “weak” opioids (e.g., codeine, tramadol) did not demonstrate efficacy, while the two that included the so-called “strong” opioids (morphine, oxycodone) were associated

with significant decreases in pain severity. The standardized mean difference (SMD) between opioid and comparison groups, although statistically significant, tended to be stronger when opioids were compared with placebo (SMD = 0.60) than when strong opioids where compared with non-opioid pain medications (SMD = 0.31). Other reviews have also found favorable evidence that opioid treatment for CNMP leads to reductions in pain severity, although evidence for increase in function is absent or less robust (Chou, Clark, &Helfand, 2003; Eisenberg, McNicol, & Carr, 2005). Little or no support for the efficacy of opioid treatment was reported in two systematic reviews of chronic back pain (Deshpande, Furlan, Mailis-Gagnon, Atlas, & Turk, 2007; Martell, et al., 2007). Because patients with a history of substance abuse typically are excluded from these studies, they provide no guidance whatsoever about the effectiveness of opioids in these populations.

Adding further to the controversy over the utility of opioid analgesics for CNMP is the absence of epidemiological evidence that an increase in the medical use of opioids has resulted in a lower prevalence of chronic pain. Noteworthy is a Danish study of a national random sample of 10,066 respondents (Eriksen, Sjøgren, Bruera, Ekholm, & Rasmussen, 2006). Denmark is known for having an extremely high national usage of opioids for CNMP and this use has increased by more than 600% during the past two decades (Eriksen, 2004). Among respondents reporting pain (1,906), 90% of opioid users reported moderate to very severe pain, compared with 46% of non-opioid users; opioid use was also associated with poor quality of life and functional disturbance (e.g., unemployment).

Although this epidemiological study may be interpreted as demonstrating that opioid treatment for CNMP has little benefit, the authors acknowledge that these disquieting findings do not indicate causality and could be influenced by the possibility of widespread undertreatment, leading to poorly managed pain. This latter interpretation is supported by a commentary on the Ericksen et al. study (Keane, 2007). Keane notes that among the 228 pain patients receiving opioids only 57 (25%) were using strong opioids, while the remainder was using weak opioids. European (as well as United States) clinical guidelines generally recommend long-acting formulations of strong

opioids for the treatment of chronic moderate to severe pain, which may be supplemented with short-acting opioids for breakthrough pain (Pain Society, 2004; OQP, 2003; Gourlay, 1998; Vallerand, 2003; Fine &Portenoy, 2007).

The possibility of inappropriate opioid treatment is further supported by another Danish study that assigned pain patients who were on opioid therapy to either a multidisciplinary pain center (MPC) or to general practitioners (GP) who had received initial supervision from the MPC staff (Eriksen, Becker, &Sjegren, 2002). At intake, a substantial number of patients in both groups were apparently receiving inappropriate opioid therapy for chronic pain (60% were being treated with short-acting opioids and 49% were taking opioids on demand). At the 12 month follow-up, 86% of MPC patients were receiving long-acting opioids and 11% took opioids on demand. There was no change in the administration pattern in the GP group. These findings suggest that a significant proportion of opioid-treated CNMP patients may be receiving inappropriate opioid treatment and that educating general practitioners in pain medicine may require more than initial supervision.

It is generally acknowledged that there is a wide degree of variance in the prescribing patterns of opioids for chronic pain (Lin, Alfandre, & Moore, 2007; Trescot et al., 2006). Some opioid treatment practices persist despite evidence that they might be harmful or have little benefit, such as the over-prescribing of propoxyphene among the elderly (Barkin, Barkin, &Barkin, 2006; Singh, Sleeper, & Seifert, 2007). Nursing home patients being treated with opioids have been found to be inadequately assessed for pain and to be more likely treated with short-acting rather than long acting opioids (Fujimoto &Coluzzi, 2000). A substantial number of physicians are reluctant or unwilling to prescribe long-acting opioids to treat CNMP, even when it may be medically appropriate (Nwokeji, et al., 2007).

Controversy about the long-term effectiveness of opioid treatment also has focused on the potential clinical implications of opioid-induced hyperalgesia. As noted earlier, exposure to opioids can result in an increased sensitivity to noxious stimuli in animals, and an increased perception of some types of experimental pain in humans (c.f., Koppert&Schmeltz, 2007; Angst & Clark, 2006). Anecdotal reports of hyperalgesia

occurring with very high or escalating doses of opioids (Angst & Clark, 2006) has been viewed as a clinical correlate of these experimental findings. The extent to which this phenomenon is relevant to the long-term opioid therapy administered to most patients with chronic pain is unknown. Although experimental evidence suggests that opioid-induced hyperalgesia might limit the clinical utility of opioids in controlling chronic pain (Chu, Clark, &Angst., 2006), there have been no reports of observations in the clinical literature to suggest that it should be a prominent problem. More research is needed to determine whether the physiology underlying opioid-induced hyperalgesia may be involved in a subgroup of patients who develop problems during therapy, such as loss of efficacy (tolerance) or progressive pain in the absence of a well defined lesion.

Outcome studies of long term use of opioids are compromised by methodological limitations which make it difficult to acquire evidence of efficacy (Noble, Tregear, Treadwell, &Schoelles, 2007). Methodological limitations may be unavoidable because of the ethical and practical challenges associated rigorous studies such as randomized controlled trials. Guidelines for opioid therapy must now be based on limited evidence; future evidence may be acquired by utilizing other study designs (Noble et al., 2007) such as practical clinical trials (Tunis, Stryer, & Clancy, 2003). These studies should include at least three criteria to reflect a positive treatment response: i.e., reduction of pain severity (derived from subjective reports or scores on pain scales), recovery of function (improved scores on instruments that measure some aspect of function), and quality of life.

Guidelines for the use of opioids for the treatment of chronic pain have been published (AAFP et al., 1996–2002; OQP, 2003), and recent guidelines have emphasized the need to initiate, structure and monitor therapy in a manner that both optimizes the positive outcomes of opioid therapy (analgesia and functional restoration) and minimize the risks associated with abuse, addiction and diversion (Portenoy et al., 2004). These guidelines discuss patient selection (highlighting the likelihood of increased risk among patients with prior histories of substance use disorders), the structuring of therapy to provide an appropriate level of monitoring and a presumably lessened risk of aberrant drug-related behavior, the ongoing assessment of drug-related behaviors and the need

to reassess and diagnose should these occur, and strategies that might be employed in restructuring therapy should aberrant behaviors occur and the clinician decide to continue treatment. They also note that therapy should be undertaken initially as a trial, which could lead to the decision to forego more therapy, and that an “exit strategy” must be understood to exist should the benefits in the individual be outweighed by the burdens of treatment.

The relatively recent recognition that guidelines for the opioid treatment of chronic pain must incorporate both the principles of prescribing as well as approaches to risk assessment and management may represent an important turning point for this approach to pain management. Acknowledging that prescription drug abuse has increased during the past decade, a period during which the use of opioid therapy by primary care physicians and pain specialists has accelerated, pain specialists and addiction medicine specialists now must collaborate to refine guidelines, help physicians identify the subpopulations that can be managed by primary care providers, and discover safer strategies that may yield treatment opportunities to larger numbers of patients.

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Treating Patients with Addictive Disorders

Safe and effective pain treatment is especially important for persons with a drug use history because inadequate treatment or lack of treatment for pain may have problematic consequences, such as illicit drug use (e.g., heroin), misuse of prescription opioids and other pain medications (e.g., benzodiazipines), psychiatric distress, functional impairment and a tendency for health providers to attribute pain complaints and requests for pain medication to an addictive disorder rather than to a pain disorder (Gureje, et al., 2001; Scimeca, Savage, Portenoy, &Lowinson, 2000). Undertreatment of pain among addicted persons may lead to the adverse medical, social and personal consequences associated with continued drug-seeking behavior (Savage, 1996). Pain complaints may be most problematic among persons with opioid addiction, as this group may have lower tolerance for pain than other addicted populations (Compton,

1994; Compton, Charuvastra, & Ling, 2001). Pain and opioid addiction may be further intertwined among persons who have a history of abusing controlled opioid pain medications, such as oxycodone or hydrocodone.

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A Possible Role on the use of Buprenorphine for the Treatment of Chronic Pain

Increasing interest in developing clinical protocols for opioid treatment of chronic pain in the population with substance abuse histories has highlighted the role of opioid medications that may have lower abuse potential. One medication that is beginning to be examined is buprenorphine, a partial opioid mu agonist that is well recognized as an analgesic (Johnson, Fudala, & Payne, 2005). In 2002, a sublingual tablet (both in mono form – Subutex® - and combined with naloxone - Suboxone®) was approved by the U.S Food and Drug Administration as a Schedule III medication for the treatment of opioid dependence. In numerous controlled clinical trials, it has been demonstrated to be highly efficacious in reducing illicit opioid use and promoting treatment retention among opioid abusers (e.g., Johnson, Strain, & Amass, 2003; Kakko, Svanborg, Kreek, Heilig, 2003; O'Connor et al., 1998; Fudala et al., 2003). In opioid addicts, it suppresses the craving and withdrawal symptoms associated with opioid use and also blocks the euphoric effects of subsequent opioid use (See Bickel & Amass, 1995 for a review).

As a partial mu-agonist, buprenorphine has a ceiling effect on its agonist activity (Lewis, 1985; Walsh, Preston, Bigelow &Stitzer, 1995). It is less likely than a full agonist to cause respiratory depression in opioid-naïve patients (Cowan, Lewis & Macfarlane, 1977). This property of buprenorphine increases its safety profile by reducing the risk of accidental overdose (Walsh, Preston, Stitzer, Cone & Bigelow, 1994). The partial agonism of buprenorphine would presumably yield a ceiling effect for analgesia as well, which would limit the clinical use of the drug in pain management, but there is some question about the extent of this ceiling effect in practice (Dahan, et al., 2006).

Although the combination buprenorphine/naloxone tablet (Suboxone) may precipitate withdrawal in opioid-tolerant persons if it is injected, making it relatively unattractive for diversion (CSAT, 2004), there is nevertheless evidence of diversion, as would be

expected with any psychoactive drug that has hedonic properties (Cicero &Inciadi, 2005; Smith, Bailey, Woody, &Kleber, 2007). Rates of abuse are relatively low compared to full mu agonists and buprenorphine rarely is endorsed as a primary drug of abuse (Cicero, Suratt, &Inciardi, 2007; Rosenblum et al., 2007; SAMHSA, 2006).

In Europe, a transdermal formulation of buprenorphine has been approved for the treatment of chronic pain (e.g., Griessinger, Sittl, &Likar, 2005; Sittl, 2005). In post-marketing surveillance studies and in a multicenter randomized controlled clinical trial, the transdermal patches were reported to be effective and well-tolerated in the treatment of cancer and non-cancer chronic pain (Griessinger et al., 2005; Sittl, 2005; Sorge and Stittl, 2004; Sittl, Nuijten, &Nautru, 2006). A transdermal formulation of buprenorphine is not presently available in the United States.

The off-label use of sublingual buprenorphine tablets to treat chronic pain has been described in two clinical reports, one describing its use in a series of chronic pain patients who were responding poorly to other opioid analgesics (Malinoff et al., 2005) and the other describing the response of patients with both pain and addiction (Heit&Gourlay, 2008). In both of these reports, the authors reported that their patients were successfully treated with buprenorphine, e.g., pain relief and improved mood and functioning.

In a similar manner, two earlier publications describe the open-label use of the parenteral formulation of buprenorphine administered sublingually to treat patients with chronic pain (Adriaensen, Mattelaer, &Vanmeenen, 1985; Nasar, McLeavy, & Knox, 1986). Although most patients were followed up for less than one month, both studies reported good analgesia and low incidence or time-limited unwanted side effects. There is also evidence from several preclinical studies and one study with human subjects that, in contrast to pure mu-agonists, buprenorphine exerts a lasting anti-hyperalgesic effect (Hans, 2007; Koppert, et al., 2005). The transdermal trials conducted in Europe, the anecdotal reports of sublingual administration in North America, and buprenorphine's comparatively high safety profile suggest that it would be valuable to systematically study buprenorphine as a treatment of pain in patients with substance use disorders.

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Conclusion

Opioids are among the most effective medications for moderate to severe pain. Although there is a consensus on their utility as a treatment for chronic cancer pain, their long-term use for chronic non-malignant pain remains controversial. Several medical professional organizations acknowledge the utility of opioid therapy and many case series and large surveys report satisfactory reductions in pain, improvement in function and minimal risk of addiction. However, the clinical trials that have been conducted do not provide adequate evidence of long-term effectiveness. Despite the consensus of pain specialists, and the eminently ethical and medically justified commentaries to consider opioid therapy in the armamentarium of treatments for moderate to severe pain (Brennan, Carr, & Cousins, 2007), there is concern that the pendulum has swung from undertreatment to overtreatment (White &Kehlen, 2007). This controversy is enhanced by the increased prevalence of prescription opioid abuse, which has developed concomitantly with an increase in opioid administration in the clinic. The resolution of this controversy will require much more research and the acceptance of treatment guidelines that recognize the dual obligations of the prescriber: to optimize the balance between analgesia and side effects, and promote other favorable outcomes, while concurrently assessing and managing the risks associated with abuse, addiction and diversion. At this juncture, it is important that the opioid treatment debate evolve from a discussion focused on “too little” or “too much” to one focused on identification and training of best treatment practices. Improvement in opioid therapy can occur through research and training to aid practitioners to determine the appropriate patient subpopulations and treatment protocols to achieve satisfactory outcomes.

Finally, it is imperative to advance a research agenda that leads to the identification of methods that would enhance pain relief while reducing the likelihood of addiction and other adverse events when opioids are selected for therapy. This should include the testing of novel medications that may be safer or more differentially effective for select treatment populations (as the proposal to test buprenorphine with high risk patients,

discussed above) and the evaluation of treatment protocols incorporating risk management techniques.

Data from the 2012 National Health Interview Study showed that more than 25 million American adults had pain every day for the preceding three months.

1 Chronic pain can be debilitating and have a significant socioeconomic impact.

2 Beyond surgery and other interventions, both prescription and nonprescription medications have been standard protocol to help mitigate chronic pain. Long-term use of pharmacologics can have unwanted side effects and a high risk of addiction, especially with opioids. Pain is one of the leading reasons Americans turn to complementary healing modalities such as yoga, massage, meditation, and nutritional supplements that may help attenuate pain.

Many individuals with chronic pain have elevated levels of proinflammatory cytokines in blood and tissues, a normal biologic process in response to injury, infection, or irritation.

If the inflammatory process persists, it can develop into a chronic condition associated with chronic pain. Emerging literature suggests certain nutrients may help alleviate chronic pain through management of inflammation via oxidative stress. As many whole foods comprise bioactive compounds with anti-inflammatory effects, diet and nutrition should be integrated in the approach to treating older adults with chronic pain.

Anti-Inflammatory Diet

The United States' food supply is flooded with empty-calorie processed foods containing unhealthful fats, refined carbohydrates, sugar, and sodium. This Western diet is low in fiber, micronutrients, and antioxidants, and is considered proinflammatory. Studies looking at the influence of diet on inflammatory markers show that consumption of foods

high in fiber, healthful oils, fruits, vegetables, and those low in sugars, starchy carbohydrates, and unhealthful fats can reduce inflammation and disease.3

Consumption of fruits and vegetables, which contain many vitamins, minerals, and antioxidants, is inversely associated with inflammation and oxidative stress; the higher the intake of plant foods, the lower the occurrence of oxidative stress.4

Specifically, to reduce proinflammatory cytokines and reactive oxygen species, a minimum daily intake of five servings of fruits and vegetables is recommended.

High–glycemic index foods such as white bread are rapidly digested, cause substantial increases in blood sugar levels after being eaten, and may contribute to oxidative stress and low-grade inflammation, both in acute and chronic pain.

Whole grain foods have a low glycemic index and are rich in bioactive compounds (eg, polyphenols, phytic acid, and lignin) with anti-inflammatory properties, including the reduction of free radicals and the activation of antioxidant enzymes. A recent study confirmed that a low–glycemic index diet was more effective in reducing chronic inflammation as measured by lower concentrations of C-reactive protein than was a high–glycemic index diet.4

Extra virgin olive oil (EVOO) is the main source of fat in the Mediterranean diet. The high concentration of monounsaturated fat and many bioactive compounds such as polyphenols in EVOO characterize its anti-inflammatory and antioxidant properties. (Seed oils don’t have the same benefit as EVOO.) This could explain why the incidence of cancer and heart diseases is lower in the Mediterranean basin than in other geographic areas. When phenolic phytochemicals were extracted from EVOO and evaluated for their nutraceutical properties, they were found to be effective in treating knee pain in early-stage knee osteoarthritis.4

Omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) are essential and must be obtained from the diet. Western diets tend to be higher in omega-6 PUFAs than omega-3s (ranging from a 10:1 to 20:1 ratio or higher), with each PUFA having an

opposite function along the cyclooxygenase pathway—the enzymatic route that converts fatty acids to prostaglandins that mediate inflammation and pain.

Omega-6 PUFAs stimulate inflammation, whereas omega-3 PUFAs decrease inflammation. The predominant omega-6 PUFA is linoleic acid, which is found in corn, sunflower, safflower, soybean, and sesame oils, as well as in nuts and seeds. In a randomized controlled trial involving 56 patients, omega-3 fats were increased and omega-6 fats were decreased, resulting in reduced headache pain,3 although there are few other studies that suggest a diet higher in omega-6 PUFAs compared with omega-3 PUFAs increases chronic inflammation.5

The most potent omega-3 PUFAs—EPA and DHA—are found mainly in cold-water fish, such as salmon, mackerel, tuna, herring, pompano, swordfish, trout, and sardines. Another omega-3 fat, alpha-linolenic acid (ALA), is found in vegetable oils (eg, soybean, canola), nuts (especially walnuts), ground flaxseed and flaxseed oil, leafy vegetables, and some animal fat, especially from grass-fed livestock. The human body generally uses ALA for energy, because it's inefficient in converting it into EPA and DHA,6 especially in aging.4

The strongest evidence for the dietary benefits of omega-3 fats pertains to their ability to reduce potentially fatal arrhythmias.7 Omega-3 fats also lower blood pressure and heart rate, improve blood vessel function, and—at higher doses than those typically found in the diet—may lower triglycerides and ease inflammation. There's evidence that omega-6 fats also positively influence cardiovascular risk factors, but, as they are ubiquitous in the diet, it's only prudent to increase consumption of omega-3 fats.

