

**MINISTRY OF PUBLIC HEALTH OF UKRAINE
ZAPOROZHYE STATE MEDICAL UNIVERSITY
DEPARTMENT OF GENERAL PRACTICE – FAMILY MEDICINE**

**MEDICAL CARE IN THE CASE OF CHRONIC PAIN IN THE
PRACTICE OF FAMILY DOCTOR / GENERAL PRACTITIONER**

**The teaching textbook for the practical classes and individual work
for 6th-years students of international faculty
(speciality «General medicine»)
Discipline: «General practice – family medicine»**

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Readers:

Kuryata O.V. – Doctor of Medical Sciences, Professor, head of Hospital therapy № 1 and profpathology department, Dnepropetrovsk State Medical Academy MoH of Ukraine.

Fushtey I.M. - Doctor of Medical Sciences, Professor, Head department of therapy, clinical pharmacology and endocrinology, Zaporozhye medical academy of postgraduate education MRH of Ukraine

Writers:

Mykhailovska N.S. - Doctor of Medical Sciences, Professor, Head of the department of General practice – family medicine, Zaporozhye State Medical University;

Grytsay A.V. - PhD, associate professor of General practice – family medicine department, Zaporozhye State Medical University.

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PREFACE

The family doctor has to provide medical care in the cases of chronic pain: Chronic pain syndrome, Cervical Myofascial Pain, Fibromyalgia, Complex Regional Pain Syndromes. Timely diagnostics and ability to cure in the case of chronic pain syndrome in out-patient clinic by family doctor lead to prevention of complication, further disease progression, and improve the treatment result.

The approach considerations, principles of treatment and management in the case of chronic pain syndrome by general practitioner – family doctor are recited in the textbook. The algorithm of physical therapy and the characteristics of chronic pain syndrome medications were recommended for family doctor.

The necessity of this textbook is conditioned by absence of such workbooks, which satisfy requirements of basic parts of academic subject «General practice – family medicine».

This textbook can be recommended for students of institutes of higher education (IV accreditation level) in the study of appropriate topic, intern, general practitioner – family doctor, other specialists.

MEDICAL CARE IN THE CASE OF CHRONIC PAIN IN THE PRACTICE OF FAMILY DOCTOR / GENERAL PRACTITIONER

I. Actuality of the theme

The task of medicine is to preserve and restore health and to relieve suffering. Understanding pain is essential to both these goals. Because pain is universally understood as a signal of disease, it is the most common symptom that brings a patient to a physician's attention. The function of the pain sensory system is to detect, localize, and identify tissue-damaging processes. Since different diseases produce characteristic patterns of tissue damage, the quality, time course, and location of a patient's pain complaint and the location of tenderness provide important diagnostic clues and are used to evaluate the response to treatment.

II. Study purposes: to learn the basic organizational, diagnostic and therapeutic features of surgical patients (obstetrics and gynecology, surgery, traumatology and orthopedics, urology, proctology, oncology, ophthalmology, otolaryngology, dentistry, resuscitation and intensive therapy) in practice of FD; to diagnose the medical condition of pain in the chest, abdomen during initial contact with patient and determine the indications for urgent hospitalization in the pre-admission stage in the case of pain.

III. Concrete purposes of the module:

- to know the features inter-sectorial interrelation of FD in outpatient clinic;
- to evaluate the benefits of the FD in the proceedings of preventive measures;
- to identify diseases and conditions that require emergency care;
- to assess the patient's condition and provide appropriate medical care in emergency case in FD practice;
- to know dosage, indications and contraindications for drug in emergency case;
- to identify emergency cases in FD practice.

IV. A student must be able:

- to know the clinical presentations of disease with abdominal pain: acute appendicitis, pancreatitis, cholecystitis, peptic ulcer and its complications, acute gynecological diseases, ectopic pregnancy, renal colic, and inflammatory diseases of the kidneys and urinary tract.
- to know the clinical presentations of disease with chest pain: various forms of CHD, pericarditis, myocarditis, pulmonary embolism, dissecting aortic aneurysm, pneumothorax, dry pleurisy, lesions of peripheral nerves, spine and muscles.
- to identify the acute coronary syndrome with ST segment elevation, ST-segment elevation without clinical characteristics of acute coronary syndrome, therapeutic approach of pre-admission and emergency care.
- to know the characteristics of pain in the extremities and clinical signs of acute lesions of veins and arteries.

V. Practical skills:

The examination of patients in the surgical clinic by ophthalmologist, otolaryngologist, urologist, gynecologist or family doctor. In the case of pain propose the algorithms and differential diagnosis of medical care in the pre-admission stage.

VI. Basic questions after a theme:

- Surgical diseases, symptoms and syndromes, the prevention, diagnosis and treatment of patients by a family doctor.
- Surgical diseases, symptoms and syndromes, which are the indication for refer to specialists for making final diagnosis, differential diagnosis, planning a therapeutic approach.
- Surgical diseases, symptoms and syndromes, for which the FD may prescribe treatment and rehabilitation for patients according to the recommendations of specialists, may conduct clinical supervision under patients.
- Surgical diseases, symptoms and syndromes, which require FD and medical specialist's supervision for implementation of working and final diagnosis, treatment, rehabilitation of patients.

- Surgical diseases that require treatment and clinical supervision of doctors.
- Surgical diseases that need emergency or planned hospitalization of patients.
- Differential diagnosis of acute and chronic pain, somatic and psychosomatic disorders.
- Diagnosis of pain in various clinical situations and treatment.
- Method of patient's help in the case of acute coronary syndrome at the pre-admission stage.
- The therapeutic approach for patient with acute arterial occlusion.
- Pathophysiological changes in the case of insects stinging, serpents, emergency.

V. Tasks for independent training and correction of initial level of knowledge

1. The patient complains for pain in the left upper quadrant of abdomen, weakness, vomiting, dizziness, which appeared 5 hours ago. Hypotension, tachycardia. Medical history: 10 days ago blunt trauma of abdomen. What is the working diagnosis?

- A. Rupture of the spleen;**
- B. Rupture of the liver;
- C. Rupture of intestine;
- D. Peritonitis;
- E. Perforated ulcer.

2. Two days ago the patient felt a sharp pain in the right upper quadrant of abdomen with irradiation under the right scapula. Next day he had vomiting. The right half of the abdomen is tense. Positive symptoms of Ortner, Musset. What is the working diagnosis?

- A. Acute pancreatitis;
- B. Mesenteric ischemia;
- C. Acute intestinal obstruction;
- D. Biliary colic;
- E. Acute cholecystitis.**

3. In the case of angina the typical pain is:

A. Pressing, squeezing, localized behind the breastbone.

B. Burning heart pain.

C. Barbed heart pain associated with movements or breathing.

D. Feeling of discomfort in the pericardial region during physical or emotional stress

E. Feeling heterogenous object under the sternum.

4. The 21 years old patient admitted to the doctor. She complained for lower abdomen pain spreading to the anus, weakness, which came on the 12th day of the menstrual cycle. BP 70/40 mm Hg, HR 120 per min. What is the working diagnosis?

A. Ectopic pregnancy;

B. Torsion of ovarian cyst;

C. Acute appendicitis;

D. Acute pelvioperitonit;

E. Ovarian apoplexy.

5. The 43 years old patient complains for right lumbar pain spreading to the lower abdomen. Patient was motionless, groaning. HR 100 per min, BP 130/70 mm Hg. The muscles tension in the right iliac region. Negative Lassega, Schetkina, Ortner signs. Positive Pasternatsky sign. What is the working diagnosis?

A. Perforated duodenal ulcer;

B. Renal colic;

C. Radiculitis;

D. Acute appendicitis;

E. Acute cholecystitis.

6. The pain in the case of angina of effort is characterized by:

A. without precursors, sudden, pain on activity, gradually increases on the peak of intensity in the form of crescendo;

B. after auras;

C. maximum intensity at the beginning;

- D. pain grows undulating;
- E. 4-6 hours after loading, maximum on 2-3 days.

7. Chronic pain syndrome is ongoing pain lasting longer than.

- A. 6 months
- B. 3 months.**
- C. 1 months.
- D. 8 weeks.
- E. 6 weeks.

8. Chronic pain syndrome can affect patients in various ways. Which effects in the patient's life are leading?

- A. depressed mood, fatigue.
- B. reduced activity and libido.
- C. excessive use of drugs and alcohol, dependent behavior.
- D. disability out of proportion with impairment.
- E. All of mentioned above.**

9. Chronic pain may lead to next changes in patient's life:

- A. prolonged physical suffering
- B. loss of employment
- C. marital or family problems
- D. various adverse medical reactions from long-term therapy
- E. All of mentioned above.**

10. The goal of pharmacotherapy of chronic pain syndrome is to reduce morbidity and prevent complications. For this purpose we use the following medication:

- A. Nonsteroidal anti-inflammatory drugs, Muscle relaxants, Antidepressants
- B. Corticosteroids, Muscle relaxants
- C. Nonsteroidal anti-inflammatory drugs, Corticosteroids.
- D. Nonsteroidal anti-inflammatory drugs, physical therapy
- E. All of mentioned above.**

1. Chronic pain syndrome

1.1. Background

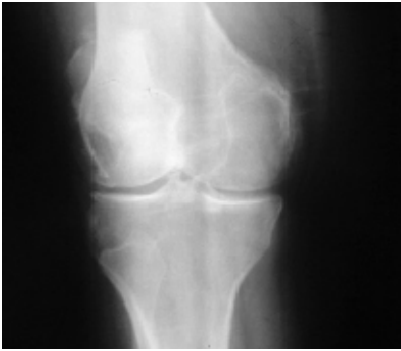
«Chronic pain patients are very demanding patients.»
Dr. Henry Kroll

Chronic pain syndrome (CPS) is a common problem that presents a major challenge to health-care providers because of its complex natural history, unclear etiology, and poor response to therapy. CPS is a poorly defined condition. Most authors consider ongoing pain lasting longer than 6 months as diagnostic, and others have used 3 months as the minimum criterion. In chronic pain, the duration parameter is used arbitrarily. Some authors suggest that any pain that persists longer than the reasonably expected healing time for the involved tissues should be considered chronic pain.

CPS is a constellation of syndromes that usually do not respond to the medical model of care. This condition is managed best with a multidisciplinary approach, requiring good integration and knowledge of multiple organ systems. (The images below demonstrate conditions associated with CPS.) [1].



Sagittal magnetic resonance imaging (MRI) scan of the cervical spine in a patient with cervical radiculopathy. This image reveals a C6-C7 herniated nucleus pulposus [1].



Osteoarthritis of the knee, Kellgren stage III [1].



Changes in the hand caused by rheumatoid arthritis (*Photograph by David Effron MD, FACEP*) [1].