Dietary guidelines recommend eating 8 oz (approximately two servings) of seafood per week, particularly fatty, darker meat fish that are richer in EPA and DHA.

There are many nutritional supplements that offer omega-3 fats, but the source, dosage, and interactions with medications all should be considered. Various research has found that subjects used fewer NSAIDs when they were treated with omega-3 fats for rheumatoid arthritis, and an analgesic effect has been shown with supplementation for

inflammatory joint pain.3 Omega-3 supplement doses used in many studies range from 3,000 to 4,000 mg of combined EPA and DHA, which usually can be found in 6,000 to 8,000 mg of fish oil. In most good-quality microdistilled fish oil preparations, EPA and DHA combined will be about one-half the amount of the dosage. For example, a 1,000-mg capsule may have 230 mg of EPA and 270 mg of DHA for a total of 500 mg of the omega-3 PUFAs.

High red meat consumption is associated with elevated plasma concentrations of inflammatory biomarkers. An eight-week intervention in which two groups of subjects were given either meat or legumes for protein showed a significant difference in the inflammatory marker for high sensitivity C-reactive protein from -1.3 (meat) to 1.7 (legumes, p=0.019).4 Legumes and other plant foods high in water-insoluble fiber are also beneficial for any patient with chronic pain who may suffer from opioid-induced constipation. Red wine is rich in numerous molecules that fight inflammation and oxidation, in particular flavonoids.3 Moderate consumption—a 5-oz glass daily for women (up to 2 for men)—merits consideration in the absence of opioid use.

Turmeric and ginger are related tubers that have been studied extensively for their anti-inflammatory properties. A systematic review of ginger concluded that it's a powerful anti-inflammatory that's useful in treating pain because it disrupts the cyclooxygenase-2 pathway that promotes inflammation.3

Although curcumin, the active component of turmeric, has been found to have effects similar to those of ibuprofen for osteoarthritis of the knee and to be useful for postoperative pain,3 several well-controlled clinical studies have failed to show clinical benefits with curcumin.8 The bioavailability of curcumin may explain differing research outcomes. Formulations of bioavailability-enhanced curcumin have been shown to overcome absorption issues and are now the most commonly used types of curcumin supplements.9 The turmeric root or rhizome made into a powder or extract appears to be the active form (compared with the leaf and flower) with a suggested dose of 1,000 mg. The optimal dose of curcumin hasn't yet been established.

Nutritional Supplements

Glucosamine and chondroitin are naturally occurring substances in the body and are the major structural components of cartilage, the tough, elastic connective tissue found in joints.

Although consumers commonly use them as nutritional supplements for knee pain, research is mixed on the efficacy of glucosamine and/or chondroitin for reducing pain, perhaps due to the variation that exists among different trial protocols. A 16-week double-blinded, randomized, placebo-controlled trial of 34 males found that a combination of glucosamine hydrochloride (1,500 mg/day) and chondroitin sulfate (1,200 mg/day) relieved symptoms of degenerative joint disease of the knee and lower back.10 The visual analog scale for pain recorded at clinic visits decreased by 26.6%. Similarly, a systematic meta-analysis showed that glucosamine and chondroitin was efficacious for treatment of osteoarthritis.11

However, another randomized controlled trial of 205 subjects with knee osteoarthritis showed that glucosamine was no more effective than placebo.12 In addition, a multicenter, double-blinded, placebo-controlled trial evaluated 1,583 randomly assigned patients with symptomatic knee osteoarthritis, but neither glucosamine nor chondroitin sulfate reduced pain effectively overall in the group of patients with knee osteoarthritis.13

Another similar multicenter trial randomly assigned 605 patients with chronic knee pain to four groups taking glucosamine, chondroitin, both, or a placebo.14 All four groups demonstrated a reduction in knee pain, with the glucosamine and chondroitin combination group demonstrating significant reduction in joint space narrowing at the two-year follow-up visit. Overall, a critical review of the use of these nutritional supplements summarized that treatment produced conflicting evidence.2 Taken in appropriate amounts, glucosamine and chondroitin generally are considered safe for healthy people not taking any other medications. In some individuals, glucosamine can

cause gastrointestinal discomfort, drowsiness, skin reactions, and headache, while chondroitin occasionally can cause stomach upset.13

Vitamins, Minerals, and Water

Deficiencies of vitamin D have been consistent among populations within the Northern Hemisphere and appear to be more common in the elderly.15,16 Those with chronic pain have more significant deficiencies.17,18 Data from literature have explained the link between vitamin D and chronic pain, demonstrating that low levels of vitamin D are associated with increased central hypersensitivity, such as increased sensitivity to mechanical pain and severity of somatic symptoms in chronic pain patients.4 An improvement in pain has been shown with mere supplementation of vitamin D.19 The Recommended Dietary Allowances (RDAs) for both men and women aged 70 and older increase from the recommendation for those under age 70 of 600 IU to 800 IU per day, with the Tolerable Upper Intake Level set at 4,000 IU per day.20

Vitamin B12 is required for proper red blood cell formation, neurological function, and DNA synthesis.21 Deficiencies of vitamin B12 are well known to contribute to neurologic dysfunction and chronic pain.3 Recent human studies have shown that the intramuscular injection of vitamin B12 is significantly important for the treatment of localized pain in the spine.4

In food, vitamin B12 is bound to protein but is released during digestion by the activity of hydrochloric acid and gastric protease in the stomach. It then combines with intrinsic factor, a glycoprotein secreted by the stomach's parietal cells, for absorption. Older people are at an increased risk of vitamin B12 deficiency for several reasons. Atrophic gastritis affects 10% to 30% of older adults and decreases secretion of hydrochloric acid in the stomach, resulting in decreased absorption of vitamin B12. Pernicious anemia, a condition that affects 1% to 2% of older adults, is characterized by a lack of intrinsic factor; thus, individuals cannot properly absorb B12 in the gastrointestinal tract. Pernicious anemia typically is treated with intramuscular vitamin B12. However,

approximately 1% of oral vitamin B12 can be absorbed passively in the absence of intrinsic factor, suggesting that high oral doses also may be an effective treatment.

Older individuals with gastrointestinal disorders, such as celiac or Crohn's disease, or those who have had gastrointestinal surgery, may also be at risk of vitamin B12 deficiency. The Institute of Medicine recommends that adults older than 50 obtain most of their vitamin B12 from vitamin supplements or fortified foods, though some elderly patients with atrophic gastritis require doses much higher than the RDA to avoid subclinical deficiency. Vitamin B12 injections in patients with pain who weren't B12 deficient resulted in reduced pain scores and less analgesic use in both active treatment arms of a double-blinded, placebo-controlled crossover trial.3

Magnesium is an abundant mineral in the body and naturally present in many foods, but older adults have lower intakes, and magnesium absorption from the gut decreases while renal magnesium increases with age. In addition, some medications (including bisphosphonates, antibiotics, diuretics, and protein pump inhibitors) can alter magnesium status, which can further decrease risk of magnesium depletion.22

Magnesium deficiency is related to factors that promote migraine headaches, including neurotransmitter release and vasoconstriction. Although research on the use of magnesium supplements to prevent or reduce symptoms of migraines is limited, the American Academy of Neurology and the American Headache Society concluded that magnesium therapy is "probably effective" for migraine prevention.23 Magnesium also is being studied for its role in neuropathic pain.3

In clinical trials, most authors confirmed that magnesium reduces opioid consumption and alleviates postoperative pain scores while not increasing the risk of side effects after opioids.4 Nuts, legumes, spinach, and cereals are all good sources of magnesium in the diet that help meet the RDA for older adults; men need 420 mg per day, and women need 320 mg per day.

Water is an essential nutrient and indispensable as a universal solvent for all physiological processes and biochemical reactions. The aging process alters important

physiological control systems associated with thirst and satiety, as sensitivity of thirst receptors declines with age. Thus, dehydration is a common problem for older adults. Hydration status is significantly correlated with pain, although it's unclear whether the mechanism of action involves a cerebrovascular response or an increase in blood cortisol concentration.24 Regardless, adequate water intake for the elderly is particularly important in the presence of chronic pain.

Management of Chronic Pain: A Food Pyramid

Given the anti-inflammatory properties of many food constituents and the fact that lower markers of inflammation and oxidative stress correspond with lower chronic pain, a recent research review evaluated existing evidence to determine whether there was an optimal diet therapy for the management of chronic pain.4 Results from an analysis of 172 scientific papers led study authors to design a hypothetical nutritional pyramid to serve as an integrative tool in the treatment of chronic pain as well as to help other researchers focus on the often-ignored possible connections between nutrition and chronic pain. The eating pattern described in this pyramid recommended for chronic pain is very similar to the Mediterranean diet. The base of the pyramid recommends 1.5 to 2 L of water daily. From there, foods are recommended in descending order of priority and inclusion: vegetables and fruits, nutrient-dense carbohydrates and whole grains, EVOO, red wine, yogurt, spices, seeds and nuts, legumes, fish, eggs, fresh cheese, poultry, red or processed meat, and sweets, along with daily nutritional supplements of vitamins B12 and D and omega-3.

Drug–Nutrient Interactions and the Microbiome

NSAIDs may contribute to nutritional deficiencies from intestinal malabsorption and disruption of the microbiome, the masses of microorganisms that inhabit the body and outnumber an individual's human cells by 10:1.3 The balance of microorganisms may influence health or disease by affecting the absorption of nutrients, causing or preventing excessive gut permeability, affecting the function of the immune system, and stimulating unhealthy fermentation within the gut. They also may be responsible for

some forms of abdominal pain. The microbiome is also adversely affected by processed foods and many other drugs commonly used in physical medicine and rheumatology practices, such as protein pump inhibitors, antibiotics, steroids, and hormones. Consuming yogurt daily can help prevent the alteration of the microbiotaby opioid therapy as well as counteract the inflammatory state that characterizes chronic pain patients.4

Diet and Nutrition in Patient Evaluation

Nutrition is an important element of health in the older population and can affect the aging process. Older adults often have reduced appetite and energy expenditure, which, coupled with a decline in biological and physiological functions such as reduced lean body mass, changes in cytokine and hormonal levels, and changes in fluid electrolyte regulations, delay gastric emptying and diminish senses of smell and taste.25 Across the health continuum, a Mediterranean-type diet—deemed the 2019 diet of the year by ***U.S. News & World Report***—appears to have the most benefits.26 Thus, implementing the Mediterranean diet as MNT in the management of chronic pain in older adults can be only beneficial. In addition, a good-quality daily multivitamin and one or a few other individual nutritional supplements may be indicated.

The vast majority of injections done for the diagnosis or treatment of chronic pain are performed on an outpatient basis. Some are performed on inpatients, who may be already hospitalized for other reasons. All of them may be performed under fluoroscopic (x-ray) guidance but are sometime performed in the office without x-ray. For any nerve block, you need to tell your doctor if you are allergic to contrast dye or if you think you may be pregnant. Below is a brief description of some of the more commonly performed nerve blocks by pain management specialists.

- **Epidural Steroid injection**: Epidural steroid injection is an injection performed in the back or neck in an attempt to place some anti-inflammatory steroid with or without a local anesthetic into the epidural space close to the inflamed area that is causing the pain. These injections are generally done for pain involving the back and leg or the

neck and arm/hand. They may be done under x-ray guidance. Common side effects include soreness of the back or neck at the point where the needle enters the skin, there may be some temporary numbness in the involved extremity but persistent numbness or weakness (lasting over 8 hours) should be reported to your doctor. Epidural steroid injections may be placed in the lumbar (low back), thoracic (mid back), or cervical (neck) regions.

- **Facet Joint Injection**: The facet joints assist with movement of the spine both in the neck and back. Injection into these joints can provide relief of neck and back pain; these injections are always performed under x-ray guidance. Common side effects include soreness in the neck or back when the needle was inserted. You will be on your stomach for this injection if it is done for back pain; however you may either be on your stomach or back if the injection is performed for neck pain, depending on the preference of the physician. A needle is placed in your neck or back and advanced to the level of the joint under x-ray visualization. Contrast dye is used if the needle is put within the joint, and sometimes used if the injection is designed to numb the nerves to the joint. This block is often a diagnostic block and a more long lasting injection may be indicated if you have significant pain relief from this injection.
- **Lumbar Sympathetic Block**: A lumbar sympathetic nerve block is performed for pain in the leg that is thought to be caused by complex regional pain syndrome type I (or CRPS I). These injections are often performed under fluoroscopic (x-ray) guidance. Local anesthetic is placed near to the lumbar sympathetic chain in order to relieve the pain. Your leg will likely become warm immediately following the injection: this is an expected effect and not a complication. Back soreness is one of the more common side effects. If you feel any sharp pains down your leg or to your groin during the injection, you should let the physician know immediately. There may be some temporary numbness following the injection but if there is persistent numbness or weakness (> 8 hours) the doctor should be notified. You will be lying on your stomach for this injection. The injection is done from the back, in the lower aspect of the back. A needle is placed, often under x-ray guidance, to a spot just to the side and approaching the front part of the spine where the ganglion is located. If it is done under x-ray, a small amount of dye is injected to make sure the needle is in

the right spot. After the doctor is satisfied that the contrast dye is in the right place, they will inject numbing medicine then remove the needle.

- **Celiac Plexus Block**: A celiac plexus block is generally performed to relieve pain in patients with cancer of the pancreas or other chronic abdominal pains. A needle is placed via your back that deposits numbing medicine to the area of a group of nerves called the celiac plexus. This injection is often performed as a diagnostic injection to see whether a more permanent injection may help with the pain. If it provides significant pain relief then the more long lasting injection may be done. This injection is usually performed under x-ray guidance. You will be lying on your stomach for this injection. The needle is place via the mid back and placed just in front of the spine. Contrast dye is injected to confirm that the needle is in the right spot; followed by some numbing medicine.
- **Stellate Ganglion Block**: A stellate ganglion block is an injection that can be performed for the diagnosis of complex regional pain syndrome of the arm or hand or for treatment of pain to that area. It can also be used to help to improve blood flow to the hand or arm in certain conditions that result in poor circulation of the hand. Side effects may include soreness in the neck where the needle was placed. In some instances the side effects may include droopiness of your eyelid on the side that is injected, along with a temporarily stuffy nose and sometimes temporary difficulty in swallowing. This injection is performed with or without x-ray guidance. You will be lying on your back for this injection with your mouth slightly open. It is very helpful to the doctor if you try not to swallow during the injection. If this injection is performed under x-ray the doctor will first inject a small amount of contrast to confirm the placement of the needle then inject some numbing medicine.

Headache is one of the most common reasons patients seek help from family physicians. The estimated lifetime prevalence of headache is 66%: 14% to 16% for migraine, 46% to 78% for tension-type headache, and 0.1% to 0.3% for cluster headache.[1–3] In Canada, at least 2.6 million adult women and nearly 1 million men experience migraine.[4] About 90% of migraine sufferers report moderate to severe pain, with 75% reporting impaired function and 33% requiring bed rest during an attack.[5] The economic effects of headache are also substantial. It is estimated that headache accounts for 20% of work absences.[6]

Vast quantities of over-the-counter medications are taken for headache disorders, and treatment is often suboptimal.[1,7] Although most migraine sufferers use acute treatment to relieve their headaches, a substantial number of people who might benefit from prophylactic therapy do not receive it—more than 1 in 4 migraineurs are candidates for preventive therapy.[5,8]

Better information and education for patients and health professionals is essential to improving management of headache in primary care, which should lead to prompt diagnosis and more effective treatment.[9] To help address this, a consortium of organizations and clinicians from Alberta developed the *Guideline for Primary Care Management of Headache in Adults.*[10]

Go to:

Scope

The Alberta guideline is intended to assist any primary care practitioner responsible for the assessment and management of headaches in adults. The guideline's main focus is primary headache disorders (eg, migraine, tension-type, and cluster headache) and medication-overuse headache. Some advice is also provided for the diagnosis and investigation of secondary headache disorders and the management of cervicogenic headache and temporomandibular joint disorder. The guideline will be helpful to a range of primary health care professionals, including family physicians, physical therapists, occupational therapists, nurses, nurse practitioners, pharmacists, psychologists, and chiropractors.

Go to:

Development

Leadership

The lead organizations involved in developing the guideline were Toward Optimized Practice (TOP), which develops and disseminates primary care guidelines in Alberta, and the Institute of Health Economics (IHE). Three multidisciplinary committees were formed to coordinate guideline production.

- The Steering Committee provided operational oversight.
- The Guideline Development Group (GDG) formulated the recommendations and comprised 9 family physicians, 2 neurologists, an osteopathic physician, a chiropractor, 2 physical therapists, an occupational therapist, a nurse, a pharmacist, 2 psychologists, and a health technology assessment specialist.
- The Advisory Committee advised the Steering Committee on strategic matters and included representatives from the Alberta College of Family Physicians, the Alberta College of Physicians and Surgeons, Alberta Health Services, Alberta Health, the Pain Society of Alberta, and a chronic pain patient advocacy group, as well as experts in guideline development and dissemination.

A research team of health technology assessment researchers with methodologic expertise from the IHE assisted the Steering Committee and GDG.[11]

Literature review

The Alberta guideline was developed using a guideline adaptation process, which takes advantage of existing high-quality guidelines and allows guideline developers to modify the recommendations from these seed guidelines to meet the needs of the local health care setting.[12] Guideline adaptation is a popular alternative to de novo guideline development owing to the need to reduce duplication and constrain costs in the creation of evidence-informed guidelines.[13–15]

The research team collaborated with experienced medical librarians to systematically search for existing clinical practice guidelines (CPGs) published between January 2000 and May 2011. The search identified 64 guidelines, 18 of which were deemed relevant after application of specific selection criteria developed by the research team and content experts from the GDG.[11] The quality of the guidelines was appraised independently by 2 reviewers (C.M. and N.A.S.) using the AGREE (Appraisal of Guidelines for Research and Evaluation) instrument,[16,17] which was modified to reduce the subjectivity of the item scoring and to enable the differentiation of good- from poor-quality guidelines.[18] Although an updated AGREE tool was published in May 2009,[19,20] the research team elected to use the original instrument in order to maintain consistency with previous guidelines produced by TOP and the IHE. Of the 18 potentially eligible guidelines, 6 were scored as good quality and were chosen as seed guidelines.