Approximately 35% of Americans have some element of chronic pain, and approximately 50 million Americans are disabled partially or totally due to chronic pain. Chronic pain is reported more commonly in women.

1.2. Complications

CPS can affect patients in various ways. Major effects in the patient's life are depressed mood, fatigue, reduced activity and libido, excessive use of drugs and alcohol, dependent behavior, and disability out of proportion with impairment.

Chronic pain may lead to prolonged physical suffering, marital or family problems, loss of employment, and various adverse medical reactions from long-term therapy.

Parental chronic pain increases the risk of internalizing symptoms, including anxiety and depression, in adolescents [23].

A study by van Tilburg et al indicates that adolescents who have chronic pain and depressive thoughts are at increased risk for suicide ideation and attempt[1].

1.3. Etiology

The pathophysiology of chronic pain syndrome (CPS) is multifactorial and complex and still is poorly understood.

Some authors have suggested that CPS might be a learned behavioral syndrome that begins with a noxious stimulus that causes pain. This pain behavior then is rewarded externally or internally. Thus, this pain behavior is reinforced, and then it occurs without any noxious stimulus.

Internal reinforcers are relief from personal factors associated with many emotions (eg, guilt, fear of work, sex, responsibilities).

External reinforcers include such factors as attention from family members and friends, socialization with the physician, medications, compensation, and time off from work.

Patients with several psychological syndromes (eg, major depression, somatization disorder, hypochondriasis, conversion disorder) are prone to developing CPS.

In one study, a connection was found in women between the number of active myofascial trigger points (MTrPs) and the intensity of spontaneous pain, as well as widespread mechanical hypersensitivity. Nociceptive inputs from these MTrPs may be linked to central sensitization [2].

Various neuromuscular, reproductive, gastrointestinal (GI), and urologic disorders may cause or contribute to chronic pain. Sometimes multiple contributing factors may be present in a single patient.

1. Musculoskeletal disorders associated with chronic pain include the following:

- Osteoarthritis/degenerative joint disease/spondylosis (see the image below).
- Rheumatoid arthritis (see the image below) T1-weighted sagittal magnetic resonance imaging (MRI) scan of the cervical spine in a patient with rheumatoid arthritis shows basilar invagination with cranial migration of an eroded odontoid peg. There is minimal pannus. The tip of the peg indents the medulla, and

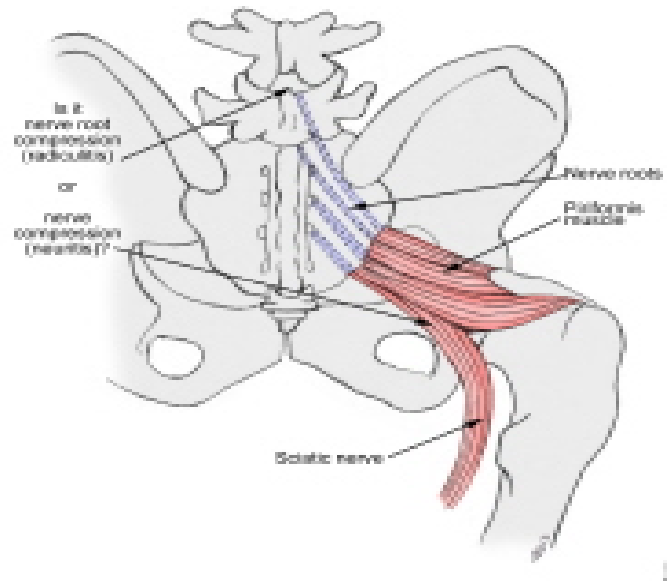
there is narrowing of the foramen magnum, due to the presence of the peg. Inflammatory fusion of several cervical vertebral bodies is shown.

T1-weighted sagittal magnetic resonance imaging (MRI) scan of the cervical spine in a patient with rheumatoid arthritis [1].



- Lyme disease
- Reiter syndrome
- Disk herniation/facet osteoarthropathy
- Fractures/compression fracture of lumbar vertebrae
- Faulty or poor posture
- Fibromyalgia [3,4,5,6,7]
- Polymyalgia rheumatica
- Mechanical low back pain
- Chronic coccygeal pain
- Muscular strains and sprains
- Pelvic floor myalgia (levator ani spasm)
- Piriformis syndrome (see the image below)
- Rectus tendon strain
- Hernias (eg, obturator, sciatic, inguinal, femoral, spigelian, perineal, umbilical)
- Abdominal wall myofascial pain (trigger points)
- Chronic overuse syndromes (eg, tendonitis, bursitis)

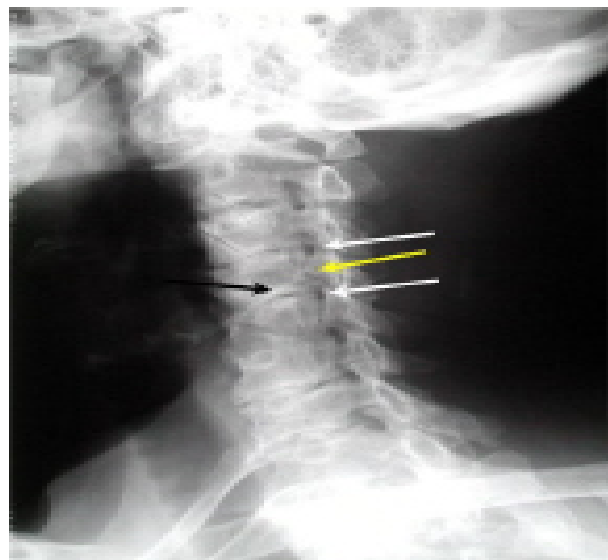
Nerve irritation in the herniated disk occurs at the root (sciatic radiculitis). In piriformis syndrome, the irritation extends to the full thickness of the nerve (sciatic neuritis) [11].



2. **Neurologic disorders** associated with chronic pain include the following:

- Brachial plexus traction injury
- Cervical radiculopathy
- Thoracic outlet syndrome
- Spinal stenosis (see the image below)

Oblique view of the cervical spine demonstrates 2 levels of foraminal stenosis (white arrows) resulting from facet hypertrophy (yellow arrow) and uncovertebral joint hypertrophy [9].



- Arachnoiditis
- Metabolic deficiency myalgias
- Polymyositis
- Neoplasia of spinal cord or sacral nerve
- Cutaneous nerve entrapment in surgical scar

- Postherpetic neuralgia (shingles) [8,9]
- Neuralgia (eg., iliohypogastric, ilioinguinal, or genitofemoral nerves)
- Polyneuropathies
- Polyradiculoneuropathies
- Mononeuritis multiplex
- Chronic daily headaches
- Muscle tension headaches
- Migraine headaches
- Temporomandibular joint dysfunction
- Temporalis tendonitis
- Sinusitis
- Atypical facial pain
- Trigeminal neuralgia
- Glossopharyngeal neuralgia
- Nervus intermedius neuralgia
- Sphenopalatine neuralgia
- Referred dental or temporomandibular joint pain
- Abdominal epilepsy
- Abdominal migraine
- Stroke (central poststroke pain) [10].

3. **Urologic disorders** associated with chronic pain include the following:

- Bladder neoplasm
- Chronic urinary tract infection
- Interstitial cystitis
- Radiation cystitis
- Recurrent cystitis
- Recurrent urethritis
- Urolithiasis
- Uninhibited bladder contractions (detrusor-sphincter dyssynergia)
- Urethral diverticulum
- Chronic urethral syndrome
- Urethral carbuncle

- Prostatitis
- Urethral stricture
- Testicular torsion
- Peyronie disease

4. **Gastrointestinal disorders** associated with chronic pain include the following:

- Chronic visceral pain syndrome
- Gastroesophageal reflux
- Peptic ulcer disease
- Pancreatitis
- Chronic intermittent bowel obstruction
- Colitis (see the image below)

Severe colitis noted during colonoscopy. The mucosa is grossly denuded, with active bleeding noted. This patient had her colon resected very shortly after this view was obtained [1].



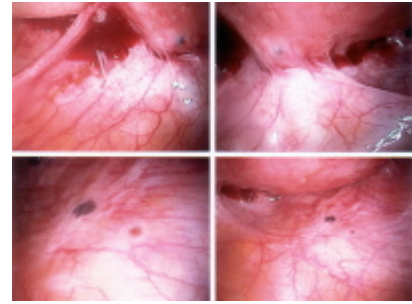
- Chronic constipation
- Diverticular disease
- Inflammatory bowel disease
- Irritable bowel syndrome

5. **Reproductive disorders (extrauterine)**

Extrauterine reproductive disorders associated with chronic pain include the following:

- Endometriosis (see the image below)

Active endometriosis with red and powder-burn lesions; adhesions from old scarring are present [15].



- Adhesions
- Adnexal cysts
- Chronic ectopic pregnancy
- Chlamydial endometritis or salpingitis
- Endosalpingiosis
- Ovarian retention syndrome (residual ovary syndrome)
- Ovarian remnant syndrome
- Ovarian dystrophy or ovulatory pain
- Pelvic congestion syndrome
- Postoperative peritoneal cysts
- Residual accessory ovary
- Subacute salpingo-oophoritis
- Tuberculous salpingitis

Uterine reproductive disorders associated with chronic pain include the following:

- Adenomyosis
- Chronic endometritis
- Atypical dysmenorrhea or ovulatory pain
- Cervical stenosis
- Endometrial or cervical polyps
- Leiomyomata
- Symptomatic pelvic relaxation (genital prolapse)

An intrauterine contraceptive device can also be associated with chronic pain.

6. **Psychological disorders** associated with chronic pain include the following:

- Bipolar personality disorders
- Depression
- Porphyria
- Sleep disturbances

7. **Other.** The following disorders can also be associated with chronic pain:

- Cardiovascular disease (eg, angina)
- Peripheral vascular disease
- Chemotherapeutic, radiation, or surgical complications

1.4. Fibromyalgia risk

Results from a study by Mork et al indicated that women who are overweight or obese have a 60-70% greater risk of developing fibromyalgia than do women of normal weight, with body mass index (BMI) being an independent risk factor for the condition. The report looked at whether physical exercise and high BMI influence the occurrence of fibromyalgia. The study included 15,990 women, none of whom at baseline had fibromyalgia or any other physical impairment. By 11-year follow-up, incident fibromyalgia had reportedly occurred in 380 women. The authors noted that only a weak association typically existed between exercise level and fibromyalgia risk.

In overweight or obese women in the study who exercised for at least 1 hour each week, the relative risk for fibromyalgia (in comparison with women of normal weight and a similar activity level) was 1,72, while in overweight or obese women who did not exercise or who did so for less than an hour per week, the relative risk was 2.09 [3].