Two reviewers (C.M. and N.A.S.) extracted the following information into standardized evidence tables: the source of the guideline, the recommendations, the number and types of studies used to create the recommendations (eg, 5 randomized controlled trials), and the strength of the recommendations. A total of 187 recommendations were tabulated. Discordant recommendations were highlighted in the tables.

Practice recommendations

The GDG reviewed the 6 seed guidelines, their companion documents, and the evidence tables during 13 half-day meetings: 1 face-to-face meeting and 12 Web conferences using WebEx (Cisco Systems Inc), which allowed all GDG members to view documents simultaneously and to register their preferences using an online voting system. The 2 GDG cochairs (W.J.B. and P.T.) led all sessions and conducted roundtable discussions for every recommendation to ensure that each GDG member had a voice in the process.

In some cases, the GDG requested additional evidence to resolve uncertainties or disagreements regarding interpretation of the evidence from the seed guidelines or when new interventions were considered that had not been included in the seed guidelines. These “parking lot” requests triggered examination of individual research studies cited by the seed guidelines, as well as additional systematic reviews on headache disorders identified by a supplementary search for literature published between January 2000 and October 2010.[11] The parking lot items were referred for further analysis to ad hoc GDG subcommittees that included one or both cochairs, one IHE researcher, and at least one volunteer from the GDG with expertise in the relevant area. Consensus-based decisions made by the subcommittees were then presented to the GDG for final approval. Occasionally new recommendations were generated from parking lot item discussions. A special GDG subcommittee, which included a neuroradiologist, was created for the diagnostic

imaging recommendations. The 23-month guideline development process resulted in 91 draft recommendations.

Each recommendation in the Alberta guideline came from 1 or more seed guidelines, was based on evidence from systematic reviews or quasi-systematic reviews, or was created by the GDG members, based on their collective professional opinion and an analysis of relevant evidence. The original wording of the recommendations was retained whenever possible, and designations were used (eg, *SR* for systematic review, *CS* for case series) to maintain a link to the evidence cited by the seed guidelines. The principles outlined in the GuideLineImplementability Appraisal tool, which is designed for appraising the implementability of CPGs, were used as a guide when crafting the recommendations.[21],[22] Standardized definitions for the types of recommendations made in the Alberta CPG were constructed from the evidence-rating scales used by the seed guidelines. The recommendations were categorized as *do* when the evidence supported the intervention, *do not do* when the evidence suggested the intervention was ineffective or harmful, or *do not know* when the evidence was equivocal, conflicting, or insufficient.

A series of companion documents were created, adapted, or adopted to support the implementation of the guideline. These included a quick reference algorithm, a summary document, patient education sheets, and practice tools (a medication table, a headache history form, a patient diary, and a video demonstrating physical examination of the neck).[10]

The draft guideline was reviewed by the Advisory Committee, a focus group of primary care physicians, and attendees at 2 Alberta physician conferences. The patient information sheets were reviewed by focus groups of patients and laypeople. The feedback was incorporated into the final documents, which were approved by the GDG in February 2012.

Go to:

Main message

The seed guidelines are listed in Table 1.[23–31] The Alberta guideline's 91 recommendations are organized into 6 sections. The full guideline and accompanying documents are available from the TOP website.[10] The quick reference algorithm[*] information is provided in Figure 1 and Tables 2 2 to to44.[10] Some general practice points are summarized in **Box 1**.

Box 1.

General practice points for managing primary headache in adults

The following are general practice points for the management of primary headache in adults:

- Rule out secondary headache when diagnosing a primary headache disorder
- Neuroimaging is not indicated in patients with recurrent headache with the clinical features of migraine, normal neurologic examination findings, and no red flags

- Neuroimaging, sinus or cervical spine x-ray scans, and electroencephalograms are not recommended for the routine assessment of patients with headache: history and physical and neurologic examination findings are usually sufficient to make a diagnosis of migraine or tension-type headache
- Migraine is by far the most common headache type in patients seeking help for headache from physicians
- Migraine is historically underdiagnosed and undertreated; many patients with migraine are not diagnosed with migraine when they consult a physician
- Migraine should be considered in patients with recurrent moderate or severe headaches and normal neurologic examination findings
- Patients consulting for bilateral headaches that interfere with their activities are likely to have migraine rather than tension-type headache and might require migraine-specific medication
- Consider a diagnosis of migraine in patients with a previous diagnosis of recurring "sinus" headache
- Medication overuse is considered to be present when patients with migraine or tension-type headache use combination analgesics, opioids, or triptans on ≥ 10 d/mo or acetaminophen or NSAIDs on ≥ 15 d/mo
- Comprehensive migraine therapy includes management of lifestyle factors and triggers, acute and prophylactic medications, and migraine self-management strategies
- A substantial number of people who might benefit from prophylactic therapy do not receive it

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NSAID—nonsteroidal anti-inflammatory drug.

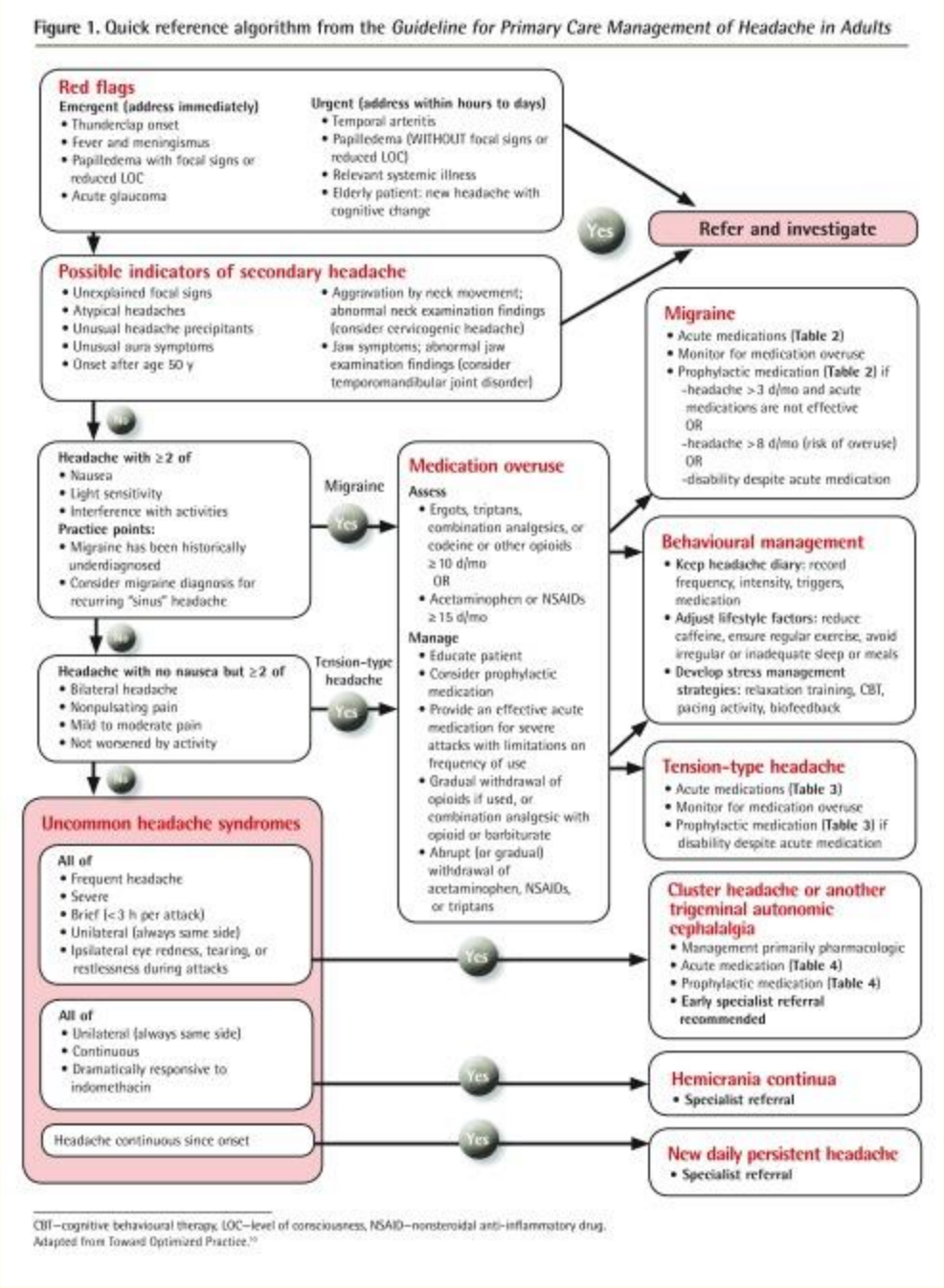

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Figure 1.

Quick reference algorithm from the *Guideline for Primary Care Management of Headache in Adults*

CBT—cognitive behavioural therapy, LOC—level of consciousness, NSAID—nonsteroidal anti-inflammatory drug.

Adapted from Toward Optimized Practice.[10]

Table 1.

US Headache Consortium,[23]–[26] 2000	US: Neuroimaging in patients with nonacute headache[23]; pharmacologic management of acute migraine attacks[24]; pharmacologic prevention of migraine[25]; behavioural and physical treatment of migraine[26]

Table 2.

Migraine medications: *A) Acute migraine medications. B) Prophylactic migraine medications.*

A)

TYPE	ACUTE MEDICATIONS
First line	Ibuprofen 400 mg, ASA 1000 mg, naproxen sodium 500–550 mg, acetaminophen 1000 mg
Second line	Triptans: oral sumatriptan 100 mg, rizatriptan 10 mg, almotriptan 12.5 mg, zolmitriptan 2.5 mg, eletriptan 40 mg, frovatriptan 2.5 mg, naratriptan 2.5 mg • Subcutaneous sumatriptan 6 mg if the patient is vomiting early in the attack. Consider for attacks resistant to oral triptans • Oral wafer: rizatriptan 10 mg or zolmitriptan 2.5 mg if fluid ingestion worsens nausea • Nasal spray: zolmitriptan 5 mg or sumatriptan 20 mg if patient is nauseated

A)

TYPE	ACUTE MEDICATIONS
	Antiemetics: domperidone 10 mg or metoclopramide 10 mg for nausea
Third line	Naproxen sodium 500–550 mg in combination with a triptan
Fourth line	Fixed-dose combination analgesics (with codeine if necessary; not recommended for routine use)

B)

PROPHYLACTIC MEDICATIONS	STARTING DOSE	TITRATION,* DAILY DOSE INCREASE	TARGET DOSE OR THERAPEUTIC RANGE†	NOTES
First line				
• propranolol	20 mg twice daily	40 mg/wk	40–120 mg twice daily	Avoid in asthma

A)

TYPE	ACUTE MEDICATIONS			
• metoprolol	50 mg twice daily	50 mg/wk	50–100 mg twice daily	Avoid in asthma
• nadolol	40 mg/d	20 mg/wk	80–160 mg/d	Avoid in asthma
• amitriptyline	10 mg at bedtime	10 mg/wk	10–100 mg at bedtime	Consider if patient has depression, anxiety, insomnia, or tension-type headache
• nortriptyline	10 mg at bedtime	10 mg/wk	10–100 mg at bedtime	Consider if patient has depression, anxiety, insomnia, or tension-type headache

A)

TYPE	ACUTE MEDICATIONS			
Second line				
• topiramate	25 mg/d	25 mg/wk	50 mg twice daily	Consider as a first-line option if the patient is overweight
• candesartan	8 mg/d	8 mg/wk	16 mg/d	Few side effects; limited experience in prophylaxis
• gabapentin	300 mg/d	300 mg every 3–7 d	1200–1800 mg/d divided into 3 doses	Few drug interactions
Other				

A)

TYPE	ACUTE MEDICATIONS			
• divalproex	250 mg/d	250 mg/wk	750–1500 mg/d divided into 2 doses	Avoid in pregnancy or when pregnancy is possible
• pizotifen	0.5 mg/d	0.5 mg/wk	1–2 mg twice daily	Monitor for somnolence and weight gain
• onabotulinumtoxin A	155–195 units	No titration needed	155–195 units every 3 mo	For chronic migraine only (headache on ≥ 15 d/mo)
• flunarizine	5–10 mg at bedtime	No titration needed	10 mg at bedtime	Avoid in patients with depression

A)

TYPE	ACUTE MEDICATIONS			
• venlafaxine	37.5 mg/d	37.5 mg/wk	150 mg/d	Consider for migraine in patients with depression
Over the counter				
• magnesium citrate	300 mg twice daily	No titration needed	300 mg twice daily	Effectiveness might be limited; few side effects
• riboflavin	400 mg/d	No titration needed	400 mg/d	Effectiveness might be limited; few side effects
• butterbur	75 mg twice daily	No titration needed	75 mg twice daily	Effectiveness might be limited; few side effects

A)

TYPE	ACUTE MEDICATIONS			
• coenzyme Q10	100 mg 3 times daily	No titration needed	100 mg 3 times daily	Effectiveness might be limited; few side effects

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ASA—acetylsalicylic acid.

*Dosage can be increased every 2 wk to avoid side effects. For most drugs, slowly increase to the target dose; a therapeutic trial requires several months. The expected outcome is reduction not elimination of attacks.
†If the target dose is not tolerated, try a lower dose. If the medication is effective and tolerated, continue it for at least 6 mo. If several preventive drugs fail, consider a specialist referral.

Adapted from Toward Optimized Practice.[10]

Table 3.

Medications for tension-type headache

MEDICATION	DOSE
Acute	
Ibuprofen	400 mg
ASA	1000 mg

MEDICATION	DOSE
Naproxen sodium	500–550 mg
Acetaminophen	1000 mg
Prophylactic	
First line	
• amitriptyline	10–100 mg/d
• nortriptyline	10–100 mg/d
Second line	
• mirtazapine	30 mg/d
• venlafaxine	150 mg/d

ASA—acetylsalicylic acid.

Adapted from Toward Optimized Practice.[10]

Table 4.

Medications for cluster headache: *Consider early specialist referral.*

MEDICATION	DOSE
Acute	
Subcutaneous sumatriptan	6 mg
Intranasal zolmitriptan	5 mg
100% oxygen	12 L/min for 15 min through non-rebreathing mask
Prophylactic*	
First line	
• verapamil	240–480 mg/d (higher doses might be required)
Second line	
• lithium	900–1200 mg/d

MEDICATION	DOSE
Other	
• topiramate	100–200 mg/d
• melatonin	Up to 10 mg/d

*If the patient has more than 2 attacks daily, consider transitional therapy while verapamil is built up (eg, 60 mg of prednisone for 5 d, then reduced by 10 mg every 2 d until discontinued).

Adapted from Toward Optimized Practice.[10]

Section 1: headache diagnosis and investigation

Box 2 presents important elements of the history for patients presenting with first-time headache or a change in headache pattern. **Box 3** presents an approach to the physical examination specifically for primary care providers.[29] **Box 4** presents red flags and other potential indicators of secondary headache.[29] Table 5 presents a simplified strategy for diagnosing primary headache disorders.[32],[33]

Box 2.

Important elements of the headache history in patients presenting with headache for the first time or those with a change in headache pattern

Explore the following important elements of the headache history:

- Headache onset (thunderclap, head or neck trauma), previous attacks (progression of symptoms), duration of attacks (< 3 hours, > 4 hours, continuous), days per month with headache
- Pain location (unilateral, bilateral, associated neck pain, etc)
- Headache-associated symptoms (nausea, vomiting, photophobia, conjunctival injection,

rhinorrhea, etc)

- Relationship of headache attacks to precipitating factors (stress, posture, cough, exertion, straining, neck movement, jaw pain, etc)
- Headache severity and effect on work and family activities
- Acute and preventive medications tried, response, and side effects
- Presence of coexistent conditions that might influence treatment choice (insomnia, depression, anxiety, hypertension, asthma, and history of heart disease or stroke)

Based on expert opinion of the Guideline Development Group.

Box 3.

Approach to the physical examination of a patient presenting with headache for the first time or with a change in headache pattern

The physical examination should incorporate the following elements:

- Screening neurologic examination
    - -general assessment of mental status
    - -cranial nerve examination
        - —fundoscopy, pupils, eye movements, visual fields, evaluation of facial movements for asymmetry and weakness
    - -assessment for unilateral limb weakness, reflex asymmetry, and coordination in the arms
    - -assessment of gait, including heel-toe walking (tandem gait)
- Neck examination
    - -posture, range of motion, and palpation for muscle tender points
- Blood pressure measurement
- If indicated by other neurologic symptoms or signs on screening examination, a focused

neurologic examination (eg, lower cranial nerve examination in a patient with dysarthria, or plantar responses in a patient with reflex asymmetry)

- If indicated by associated jaw complaints, an examination for temporomandibular disorders
    - -assessment of jaw opening
    - -palpation of muscles of mastication for tender points

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Based on the Scottish Intercollegiate Guidelines Network guideline[29] and expert opinion of the Guideline Development Group.

Box 4.

Red flags and other potential indicators of secondary headache: *Appropriate referral or investigation should be considered.*

Red flags: emergent (address immediately)

- Thunderclap onset
- Fever and meningismus
- Papilledema with focal signs or reduced level of consciousness
- Acute glaucoma

Red flags: urgent (address within hours to days)

- Temporal arteritis
- Papilledema without focal signs or reduced level of consciousness
- Relevant systemic illness
- Elderly patient: new headache with cognitive change

Other possible indicators of secondary headache (less urgent)

- Unexplained focal signs
- Atypical headaches (not consistent with migraine or tension-type headache)
- Unusual headache precipitants
- Unusual aura symptoms
- Onset after age 50 y
- Aggravation by neck movement; abnormal neck examination findings (consider cervicogenic headache)
- Jaw symptoms; abnormal jaw examination findings (consider temporomandibular joint disorder)

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Based on the Scottish Intercollegiate Guidelines Network guideline[29] and expert opinion of the Guideline Development Group.

Table 5.