2. Clinical Presentation

2.1. History

Because of the complex etiology and the frequent presence of associated disorders, a general and open-minded approach to the assessment of the patient is needed. Obtaining the history of patients whose symptoms suggest chronic pain syndrome (CPS) is important. A thorough history is necessary for the physician to direct further evaluation and appropriate consultations and to avoid repeating invasive and expensive procedures.

A detailed review of the musculoskeletal, reproductive, GI, urologic, and neuropsychological systems must be obtained. As needed, specific questions should be asked of particular patients, depending on their associated disorders.

Focus the history on a characterization of the patient's pain. Obtaining the characteristics of the pain helps to establish appropriate diagnostic and therapeutic plans.

- Pain location:
the location of pain is an important part of the history;
ask the patient to describe the type of pain and the location on a pain diagram (anterior/posterior and lateral view of human picture)
- Precipitating factors:
ask questions about factors that provoke or intensify pain;
this information may provide clues concerning possible etiologies or associated disorders
- Alleviating factors: ask the patient if any factors help to alleviate the pain; for example, rest may decrease pain of musculoskeletal origin
- Quality of pain:
ask the patient to describe the quality of pain:
various terms can be used to describe the quality of pain, including throbbing, pounding, shooting, pricking, boring, stabbing, lancinating, sharp, cutting, lacerating, pressing, cramping, crushing, pulling, pinching, stinging, burning, splitting, penetrating, piercing, squeezing, and dull aching,

- Radiation of pain: ask the patient if the pain spreads or radiates; spreading or radiating pain is a characteristic of neuropathic pain
- Severity or intensity of pain:
use some type of rating system to evaluate pain severity or intensity with a degree of objectivity and reproducibility;
different types of pain scales may be used, with numerical scales being more useful and reliable (the visual analog scale [VAS] is one of the commonly used numerical scales).

The Pain Sensitivity Questionnaire can be used to measure general pain perception (pain perception outside the clinical pain site) in patients with chronic pain [12].

A 2012 meta-analysis indicates that athletes exhibit higher pain tolerance than normally active subjects, suggesting that regular physical activity is associated with alterations in the perception of pain [13].

Obtain history specific to the following systems and related disorders:

- Musculoskeletal
- Neurologic
- Gynecologic and obstetric
- Urologic
- GI

In addition, a good psychosocial or psychosexual history is needed when organic diseases are excluded or coexisting psychiatric disorders are suggested. Obtain sufficient history to evaluate depression; anxiety disorder; somatization; physical or sexual abuse; drug abuse/dependence; and family, marital, or sexual problems. Somatization is a commonly associated psychological disorder in women with chronic pain. Somatization scales can be used for evaluation [14].

Sternbach's 6 *D*'s of CPS are as follows:

- Dramatization of complaints
- Drug misuse
- Dysfunction/disuse

- Dependency
- Depression
- Disability

2.2. Physical Examination

Good rapport, tolerance, and an open-minded approach are important when evaluating any patient with chronic pain. A thorough systematic examination usually leads to an appropriate diagnosis and therapy. Patients often have Waddell signs. The disability is usually out of proportion to the impairment and the objective findings.

A patient with chronic pain syndrome (CPS) may exhibit exaggerated pain behavior. Sensations may seem to be hysterical or appear non-anatomic or non-physiologic, but the patient always should be taken seriously and appropriate conservative steps should be taken.

Detailed examination of the musculoskeletal system is important.

Examination of various other systems (eg, GI, urologic, neurologic) also should be performed.

2.3. Consultations

Consultation with a psychologist, urologist, neurologist, obstetrician-gynecologist, GI specialist, or other appropriate specialist is very important, especially before considering invasive or aggressive management of a patient with chronic pain syndrome (CPS).

The high incidence of personality pathology in CPS may represent an exaggeration of maladaptive personality traits and coping styles caused by chronic, intense pain. A psychological evaluation should be performed to identify the stressor and to obtain information about the distress of the patient. The evaluation should consist of a structural clinical interview and a personality measure (eg, Minnesota Multiphasic Personality Scale, Hopelessness Index).

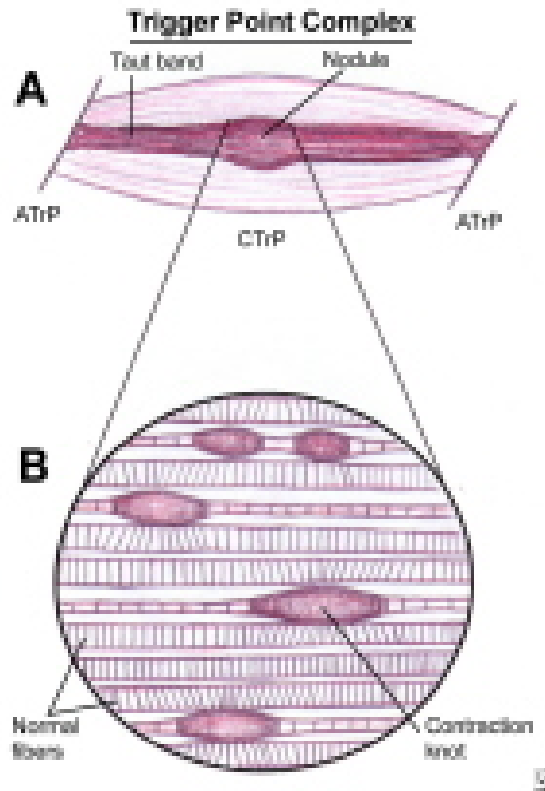
3. Differential Diagnoses. Diagnostic Considerations

- Achilles Tendon Injuries and Tendonitis
- Adhesive Capsulitis
- Brachial Neuritis
- Carpal Tunnel Syndrome
- Cervical Disc Disease
- Cervical Myofascial Pain
- Cervical Spondylosis
- Cervical Sprain and Strain
- Complex Regional Pain Syndromes
- Fibromyalgia

3.1. Cervical Myofascial Pain

Background. Pain attributed to muscle and its surrounding fascia is termed myofascial pain, with cervical myofascial pain thought to occur following either overuse or trauma to the muscles that support the shoulders and neck. In the cervical spine, the muscles most often implicated in myofascial pain are the trapezius, levator scapulae, rhomboids, supraspinatus, and infraspinatus [1].

Myofascial pain in any location is characterized on examination by the presence of trigger points located in skeletal muscle. A trigger point is defined as a hyperirritable area located in a palpable, taut band of muscle fibers (see the image below).



Schematic of a trigger point complex of a muscle in longitudinal section. A: The central trigger point (CTrP) in the endplate zone contains numerous electrically active loci and numerous contraction knots. A taut band of muscle fibers extends from the trigger point to the attachment at each end of the involved fibers. The sustained tension that the taut band exerts on the attachment tissues can induce a localized enthesopathy that is identified as an attachment trigger point (ATrP). B: Enlarged view of part of the CTrP shows the distribution of 5 contraction knots. The vertical lines in each muscle fiber identify the relative spacing of its striations. The space between 2 striations corresponds to the length of 1 sarcomere. The sarcomeres within one of these enlarged segments (ie, contraction knot) of a muscle fiber are markedly shorter and wider than the sarcomeres in the neighboring normal muscle fibers, which are free of contraction knots [23].

Descriptions of myofascial pain date back to the mid-19th century, when Frohriepp described *muskelschwiele*, or muscle calluses. He characterized these calluses as tender areas in muscle that felt like a cord or band associated with rheumatic complaints. In the early 1900s, Gowers first used the term fibrositis to describe muscular rheumatism associated with local tenderness and regions of palpable hardness.

In 1938, Kellgren described areas of referred pain associated with tender points in muscle. In the 1940s, Janet Travell, MD, began writing about myofascial trigger points. Her text, written in conjunction with David Simons, MD, continues to be viewed as the foundational literature on the subject of myofascial pain [2].

The primary concern for patients with cervical myofascial pain is chronicity. Recurrence of myofascial pain is a common scenario. Prompt treatment prevents

other muscles in the functional unit from compensating and, consequently, producing a more widespread and chronic problem. Migraine headaches and muscle contraction headaches are known to occur frequently in the patient with myofascial pain [3]. Temporomandibular joint (TMJ) syndrome also may be myofascial in origin.

Etiology. Cervical myofascial pain is thought to occur following either overuse or trauma to the muscles that support the shoulders and neck. Common scenarios among patients are recent involvement in a motor vehicle accident or performance of repetitive upper extremity activities.

In the cervical spine, the muscles most often implicated in myofascial pain are the trapezius, levator scapulae, rhomboids, supraspinatus, and infraspinatus [1]. Trapezial myofascial pain commonly occurs when a person with a desk job does not have appropriate armrests or must type on a keyboard that is too high.

Other issues that may play a role in the clinical picture of cervical myofascial pain include endocrine dysfunction, chronic infections, nutritional deficiencies, poor posture, and psychological stress.

Epidemiology. Occurrence in the United States: myofascial pain is thought to occur commonly in the general population. As many as 21% of patients seen in general orthopedic clinics have myofascial pain. Of patients seen at specialty pain management centers, 85-93% have a myofascial pain component to their condition.

Sex- and age-related demographics: cervical myofascial pain occurs in both sexes, but with a predominance among women. Myofascial pain seems to occur more frequently with increasing age until midlife. The incidence declines gradually after middle age.

Prognosis. When the patient with cervical myofascial pain undergoes appropriate treatment (eg, physical therapy, massage therapy, stretch and spray, trigger point injections), the prognosis is generally good. However, recurrence can be a common scenario. Outcomes seem to be better when treatment is initiated

early in order to prevent compensation patterns that exacerbate pain. Increased mortality is not associated with cervical myofascial pain.

The patient disability in chronic myofascial pain is most strongly linked to the duration of pain [1].

History. The diagnosis of myofascial pain is clinical, with no confirmatory laboratory tests available. The patient with cervical myofascial pain may present with a history of acute trauma associated with persistent muscular pain. However, myofascial pain can also manifest insidiously, without a clear antecedent accident or injury. It may be associated with repetitive tasks, poor posture, stress, or cold weather. Typical findings reported by patients also include the following:

- Cervical spine range of motion (ROM) is often limited and painful
- The patient may describe a lumpiness or painful bump in the trapezius or cervical paraspinal muscles
- Massage is often helpful, as is superficial heat
- The patient's sleep may be interrupted because of pain
- The cervical rotation required for driving is difficult to achieve
- The patient may describe pain radiating into the upper extremities, accompanied by numbness and tingling, making discrimination from radiculopathy or peripheral nerve impingement difficult
- Dizziness or nausea may be a part of the symptomatology
- The patient experiences typical patterns of radiating pain referred from trigger points

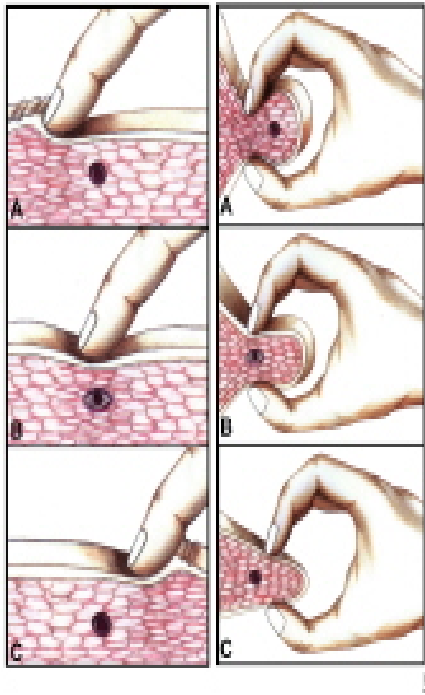
Physical Examination. Common findings include the following:

- Patients with cervical myofascial pain often present with poor posture; they exhibit rounded shoulders and protracted scapulae
- Trigger points frequently are noted in the trapezius, supraspinatus, infraspinatus, rhomboids, and levator scapulae muscles
- The palpable, taut band is noted in the skeletal muscle or surrounding fascia; a local twitch response often can be reproduced with palpation of the area

- ROM of the cervical spine is limited, with pain reproduced in positions that stretch the affected muscle
- While the patient may complain of weakness, normal strength in the upper extremities is noted on physical examination
- Sensation typically is normal when tested formally; no long tract signs are observed on examination

Myofascial pain in any location is characterized on examination by the presence of trigger points located in skeletal muscle. A trigger point is defined as a hyperirritable area located in a palpable, taut band of muscle fibers. According to Hong and Simon's review on the pathophysiology and electrophysiologic mechanisms of trigger points, the following observations help to define them further [4]:

- Trigger points are known to elicit local pain and/or referred pain in a specific, recognizable distribution
- Palpation in a rapid fashion (ie, snapping palpation) may elicit a local twitch response, a brisk contraction of the muscle fibers in or around the taut band; the local twitch response also can be elicited by rapid insertion of a needle into the trigger point (see the images below)
- Restricted ROM and increased sensitivity to stretch of muscle fibers in a taut band are noted frequently
- The muscle with a trigger point may be weak because of pain; usually, no atrophic change is observed
- Patients with trigger points may have associated localized autonomic phenomena (eg, vasoconstriction, pilomotor response, ptosis, hypersecretion)
- An active myofascial trigger point is a site marked by generation of spontaneous pain or pain in response to movement; in contrast, latent trigger points may not produce pain until they are compressed.



Cross-sectional drawing shows flat palpation of a taut band and its trigger point. Left: A. The skin is pushed to one side to begin palpation.

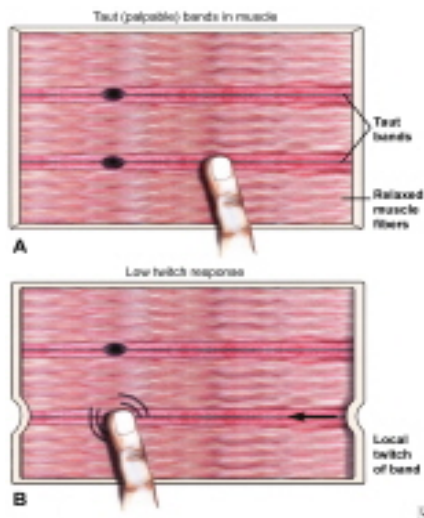
B. The fingertip slides across muscle fibers to feel the cord-line texture of the taut band rolling beneath it.

C. The skin is pushed to the other side at completion of the movement. This same movement performed vigorously is called snapping palpation.

Right: A. Muscle fibers are surrounded by the thumb and fingers in a pincer grip.

B. The hardness of the taut band is felt clearly as it is rolled between the digits.

C. The palpable edge of the taut band is sharply defined as it escapes from between the fingertips, often with a local twitch response [12].



Longitudinal schematic drawing of taut bands, myofascial trigger points, and a local twitch response.

A: Palpation of a taut band (straight lines) among normally slack, relaxed muscle fibers (wavy lines).

B: Rolling the band quickly under the fingertip (snapping palpation) at the trigger point often produces a local twitch response, which usually is seen most clearly as skin movement between the trigger point and the attachment of the muscle fibers [12].

Approach Considerations

The diagnosis of myofascial pain is clinical, with no confirmatory laboratory tests available. In addition, imaging studies often reveal nonspecific change only and typically are not helpful in making the diagnosis of cervical myofascial pain.

However, cervical myofascial pain can be present at the same time as other, more serious medical conditions. If the patient's symptoms are resistant to traditional treatment for cervical myofascial pain, further workup is indicated. If a

history of trauma exists, order cervical flexion/extension films to rule out the possibility of instability.

Magnetic resonance imaging (MRI) may be helpful in ruling out any significant abnormality within the structure of the cervical vertebrae or spinal canal. The cervical discs also may be evaluated. If the pain is in the shoulders or chest wall, be aware that visceral pain may refer to these areas and even produce some myofascial findings on examination. Be open-minded to the possibility that another problem also may be present.

It may also be reasonable, depending on the clinical presentation, to check for indicators of inflammation, assess thyroid function, and perform a basic metabolic panel to rule out a concomitant medical illness.

Travell and Simons described a study looking at lactate dehydrogenase (LDH) isoenzymes in which a shift was noted in the distribution of the isoenzymes, with higher levels of LDH1 and LDH2, while the total LDH remained within normal limits [2].

Electrophysiological Studies

Several research articles have attempted to identify changes on electromyograms/nerve conduction velocity studies that may be unique to patients with myofascial pain. The research has been somewhat contradictory, with some studies finding no real electromyographic activity and others finding nonspecific electrical activity.

The low-amplitude action potentials recorded at the region of the myofascial trigger point. Spontaneous electrical activity apparently can be detected using high-sensitivity recordings at the site of the trigger point. The spontaneous electrical activity may be a type of endplate potential.

The sonoelastography can classify myofascial trigger points by active, latent, and normal sites. Assessing the trigger point areas and pulsatility index may help in determining myofascial pain syndrome's natural history [5].

Treatments for cervical myofascial pain include physical therapy, trigger point injection, stretch-and-spray therapy, and ischemic compression. Injection of

botulinum toxin has also been used, although this procedure has received mixed reviews in the literature.

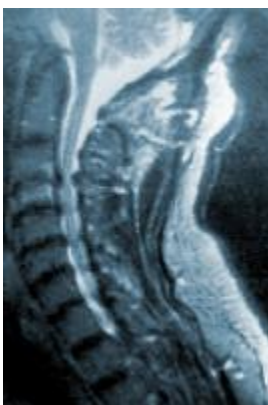
Various pain-relieving medications can also be employed in treatment, including the following:

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Tricyclic antidepressants
- Muscle Relaxants
- Nonnarcotic analgesics
- Anticonvulsants

3.2. Cervical Spondylosis

Background. Cervical spondylosis is a chronic degenerative condition of the cervical spine that affects the vertebral bodies and intervertebral disks of the neck (in the form of, for example, disk herniation and spur formation), as well as the contents of the spinal canal (nerve roots and/or spinal cord). Some authors also include the degenerative changes in the facet joints, longitudinal ligaments, and ligamentum flavum.

Spondylosis progresses with age and often develops at multiple interspaces. Chronic cervical degeneration is the most common cause of progressive spinal cord and nerve root compression. Spondylotic changes can result in stenosis of the spinal canal, lateral recess, and foramina. Spinal canal stenosis can lead to myelopathy, whereas the latter 2 can cause radiculopathy. (See image below)



A T2-weighted cervical magnetic resonance imaging scan shows obliteration of the subarachnoid space as a result of spondylotic changes [12].

Pathophysiology. Intervertebral disks lose hydration and elasticity with age, and these losses lead to cracks and fissures. The surrounding ligaments also lose

their elastic properties and develop traction spurs. The disk subsequently collapses as a result of biomechanical incompetence, causing the annulus to bulge outward. As the disk space narrows, the annulus bulges, and the facets override. This change, in turn, increases motion at that spinal segment and further hastens the damage to the disk. Annulus fissures and herniation may occur. Acute disk herniation may complicate chronic spondylotic changes.

As the annulus bulges, the cross-sectional area of the canal is narrowed. This effect may be accentuated by hypertrophy of the facet joints (posteriorly) and of the ligamentum flavum, which becomes thick with age. Neck extension causes the ligaments to fold inward, reducing the anteroposterior (AP) diameter of the spinal canal.

As disk degeneration occurs, the uncinete process overrides and hypertrophies, compromising the ventrolateral portion of the foramen. Likewise, facet hypertrophy decreases the dorsolateral aspect of the foramen. This change contributes to the radiculopathy that is associated with cervical spondylosis. Marginal osteophytes begin to develop. Additional stresses, such as trauma or long-term heavy use, may exacerbate this process. These osteophytes stabilize the vertebral bodies adjacent to the level of the degenerating disk and increase the weight-bearing surface of the vertebral endplates. (See images below) The result is decreased effective force on each of these structures.



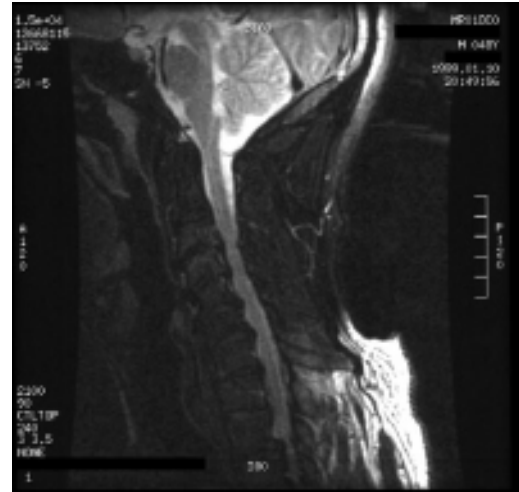
A cervical myelogram shows advanced spondylotic changes and multiple compression of the spinal cord by osteophytes [12].

A 59-year-old woman presented with a spastic gait and weakness in her upper extremities. A T2-weighted sagittal magnetic resonance imaging scan shows cord compression from cervical spondylosis, which caused central spondylotic myelopathy. Note the signal changes in the cord at C4-C5, the ventral osteophytosis, buckling of the ligamentum flavum at C3-C4, and the prominent loss of disk height between C2 and C5 [1].