Diagnosing primary headache syndromes

DESCRIPTION	HEADACHE SYNDROME

Patients with recurrent headache attacks and normal neurologic examination findings (in some patients other clinical symptoms might also need to be considered)*	• Diagnose migraine without aura (migraine with aura if an aura is present) if they have at least 2 of the following:
	  • -nausea during the attack
	  • -light sensitivity during the attack
	  • -some of the attacks interfere with their activities
	• Diagnose episodic tension-type headache† if headache attacks are not associated with nausea,

DESCRIPTION	HEADACHE SYNDROME
	and have at least 2 of the following: • -bilateral headache • -nonpulsating pain • -mild to moderate intensity • -headache is not worsened by activity • Diagnose cluster headache or another trigeminal autonomic cephalalgia if headache attacks meet all the following criteria: • -frequent • -severe • -brief (duration < 3 h) • -unilateral • -ipsilateralconjunctival injection, tearing, or restlessness during the attacks (ipsilateral ptosis or miosis might be present on examination). Neurologist referral recommended
Patients with headache on ≥ 15 d/mo for > 3 mo and with normal neurologic examination findings‡	• Diagnose chronic migraine if headaches meet migraine diagnostic criteria (above) or are quickly aborted by migraine-specific medications (triptans or ergots) on ≥ 8 d/mo • -Chronic migraine with medication overuse if the patient uses ergots, triptans, opioids, or combination analgesics on ≥

DESCRIPTION	HEADACHE SYNDROME
	10 d/mo or uses plain acetaminophen or NSAIDs on ≥ 15 d/mo • -Chronic migraine without medication overuse if patients do not have medication overuse as defined above • Diagnose chronic tension-type headache if headaches meet episodic tension-type headache diagnostic criteria (above), except mild nausea might be present
Patients with continuous daily headache for > 3 mo with normal neurologic examination findings[§]	• Diagnose hemicrania continua[‖] (neurologist referral recommended) if the headache • -is strictly unilateral • -is always on the same side of the head (ptosis or miosis might be present on examination) • -responds dramatically to indomethacin • Diagnose new daily persistent headache[‖] if the headache is unremitting since its onset. It is important to consider secondary headaches in these patients. Neurologist referral recommended

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NSAID—nonsteroidal anti-inflammatory drug.

[*]Modified from the International Classification of Headache Disorders[32]; data from Lipton et al[33]; and based on expert opinion of the Guideline Development Group.
[†]If patients do not meet migraine diagnostic criteria.
[‡]Modified from the International Classification of Headache Disorders[32] and based on expert opinion of the Guideline Development Group.

[§]Modified from the International Classification of Headache Disorders[32] and based on expert opinion of the Guideline Development Group.
[‖]This less common headache syndrome should be considered in patients with continuous headache.

Section 2: migraine

A comprehensive approach to migraine management is summarized in **Box 5**. Section 2 of the guideline contains recommendations for lifestyle management, acute treatment, prophylaxis, menstrual migraine, and migraine treatment during pregnancy. The full guideline provides a detailed medication table for migraine that includes available formulations, usual doses, relative and absolute contraindications, and adverse events. **Boxes 6** and **7** show the indications and considerations for prescribing prophylactic drugs for migraine.[28],[29] Recommended medications are outlined in Table 2.[10]

Box 5.

Comprehensive migraine management

Consider the following when managing patients with migraine:

- Pay attention to lifestyle and specific migraine triggers in order to reduce the frequency of attacks. Lifestyle factors to avoid include the following:
    - -irregular or skipped meals
    - -irregular or too little sleep
    - -a stressful lifestyle
    - -excessive caffeine consumption
    - -lack of exercise
    - -obesity
- Use acute pharmacologic therapy for individual attacks
- Use prophylactic pharmacologic therapy, when indicated, to reduce attack frequency
- Use nonpharmacologic therapies
- Evaluate and treat coexistent medical and psychiatric disorders

- Encourage patients to participate actively in their treatment and to employ self-management principles:
    - -self-monitoring to identify factors influencing migraine
    - -managing migraine triggers effectively
    - -pacing activity to avoid triggering or exacerbating migraine
    - -maintaining a lifestyle that does not worsen migraine
    - -practising relaxation techniques
    - -maintaining good sleep hygiene
    - -developing stress management skills
    - -using cognitive restructuring to avoid catastrophic or negative thinking
    - -improving communication skills to talk effectively about pain with family and others
    - -using acute and prophylactic medication appropriately

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Based on expert opinion of the Guideline Development Group.

Box 6.

Pharmacologic prophylaxis for migraine

Prophylactic medication is indicated in the following circumstances:

- Recurrent migraine attacks are causing considerable disability despite optimal acute drug therapy
- Frequency of acute medication use is approaching levels that place the patient at risk of medication-overuse headache
    - -acute medications are used on ≥ 10 d/mo for triptans, ergots, opioids, and combination analgesics

    - -acute medications are used on ≥ 15 d/mo for acetaminophen and NSAIDs
- Recurrent attacks with prolonged aura are occurring (hemiplegic migraine, basilar-type migraine, etc)
- Contraindications to acute migraine medications are making symptomatic treatment of migraine attacks difficult

NSAID—nonsteroidal anti-inflammatory drug.

Based on expert opinion of the Guideline Development Group.

Box 7.

Pharmacologic prophylaxis for migraine

Consider the following when prescribing prophylactic medication:

- Educate patients on the need to take the medication daily and according to the prescribed frequency and dosage
- Ensure that patients have realistic expectations as to what the likely benefits of pharmacologic prophylaxis will be:
    - -Headache attacks will likely not be abolished completely
    - -A reduction in headache frequency of 50% is usually considered worthwhile and successful
    - -It might take 4–8 wk for substantial benefit to occur
    - -If the prophylactic drug provides substantial benefit in the first 2 mo of therapy, this benefit might increase further over several additional months of therapy
- Evaluate the effectiveness of therapy using patient diaries that record headache frequency, drug use, and disability levels
- For most prophylactic drugs, initiate therapy with a low dose and increase the dosage gradually to minimize side effects
- Increase the dose until the drug proves effective, until doselimiting side effects occur, or

until a target dose is reached

- Provide an adequate drug trial. Unless side effects mandate discontinuation, continue the prophylactic drug for at least 6–8 wk after dose titration is completed
- Because migraine attack tendency fluctuates over time, consider gradual discontinuation of the drug for many patients after 6 to 12 mo of successful prophylactic therapy, but preventive medications can be continued for much longer in patients who have experienced substantial migraine-related disability

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Based on Géraud et al[28] and the Scottish Intercollegiate Guidelines Network guidelines.[29]

Section 3: tension-type headache

This section contains recommendations on lifestyle, acute and prophylactic drug therapy, and management of tension-type headache during pregnancy. Recommended medications are outlined in Table 3.[10]

Section 4: medication-overuse headache

Migraine sufferers are particularly prone to developing medication-overuse headache. Recommendations for diagnosis and management of medication-overuse headache are shown in **Boxes 8** and **9**.[29]

Box 8.

Diagnosis of medication-overuse headache

Consider the following in the diagnosis of medication-overuse headache:

- Consider a diagnosis of medication overuse headache in patients with headache on ≥ 15 d/mo and assess patients for possible medication overuse (use of triptans, ergots, combination analgesics, or opioid-containing medications on ≥ 10 d/mo, or use of acetaminophen or NSAIDs on ≥ 15 d/mo)
- When medication-overuse headache is suspected, the patient should also be evaluated for the presence of the following:
    - -psychiatric comorbidities (depression and anxiety); these might need to be

considered in planning an overall treatment strategy

- -psychological and physical drug dependence
- -use of inappropriate coping strategies. Rather than relying on medication as a main coping strategy, patients with suspected medication overuse might benefit from training in and development of more adaptive self-management strategies (eg, identification and management of controllable headache triggers, relaxation exercises, effective stress management skills, and activity pacing)

- Headache diaries that record acute medication intake are important in the prevention and treatment of medication-overuse headache

NSAID—nonsteroidal anti-inflammatory drug.

Based on the Scottish Intercollegiate Guidelines Network guideline[29] and expert opinion of the Guideline Development Group.

Box 9.

Management of medication-overuse headache

Treatment plans for patients with medication-overuse headache should include the following:

- Patient education. Patients need to understand that
  - -acute medication overuse can increase headache frequency
  - -when medication overuse is stopped, headache might worsen temporarily and other withdrawal symptoms might occur
  - -many patients will experience a long-term reduction in headache frequency after medication overuse is stopped
  - -prophylactic medications might become more effective
- A strategy for cessation of medication overuse
  - -abrupt withdrawal should be advised for patients with suspected medication-overuse headache caused by simple analgesics (acetaminophen, NSAIDs) or

triptans; however, gradual withdrawal is also an option

    - -gradual withdrawal should be advised for patients with suspected medication-overuse headache caused by opioids and opioid-containing analgesics

- Provision of a prophylactic medication while medication overuse is stopped. While many prophylactic agents are used (tricyclics, β-blockers, etc), drugs with the best evidence for efficacy in chronic migraine with medication overuse are

    - -onabotulinumtoxinA, 155 units to 195 units injected at intervals of 3 mo by clinicians experienced in its use for headache

    - -topiramate with slow titration to a target dose of 100 mg/d

- A strategy for the treatment of remaining severe headache attacks with limitations on frequency of use (eg, a triptan for patients with analgesic overuse, dihydroergotamine for patients with triptan overuse, etc)

- Patient follow-up and support

Open in a separate window

NSAID—nonsteroidal anti-inflammatory drug.

Based on the Scottish Intercollegiate Guidelines Network guideline[29] and expert opinion of the Guideline Development Group.

Section 5: cluster headache

Cluster headache is managed with a number of pharmacologic therapies. These can be initiated and monitored in primary care, but early specialist referral is recommended because this headache type is uncommon, disabling, and challenging to manage. Recommended medications are outlined in Table 4.[10]

Section 6: other headache disorders

This section of the guideline focuses on hemicrania continua, cervicogenic headache, and headache secondary to temporomandibular joint disorders. Treatment of these conditions will likely involve referral to an appropriately trained therapist or specialist.

Go to:

Implementation and update plans

The guideline has been disseminated through presentations and workshops at provincial, regional, and national conferences. It is also listed in the CMA Infobase,[34] where it was among

the 10 most downloaded guidelines for nearly 6 months. It also appears on the Michael G. DeGroote National Pain Centre website[35] and is listed by the US National Guideline Clearing House.[36] A pilot project is under way at the University of Calgary in Alberta to present the headache guideline using interactive webinars.

The evidence base for the Alberta CPG will be assessed annually and will be updated when new evidence is found that changes the recommendations.

Go to:

Limitations

The guideline adaptation process precluded an in-depth analysis of the validity or a formal assessment of the strength and quality of the underlying empirical evidence, which made categorizing the strength and type of recommendations problematic. To counter this problem, standardized definitions were constructed for the types of recommendations made in the Alberta CPG (eg, what constituted a *do* or *do not do* recommendation) from the overlapping evidence-rating scales used by the seed guidelines, and designations were used (eg, *SR* for systematic review) to maintain a link to the evidence type referenced by the seed guidelines in support of their recommendations.[10,11]

The lack of high-quality scientific evidence for headache investigations, diagnosis, red flags, and specialist referral meant that many recommendations in these areas relied on the opinions of the GDG or the experts who developed the seed guidelines. However, these issues were overcome by using credible seed guidelines, scrupulously listing the evidence type and source for all recommendations, and clearly documenting the subjective contextualization process.

Adaptation processes are limited by the time lag between the publication of primary studies and their incorporation into guidelines, which means that recently published evidence was not necessarily incorporated into the Alberta CPG and that not all of the treatment options available were covered by the seed guidelines. To help offset this, the research team updated searches regularly throughout the Alberta guideline adaptation process.

There was debate among the GDG members about incorporating newly emerging headache treatments that were not identified in the seed guidelines. A conservative approach was adopted whereby a recommendation for an emerging intervention was created only if it had been assessed in a systematic review.

None of the seed guidelines included formal economic evaluations or cost analyses, nor did they discuss the economic implications of their recommendations. Owing to time and resource constraints, a formal cost analysis or economic evaluation of the effect of the Alberta CPG was not conducted. However, any statements on economic aspects made by the seed guidelines were noted in the accompanying background document.[11]

Go to:

Conclusion

The format and brevity of the *Guideline for Primary Care Management of Headache in Adults* reflects its intent—to provide Canadian primary care providers across multiple disciplines

with a comprehensive suite of resources for assessing and managing headaches in adults. A guideline summary and algorithm, as well as practice tools and patient information sheets, are provided to support comprehensive headache management that emphasizes patient engagement and self-management, as well as evidence-informed interventions.

Most persons will experience acute low back pain during their lifetime. The first episode usually occurs between 20 and 40 years of age. For many, acute low back pain is the first reason to seek medical care as an adult. Pain can be moderate to severe and debilitating, causing anxiety. Many cases are self-limited and resolve with little intervention.

However, 31 percent of persons with low back pain will not fully recover within six months,1 although most will improve. Recurrent back pain occurs in 25 to 62 percent of patients within one to two years, with up to 33 percent having moderate pain and 15 percent having severe pain.2-4 Acute low back pain can be defined as six to 12 weeks of pain between the costal angles and gluteal folds that may radiate down one or both legs (sciatica). Acute low back pain is often nonspecific and therefore cannot be attributed to a definite cause. However, possible causes of acute low back pain (e.g., infection, tumor, osteoporosis, fracture, inflammatory arthritis) need to be considered based on the patient's history and physical examination. Table 1 presents the differential diagnosis of acute low back pain.5,6 The goals of treatment for acute low back pain are to relieve pain, improve function, reduce time away from work, and develop coping strategies through education. Optimizing treatment may minimize the development of chronic pain, which accounts for most of the health care costs related to low back pain.7

History and Physical Examination

An accurate history and physical examination are essential for evaluating acute low Acute low back pain is one of the most common reasons for adults to see a family physician. Although most patients recover quickly with minimal treatment, proper evaluation is imperative to identify rare cases of serious underlying pathology. Certain

red flags should prompt aggressive treatment or referral to a spine specialist, whereas others are less concerning. Serious red flags include significant trauma related to age (i.e., injury related to a fall from a height or motor vehicle crash in a young patient, or from a minor fall or heavy lifting in a patient with osteoporosis or possible osteoporosis), major or progressive motor or sensory deficit, new-onset bowel or bladder incontinence or urinary retention, loss of anal sphincter tone, saddle anesthesia, history of cancer metastatic to bone, and suspected spinal infection. Without clinical signs of serious pathology, diagnostic imaging and laboratory testing often are not required. Although there are numerous treatments for nonspecific acute low back pain, most have little evidence of benefit. Patient education and medications such as nonsteroidal anti-inflammatory drugs, acetaminophen, and muscle relaxants are beneficial. Bed rest should be avoided if possible. Exercises directed by a physical therapist, such as the McKenzie method and spine stabilization exercises, may decrease recurrent pain and need for health care services. Spinal manipulation and chiropractic techniques are no more effective than established medical treatments, and adding them to established treatments does not improve outcomes. No substantial benefit has been shown with oral steroids, acupuncture, massage, traction, lumbar supports, or regular exercise programs. (Am Fam Physician. 2012;85(4):343-350. Copyright © 2012 American Academy of Family Physicians.) ▲ Patient information: Handouts on this topic are available at http:// familydoctor.org/family doctor/en/diseasesconditions/low-back-pain. html and http://www. knowyourback.org/ Documents/acute_lbp.pdf. ILLUSTRATION BY CRAIG ZUCKERMAN   Table 1. Differential Diagnosis of Acute Low Back Pain Diagnosis Key clinical clues Intrinsic spine Compression fracture History of trauma (unless osteoporotic), point tenderness at spine level, pain worsens with flexion, and while pulling up from a supine to sitting position and from a sitting to standing position Herniated nucleus pulposus Leg pain is greater than back pain and worsens when

sitting; pain from L1-L3 nerve roots radiates to hip and/or anterior thigh, pain from L4-S1 nerve roots radiates to below the knee Lumbar strain/sprain Diffuse back pain with or without buttock pain, pain worsens with movement and improves with rest Spinal stenosis Leg pain is greater than back pain; pain worsens with standing and walking, and improves with rest or when the spine is flexed; pain may be unilateral (foraminal stenosis) or bilateral (central or bilateral foraminal stenosis) Spondylolisthesis Leg pain is greater than back pain; pain worsens with standing and walking, and improves with rest or when the spine is flexed; pain may be unilateral or bilateral Spondylolysis Can cause back pain in adolescents, although it is unclear whether it causes back pain in adults; pain worsens with spine extension and activity Spondylosis (degenerative disk or facet joint arthropathy) Similar to lumbar strain; disk pain often worsens with flexion activity or sitting, facet pain often worsens with extension activity, standing, or walking Systemic Connective tissue disease Multiple joint arthralgias, fever, weight loss, fatigue, spinous process tenderness, other joint tenderness Inflammatory spondyloarthropathy Intermittent pain at night, morning pain and stiffness, inability to reverse from lumbar lordosis to lumbar flexion Malignancy Pain worsens in prone position, spinous process tenderness, recent weight loss, fatigue Vertebral diskitis/ osteomyelitis Constant pain, spinous process tenderness, often no fever, normal complete blood count, elevated erythrocyte sedimentation rate and/ or C-reactive protein level Referred Abdominal aortic aneurysm Abdominal discomfort, pulsatile abdominal mass Gastrointestinal conditions: pancreatitis, peptic ulcer disease, cholecystitis Abdominal discomfort, nausea\vomiting, symptoms often associated with eating Herpes zoster Unilateral dermatomal pain, often allodynia, vesicular rash Pelvic conditions: endometriosis, pelvic inflammatory disease, prostatitis Discomfort in lower abdomen, pelvis, or hip Retroperitoneal conditions: renal colic, pyelonephritis Costovertebral angle pain, abnormal urinalysis results, possible fever Information from references 5 and 6. Acute Low Back Pain February 15, 2012 ◆Volume 85, Number 4 www.aafp.org/afp American Family Physician 345 back pain. Often, patients awaken with morning pain or develop pain after minor forward bending, twisting, or lifting. It is also important to note whether it is a first episode or a recurrent episode. Recurrent episodes usually are more painful with increased symptoms. Red flags are often used to distinguish a common, benign

episode from a more significant problem that requires urgent workup and treatment (Table 2). 5,6,8 A recent study shows that some red flags are more important than others, and that red flags overall are poor at ruling in more serious causes of low back pain.8 Patients with back pain in the primary care setting (80 percent) tend to have one or more red flags, but rarely have a serious condition.8 However, physicians should be aware of the signs and symptoms of caudaequina syndrome, major intra-abdominal pathology, infections, malignancy, and fractures (Tables 15,6 and 25,6,8). Caudaequina syndrome and infections require immediate referral. Family physicians should rely on a comprehensive clinical approach rather than solely on a checklist of red flags. Pain from spine structures, such as musculature, ligaments, facet joints, and disks, can refer to the thigh region, but rarely to areas below the knee. Pain related to the sacroiliac joint often refers to the thigh, but can also radiate below the knee. Irritation, impingement, or compression of the lumbar root often results in more leg pain than back pain. Pain from the L1-L3 nerve roots will radiate to the hip and/or thigh, whereas pain from the L4-S1 nerve roots will radiate below the knee. Neurologic examination of the lower extremities includes strength, sensation, and Acute low back pain is often nonspecific and therefore cannot be attributed to a definite cause. Table 2. Red Flags for Serious Etiologies of Acute Low Back Pain Possible etiology History findings Physical examination findings Cancer Strong: Cancer metastatic to bone Intermediate: Unexplained weight loss Weak: Cancer, pain increased or unrelieved by rest Weak: Vertebral tenderness, limited spine range of motion Caudaequina syndrome Strong: Bladder or bowel incontinence, urinary retention, progressive motor or sensory loss Strong: Major motor weakness or sensory deficit, loss of anal sphincter tone, saddle anesthesia Weak: Limited spine range of motion Fracture Strong: Significant trauma related to age* Intermediate: Prolonged use of steroids Weak: Age older than 70 years, history of osteoporosis Weak: Vertebral tenderness, limited spine range of motion Infection Strong: Severe pain and lumbar spine surgery within the past year Intermediate: Intravenous drug use, immunosuppression, severe pain and distant lumbar spine surgery Weak: Pain increased or unrelieved by rest Strong: Fever, urinary tract infection, wound in spine region Weak: Vertebral tenderness, limited spine range of motion NOTE: Presence of one or two weak or intermediate red flags may warrant observation because few

patients will be significantly harmed if diagnosis of a serious cause is delayed for four to six weeks. Presence of any strong red flag warrants more urgent workup and probable referral to a spine subspecialist. *—Fall from a height or motor vehicle crash in a young patient, minor fall or heavy lifting in a patient with osteoporosis or possible osteoporosis. Information from references 5, 6, and 8. Acute Low Back Pain 346 American Family Physician www.aafp.org/afp Volume 85, Number 4 ◆February 15, 2012 reflex testing (Table 3), even in the absence of significant sciatica. A straight leg raise test is positive for L4-S1 nerve root pain if it radiates below the knee. A reverse straight leg raise test (extending hip and flexing knee while in the prone position) is positive for L3 nerve root pain if it radiates into the anterior thigh. A central, paracentral, or lateral disk herniation may affect different nerve roots at the same level. Examination of the lumbosacral, pelvic, and abdominal regions may provide clues to underlying abnormalities relating to back pain (Table 15,6 and 25,6,8).

Diagnostic Workup

Imaging is not warranted for most patients with acute low back pain. Without signs and symptoms indicating a serious underlying condition, imaging does not improve clinical outcomes in these patients.9-11 Even with a few weaker red flags, four to six weeks of treatment is appropriate before consideration of imaging studies.8-10 If a serious condition is suspected, magnetic resonance imaging (MRI) is usually most appropriate. Computed tomography is an alternative if MRI is contraindicated or unavailable.10 Clinical correlation of MRI or computed tomography findings is essential because the likelihood of false-positive results increases with age.12-14 Radiography may be helpful to screen for serious conditions, but usually has little diagnostic value because of its low sensitivity and specificity.10 Laboratory tests such as complete blood count with differential, erythrocyte sedimentation rate, and C-reactive protein level may be beneficial if infection or bone marrow neoplasm is suspected. These tests may be most sensitive in cases of spinal infection because lack of fever and a normal complete blood count are common in patients with spinal infection.15 Because laboratory testing

lacks specificity, MRI with and without contrast media and, in many cases, biopsy are essential for accurate diagnosis.15

Treatment of Nonspecific Pain

Many treatments are available for acute low back pain, but strong evidence for their benefit is lacking. Based on the evidence, a reasonable approach to treatment is described in Table 4.

RECOMMENDED

Medications:Nonsteroidal anti-inflammatory drugs (NSAIDs) are often first-line therapy for low back pain. Low-quality evidence suggests that they are effective for short-term symptom relief, compared Table 3. Neurologic Examination Findings in Patients with Acute Low Back Pain Affected nerve root Motor deficit Sensory deficit Reflex Disk herniation Central Paracentral Lateral L3 Hip flexion Anterior/medial thigh Patella Above L2-L3 L2-L3 L3-L4 L4 Knee extension Anterior leg/medial foot Patella Above L3-L4 L3-L4 L4-L5 L5 Dorsiflexion\great toe Lateral leg/dorsal foot Medial hamstring Above L4-L5 L4-L5 L5-S1 S1 Plantar flexion Posterior leg/lateral foot Achilles tendon Above L5-S1 L5-S1 None Table 4. Approach to the Treatment of Nonspecific Acute Low Back Pain First visit Patient education Reassure the patient that the prognosis is often good, with most cases resolving with little intervention Advise the patient to stay active, avoiding bed rest as much as possible, and to return to normal activities as soon as possible Advise the patient to avoid twisting and bending Initiate trial of a nonsteroidal anti-inflammatory drug or acetaminophen Consider a muscle relaxant based on pain severity Consider a short course of opioid therapy if pain is severe Consider referral for physical therapy (McKenzie method and/or spine stabilization) if it is not the first episode Second visit* Consider changing to a different nonsteroidal anti-inflammatory drug Consider referral for physical therapy (McKenzie method and/or spine stabilization) if not done at initial visit Consider referral to a spine subspecialist if pain is severe or limits function *—Two to four weeks after the initial visit, if the patient has not significantly improved. Acute Low Back Pain February 15,

 with placebo.16 No patient characteristics at baseline can predict the success of NSAID therapy.17 Moderate evidence suggests that no one NSAID is superior, and switching to a different NSAID may be considered if the first is ineffective. Whether NSAIDs are more effective than acetaminophen is unknown, but the addition of an NSAID to acetaminophen therapy is no more beneficial than acetaminophen alone.16,18 Moderate-quality evidence shows that nonbenzodiazepine muscle relaxants (e.g., cyclobenzaprine [Flexeril], tizanidine [Zanaflex], metaxalone [Skelaxin]) are beneficial in the treatment of acute low back pain. Most pain reduction from these medications occurs in the first seven to 14 days, but the benefit may continue for up to four weeks.19,20 However, nonbenzodiazepine muscle relaxants do not affect disability status.19,20 Very low-quality evidence shows that a short course (up to five days) of oral diazepam (Valium) may also be beneficial for pain relief.19 Because all muscle relaxants have adverse effects, such as drowsiness, dizziness, and nausea, they should be used cautiously. Diazepam and carisoprodol (Soma) use should be brief to decrease the risk of abuse and dependence. There is also moderate-quality evidence that muscle relaxants combined with NSAIDs may have additive benefit for reducing pain.19 Opioids are commonly prescribed for patients with severe acute low back pain; however, there is little evidence of benefit. Three studies showed no difference in pain relief or time to return to work between oral opioids and NSAIDs or acetaminophen, and there is risk of harmful dose escalation over time with opioids, especially with purer formulations.16,21 Although epidural steroid injections are not beneficial for isolated acute low back pain, they may be helpful for radicular pain that does not respond to two to six weeks of noninvasive treatment. Transforaminal injections appear to have more favorable short- and long-term benefit than traditional interlaminar injections.22 Patient Education. Patient education involves a discussion of the often benign nature of acute back pain and reassurance that most patients need little intervention for significant improvement. Patients should be advised to stay as active as possible, within pain limits; to avoid twisting and bending, particularly when lifting; and to return to normal activities as soon as possible. The goal is to reduce worry about back pain and to teach ways to avoid worsening of pain or pain recurrence. High-quality evidence shows that individual

patient education of greater than two hours is more effective than no education or less-intense education for pain that persists for four weeks or more.23 Moderatequality evidence shows that less-intense individual education and advice to stay active have small benefits and are at least as effective as other back pain interventions.23,24 It is unclear whether patient education and advice for patients with acute low back pain are cost-effective.25

ACCEPTABLE

Physical Therapy. Physical therapists often recommend the McKenzie method or spine stabilization exercises for the treatment of low back pain. The McKenzie method is described at http://www.mckenziemdt.org/ approach.cfm, and a video demonstration is available at http://www.youtube.com/ watch?v=wBOp-ugJbTQ. The McKenzie method has been shown to be slightly more effective than other common low back pain treatments; however, the difference is not clinically significant,26,27 and evidence on its effect on disability is conflicting.26,27 There also do not appear to be good long-term benefits with the McKenzie method, other than decreased need for health care services.27 Spine stabilization exercises have been shown to decrease pain, disability, and risk of recurrence after a first episode of back pain.28 According to moderate-quality evidence, physical therapist–directed home exercise programs for acute back pain can reduce the rate of recurrence, increase the time between episodes of back pain, and decrease the need for health care services. Therefore, most of these exercise programs are cost-effective treatments for acute low back pain.29-31 Imaging is not warranted for most patients with acute low back pain. Acute Low Back Pain 348 American Family Physician www.aafp.org/afp Volume 85, Number 4 ◆ February 15, 2012 Application of Ice or Heat. Low-quality evidence shows that in the first five days of acute low back pain, the use of heat treatments may be more effective for reducing pain and disability than nonheat wraps, NSAIDs, or acetaminophen, but shows no difference between heat application and McKenzie therapy at seven days.32 A lowquality study found that heat therapy in conjunction with education or NSAIDs is more effective than

education or NSAIDs alone at 14 days.33 Ice and heat therapy have similar analgesic effects.32

UNSUPPORTED

Oral Steroids. A short course of oral corticosteroids has questionable benefit for patients with acute radicular leg pain.34 However, there are no studies to support the use of oral steroids for isolated acute low back pain. Acupuncture. Several low-quality trials show that acupuncture has minimal or no benefit over sham treatment, naproxen (Naprosyn), or the Chinese herbal therapy moxibustion.35,36 Although evidence to support its effectiveness is limited, acupuncture may be cost-effective in patients with pain lasting longer than four weeks.25 Exercise. Aerobic conditioning, strengthening exercises, flexibility exercises, or a combination of these exercises is no more effective than other treatments in patients with acute low back pain.37-39 Lumbar Support. It is unclear whether lumbar support is more effective than no intervention or other treatments for acute low back pain.40 Massage. There is insufficient evidence to recommend for or against massage therapy for acute low back pain.41,26 It is unlikely to be cost-effective.25 Spinal Manipulation and Chiropractic Techniques. Low-quality evidence shows that spinal manipulation may be more effective than sham treatments in the short-term reduction of pain (less than six weeks), but no more effective in reducing disability.18,20,42,43 There is little evidence that manipulation is costeffective for treating acute low back pain.25 Although chiropractic techniques are considered safe if performed by a well-trained chiropractor, a systematic review found that SORT: KEY RECOMMENDATIONS FOR PRACTICE Clinical recommendation Evidence rating References Red flags are common in patients with acute low back pain and do not necessarily indicate serious pathology; therefore, physicians should rely on a comprehensive clinical approach to evaluating red flags in these patients. C 5, 6, 8 Without findings suggestive of serious pathology, imaging is not indicated in patients with acute low back pain. C 8-11 Nonsteroidal anti-inflammatory drugs, acetaminophen, and muscle relaxants are effective treatments for nonspecific acute low back pain. A 16-20 Patient education that includes advice to stay active, avoid aggravating movements,

and return to normal activity as soon as possible and a discussion of the often benign nature of acute low back pain is effective in patients with nonspecific pain. B 23, 24 Although regular exercises may not be beneficial in the treatment of nonspecific acute low back pain, physical therapy (McKenzie method and spine stabilization) may lessen the risk of recurrence and need for health care services. B 26-31, 37-39 Spinal manipulation and chiropractic techniques are no more beneficial than established treatments for nonspecific acute low back pain, and their addition to established treatments does not improve outcomes. B 18, 20, 25, 42-44 Bed rest is not helpful for nonspecific acute low back pain. A 46 A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, diseaseoriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp. org/afpsort.xml. Acute Low Back Pain February 15, 2012 ◆Volume 85, Number 4 www.aafp.org/afp American Family Physician 349 these techniques (e.g., manipulation, temperature modalities, exercises, mechanical devices, patient education) provide no clinically relevant improvement in pain or disability compared with other treatments.44 Traction. High-quality trials show no evidence of benefit with traction, as a single treatment or in combination with other treatments, in patients with acute or chronic back pain.45 There are no studies on acute low back pain alone.

INADVISABLE

Bed Rest. Bed rest should not be recommended for patients with nonspecific acute low back pain. Moderate-quality evidence suggests that bed rest is less effective at reducing pain and improving function at three to 12 weeks than advice to stay active.46 Prolonged bed rest can also cause adverse effects such as joint stiffness, muscle wasting, loss of bone mineral density, pressure ulcers, and venous thromboembolism

Introduction

Pain is generally the symptom that brings a person to a healthcare practitioner looking for relief. As informed by the American Pain Society, 45% of the American population seeks medical attention for chronic pain.1 Because complaints of pain are so varied, non-specific or diverse,2 what may be tolerable at one instance suddenly becomes unbearable to the same person in another circumstance. The exact same injury to two different persons has totally different responses. This is not easily explained as the nervous system, that is chiefly responsible for pain perception and awareness. The nervous system is connected to other systems and organs in an intricate network and the pain transmission methods are equally complex. There is constant mediation of higher centres that make it even more challenging to figure out.3

Physiotherapists attempt to utilise a combination of strategies to bring pain relief to their patients. They know that pain is not only subjective, but an objective experience.

Physiotherapy Examination Guidelines for Signs and Symptoms

Quite a few individuals with pain are referred for physiotherapy (physical therapy) for an instant cure or have resigned to accepting a lifetime of pain and disability. Often, secondary gains have a larger overlay on the physiology that is causing pain and this may prove to be the most difficult hurdle for the therapist to overcome. However, a thorough examination of the patient is essential to establishing a treatment plan with attainable goals.

Range of motion of the affected and unaffected parts this may be directly impacted due to anatomical insult or maybe impaired due to protective spasm, guarding or faulty positioning. Range of the joint is not limited to the peripheral joints but the therapist also may need to assess the joint mobility of the vertebral body(ies) in the various anatomically available ranges. A working knowledge of the available joint play in each direction for different levels of the spine is essential to determine a decrease in range of motion.

Posture/Gait Deviations Deviations from the typical gait and posture may be a result of pain or may actually cause the pain. Postural deviations should be assessed not only in

the supine or prone position but also in standing and sitting which are the more functional positions that impact the patient's performance.

Pain History and Presentation

This includes observation during and after the evaluation and includes the origin/onset, site, pattern, quality, intensity, radiation, characteristics, contributing and relieving factors, previous treatments and their effectiveness, and other visceral signs and symptoms.

Palpation determining the end-feel at the available movement allows the therapist to estimate the nature of the cause of the pain. Neurological function testing involves assessing tone, reflexes, sensations and coordination.

Orthopaedic testing for stability and mobility of joints and various signs to differentially diagnose the condition/pathology.

Neural tissue tension testing involves a pressure and stretch to determine the glide of the peripheral nerve trunk and assess possible restrictions along its course.

Functional assessment is probably the most important element that a physiotherapist needs to include in a patient's assessment; the impact that pain has on the person's functional abilities can uniquely be addressed by a physiotherapist. The patient's inability or difficulty to perform Activities of Daily Living (ADLs) must be the cornerstone of the patient evaluation. Simple activities such as sit-to-stand may be a problem due to low back pain or inability to dress/undress due to shoulder pain is usually the cause the patient is looking for a physiotherapist's services. Therefore, the functional assessment should be performed in the position that the patient performs the activity in. For example, if the patient reports pain in the low back after standing, an assessment in standing should be performed to understand the impact of gravity in the functional position. Preferably, the pain-causing activity/position should be used to best understand the pathophysiology using a kinesiological framework. A movement analysis

approach may be required to determine inappropriate firing of the muscles that impact the timing of the movement.

Objective Measures of Pain Used in Physiotherapy

Pain memory is not an accurate measure of pain intensity. Researchers have demonstrated that it is worse when it comes to assessing chronic pain.3 Therefore, an objective measurement of pain on an ongoing basis while under the care of the therapist is an integral part of patient care. In addition to the measured intensity, the duration, frequency, location and description of the pain should also become a part of the ongoing assessment. Typically, the therapist will assess these elements to determine the efficacy of the treatment.

Visual Analogue Scale (VAS) is an easily understood concept but it is not found to be reliable. Also, it cannot be used in patients that have cognitive impairments or those that cannot understand an abstract concept such as a linear representation of their pain4.

Simple Descriptive Pain Scale (SDPS) is used for patients that cannot abstractly understand a pain scale. FACES is usually best used with young children and those that are unable to express their pain verbally. "Pain Drawings" may also be used.

Conditions and Treatment

Physical this involves directing the treatment interventions to the physiological and anatomical aspects. Healing the tissue that was damaged due to injury, disuse, etc. is the main focus. This is often the target for relief in acute pain that is due to a very recent injury or recurrent and repetitive physiological stress. Such physical interventions are often passive and the effect may be limited to a short duration.

Cognitive are typically based on suggestions from the clinician that encourage the patient's active participation in the healing process. This is often used in chronic pain patterns that cannot break the cycle of pain à disability/disuseà pain. This must be initiated by the patient as it focusses on addressing the patient's perception of pain and its resulting limitations.