A 48-year-old man presented with neck pain and predominantly left-sided radicular symptoms in the arm. The patient's symptoms resolved with conservative therapy. An axial, gradient-echo magnetic resonance imaging scan shows moderate anteroposterior narrowing of the cord space due to a ventral osteophyte at the C4 level, with bilateral narrowing of the neural foramina (more prominently on the left side [1]).

A 48-year-old man presented with neck pain and predominantly left-sided radicular symptoms in the arm. The patient's symptoms resolved with conservative therapy. A T2-weighted sagittal magnetic resonance imaging scan shows ventral osteophytosis, most prominent between C4 and C7, with reduction of the ventral cerebrospinal fluid sleeve [1].



Degeneration of the joint surfaces and ligaments decreases motion and can act as a limiting mechanism against further deterioration. Thickening and ossification of the posterior longitudinal ligament (OPLL) also decreases the diameter of the canal [1, 2, 3].

The blood supply of the spinal cord is an important anatomic factor in the pathophysiology. Radicular arteries in the dural sleeves tolerate compression and repetitive minor trauma poorly. The spinal cord and canal size also are factors. A congenitally narrow canal does not necessarily predispose a person to myelopathy, but symptomatic disease rarely develops in individuals with a canal that is larger than 13 mm.

Epidemiology. U.S.: cervical spondylosis is a common condition that is estimated to account for 2% of all hospital admissions. It is the most frequent cause of spinal cord dysfunction in patients older than 55 years. On the basis of radiologic findings, 90% of men older than 50 years and 90% of women older than 60 years have evidence of degenerative changes in the cervical spine [4].

Mortality/Morbidity

- The course of cervical spondylosis may be slow and prolonged, and patients may either remain asymptomatic or have mild cervical pain.
- Long periods of nonprogressive disability are typical, and in a few cases, the patient's condition progressively deteriorates.

- Morbidity ranges from chronic neck pain, radicular pain, diminished cervical range of motion (ROM), headache, myelopathy leading to weakness, and impaired fine motor coordination to quadriparesis and/or sphincteric dysfunction (eg, difficulty with bowel or bladder control) in advanced cases. The patient may eventually become chair-bound or bedridden.

No apparent correlation between race and cervical spondylosis exists.

Both sexes are affected equally. Usually starts earlier in men than in women.

Age:

- Symptoms of cervical spondylosis may appear in persons as young as 30 years but are found most commonly in individuals aged 40-60 years. Radiologic spondylotic changes increase with patient age; 70% of asymptomatic persons older than 70 years have some form of degenerative change in the cervical spine.

- When cervical spondylosis develops in a young individual, it is almost always secondary to a predisposing abnormality in 1 of the joints between the cervical vertebrae, probably as a result of previous mild trauma.

History. Common clinical syndromes associated with cervical spondylosis include the following:

- Cervical pain
 - Chronic suboccipital headache may be present. Mechanisms include direct nerve compression; degenerative disk, joint, or ligamentous lesions; and segmental instability.
 - Pain can be perceived locally, or it may radiate to the occiput, shoulder, scapula, or arm.
 - The pain, which is worse when the patient is in certain positions, can interfere with sleep.
- Cervical radiculopathy
 - Compression of the cervical nerve roots leads to ischemic changes that cause sensory dysfunction (eg, radicular pain) and/or motor dysfunction (eg, weakness). Radiculopathy most commonly occurs in persons aged 40-50 years.

- An acute herniated disk or chronic spondylotic changes can cause cervical radiculopathy and/or myelopathy
 - The C6 root is the most commonly affected one because of the predominant degeneration at the C5-C6 interspace; the next most common sites are at C7 and C5.
 - Most cases of cervical radiculopathy resolve with conservative management; few require surgical intervention.
 - Cervical myelopathy:
 - Cervical spondylotic myelopathy is the most serious consequence of cervical intervertebral disk degeneration, especially when it is associated with a narrow cervical vertebral canal. (See image below)
 - Cervical myelopathy has an insidious onset, which typically becomes apparent in persons aged 50-60 years. Complete reversal is rare once myelopathy occurs.
 - Involvement of the sphincters is unusual at presentation, as based on the patient's perception of symptoms.
 - Five categories of cervical spondylotic myelopathy are described; these are based on the predominant neurologic findings, as follows:
 - Transverse lesion syndrome: corticospinal and spinothalamic tracts, as well as the posterior columns, are involved.
 - Motor syndrome: this primarily involves the corticospinal or anterior horn cells.
 - Central cord syndrome: motor and sensory involvement is greater in the upper extremities than the lower extremities [5].
 - Brown-Séquard syndrome: unilateral cord lesion with ipsilateral corticospinal tract involvement and contralateral analgesia are present below the level of the lesion.
 - Brachialgia and cord syndrome: predominant upper limb pain is present, with some associated long-tract involvement.
 - Less common manifestations:

- Primary sensory loss may be present in a glovelike distribution.
- Tandem spinal stenosis is a simultaneous cervical and lumbar stenosis resulting from spondylosis. It is a triad of findings: neurogenic claudication, complex gait abnormality, and a mixed pattern of upper and lower motor neuron signs.
 - Dysphagia may be present if the spurs are large enough to compress the esophagus.
 - Vertebrobasilar insufficiency and vertigo may be observed.
 - Elevated hemidiaphragm, caused by spondylotic compression of C3-C4, may be another finding.

Physical examination. Findings at physical examination may include the following:

- Spurling sign: radicular pain is exacerbated by extension and lateral bending of the neck toward the side of the lesion, causing additional foraminal compromise.
- Lhermitte sign: this generalized electrical shock sensation is associated with neck extension.
- Hoffman sign: reflex contraction of the thumb and index finger occurs in response to nipping of the middle finger. This sign is evidence of an upper motor neuron lesion. May be insignificant if present bilaterally.
 - Distal weakness
 - Decreased ROM in the cervical spine, especially with neck extension
 - Hand clumsiness
 - Loss of sensation
 - Increased reflexes in the lower extremities and in the upper extremities below the level of the lesion
 - A characteristically broad-based, stooped, and spastic gait
 - Extensor planter reflex in severe myelopathy

Causes

- Age: This is a disease observed most commonly in elderly individuals.

- Among persons younger than 40 years, 25% have degenerative disk disease (DDD), and 4% have foraminal stenosis, as confirmed with magnetic resonance imaging (MRI).
- In persons older than 40 years, almost 60% have DDD, and 20% have foraminal stenosis, as confirmed with MRI.
 - Trauma: the role of trauma in spondylosis is controversial.
- Repetitive, subclinical trauma probably influences the onset and rate of progression of spondylosis.
 - Work activity: Cervical spondylosis is significantly higher in patients who carry loads on their head than in those who do not.
 - Genetics: The role of genetics is unclear. However, a retrospective, population-based study by Patel et al shows that genetics may play a role in the development of cervical spondylotic myelopathy (CSM). An abundance of cases showing relatedness, as well as a considerable amount of elevated relative risks to close and distant relatives, advances the idea of an inherited predisposition to CSM[6].
- Patients older than 50 years who have normal cervical spine radiographic findings are significantly more likely to have a sibling with normal or mildly abnormal radiographic results.

Cervical Spondylosis Workup

Laboratory Studies: usually, no specific findings are present. Other findings may include those related to an underlying etiologic or pathogenetic disorder that initiates the spondylotic changes.

Imaging Studies

- Plain cervical radiography is routine in every patient with suspected cervical spondylosis.
 - This examination is valuable in evaluating the uncovertebral and facet joints, the foramen, intervertebral disk spaces, and osteophyte formation.
 - In select circumstances, flexion-extension views may be needed to detect instability.

- Myelography, with computed tomography (CT) scanning, is usually the imaging test of choice to assess spinal and foraminal stenosis [7].
 - Because myelography method is invasive, most physicians depend on MRI in diagnosing cervical spondylosis [7].
 - Myelography adds anatomic information in evaluating spondylosis.
 - Myelography may be especially useful in visualizing the nerve root takeoff.
 - CT scanning, with or without intrathecal dye, can be used to estimate the diameter of the canal.
 - CT scans may demonstrate small, lateral osteophytes and calcific opacities in the middle of the vertebral body.
- MRI is a considerable advance in the use of imaging to diagnose cervical spondylosis. It offers the following advantages:
 - Direct imaging in multiple planes
 - Better definition of neural elements
 - Increased accuracy in evaluating intrinsic spinal cord diseases
 - Noninvasiveness
 - Myelogramlike images
- High-signal-intensity lesions can be seen on magnetic resonance images of spinal cord compression; this finding indicates a poor prognosis.
- False-positive and false-negative MRI results occur frequently in patients with cervical radiculopathy; therefore, MRI results and clinical findings should be used when interpreting root compression [8].

Other Tests

- Electromyography is useful in evaluating radiculopathy caused by spondylosis, but it may have only limited value in assessing myelopathy.
- In myelopathy, somatosensory evoked potential (SSEP) responses are delayed or have low amplitude [9].
- Cortical motor evoked potentials (MEP) may be more sensitive than SSEPs in evaluating spinal cord dysfunction [10, 11].

- As an invasive procedure, cervical discography is not commonly used in the evaluation of cervical spondylosis.
- Urodynamic studies may be helpful in evaluating bladder incontinence.

Histologic Findings: thinning and fragmentation of the articular cartilage may be observed. The normal smooth, white articular surface becomes irregular and yellow. Continued loss of articular cartilage leads to exposure of areas of subchondral bone, which appear as shiny foci on the articular surface (eburnation). Fibrosis, increased bone formation, and cystic changes frequently occur in the underlying bone. Loss of articular cartilage stimulates new bone formation, usually in the form of nodules (osteophytes) at the bone edges.

Treatment & Management. Rehabilitation Program

Physical Therapy

- Immobilization of the cervical spine is the mainstay of conservative treatment for patients with cervical spondylosis. Soft cervical collars are recommended for daytime use only, but they are unable to appreciably limit the motion of the cervical spine. Molded cervical pillows can better align the spine during sleep and provide symptomatic relief for some patients.
- Mechanical traction is a widely used technique. This form of treatment may be useful because it promotes immobilization of the cervical region and widens the foraminal openings.
- The use of cervical exercises has been advocated in patients with cervical spondylosis. Isometric exercises are often beneficial to maintain the strength of the neck muscles. Neck and upper back stretching exercises, as well as light aerobic activities, also are recommended.
- Passive modalities generally involve the application of heat to the tissues in the cervical region, either by means of superficial devices (eg, moist-heat packs) or mechanisms for deep-heat transfer (eg, ultrasound, diathermy).
- Manual therapy, such as massage, mobilization, and manipulation, may provide further relief for patients with cervical spondylosis.

Occupational Therapy: patients with upper extremity weakness often lose their ability to perform activities of daily living (ADL), vocational activities, or recreational activities. Disability can be improved with specific strengthening exercises of the upper extremities, special splinting to compensate for weakness, and the use of assistive devices that allow the patient to perform previously impossible activities.

Medical Issues/Complications

Cervical spondylosis may result in complications, including the following:

- Cervical myelopathy
- Paraplegia
- Tetraplegia
- Recurrent chest infection
- Pressure sores
- Recurrent urinary tract infection

Surgical Intervention. Indications for surgery include the following:

- Progressive neurologic deficits
- Documented compression of the cervical nerve root and/or spinal cord
- Intractable pain

The aims of surgery are to relieve pain and neuronal structure compression, as well as, in select cases, to achieve stabilization.

Consultations with the following specialists may be helpful:

- Psychologist or psychiatrist
- Neurologist
- Neurosurgeon and/or orthopedic spinal surgeon
- Urologist
- Internist
- Occupational therapist
- Physical therapist
- Recreational therapist
- Social worker

Other Treatment

Injection: Cervical, zygapophyseal, intra-articular steroid injection can be helpful for active synovitis. The facet injections can be diagnostic and therapeutic. Mechanical facet pain is better evaluated with facet joint nerve blocks. Long-term relief can often be accomplished with a rhizotomy procedure. Cervical epidural block might be beneficial in cervical spondylosis, especially if an inflammatory component is present. Epidural and selective nerve root blocks can be diagnostically and therapeutically helpful in cases of radiculopathy. Trigger-point injections may be helpful.

Treatment of bowel and bladder dysfunction. Some patients with bowel dysfunction may benefit from a daily suppository, enema, or oral laxative. The administration should be followed by digital stimulation so that the patient's defecation occurs at a predictable time. Evaluate bladder incontinence with urodynamic studies. Pharmacologic intervention is possible in some patients, but many individuals need an intermittent catheterization program and control of fluid intake.

Rehabilitative nursing. A nurse should be involved in the educational process regarding the development of an effective bowel and/or bladder program and the prevention of pressure sores.

Psychosocial support. Patients with significant disability often react with fear, anxiety, or depression. Postoperative depression is significantly associated with pain intensity, pain interference, and pain-related disability [17]. Referral to a psychologist or psychiatrist for psychotherapy, pharmacotherapy, and/or family counseling may be indicated.

Medication Summary. The goal of pharmacotherapy is to reduce morbidity and prevent complications:

1. Nonsteroidal anti-inflammatory drugs
2. Corticosteroids
3. Muscle relaxants
4. Antidepressants

Prognosis

- Cervical spondylosis is a slowly progressive, chronic joint disability, especially when it is associated with neuronal compression.
- Cervical spondylotic myelopathy is the most serious consequence.
- High – signal-intensity lesions can be seen on magnetic resonance images of spinal cord compression; this finding indicates a poor prognosis.

3.3. Cervical Sprain and Strain

Background. Cervical strain is one of the most common musculoskeletal problems encountered by generalists and neuromusculoskeletal specialists in the clinic.



Radiograph of the cervical spine shows a normal lordotic curve [1].

Whiplash, one of the most common sequela of nonfatal car injuries, is one of the most poorly understood disorders of the spine, and the severity of the trauma is often not correlated with the seriousness of the clinical problems [1]. A history of neck injury is a significant risk factor for chronic neck pain [2]. Pretorque of the head and neck increases facet capsular strains, supporting its role in the whiplash mechanism [3].

The following system for classifying the severity of cervical sprains [4]:

- 0 - No neck pain complaints, no physical signs

- 1 - Neck pain complaints, only stiffness or tenderness, no other physical signs
- 2 - Neck complaints and musculoskeletal signs (decreased range of motion [ROM] and point tenderness)
- 3 - Neck complaints and neurologic signs (weakness, sensory and reflex changes)
- 4 - Neck complaints with fracture and/or dislocation

Pathophysiology. Relevant anatomy and physiology. Consistent with known biologic models, injuries to bony, articular (disks and facets), nerve (including root and spinal cord), and soft (ligament, tendon, muscle) tissues of the cervical spine are the most likely sources of dysfunction and pain. Cervical strain is produced by an overload injury to the muscle-tendon unit because of excessive forces on the cervical spine. The cause is thought to be the elongation and tearing of muscles or ligaments. Secondary edema, hemorrhage, and inflammation may occur.

Many cervical muscles do not terminate in tendons but attach directly to the periosteum. Muscles respond to injury by contracting, with surrounding muscles recruited in an attempt to splint the injured muscle. Myofascial pain syndrome, which is thought to be the resultant clinical picture, may be a secondary tissue response to disk or facet-joint injury.

Facet capsular ligaments have been shown to contain free (nociceptive) nerve endings, and distending these ligaments by administering facet joint injections has produced whiplash-like pain patterns in healthy individuals. The cervical facet capsular ligaments may be injured under whiplash-like loads of combined shear, bending, and compression forces; this mechanism provides a mechanical basis for injury caused by whiplash loading [5].

Chronic pain associated with cervical strains is most likely to affect the zygapophysial (facet) joints, intervertebral disks, and upper cervical ligaments. The C2-C3 facet joint is the most common source of referred pain in patients with a dominant complaint of headache (60%). The C5-C6 region is the most common

source of cervical, axial, and referred arm pain. Cervical facet joint pain is typically a unilateral, dull, and aching neck pain with occasional referral into the occiput or interscapular regions. The cervical facet joints can be responsible for a substantial portion of chronic neck pain. The cervical facet joints refer pain overlapping with both myofascial and diskogenic pain patterns.

Neuroanatomic studies reveal that the facet joint is richly innervated and contains free and encapsulated nerve endings. The facet capsule is richly innervated with C fibers and A-delta fibers. Many of these nerves are at a high threshold and likely to indicate pain. Local pressure and capsular stretch can mechanically activate these nerves. These neurons can be sensitized or excited by naturally occurring inflammatory agents, including substance P and phospholipase A.

Physiologic changes in the spinal cord, particularly the pain complexes of the dorsal horn, implicate excitatory amino acids, such as substance P, glutamate, gamma-aminobutyric acid (GABA), and N -methyl-D-aspartate (NMDA), as well as other factors that sensitize the dorsal horn in chronic pain. The mechanism is massive input of noxious stimuli from cervical spine injury [7].

In lumbar spine studies, inflammatory cytokines are found at high levels in facet joint tissue when a degenerative disorder is present. Facet joints are covered by hyaline cartilage and enclosed with synovium and joint capsules. This basic structure is found throughout the spine and in the joints of the arms and the legs[8].

The zygapophysial joints are injured in cases of whiplash. Clinical studies have shown that pain in the zygapophysial joint is common in patients with chronic neck pain after whiplash injury [9]. Injury was sustained to cervical facet capsular ligaments as a result of the combined shear, bending, and compression load levels that occur in rear-end impacts [10].

An overload injury to the muscle-tendon unit produces cervical strain because of excessive forces on the cervical spine. This injury is accompanied by elongation and tearing of muscles or ligaments, secondary edema, hemorrhage, and inflammation. Many cervical muscles attach directly to bone (periosteum), and the

muscle response to injury is contraction, with surrounding muscles recruited to splint the injured muscle.

Classic mechanism of whiplash injury. A collision in any direction can cause chronic whiplash [11].

The classic whiplash scenario in which the patient's car has been struck from behind (ie, rear ended) [12]. This type of accident typically occurs in the following manner:

- At the time of impact, the vehicle suddenly accelerates forward. About 100 ms later, the patient's trunk and shoulders follow, induced by a similar acceleration of the car seat.
- The patient's head, with no force acting on it, remains static in space. The result is forced extension of the neck, as the shoulders travel anteriorly under the head. With this extension, the inertia of the head is overcome, and the head accelerates forward.
- The neck then acts as a lever to increase forward acceleration of the head, forcing the neck into flexion.

Frontal impact causes middle C2-C3 to C4-C5 and lower C6-C7 and C7-Th1 injury [13]. Direct facial impact has shown a flexion motion of the upper or middle cervical spine, with extension of the lower cervical spine [14].

The forces involved in an impact speed of 20 mph (32 km/h) cause the human head to reach a peak acceleration of 12G during extension. If the head is in slight rotation, a rear impact forces the head into further rotation before extension, pre-stressing various cervical structures, such as the capsules of the zygapophysial joints, intervertebral disks, and the alar ligament complex. These structures are thus rendered susceptible to injury. Muscle injury may be less likely after low-velocity impacts with head rotation at the time of impact than they are in other mechanisms [15, 16, 17, 18, 19].

When a rear impact is offset to the subject's left, it not only results in increased electromyographic activity in both sternocleidomastoids, it also causes the splenius capitis contralateral to the direction of impact to bear part of

the force, thus causing injury. Which muscle responds most to a whiplash-type injury is determined by the direction of head rotation. The sternocleidomastoid on the right responds most with the head rotated to the left, and vice versa. Measures to prevent whiplash injury need to account for the symmetric muscle response caused by victims looking to the right or left at the time of collision.

Lower cervical facet joints respond with a shear plus distraction mechanism in the front and shear plus compression in the back. In studies, females were more likely to be injured than were males, possibly owing to sex-related genetic, hormonal, structural, or tolerance differences [20].

Head-turned rear impact also causes significantly greater injury at C0-C1 and C5-C6 as compared with head-forward rear and frontal impacts. Multiplanar injury that occurs at C5-C6 and C6-C7 has also been found to occur with head-turned impact [21]. Head-turned rear impacts up to 8 G do not typically injure the alar, transverse, and apical ligaments [22].

Head-turned impact also causes dynamic cervical intervertebral narrowing, indicating potential ganglion compression even in patients with a non-stenotic foramen at C5-C6 and C6-C7. In patients with a stenotic foramen, the risk greatly increases to include C3-C4 through C6-C7 [23].

A rear-end collision is most likely to injure the lower cervical spine, with intervertebral hyperextension at a peak acceleration of 5 G and above [24, 25]. The first substantial increase in intervertebral flexibility occurs at C5-C6 following 5-G acceleration. At accelerations faster than this, the injuries spread to the surrounding levels (C4-C5 to C4-Th1). The 2 injury phases during whiplash are (1) hyperextension at C5-C6 and C6-C7 and mild flexion at C0-C4 and (2) hyperextension of the entire cervical spine [25].

An instantaneous change occurs in the pivot point at C5-C6, causing a jamming effect of the inferior facet of C5 on the superior facet of C6 [7]. The non-physiologic kinematic responses that occur during a whiplash impact may induce stresses in upper cervical neural structures or in lower facet joints. The result may be compromise sufficient to elicit neuropathic or nociceptive pain [25].