Behavioural changes on part of the patient are probably the most effective methods to bring about long term pain relief. Exercises, biofeedback, relaxation techniques, etc. are examples. There is a learning period where the patient is trained to perform these methods and when trained is able to perform them independently.

Physiotherapy treatment for pain using physical agents may be traced back to ancient Rig Veda talks of using light and heat to relieve pain. In early 250 A.D. Romans used electric eels to treat pain due to gout, headaches, etc. As technology advanced, we currently use various modalities in the form of LASERs, electrical stimulation, ultrasound and heat in addition to other manual therapy forms (Figure 1).

Laser used by physiotherapists are: Ruby, Gallium Arsenide (GaAs), diode with different wavelengths. The authors have used GaAs with pulsed Infrared (904nm wavelength with 1.5 to 2 cm depth of penetration) with good results. Laser causes release of ACTH and beta-endorphins, reduction of prostaglandin E and SOD activity, immunostimulant, balance of intra-extra cellular activities and accelerates ATP and collagen synthesis. Laser is contra indicated over eyes, cancerous lesions, pregnancy, pacemakers, thrombosis and photochemical drugs.

Commonly used physical agents in physiotherapy are heat, electricity, light, sound, and cold. Most of these agents are used to improve the lymphatic and blood circulation to the area due to a local vasodilation effect and possible muscle relaxation.

Thermotherapy or the use of heat is likely to decrease excitability of muscle spindles and increase activity of Golgi tendon organs and result in decreased muscle spasm. Sedation of sensory nerve endings if the heat is mild may also promote pain relief. Also, gating at the spinal cord level may raise the pain threshold level and therefore allow the

patient to perform with decreased difficulty.8 Several modalities may be used to deliver localised heat in a controlled and safe manner. Superficial heat can be delivered using conduction techniques such as moist heat packs or paraffin wax baths. The depth of penetration using such techniques is less than 1 cm. Fluidotherapy is an example of the use of convection heat that is produced when molecules are agitated and emit heat due to this excitation. This is generally used for hands and feet which are "immersed" in the machine that produces heat. Radiation may be used to heat large body parts that are not bony and infrared is commonly used examples of this.

Heat to deeper tissues can be delivered using energy conversion techniques such as diathermy or ultrasound. Shortwave diathermy uses a constantly reversing and oscillating magnetic field which heats up the tissue temperature. It is used generally for moderate to large body parts and is contraindicated in patients with underlying cancer, multiple sclerosis, any metallic implants including pacemakers. Its use is generally avoided during pregnancy or over growing epiphysis and over eyes.9 Ultrasound is sound waves transmitted at a high frequency of 1-3 MHz. The higher the frequency the lesser is the depth of penetration. It can heat up tissues 2-5 cm.10 depending on the frequency employed. The advantage of ultrasound is dual it has thermal effects in the treated area but also has non thermal effects due to the mechanical properties of the sound head being physically in contact with the body. Because of its effect on A and C fibres, it can provide pain relief and decrease muscle spasm.11 Since the conducer, or treatment head, is in close contact with the treated area, it is used to obtain localised relief. Ultrasound can cause micro streaming and this improves metabolic processes, enzyme activity and alters the ion exchange speed in the area treated. When pain-relieving ions are introduced using ultrasound, the technique is referred to as "phonophoresis". Commonly used chemicals introduced in this manner are lidocaine, hydrocortisone or NSAIDs like piroxicam for pain relief or decreasing inflammation. Medication molecules were found to travel up to tissue depth distances of two inches12. Cryotherapy, uses the physiological effects of cold, is generally considered in the treatment of acute inflammatory conditions and muscle spasm. Cooling causes the large myelinated and small unmyelinated nerve fibres to decrease their nerve

conductivity. Pain perception and contractility of the muscles, therefore, decreases and consequently, muscle spasm is diminished. Initially, the blood flow to the area decreases but after 15 minutes, it increases. It is contraindicated in patients with Raynaud's phenomenon and used cautiously when treating people with peripheral vascular disease, circulatory problems or sensory loss. Therapeutically, cryotherapy is used either by a direct application of a cold/ice pack or by a vapocoolant spray usually prior to manual therapy techniques deep friction tissue or stretching. The latter is generally used in treatment of trigger points. Cryotherapy has been found to be particularly helpful in acute rheumatoid arthritis by improving function.

Transcutaneous Electrical Nerve Stimulation (TENS), as the name suggests, employs electricity to control pain (Figure 2). While the exact mechanism of TENS is not sufficiently clear, the working theory is that the large diameter A beta fibres are specifically stimulated.13 The two mechanisms generally attributed for this physiological effect of electricity are the "gate control theory" or through the stimulation of tonic descending pathways that inhibit pain. Recent research has also demonstrated that low frequency TENS can increase the level of endogenous opiates in the nervous system. The gate control mechanism at the spinal cord level produces moderate paraesthesia when sensory-level TENS (high rate) is used.14 When low rate TENS is used, it may produce muscle contractions and this is thought to produce opiates in the CNS that can bring pain relief.15 This has been more beneficial in chronic pain as the pain relief lasts for a few days as compared to the high rate TENS where pain may be alleviated for a few hours. Therefore, adjusting the TENS parameters is essential to pain relief and an understanding of electrophysiology is necessary. It is contraindicated, like all electrical stimulation, in patients that have a pacemaker, and in patients that are pregnant. Patients that may have sensory disturbances, caution must be exercised and the patient closely monitored. One of the benefits of TENS is its ease of application and portability and therefore it can be taught to the patient or caregiver to use on a regular basis, without being dependent on the therapist.

Iontophoresis is a method to introduce chemical ions using a small electrical current through the skin (Figure 3). Chemical ions of medication are used in a gel form that is

applied to the skin and the direct current introduced via the electrode that is placed over the skin. Lidocaine, hydrocortisone, iodine, methyl salicylate, acetic acid are examples of chemical substances used for pain relief or reduction of muscle spasm. Allergic reaction to the medication is a contraindication of this method.16

Manual therapy techniques such as gentle massage have been used for centuries. It improves local circulation from the mechanical forces on the area treated and may also be eliciting the gating mechanism at the spinal cord level.17 Contraindications for massage include dermatological conditions, acute infection or thromboembolism. One of the techniques that have gained a lot of attention is lymphatic massage which is used for patients post mastectomy where pain and swelling can be disabling. Myofascial release is another specialised technique that works on realigning the fascia layers and allowing the myofascium to function properly.18 Joint mobilisation is one of the most commonly used manual therapy techniques by physiotherapists around the world. By guided and controlled passive oscillations in specific directions and amplitude, collagen fibres in the joint and surrounding areas are loosened. This produces pain relief and regains joint mobility to improve function. Based on the amplitude and force applied, mobilisation is characterised from Grade I to V. It is contraindicated in patients that may have osteoporosis, malignancy, vascular disease, acute infection in the area treated, etc.

Cognitive strategies such as relaxation techniques, body imaging, humour, hypnosis, etc. are also potentially used for pain relief and may be included modalities in addition to the physical agents.

While physical modalities and manual techniques are important, these are best used as adjuncts to an exercise programme. The most important aspect of a pain management programme that is developed and executed by a physical therapist is a patient-centred exercise programme. Range of motion, stretching, or strengthening exercises are all beneficial to improve mobility, strength and muscle tone. Aerobic exercises may be incorporated as well if cardiovascular fitness needs improvement. One of the other desirable effect of sufficient intensity of exercise is the release of beta-endorphin levels

which in turn can help alleviate pain and improve mood. Exercise programme may target specific muscles or muscle groups for strengthening or joints for stretching to improve mobility. To optimise compliance, it is necessary that the patient becomes an active partner in the development of the programme rather than a passive recipient. Exercises should be 'tailor made' to suit each individual. Pain relief that is aimed at improving the overall quality of life is the ultimate goal of a physical therapy programme. While temporary relief obtained with the use of modalities may appeal to most patients, the long term effect of exercise should be emphasised right from the first session of therapy. An intelligently designed exercise programme that is prescribed to the patient, with the patient's needs and lifestyle in mind, should become the cornerstone of a pain management programme.

Conclusion and Follow Up

Physiotherapy must be started as early as possible to minimise pain, stiffness, contractures and deformities. Ergonomic guidance must be followed regularly. Follow up is equally important specially for chronic spinal and arthritis pain. Exercises should be done under the guidance of qualified Physiotherapist and progressive exercises to be given as patient improves.

INTRODUCTION

Ozone (O_3), a gas discovered in the mid-nineteenth century, is a molecule consisting of three atoms of oxygen in a dynamically unstable structure due to the presence of mesomeric states. The gas is colorless, acrid in odour and explosive in liquid or solid form. It has a half-life of 40 min at 20°C and about 140 min at 0°C. Its basic function is to protect humans from harmful effects of UV radiation. Ozone occurs at less than 20 $\mu g/m^3$ from the Earth's surface at concentrations that are perfectly compatible with life. Although O_3 has dangerous effects, yet researchers believe it has many therapeutic effects.[1–3] The beginning of precise medical

O_3 generators has only recently allowed the mechanisms, action and possible toxicity of O_3 to be evaluated by clinical trials.[2] Ozone has a capacity to oxidize organic compounds,[4] and has well-known toxic effects on the respiratory tract when present in smog.[5–6] In medical use the gas produced from medical grade oxygen is administered in precise therapeutic doses, and never via inhalation, and advocates that it has excellent health benefits in dental caries, decrease blood cholesterol and stimulation of antioxidative responses, modifies oxygenation in resting muscle and is used in complementary treatment of hypoxic and ischemic syndromes.[7–10]

Go to:

HISTORY OF OZONE THERAPY

Ozone therapy has been utilized and extensively studied for many decades altogether. Its effects are proven, consistent and with minimal side effects. Medical O_3, used to disinfect and treat disease, has been around for over 150 years. Used to treat infections, wounds and multiple diseases, O_3's effectiveness has been well-documented. It has been used to disinfect drinking water before the turn of the last century. Ozone was known to treat as many as 114 diseases.[11] Ozone therapy has been in use since the 1800s and in 1896 the genius Nikola Tesla patented the first O_3 generator in the US, later forming the "Tesla Ozone Company."[12] During the first world war (1914-18) doctors familiar with O_3's antibacterial properties, and with few other medical resources available to them applied it topically to infected wounds and discovered O_3 not only remedied infection, but also had hemodynamic and anti-inflammatory properties.[13] In the late 1980s, reports had emerged that German physicians were successfully treating HIV patients with 03-AHT (Autohemotherapy). There was then no pharmaceutical treatment for HIV and a pandemic was feared, so Canadian authorities authorized the study to test safety and efficacy of 03-AHT in AIDS patients. Ozone had shown promise in *in vitro* testing. Ozone was seen effective at disinfecting extracorporeal blood samples of HIV; unfortunately for AIDS patients, 03-AHT proved to be an *in vivo* ineffective treatment[14–15] [Table 1].

Table 1

The chronological use of ozone in medicine

Year	Use/treatment of/with ozone
1987	Abscess, acne, AIDS, allergies, cerebral sclerosis, circulatory disturbances, cirrhosis of the liver, cystitis, bedsores, gangrene, hepatitis, herpes, high cholesterol, colitis, tumors, cancer, osteomyelitis, Parkinson's, rheumatism, Raynaud's disease, scars, inflammation of the vertebrae, stomatitis, joint dystrophy, phlebitis, open sores, urology, vascular surgery, wound healing.[16]
1988	Herpes, AIDS and flu, wounds, burns, Staphylococcus infections, fungal and radiation injuries, and gangrene. Fistulae, hemorrhoids and anal infections. Diabetes and arteriosclerosis. Used in periodontal disease, mixed in water and swallowed for use on gastric cancer, and applied as a wash in intestinal or bladder inflammation. Mixed with olive oil it is used on fungal growths and skin ulcers. Ozone baths are used to irrigate the skin, to disinfect and treat eczema and skin ulcers.[17]
1989	Influence on tumor metabolism was observed, hence subsequently used in treatment of cancer.[18] There was significant increase IgG levels, hence was evaluated for its immunostimulatory activity.[19]
1990	Ozone in combination with 5-fluorouracil was shown to be synergistic *in vitro* against tumor cell suspensions, derived from the breast and the colon.[20] Ozonation of blood was carried out to treat viral diseases. Ozonation of blood was found to increase the release of lymphokines and the stimulation of peripheral blood mononuclear cells.[21]
1991	Ozone was found to have germicidal activity by the virtue of its oxidative destruction of micro-organisms including viruses and bacteria[22]
1992	Ozone therapy was used in rhinoplasty and it was found that there was a significant reduction in the postoperative complications.[23]
1993	Ozonated saline used as irrigating solution and was found to reduce abscess formation in the rats with fecal slurry in the peritoneal cavity.[24]

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SARS AND OZONE

Ozone is a naturally occurring energy-rich molecule embodying unique physico-chemical and biological properties suggesting a possible role in the therapy of SARS, either as a monotherapy or, more realistically, as an adjunct to standard treatment regimens. Owing to the excess energy contained within the O_3 molecule, it is theoretically likely that O_3, unlike organism-specific antiviral options available today, will show effectiveness across the entire genotype and subtype spectrum of SARS.[25]

Go to:

MECHANISM OF ACTION

Inactivation of bacteria, viruses, fungi, yeast and protozoa: Ozone therapy disrupts the integrity of the bacterial cell envelope through oxidation of the phospholipids and lipoproteins. In fungi, O_3 inhibits cell growth at certain stages. With viruses, the O_3 damages the viral capsid and upsets the reproductive cycle by disrupting the virus-to-cell contact with peroxidation. The weak enzyme coatings on cells which make them vulnerable to invasion by viruses make them susceptible to oxidation and elimination from the body, which then replaces them with healthy cells.[26]

Stimulation of oxygen metabolism: Ozone therapy causes an increase in the red blood cell glycolysis rate. This leads to the stimulation of 2,3-diphosphoglycerate which leads to an increase in the amount of oxygen released to the tissues. Ozone activates the Krebs cycle by enhancing oxidative carboxylation of pyruvate, stimulating production of ATP. It also causes a significant reduction in NADH and helps to oxidize cytochrome C. There is a stimulation of production of enzymes which act as free radical scavengers and cell-wall protectors: glutathione peroxidase, catalase and superoxide dismutase. Production of prostacyline, a vasodilator, is also induced by O_3 [Figure 1].[25]

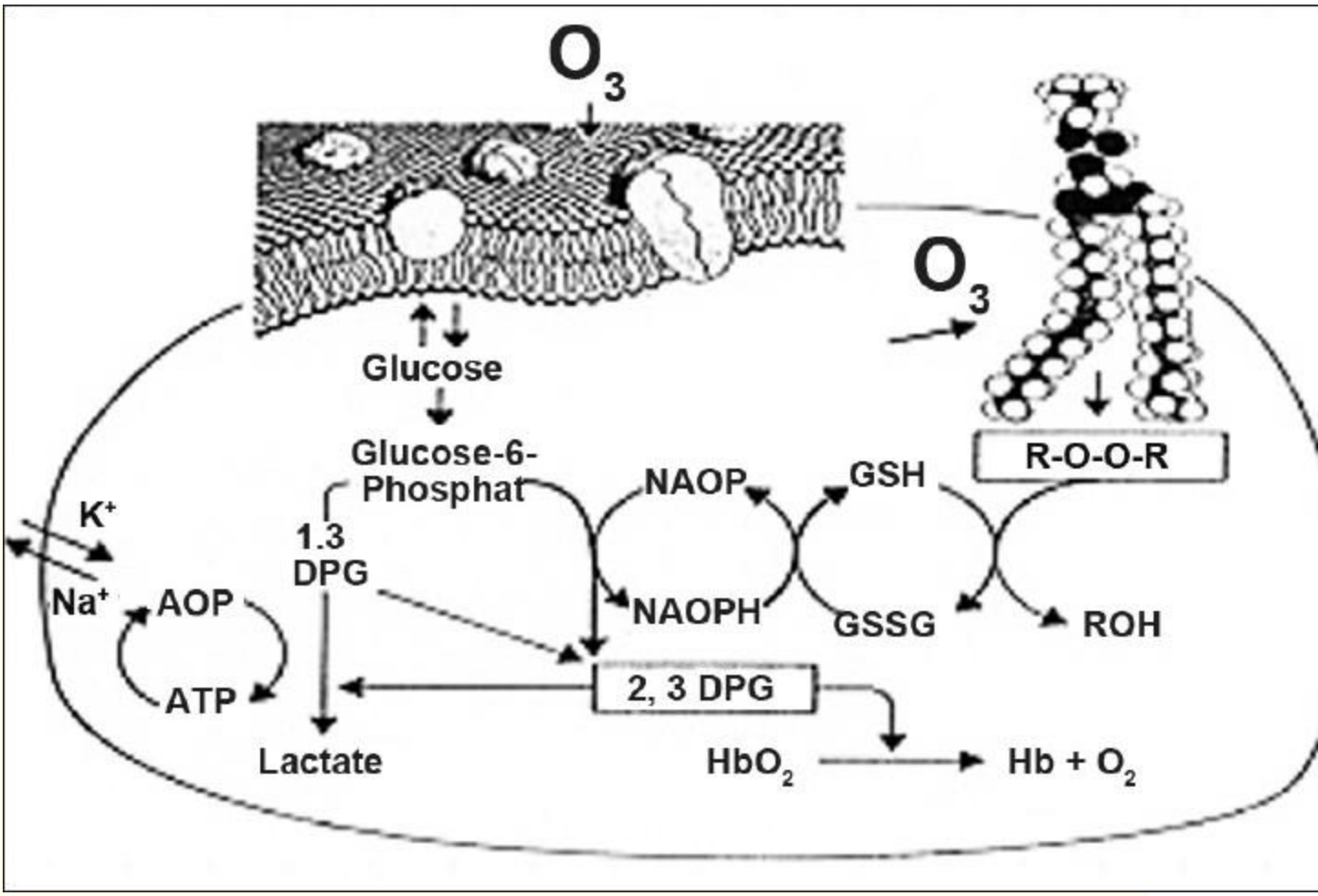

Figure 1

Action of ozone on RBC Metabolism[27]