The muscular component of the head-neck complex plays a central role in the abatement of higher acceleration levels; it may be a primary site of injury in the whiplash phenomenon. Muscle responses are greater with faster accelerations than with slower ones [2,8]. Cervical muscle strains induced during a rear-end impact are greater than the injury threshold that had previously been reported for a single stretch of active muscle, with larger strains in the extensor muscles being consistent with clinical reports of pain in the posterior cervical region after the occurrence of a rear-end impact [2,9].

The risk of whiplash injury in motor vehicle collisions increases when subjects are surprised and unprepared for the impact [3].

Complications. Cervical myeloradiculopathy is a complication of flexion/extension injuries in patients with underlying spondylosis. Cervical disks may become painful as part of the degenerative process, because of repetitive microtrauma or a single excessive load. Pain due to a disk injury may result from annular tears with inflammation or compression of the local nervous or vascular tissue.

Cord compression after whiplash due to physiologic extension loading is not likely. However, individuals with a narrow spinal canal have an increased risk of quadriplegia-causing injury to the spinal cord [25].

Postmortem studies have shown that ligamentous injuries are common after whiplash injuries, but disk herniation is a rare event [3].

In one study, whiplash-type distortions were associated with a 16% incidence of diskoligamentous injuries. On MRI, most patients with severe, persisting, radiating pain had large disk protrusions that were confirmed as herniations at surgery. Neck and radiating pain were alleviated with early disk excision and fusion [4].

Strain or tears of the anterior annulus and the alar portions of the posterior longitudinal ligament (when stretched by a bulging disk) are possible causes for diskogenic pain after whiplash injury. Injuries of the zygapophysial joint found in clinical and cadaveric studies include fracture, bleeding, rupture or tear of the joint

capsule, fracture of the subchondral plate, contusion of the intra-articular meniscus, and fracture of the articular surface [3,5].

Upper cervical disk protrusions as a result of cervical strain injury may result in nonspecific and shoulder pain. Motor weakness or reflex or sensory abnormalities may be limited or nonspecific. Radiculopathy is more likely than are cord signs.

MRI or computed tomography (CT) myelography are necessary for the diagnosis [3,6].

Epidemiology. Frequency. United States. Almost 85% of all neck pain is thought to result from acute or repetitive neck injuries or from chronic stresses and strain. In the general population, the 1-year prevalence rate for neck and shoulder pain is 16-18% [3,7].

Estimates indicate that more than 1 million whiplash injuries occur each year due to automobile accidents. The annual incidence of symptoms due to whiplash injury is 3,8 cases per 1000 population [3,5]. 6,2% of the US population have late whiplash syndrome [3,8].

International: The annual incidence in Switzerland is 0,44 cases per 1000 population. In Norway, a rate of 2 cases per 1000 population has been reported. The approximate annual incidence in Western countries is 1 case per 1000 population.

Mortality/Morbidity. Mortality is rare unless severe trauma causes the cervical strain, with associated brain or spinal cord trauma, respiratory compromise, or vascular injury.

Morbidity includes cervical pain syndromes with associated symptoms. Disability in acute or chronic cervical strains is responsible for significant socioeconomic costs.

Sex. Chronic neck pain is identified in 9,5% of men and in 13,5% of women.

Age. The patients with a whiplash injury are in their late fourth decade.

History. The most common symptoms of cervical disorders are suboccipital headache and/or ongoing or motion-induced neck pain. Other symptoms associated with cervical strain include the following:

- Neck pain:
 - At the time of accident, neck pain may be minimal, with an onset of symptoms occurring during the subsequent 12-72 hours.
 - Nonspecific neck and shoulder pain (a variety of cervical radiculopathies) may indicate an injury to a disk in the upper cervical spine[3,6]
- Headache is a frequent symptom of cervical strain [3,9].
 - Neck structures play a role in the pathophysiology of some headaches, but the clinical patterns have not been defined adequately.
 - Increased muscle hardness (determined by palpation) is significantly increased in patients with chronic tension-type headaches.
 - Facet joints and intervertebral disk damage have been implicated in the pathology of headaches due to neck injury [7].
 - No specific pathology on imaging or diagnostic studies has been correlated with cervicogenic headaches.
- Shoulder, scapular, and/or arm pain
- Visual disturbances (eg, blurred vision, diplopia)
- Tinnitus
- Dizziness - this may result from injury to facet joints that are supplied with proprioceptive fibers; when injured, these fibers can cause confused vestibular and visual input to the brain [7].
- Concussion
- Neurologic symptoms: these may include weakness or heaviness in the arms, numbness, and paresthesia.
- Difficulty sleeping due to pain
- Disturbed concentration and memory

- Late whiplash syndrome includes symptoms such as headache, vertigo, disturbances in concentration and memory, difficulty swallowing, and impaired vision. These cognitive impairments remain poorly understood.
- Many patients with these changes have abnormal results on single-photon emission CT (SPECT) scans or P300 event-related potentials [4].
- Bladder or bowel dysfunction: these may be symptoms of complication of myelopathy (spinal cord involvement).

The physical examination is a vital part of the diagnosis of cervical stress and strain injuries. Various signs and symptoms may be noted.

- Observation of the patient's general appearance: this may yield information about pain behavior, verbal or nonverbal.
- Spinal examination:
 - During the postural assessment, the clinician may note the following findings: stiffness of the neck, forward head, flexed neck, rounded shoulders, asymmetry of the neck or shoulders, neck tilt or rotation, and one shoulder higher or tighter than the other.
 - Palpation may reveal rigidity (loss of motion or postural abnormality), spasm tightness, muscle hardness, crepitation, swelling, enlargement of joints, tenderness, tender points, and trigger points. Palpation of the zygapophysial joints may be helpful in determining the painful joints, because of osteoarthritis or posttraumatic irritation of the joint capsule.
 - ROM: decreased active and passive ROM may be noted. Impaired cervical ROM (particularly in the sagittal plane) is useful in distinguishing between asymptomatic persons and those with persistent whiplash-associated disorders [1].
 - After acute whiplash injury, neck mobility is significantly reduced. After 3 months, however, mobility has been found to be similar between control subjects and patients with whiplash injury [43].
 - Special maneuvers: cervical neurocompression may cause parascapular or arm pain by narrowing the neural foramen (causing nerve root compression) or by causing pressure on the facet joints.

- Neurologic examination:
 - Mental status: mood disturbance, such as anxiety or depressive affect.
 - Motor function: if cervical radiculopathy is present, the strength or bulk of the upper extremities may be decreased. If myelopathy is present, weakness of upper and lower extremities may be noted.
 - Circumference: the dominant arm and forearm are usually slightly larger than are those of the nondominant side.
 - Reflexes: in cervical radiculopathy, muscle stretch reflexes (MSRs) may be decreased in a myotomal pattern in the affected upper limb; however, they should remain normal in the lower limbs. In cervical myelopathy (cervical spinal cord involvement), the MSRs arising from a given level of the cord may be decreased in the upper limbs; however, MSRs in the lower limbs may be increased, with spasticity of the lower extremities, a positive Babinski sign, and a positive Hoffman sign.
 - Sensation: if cervical radiculopathy is present, pain or 2-point discrimination of light touch may be reduced in a radicular pattern in the upper extremities.
 - Coordination: with radiculopathy or myelopathy, coordination may be decreased in the involved upper extremity.
 - Gait: in cases of cervical myelopathy, the patient's gait pattern may be abnormal as a result of spasticity. The presence of spasticity implies an upper motor neuron dysfunction, in contrast with injury to the peripheral nerves.
 - Provocative maneuvers: the Spurling test uses cervical extension and lateral bending while the examiner applies a downward axial load. This test may provoke (reduce) radicular symptoms in a patient with cervical radiculopathy.

Causes: motor vehicle accidents, lifting or pulling heavy objects, awkward sleeping positions, unusual upper-extremity work, and prolonged static positions.

Flexion/extension injuries may precipitate a myeloradiculopathic presentation in a patient with cervical spondylosis. Nerve root or spinal cord compression may occur from neural ischemia due to the preexisting stenosis that

accompanies cervical spondylosis. Flexion/extension injuries, blows to the head, or neck injury while lifting heavy objects may precipitate an acute exacerbation of cervical spondylosis.

Repetitive or abnormal postures may contribute to cervical sprains and strains.

No dose-response association between the magnitude of trauma severity and the incidence of whiplash injury was found [4].

Cervical Sprain and Strain Workup. Laboratory Studies

- Complete blood count (CBC) with differential, if infection or tumor is a concern.
- An arthritis profile, including a determination of the erythrocyte sedimentation rate (ESR), if inflammatory arthritis or polymyalgia rheumatica is suggested.

Imaging Studies

- Although not pathognomonic for sprain/strain, imaging results are important for excluding other diagnoses and more extensive injuries.
 - Motor vehicle crashes causing fatalities may also result in occult pathoanatomic lesions in the cervical intervertebral disk and zygapophysial joints. Present imaging methods do not depict these subtle lesions; hence, underreporting of pathoanatomic lesions during standard autopsy is probably common.
 - These findings may have clinical relevance in the management of road traffic trauma survivors with potentially similar pathoanatomy [4,5].
- Radiography is useful in the evaluation of cervical sprain and strain.
 - Only lateral views are needed for the initial screening of stability. Three views are obtained for the basic evaluation: anteroposterior (AP), lateral, and odontoid. Five views, including the 3 basic views plus bilateral oblique views, are used to evaluate the intervertebral foramen.
 - Flexion/extension views may be obtained if instability is suggested. Hypermobility in the lower cervical segments in 12 out of 34 patients with chronic whiplash-associated disorders were identified by a new measurement protocol

determining rotational and translational motions of segments C3-C4 and C5-C6 [4,6].

- Order radiographic studies early in any of the following cases: when significant trauma, pain, or dysfunction develops; when a chronic condition develops; or when documentation of the patient's condition is required (in instances when litigation is anticipated).

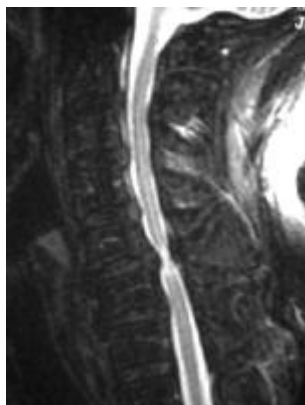
- Radiographs of the cervical spine may show straightening or reversal of the normal lordotic curve (see images below). This finding is thought to represent spasm, guarding, or splinting of the muscles that stabilize the neck. Although these findings may be seen in as many as 20% of healthy control subjects, the rates are higher in the injured population.