Activation of the immune system: Ozone administered at a concentration of between 30 and 55 µg/cc causes the greatest increase in the production of interferon and the greatest output of tumor necrosis factor and interleukin-2. The production of interleukin-2 launches an entire cascade of subsequent immunological reactions.[27]

Mechanism of action of O_3 on the human lung: Ozone exposure induces a significant mean decrement in vital capacity. It significantly increases mean airway resistance and specific airway resistance but does not change dynamic or static pulmonary compliance or viscous or elastic

work. It also significantly reduces maximal transpulmonary pressure. And further more significantly increases respiratory rate and decreased tidal volume.[27]

Go to:

CLINICAL TRIALS

The study to evaluate effect of bimosiamose on O_3-induced sputum neutrophilia: Biomosiamose is an anti-inflammatory glycomimetic and selectin inhibitor.[28] It is found effective against disease states involving inflammatory cells like for example for asthma.[29] This drug, as per last updation, was in phase 2 trials and being evaluated for its efficacy and safety in treating chronic pulmonary obstructive disease (COPD), the study is sponsored by Revotar Biopharmaceuticals AG and was carried out by NCT00962481 (ClinicalTrials.gov Identifier).[30]

Evaluate the effects of the drug (SB-656933-AAA) on the body after a single dose in subjects who have inhaled O_3: Drug SB-656933-AAA was developed by GlaxoSmithKline which was found to exhibit good activity in treating COPD as well as cystic fibrosis. This action was found to be enhanced by administration of a single dose of O_3 before administration of the aforementioned drug. This drug until latest updated data was in phase 1 stage, study was carried out by NCT00551811.[31]

Intraarticular O_3 therapy for pain control in osteoarthritis of the knee: Ozone is being currently tested for its effectiveness in relieving the pain in patients suffering from osteoarthritis of the knee. The current status of the study is phase 2 which is sponsored by Ben-Gurion University of the Negev and the study being conducted by NCT00832312.[32]

The Effect of Ozone Therapy for Lumbar-Herniated Disc: Ozone is also being evaluated for its efficacy infiltration and its effectiveness in comparison with microdiscectomy in the treatment of lumbar-herniated disc with criteria for surgery. The study is currently in its phase 2 studies, which is sponsored by Kovacs Foundation and trials being carried out by NCT00566007. The study also evaluates the efficacy of infiltration in presence of corticoids, anesthetics, which is being compared by replacing O_3 by oxygen.[33–35]

Go to:

ADVANTAGES OF OZONE THERAPY

Diabetic complications are attributed to the oxidative stress in the body, O_3 was found to activate the antioxidant system affecting the level of glycemia. Ozone prevented oxidative stress by normalizing the organic peroxide levels by activating superoxide dismutase.[36–37] Ozone was found to completely inactivate the HIV *in vitro*, this action of O_3 was dose-dependent. Concentration used for inactivation was found to be non-cytotoxic. The inactivation was owing to the reduction of the HIV p24 core protein.[38] Ozone was also found to increase the host immunity by increasing the production of cytokine.[39] In an *in vitro* study, it was observed that O_3 is very effective in reducing the concentrations of *Acinetobacterbaumannii*, Clostridium difficile and methicillin-resistant *Staphylococcus aureus* in dry as well as wet samples, hence it can be used as a disinfectant. Oxygen/ O_3 mixture was also found to prolong the appearance of arrhythmia induced by potassium chloride, aconitine, etc., in laboratory animals like rats.[40]

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DISADVANTAGES OF OZONE THERAPY

An array of ill-effects are observed owing to the reactivity of O_3 viz oxidation, peroxidation or generation of free radicals and giving rise to cascade of reactions like peroxidation of lipids leading to changes in membrane permeability,[41] lipid ozonation products (LOP) act as signal transducer molecules.[42] The main reason for this being presence of unsaturated fatty acids in both lung lining fluid and pulmonary cell bilayers, O_3 reacts with unsaturated fatty acids to give their specific products i.e., LOP, which activates the lipases triggering the release of endogenous mediators of inflammation.[43] The loss of functional groups in enzymes leading to enzyme inactivation. These reactions further results in cell injury or eventual cell death. Combinations of O_3 and NO_2 occur in photochemical smog, have hazardous effects on lung alveoli and act additively or synergistically. Dietary antioxidants or free radical scavengers like vitamin E, C, etc., can prevent aforementioned effects of O_3.[44–45]

In an *in vitro* study it was observed that arachidonic acid was oxidized in presence to O_3 to give peroxides, viz. arachidonic acid peroxides (AAP), having activity comparable to prostaglandin endoperoxides. These peroxides were fond to show following actions contraction of rabbit aortic strips and rat fundus strips in presence on indomethacin and Vane's mixture of vasoactive

hormones at doses comparable to naturally formed prostaglandin peroxides. AAP also caused aggregation of human platelets in platelet-rich plasma, but these effects were not observed in presence of indomethacin and vitamin E, which indicated that these can be used to treat such toxicity of O_3.[46]

Go to:

RECENT DEVELOPMENT

Ozone was effectively used as an antibacterial agent to treat oral infections caused by *Actinomycesnaeslundii, Lactobacilli casei* and *Streptococcus mutans*. Exposure of about 60 s exhibited 99.9% killing efficiency, but exposure for such a long period showed degradation of saliva proteins. So exposure of 10 s to 30 s was proved effective to kill significant number of bacteria.[47]

A single subcutaneous injection of O_3 in mouse with spared nerve injury of the sciatic nerve was found to decrease the neuropathic pain-type behavior. Mechanism of this action is yet unclear but O_3 was observed to regulate the expression of the genes that play vital role in onset and maintenance of allodynia.

Steroids are among the most commonly used medications in palliative care. A Canadian study of ambulatory palliative care patients with cancer demonstrated that 40% of patients were receiving corticosteroids, and dexamethasone was the medication most commonly added by palliative care specialists.[1] This study echoes European studies in which corticosteroids were among the drugs most commonly prescribed by hospital-based palliative care services.

There is evidence for the use of corticosteroids for specific indications, such as spinal cord compression,[5] raised intracranial pressure,[6] and bowel obstruction.[7] Corticosteroids are also commonly used for broader indications, such as to control pain, stimulate appetite, suppress nausea, and alleviate fatigue. However, there is little objective evidence in the literature for this broader use of corticosteroids.

Pain management

An adjuvant pain medication should be considered at all stages of the World Health Organization's pain ladder for mild to severe pain.[10] Mr C. shows evidence of mixed bony and neuropathic pain.[11] Steroids are particularly useful as adjuvant therapy for metastatic bone pain, neuropathic pain, and visceral pain.[12] As adjuvant agents, corticosteroids can directly reduce pain, reduce pain in concert with opioid use, allow for reduction of opioid dose, and have beneficial symptomatic effects outside of pain relief.

Glucocorticoids reduce pain by inhibiting prostaglandin synthesis, which leads to inflammation, and reducing vascular permeability that results in tissue edema. Glucocorticoids are also lipophilic molecules that can cross the blood-brain barrier. Research has shown that steroid receptors are found in the central and peripheral nervous systems and are responsible for growth, differentiation, development, and plasticity of neurons.[13] In particular, corticosteroids have been shown to reduce spontaneous discharge in an injured nerve, which reduces neuropathic pain.[12]

Dexamethasone is the most commonly prescribed corticosteroid for pain, but prednisone or prednisolone can also be used. An advantage of prednisolone is that the side effect of myopathy is less common. Dexamethasone causes less fluid retention than other steroids owing to the fact that it has less mineralocorticoid effect. It is also relatively more potent and, owing to dexamethasone's longer half-life, it can be taken once daily. The most appropriate dose of dexamethasone has not been determined, but a range of 2 to 8 mg orally or subcutaneously once to 3 times daily is generally accepted.

Corticosteroids have a diverse side effect profile, and side effects are not uncommon; thus, the lowest effective dose should be used. Because side effects accumulate over the long term, corticosteroids are best used for short-term therapy (1 to 3 weeks).[8,11] In palliative care, corticosteroids are used for longer than 3 weeks for cases in which prognosis is in the short to medium term and side effects are unlikely to develop in the time remaining. For cases in which corticosteroids are used in the long term, their use

should be monitored closely.[2] There is concern expressed in the literature that corticosteroids are not monitored closely enough in palliative care settings.[9]

The most frequently encountered side effects of dexamethasone are summarized in Box 1.[9,11,15] For cases in which side effects are mild or corticosteroids remain necessary to alleviate pain in the long term, medications can be prescribed to counteract side effects (eg, adjustment of diabetic medications to counteract hyperglycemia).[9] In patients at high risk of gastric bleed, gastroprotection can be prescribed concurrently with steroids. The combination of a nonsteroidal anti-inflammatory drug and a steroid increases the risk of gastric bleeding 15-fold; therefore, this combination should be avoided, particularly in the frail elderly.[16] For cases in which the use of steroids over many months is anticipated, a bisphosphonate can be considered concurrently in elderly patients and patients at risk of osteoporosis.

Box 1.

Common side effects of dexamethasone

Most frequent side effects include the following:

- increased appetite or weight gain
- proximal muscle weakness
- insomnia
- gastrointestinal side effects
- psychiatric side effects, such as delirium, depression, anxiety, and psychosis
- osteoporosis with long-term use

Less frequent side effects include the following:

- infections

- hyperglycemia
- Cushing syndrome

Life-threatening side effects include the following:

- gastrointestinal bleeds
- thromboembolism

Data from Walsh et al,[9] Pereira,[11] and Sturdza et al.[15]

Of particular concern in palliative patients is the side effect of proximal muscle myopathy when added to the weakness from terminal illness. Acute steroid myopathy is rare and occurs with high-dose parenteral treatment in the first week of treatment. More commonly, myopathy occurs as an insidious process. The muscles of the lower limbs are affected first, and patients often complain of difficulty with stairs or rising from a chair as an early symptom. Fortunately, myopathy is most often reversible upon discontinuation of the steroid. Physiotherapy is also helpful.

In terms of drug interactions, anticonvulsants accelerate the metabolism of corticosteroids, and thus higher doses might need to be used in patients taking anticonvulsants. Corticosteroids might cause an increase or decrease in phenytoin and warfarin levels, and these should be monitored in patients on concurrent therapy. Live vaccines should not be given to patients taking corticosteroids owing to their impaired immune response.

Discontinuing corticosteroid use

After 2 weeks of therapy with a steroid it can be discontinued without any adverse effects.[11] However, even low doses of corticosteroids can suppress the hypothalamic-pituitary-adrenal axis in the long term. Longer periods of treatment require a taper, the length of which depends on the duration of therapy.[15] The most appropriate method of tapering has not been determined in the literature.[17]

If patients have required steroids up to the last days of life and are no longer able to swallow, the steroids should be prescribed at full dose or tapered using the parenteral route (dexamethasone is available intravenously and subcutaneously) rather than abruptly stopping this medication.[8] If a stressful event, such as a serious infection or surgery, occurs within 1 week after discontinuation of steroid therapy, stress-dose steroid should be provided.

It is important not to mistake withdrawal from corticosteroids for advancement of progressive disease in palliative care.[8] Withdrawal symptoms from corticosteroids include pain, nausea or vomiting, weight loss, depression, fatigue, fever, dizziness, and rebound symptoms that are unmasked when there is loss of symptom control once the corticosteroid is removed. Addisonian crisis is a life-threatening complication that can cause confusion, coma, cardiovascular shock, and even death. Notably in palliative patients, corticosteroid withdrawal is known to exacerbate terminal restlessness.

Paramedicine and the emergency medical services have been moving in the direction of advancing pharmaceutical intervention for the management of pain in both acute and chronic situations. This coincides with other areas of advanced life support and patient management strategies that have been well researched and continue to benefit from the increasing evidence. Even though paramedic practice is firmly focused on pharmacological interventions to alleviate pain, there is emerging evidence proposing a range of nonpharmacological options that can have an important role in pain management. This review highlights literature that suggests that paramedicine and emergency medical services should be considering the application of complementary and alternative therapies which can enhance current practice and reduce the use of pharmacological interventions.

1. Introduction

Pain is a common complaint among patients cared for by paramedics [1]. Cases attended by paramedics involve patients who report pain as their chief complaint and symptom that instigated an ambulance call for assistance. In other cases, the sensation of pain will be a component of a constellation of symptoms, and the patient's report of pain will be an important diagnostic cue that guides the clinical examination. Paramedics will also encounter patients who report persistent pain, but where the pain is unrelated to their current health crisis.

Paramedics have an important role in identifying and reducing the burden of pain. The alleviation of pain is important from a humanitarian perspective, with freedom from pain

considered as a basic human right [2]. Pain is also associated with significant morbidity, and as the study of pain evolves, the relationship between poorly managed acute pain and the development of chronic pain syndromes is becoming recognized [3].

Patients who seek medical care may understandably expect relief from pain, with a study of patients presenting to an emergency department finding a majority that expected relief from their pain, with a significant proportion expecting complete relief [4]. Regardless of the health care setting, pain is a frequently reported symptom. For paramedics, an encounter with a patient reporting pain is a common event [5].

The provision of reassurance and comfort for the relief of pain and distress has been described as a primary goal of paramedics and emergency medical services (EMS) [6]. However, reassurance alone may provide inadequate relief of pain. Prior to the introduction of advanced levels of training and clinical guidelines for the administration of analgesics, the management of pain in patients who were injured relied on techniques such as splinting fractures so that the immobilized limb was less likely to move and exacerbate tissue injury resulting in further pain. While there are still rudimentary skills used, paramedic practice has advanced and become more specialised and now includes the administration of a range of pharmacological agents to relieve or minimize pain [7, 8]. These now include opioids, nonsteroidal anti-inflammatories, paracetamol, NMDA-receptor antagonists, methoxyflurane, and local anaesthetics for nerve blocks. Morphine is commonly used for the treatment of pain, and this drug is considered the “gold standard” against which other analgesics are measured [9]. The efficacy of opioids such as morphine and fentanyl for the management of severe pain in the paramedic practice setting has been established [10].

Over the last two decades, this escalating reliance upon pharmaceuticals for pain management practice has been borne in part by the need to respond to societal expectations. In addition, pain management has been identified as a key performance indicator by some EMS. In Australia, the Council of Ambulance Authorities (CAA) has identified that the quality of pain relief is a surrogate measure of compassion and caring and has recently recommended that EMS develop and adopt clinical performance indicators that include the reduction of pain [22]. However, this is not a binding recommendation and national data relating to the adoption of pain management performance indicators by Australian EMS is not widely available.

The acknowledgement of pain management as an important component of paramedic practice is reflected by the use of evidence-based guidelines for the relief of pain. However, these almost exclusively focus on acute pain and pharmacological interventions. References to nonpharmacological therapies in Australian clinical guidelines for paramedics are uncommon, with the exception of traditional measures such as splinting, cooling, and reassurance. References to complementary and alternative therapies such as acupuncture are rare in the paramedic literature and resources that support paramedic education [23, 24]. Although uncommon in Australian paramedic curricula, nonpharmacological therapies for pain relief feature consistently in the practice of several allied health disciplines, with cognitive-behavioral and complementary therapies included in the International Association for the Study of Pain Core Curriculum for Health Professionals [25].

Nonpharmacological interventions to alleviate pain rely on the inhibition of pain signalling. Pain arises from nociceptive transmission through small afferents to the spinal cord and then to higher brain nuclei and the cerebral cortex. Nociceptive signals are mediated by peripheral and central components that may facilitate or inhibit this input [26]. These signals are modulated by midbrain networks which exert bidirectional control over nociceptive transmission through the spinal cord. Several neurotransmitters are involved in mediating nociceptive signals including substance P which facilitates transmission and endogenous opioid-based compounds that inhibit transmission [27]. Nonpharmacological analgesia therefore involves the inhibition of nociceptive input by activating separate antinociceptive outputs. Procedures such as transcutaneous electrical nerve stimulation (TENS) and acupoint stimulation rely on inhibiting the nociceptive signal to induce an analgesic effect.

Nonpharmacological approaches to the relief of pain are more commonly associated with nonacute settings and may be classified as follows:(i)psychological interventions (including distraction, stress management, hypnosis, and other cognitive-behavioral interventions),(ii)acupuncture and acupressure,(iii)transcutaneous electrical nerve stimulation,(iv)physical therapies (including massage, heat/cold, physiotherapy, osteopathy, and chiropractic).

These approaches to pain management may complement or indeed substitute pharmacological therapy in some types of pain. Chronic pain (which is also commonly encountered in paramedic practice) is one situation where a range of interventions may be used to manage complex health problems such as cancer pain, lower back pain, and specific diseases associated with pain such as endometriosis. Evidence of efficacy is variable, and this may be due to the type of pain, type of intervention, patient characteristics, skill and experience of the clinician, and heterogeneous study populations. For example, significant variability in the efficacy of acupuncture has been reported in the literature [28].

The use of these therapies to manage acute pain, such as pain arising from trauma or tissue injury associated with inflammation or ischemia, is rarely described in the literature. The role of alternatives in pharmacotherapy is acknowledged by the Australian and New Zealand College of Anaesthetists (ANZCA), albeit as adjunctive or complementary therapy [29]. When describing pain management in the emergency health setting, the ANZCA recommends “ice, elevation, and splinting for injuries” as well as reassurance as the mainstays of nonpharmacological management of pain [29].

This paper will appraise the current evidence of nonpharmacological interventions for pain management in the paramedic practice setting, either as complementary therapies or as alternatives to pharmacological interventions. Our review will focus upon acupuncture and acupressure, TENS, and the use of warming as all simple measures that may be implemented and would potentially complement current paramedic pain management guidelines. This contributes to the knowledge base for paramedic pain management practice and should inform future research that seeks to establish the role for nonpharmacological therapies in the relief of pain. For data sources, electronic literature searches were conducted using Medline, Embase, the

Cochrane Library, and Cinahl (EBSCO). The search terms used were “paramedic” OR “CAM” OR “acupuncture” OR “acupressure” OR “TENS.”

2. Transcutaneous Electrical Nerve Stimulation (TENS)

Alternative approaches to paramedic-initiated analgesia such as TENS have been reported in the literature [30, 31]. However, research into the use of nonpharmacological interventions in paramedic practice is limited. This lack of research may reflect the developing status of paramedic practice as an allied health profession. There may also be limited impetus for research in this area if nonpharmacological interventions are deemed to be inappropriate for the management of pain associated with acute trauma or health emergencies, particularly in an environment where the time taken for each interval in the patient care process is a closely monitored performance indicator. The drive to minimize time spent with each patient is designed to improve operational effectiveness, and this may restrict the use of nonpharmacological therapies that require extended time to deliver the care compared with the intravenous titration of opioids. Furthermore, attitudes among paramedics and service providers regarding the utility of nonpharmacological interventions to relieve pain may inhibit clinical trials that compare the efficacy of these therapies.

Although TENS has been clinically used for over three decades, the mechanisms by which analgesia is produced are only recently being described [32]. Gate control theory is the most common theory used to support the effect of inhibiting pain by TENS. Gate control theory describes how a stimulus that activates nonnociceptivefibers can inhibit pain. Pain is reduced when the area is rubbed or stimulated due to activation of nonnociceptivefibers inhibiting the nociceptive response in the dorsal horn of the spinal cord [33]. In TENS, nonnociceptivefibers are selectively stimulated with electrodes in order to produce this effect and thereby inhibit pain [33].

TENS appears to produce both segmental and descending pain inhibition since inhibition remains after spinalization (removal of descending inhibition) in the animal model [34]. Adenosine also appears to play a role in TENS analgesia since caffeine (adenosine receptor antagonist) significantly reduces the analgesic effect resulting from activation of large diameter fibers [35]. Additionally, concentrations of endogenous opioids have been shown to increase in cerebrospinal fluid following TENS procedure [36].

TENS uses electric current produced by a portable device to stimulate the nerves for therapeutic purposes. Previous intervention trials investigating the effect of TENS on pain are shown in Table 1. One randomized double-blinded study investigating TENS in an EMS setting showed that TENS intervention in female patients () with acute pelvic pain (salpingitis, ovarian cyst, dysmenorrhea, vaginal infection, and vaginal trauma) reduced pain, anxiety, heart rate, nausea, and arteriolar vasoconstriction with an improvement of overall patient satisfaction compared with those () treated with sham TENS [11]. The effect of TENS producing pain relief was further supported in another study in which patients suffering from acute posttraumatic hip pain felt less

pain and anxiety with TENS intervention compared with those treated with sham TENS [12]. These observations suggest that TENS could be an effective and fast-acting pain treatment with applications within paramedic practice.

Table 1
Intervention trials investigating the effect of TENS on pain.

3. Acupuncture, Electroacupuncture, and Acupressure

Stimulation of specific points on the body, commonly known as acupuncture, is widely recognized as a therapeutic procedure used to treat pain and illness [37, 38]. Acupoint stimulation such as manual acupuncture involves the penetration and manipulation of a fine needle through the skin into specified points on the body to evoke a sensation known as *de-qi* [39]. Treatment procedures that involve acupoint stimulation also include electroacupuncture and acupressure. Electroacupuncture requires delivery of electrical current through the inserted needle. Acupressure requires the use of fingers and hands to stimulate acupoints on the body to relieve pain and clinical symptoms [40]. More than 360 acupoints are located along 14 meridian channels that cover the body in a weblike interconnecting matrix [41]. Each acupoint is recognized as having a defined therapeutic action; however, a combination of acupoints is often stimulated to induce a therapeutic effect [41].

The potential mechanism for acupuncture analgesia is via the descending pain modulation pathways. The nucleus raphe magnus (NRM) in the midbrain is a significant neural site for descending analgesia via expression of serotonin [42]. NRM inhibits ascending pain signalling by projection neurons to the dorsal horn of the spinal cord. The NRM is part of a central pain modulatory system comprising the midbrain periaqueductal grey (PAG) and the ventromedial medulla (RVM) recruited to suppress or facilitate responses to noxious stimuli (PAG-RVM system). Endogenous opioid peptides are present in the neural soma and terminals of these nuclei. Electroacupuncture has been shown to enhance the expression of serotonin and reduce the release of substance P during electroacupuncture inhibition of acute nociceptive responses [43]. The dorsolateral pontinetegmentum is another midbrain site mediating spinal cord nociceptive signalling by providing noradrenergic innervations of the spinal cord. Involvement of noradrenergic receptors in rat spinal cord has also been demonstrated during electroacupuncture analgesia [44]. Together, these studies suggest that acupuncture evokes central pathways to inhibit the pain signal.

The World Health Organisation recommends the use of acupuncture for a substantial number of diseases [37]. The efficacy of acupuncture is formally endorsed by the National Institute of Health and recognized by the American Medical Association [45]. In a Cochrane Review paper on the efficacy of acupuncture for lower back pain, the results showed that acupuncture is more effective for pain relief than no treatment or sham procedure [46]. Moreover, when acupuncture is added with conventional therapy, it was shown to relieve pain and enhance function better than conventional therapies alone.

Acupressure works with the same acupoints and meridians as acupuncture. The only difference between two interventions is that acupressure stimulates the acupoints with finger pressure rather than by fine needles. Previous intervention trials investigating the effect of acupressure on pain are shown in Table 2. In the first known study to investigate the effects of acupressure on pain in the paramedic practice setting, researchers allocated adult patients () to one of three treatment arms. Group 1 used true acupressure points LI4 (Hegu), PC9 (Zhongchong), PC6 (Neiguan), BL60 (Kunlun), and GV20 (Baihui), while Groups 2 and 3 involved sham acupressure point and no acupressure, respectively [13]. Group 1 patients reported reduced pain and anxiety with these changes which was significantly greater than either Group 2 or Group 3. Group 1 patients also demonstrated a statistically significant decrease in heart rate compared with patients that were treated with sham acupressure () or did not receive the intervention (). Patient satisfaction scores after treatment were significantly better in Group 1.

Table 2
Intervention trials investigating the effect of acupressure on pain.

In a review paper on acupressure, it was shown that this procedure was effective for pain in patients with dysmenorrhea, during labour, and in trauma [47]. In accord with this, a randomized double-blinded study in 15 patients with distal radius fracture showed that acupressure on GV20 and LI4 lowered pain, anxiety, and heart rate and raised patient general satisfaction [17]. These findings suggest that stimulation with fingers on GV20 and LI4 may be a pain management option for patients with minor trauma during ambulance transportation to a hospital. Promoting and encouraging acupressure on other acupoints that fit within the context of analgesia may create a supportive environment of pain management and is possibly an easy skill to teach all levels of paramedics.

The related technique of auricular acupressure treats the entire body through pressure on a few points in the ear. In a randomized controlled study of 36 patients with gastrointestinal illnesses (gastritis, cholecystitis, pancreatitis, and diverticulitis), researchers compared acupressure in the ear with small plastic ball at the relaxation point with a sham intervention [14]. Although both interventions showed no significant changes in blood pressure and heart rate, greater improvements in anxiety and anticipated perception of hospital treatment were reported with acupressure.

A small, randomized study showed that acupressure in the ear with 1 mm acupressure plastic beads reduced the level of pain and anxiety as indicated by a reduced heart rate in patients () with hip fracture compared with patients () in the sham group [16]. These observations suggest that the application of pressure to auricular acupoints may offer benefits for improving pain and anxiety. Comparable to auricular acupressure, Korean hand acupuncture with hand patches consisting of a hard plastic ball was also effective in producing analgesia [15]. A randomized study involving 100 patients with minor trauma was conducted, with the groups divided evenly (per group) into intervention and sham acupressure groups. Significant improvements in nausea score, vasoconstriction, and overall patient satisfaction were achieved with Korean hand acupuncture bilaterally on K-K9 point located in the middle phalanx of the fourth finger. These

simple techniques could be quite easily taught to paramedic clinicians and we would propose further experimental studies in paramedic practice. The ear is usually an area that is not injured and is out of the way of body limbs, and gaining access to apply acupressure should not be hampered by the condition of the patient. The use of acupoint pressure on the ear may prove easily accessible in a range of situations that may have positive effects which assist in relieving pain.

4. Effect of Warming Interventions on Pain

Another type of intervention that may be implemented by paramedics for pain control in specific situations is active warming or resistive heating, and this has been examined in several studies (Table 3). As opposed to passive heating, in which there is no external source of heat used other than the person's own body heat, active or resistive heating involves using an external source of heat to warm the patient. This may be in the form of a heated blanket or increased ambient temperature. A single-blinded randomized study reported that fifty patients undergoing active warming with minor trauma including limited bleeding, fractures, or contusions experienced less pain and anxiety with increased overall patient satisfaction, thermal comfort, and core temperature compared with another fifty undergoing passive warming [18]. A subsequent study, involving patients with a diagnosis of cholelithiasis, showed that warming with an electric heating blanket over the abdomen reduced pain, anxiety, and heart rate [19]. The subcutaneous temperature increased accordingly with increasing skin temperature. Another study using this technique published by the same group of researchers showed that patients complaining of abdominal pain from renal colic experienced less pain, anxiety, nausea, and heart rate with overall improvement of patient satisfaction [20].

Table 3
Intervention trials investigating the effect of active warming on pain.

Lastly, in a study of female patients with pelvic pain from cystitis, urolithiasis, cholelithiasis, appendicitis, colitis, and rectal trauma, active warming over the abdomen caused less pain, anxiety, and nausea, compared to passive warming [21]. These suggest that active warming could be an adjunct to analgesic treatment at the emergency site.

5. Conclusion

There are many reasons why paramedicine and emergency care practice has been moving in the direction of advanced pharmacological interventions for the management of pain in both acute and chronic situations. This coincides with other areas of advanced life support and patient management strategies that have been well researched and continue to benefit from the increasing evidence. Even though paramedic practice is firmly focused on pharmacological interventions to alleviate pain, there is a developing literature suggesting that a range of nonpharmacological options may also have an important role in managing pain in individuals cared for by paramedics.

As a developing profession, paramedicine should investigate multiple modalities and consider complementary and alternative therapies that could be used to enhance pain relief and potentially also reduce the reliance on pharmacological interventions as the first-line approach to alleviating pain. If proven to be efficacious, the analgesic sparing effect may translate into cost reductions and better patient outcomes with less adverse reactions. However, further research is required to develop the level of evidence required to support changes to practice. From the research that has been conducted, we can see great potential value of conducting trials into the use of complementary therapies within paramedic practice and would strongly encourage further research specifically that looks into the use of simple techniques such as acupuncture (including electroacupuncture and acupressure), TENS, and active warming.

VALUE ADDED COURSE

COMPREHENSIVE PAIN CARE

Annexure II

STUDENT ENROLLMENT LIST (JULY-DEC 2018)

S.No.	University no	Name of the student	Year / CRRI	Signature
1.	U17MB331	MUSALE VENUGOPAL RAO	II nd	
2.	U17MB332	NAMITA THARANI	II nd	
3.	U17MB333	NAYANA NANDANAN M	II nd	
4.	U17MB334	NEHA KUMARI	II nd	
5.	U17MB335	NEHA KUMARI.B	II nd	
6.	U17MB336	NIDHI SUNIL KRISHNAN	II nd	
7.	U17MB337	NIJITH KRISHNADHAS RAHAEL	II nd	
8.	U17MB338	NIKITA VERMA	II nd	
9.	U17MB339	NILUTPAL DAS	II nd	
10.	U17MB340	NISHANT BHUSAN	II nd	
11.	U17MB341	PANEM SAMIUNNU	II nd	
12.	U17MB342	PARTHA PRATIM BARUAH	II nd	
13.	U17MB343	PAYAL MOHITE	II nd	
14.	U17MB344	POOJALAKSHMI.P	II nd	
15.	U17MB345	PRACHI KUMARI	II nd	
16.	U17MB346	PRASANNA.B	II nd	
17.	U17MB347	PRAVEEN.V	II nd	
18.	U17MB348	PRITAM SAHOO	II nd	
19.	U17MB349	PRIYA SAXENA	II nd	
20.	U17MB350	PRIYADARSHINI MAITHY	II nd	

RESOURCE PERSON

DR. KALASREE

COORDINATOR

Dr S NITHIANANDAM

Annexure III

MCQ: COMPREHENSIVE PAIN CARE

1. The following are process in pain relay information except
   a. Transduction
   b. Transmission
   c. Modulation
   d. Assessment

2. Following can activate pain receptors
   a. Pressure
   b. Heat
   c. Chemical
   d. All the above

3. All are pain mediators except
   a. Prostaglandins
   b. Leukotrienes
   c. Sodium
   d. Histamine

4. The following tract is involved in pain pathway
   a. Spinothalamic
   b. Corticospinal
   c. Spinoreticular
   d. Both A&C

5. Character of RSD are
   a. Pain dispropriatial to injury
   b. Progressive worsening of pain
   c. Presistence beyond the tissue damaging process
   d. All the above

6. Following are opioid except
   a. Morphine
   b. Cocaine
   c. Oxycodone
   d. Methadone

7. Example of opioid receptors
    a. H1
    b. HT1
    c. μ
    d. β

8. Chronic pain is
    a. Pain persisting for at least 1month following usual healing time
    b. Pain that recover frequently over a period of month
    c. Pain that occurs with non healing lesion
    d. All the above

9. Following are pain scale
    a. VAS
    b. FACES
    c. SDPS
    d. All the above

10. Causalgia is
    a. Severe burning pain & sign of ANS hyperactivity
    b. Pain at site different than injury
    c. Pain after cervical injury
    d. Pain affecting sleep wake cycle

B. Neha Kumari

Annexure III

8/10

MCQ: COMPREHENSIVE PAIN CARE

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   c. Pain after cervical injury
   d. Pain affecting sleep wake cycle

Praveen. N

Annexure III

MCQ: COMPREHENSIVE PAIN CARE

9/10

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   a. Transduction
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   b. Pain at site different than injury
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   d. Pain affecting sleep wake cycle

Annexure V
Student Feedback Form

Course Name: **COMPREHENSIVE PAIN CARE**

Subject Code: **ANAES 07**

Name of Student: _____ Roll No.: _____

We are constantly looking to improve our classes and deliver the best training to you. Your evaluations, comments and suggestions will help us to improve our performance

Sl. NO	Particulars	1	2	3	4	5
1	Objective of the course is clear					
2	Course contents met with your expectations					
3	Lecturer sequence was well planned					
4	Lectures were clear and easy to understand					
5	Teaching aids were effective					
6	Instructors encourage interaction and were helpful					
7	The level of the course					
8	Overall rating of the course	1	2	3	4	5

*** Rating: 5 – Outstanding; 4 - Excellent; 3 – Good; 2– Satisfactory; 1 - Not-Satisfactory**

Suggestions if any:

Annexure V
Student Feedback Form

Course Name: **COMPREHENSIVE PAIN CARE**

Subject Code: **ANAES 07**

Name of Student: Musale Venugopal Rao Roll No.: U1TMB331

We are constantly looking to improve our classes and deliver the best training to you.

Your evaluations, comments and suggestions will help us to improve our performance

Sl. NO	Particulars	1	2	3	4	5
1	Objective of the course is clear		✓			
2	Course contents met with your expectations			✓		
3	Lecturer sequence was well planned				✓	
4	Lectures were clear and easy to understand			✓		✓
5	Teaching aids were effective					✓
6	Instructors encourage interaction and were helpful				✓	
7	The level of the course					✓
8	Overall rating of the course	1	2	3	4	5

*** Rating: 5 – Outstanding; 4 - Excellent; 3 – Good; 2– Satisfactory; 1 - Not-Satisfactory**

Suggestions if any:

Good.

Annexure V
Student Feedback Form

Course Name: **COMPREHENSIVE PAIN CARE**

Subject Code: **ANAES 07**

Name of Student: Priya Saxena Roll No.: VITMB349

We are constantly looking to improve our classes and deliver the best training to you.

Your evaluations, comments and suggestions will help us to improve our performance

Sl. NO	Particulars	1	2	3	4	5
1	Objective of the course is clear					✓
2	Course contents met with your expectations			✓		
3	Lecturer sequence was well planned				✓	
4	Lectures were clear and easy to understand					✓
5	Teaching aids were effective			✓		
6	Instructors encourage interaction and were helpful				✓	
7	The level of the course					✓
8	Overall rating of the course	1	2	3	4	5

*** Rating: 5 – Outstanding; 4 - Excellent; 3 – Good; 2– Satisfactory; 1 - Not-Satisfactory**

Suggestions if any:

Satisfactory

Date: 05.12.2018

From
Dr M Kalasree
Head Of Department Incharge
Department of Anaesthesia
Sri Lakshmi Narayana Institute of Medical Sciences
Puducherry

To
The Dean,
Sri Lakshmi Narayana Institute of Medical Sciences
Puducherry

Sub: Completion of value-added course: COMPREHENSIVE PAIN CARE

Dear Sir,

With reference to the subject mentioned above, the department has conducted the value-added course titled: Comprehensive Pain Care in July- Dec 2018 for 20 students. We solicit your kind action to send certificates for all the participants, whose name list is attached with this letter. Also, I am attaching the photographs captured during the conduct of the course.

Kind Regards,

Dr. M Kalasree

Encl: Certificates

Photographs

Sri Lakshmi Narayana Institute of Medical Sciences

Affiliated to Bharath Institute of Higher Education & Research

(Deemed to be University under section 3 of the UGC Act 1956)

CERTIFICATE OF MERIT

This is to certify that __NIKITA VERMA_____has actively participated in the Value Added Course on Comprehensive Pain Care held during July - December 2018 Organized by Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry- 605 502, India.

Dr.KALASREE M
RESOURCE PERSON

DEPARTMENT OF ANAESTHESIOLOGY
SRI LAKSHMI NARAYANA INSTITUTE
OF MEDICAL SCIENCES
OSUDU, KIRUMAMPAKKAM, PONDICHERRY-605 502

Dr. KALASREE M
COORDINATOR

Sri Lakshmi Narayana Institute of Medical Sciences

Affiliated to Bharath Institute of Higher Education & Research

(Deemed to be University under section 3 of the UGC Act 1956)

CERTIFICATE OF MERIT

This is to certify that ___NILUTPAL DAS_____ has actively participated in the Value Added Course on Comprehensive Pain Care held during July - December 2018 Organized by Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry- 605 502, India.

Dr.KALASREE M
RESOURCE PERSON

Dr.KALASREE M
COORDINATOR


COMPREHENSIVE PAIN CARE
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