- Overall, MRI is the best noninvasive and detailed imaging study for evaluating the status of the disks and spinal cord.

- Order MRI if detailed analysis of spinal structures (eg, spinal cord, disk) is indicated, as in, for example, an evaluation for underlying herniated nucleus pulposus (HNP).

- A relative number of abnormal findings on cervical spine MRI scans can be found in asymptomatic individuals. The most common findings involve disk degeneration, but nearly 10% of patients can have asymptomatic spinal cord compression [4].

- Lateral disk protrusions (see image below) are rarely found in asymptomatic patients, who usually present with concordant radiculopathy.



MRI of the cervical spine shows disk protrusion [4].

- Extruded disks are not seen in asymptomatic patients. When seen in the cervical spine, they are almost invariably associated with the patient's symptoms.
- A clearly defined extrusion, when arising from a normally hydrated disk with no osseous ridging and when compressing an appropriate nerve root concordant with the patient's symptoms, can be considered with confidence to be acute or subacute.
- MRI is indicated in patients with persistent arm pain, neurologic deficits, or clinical signs of nerve root compression.
- MRI is unable to reliably depict sources of cervical diskogenic pain, because significant annular tears often escape MRI detection [7].
- CT scanning may be performed if detailed bony imaging is indicated, such as when a fracture or instability is a concern. CT scanning may be used as an alternative to MRI in patients with claustrophobia, although disk imaging with CT scanning offers low resolution.
- CT myelography is an invasive imaging study that may be useful for a detailed analysis if plain CT scanning and MRI do not provide a definitive answer regarding the suspected pathology.
 - The degree of concordance between CT myelography and MRI is only moderately good; discrepancies are noted especially in the differentiation of disk and bony pathology.
 - A disadvantage is that lumbar puncture is required.
- Bone scanning is indicated if a spinal tumor, infection, or occult fracture is suggested.
- Videofluoroscopy is a controversial study used to evaluate increased, decreased, or abnormal segmental movement of the cervical spine.
 - Motion patterns were different between normal spines and pathologic spines [8].

- Cineradiography allows the identification of soft-tissue injuries and early subluxations of the cervical spine that may not be identified with static radiography or physical examination [9].
- Discography is used in the presurgical evaluation, to identify the level on which to operate. Significant tears are often missed with MRI, but discography can reveal a discogenic source of cervical pain. Although MRI can identify most of the painful disks, it has relatively high false-negative and false-positive rates. Discography can direct a surgeon in making critical management decisions [5].

Other Tests

- Electrodiagnostic studies
 - These physiologic studies may show nerve injury (as opposed to imaging studies, which may show only structural injury).
 - These studies should be performed and interpreted by an appropriately trained and board certified electromyographer.
- Electromyography (EMG):
 - EMG can be used to determine if radiculopathy is a factor in the patient's symptoms.
 - EMG is usually performed after 1-2 weeks (or longer), when the physiologic changes are first found.
 - In patients with acute radiculopathy, electromyographic findings include increased insertional activity, fibrillation potentials, positive sharp waves, and complex repetitive discharges.
 - Chronic radiculopathy findings are noted after a few months of nerve root involvement; they include polyphasic or broad-duration/large-amplitude motor units, drop out of motor units, decreased recruitment, and an incomplete interference pattern.
 - Findings in the posterior primary division of the nerve root are noted in the cervical paraspinous muscles.

- The anterior primary division of the nerve root findings is noted in the specific root-innervated muscles of the upper extremity.
- The accessory spinal nerve innervates the trapezius muscle, which is often a source of chronic neck pain due to spasm. Contribution from the C2-C4 motor roots is minimal and inconsistent. Electromyographic recordings from the trapezius muscle can show dysfunction of the spinal motor nerve root [1].
- When electromyographic findings of radiculopathy are interpreted, the duration of the symptoms should not influence the diagnosis [2].
- Nerve conduction studies (NCS):
 - NCS may be performed by an appropriately trained and supervised technician.
 - These tests should be interpreted by a board certified electrodiagnostic medicine specialist only with the entire clinical picture in mind.
 - An NCS is indicated if a concomitant peripheral nerve involvement is suspected and needs to be evaluated. The study would be performed, for example, when numbness of the radial aspect of the upper extremity is a symptom or when carpal tunnel syndrome versus C6 radiculopathy needs to be identified.

Rehabilitation Program. Physical Therapy. Early rehabilitation helps to prevent chronic pain and disability.

Passive modalities include the application of heat, ice, electrical stimulation, massage, myofascial release, and traction. Passive modalities are often used to decrease pain or inflammation and to facilitate participation in an active rehabilitation program, which often involves stretching and strengthening. Extended use of passive modalities without a more active program is generally inappropriate.

Active treatment refers to therapeutic exercises that are aimed at improving the patient's strength, endurance, flexibility, posture, and body mechanics. The goal is to obtain an independent home program or community fitness program at

the conclusion of formal physical therapy. The typical therapy prescription is recommended 3 times per week for 4-8 weeks.

Scientific evidence for the physiotherapeutic management of whiplash is sparse. An early, active strategy is recommended to improve functions, increase activity, and prevent chronicity [5]. In patients with whiplash-associated disorders caused by a motor vehicle collision, treatment with frequently repeated active submaximal movements combined with mechanical diagnosis and therapy is more effective in reducing pain than is a standard program of initial rest, use of a soft collar, and gradual self-mobilization [5].

In patients with whiplash-associated disorders, active intervention is more effective than standard intervention in reducing pain intensity and sick leave, as well as in retaining/regaining total ROM.

In examining the costs and consequences of 2 types of intervention after whiplash trauma in automobile crashes, active intervention using physical therapy was found to be less costly and more effective than short-term immobilization using a cervical collar followed by a gradual self-exercise program taught by a leaflet [6].

Occupational Therapy. Occupational therapy may be indicated unless a concurrent problem involves a distal upper-extremity function or ergonomic factors in causation. A workstation ergonomic evaluation may be indicated if biomechanical stresses of work activity are factors in the causation or exacerbation of the condition.

Medical Issues/Complications

- Pain complaints may escalate during the rehabilitation program.
- Pain must be treated aggressively and appropriately.
- Underlying medical conditions may need to be evaluated and treated to facilitate rehabilitation.
- The goal of therapy is functional rehabilitation and restoration with an emphasis on improving the patient's strength, endurance, and flexibility.

Surgical Intervention

- Cervical myeloradiculopathy or instability, a possible complication of cervical strain, may require surgical intervention (eg, fusion).
- The cervical radiculopathy has a better outcome with surgical intervention than with medical treatment. However, in clinical practice, many physicians believe that most patients respond well to nonsurgical treatment [6].
- In one study of patients with cervical spondylotic myeloradiculopathy, the short-term effects of surgery (eg, pain, weakness, sensory loss) were superior. However, at 1 year, no significant differences between surgically and nonsurgically treated groups were found [6].
- Severe sprains of the cervical spine may result in a traumatic rupture of the intervertebral disk and ligaments, which, if not surgically treated, can lead to a significant kyphotic deformity [6].

Consultations. A board-certified electrodiagnostic medicine specialist may be consulted for EMG and/or an NCS if radiculopathy or peripheral nerve involvement (eg, carpal tunnel syndrome) is suspected.

Surgical consultation with a neurosurgeon or orthopedic spinal surgeon may be appropriate if surgical intervention is being considered.

Psychological or psychiatric consultation may be indicated if secondary depression, anxiety, or adjustment disorder needs evaluation and treatment.

- Patients who achieve complete relief from chronic neck pain resolve all of their psychological distress. Patients with persistent neck pain also have persistent anxiety, depression, and other forms of psychological distress.
- Findings from a study of patients with whiplash-associated disorders suggested that psychosocial problems of these patients are more pronounced than their physical problems. Coping strategies seem to be a significant predictor of psychological well-being [6,7].

A functional capacity evaluation (FCE) may be required if objective evaluation of the level of ability/disability needs to be documented for litigation or for determining the patient's readiness to return to work.

The degree of neck pain or dysfunction can be evaluated by using standardized scales [2].

Other Treatment. Upon review of several trials and studies, moderate evidence exists in support of radiofrequency neurotomy. Evidence for steroid injections, botulinum treatments, and cervical discectomy is conflicting or unclear [58, 59].

1. Opioid analgesics
2. Cyclooxygenase-2 (COX-2) inhibitors
3. Nonsteroidal anti-inflammatory agents
4. Muscle relaxants
5. Tricyclic antidepressants
6. Corticosteroids

Prognosis. Short-term recovery. Many patients improve within 8 weeks, although complete resolution in this period may not be common. If pain persists for longer than 3 months, severe ligamentous, disk, or associated facet injury is suggested. Recovery after whiplash occurs mostly in the first 2-3 months after the accident. After that, recovery slows dramatically, with no further change in symptoms after 2 years.

At 6 months after the injury, 20-70% of patients with neck injury due to an automobile accident still experience pain.

Long-term recovery. Dreyer and Boden examined patients 10 years after the onset of neck pain and found that 79% had improved, 43% were pain-free, and 32% had persistent, moderate to severe pain [3,7]. In a group of patients with significant symptoms at 10 years after whiplash injury, everyone had degenerative changes on radiographs, at a significantly higher rate than that of a control group [3,5].

Whiplash patients with ongoing moderate or severe symptoms at 2-3 years continued to show decreased ROM, increased electromyographic activity during craniocervical flexion, and sensory hypersensitivity. They also showed elevated

levels of psychological distress compared with those of patients with milder symptoms or with individuals who had recovered [7].

The greatest risk for long-term symptoms occurs in patients with point tenderness and limited ROM [7,8].

The factors related to poor recovery from whiplash-associated disorder include female sex, a low level of education, high initial neck pain, severe disability, and high levels of somatization and sleep difficulties. Neck pain intensity and work disability were the most consistent predictors for poor recovery [8].

Associated comorbidities. The trauma to the cervical spine may accelerate normal age-related deterioration of the disks [3].

Increasing age, injury-related cognitive impairment, and severity of the initial neck pain were predictive of persistent symptoms at 6 months [8].

The symptomatic patients with injury-related symptoms were older and had an increased incidence of rotated or inclined head position at the time of impact, an increased prevalence of pretraumatic headache, and an increased intensity of initial neck pain and headache [8]. Symptomatic patients also had more symptoms (including those of radicular deficit), higher average scores on a multiple-symptom analysis, and more degenerative signs (osteoarthritis) on radiographs.

Disabling neck pain is associated with other comorbidities (headache, cardiovascular problems, digestive problems, low back pain) that negatively affect the patient's health. The prevalence of neck pain and disability is increased in individuals with a lifetime history of neck injury who are involved in a motor vehicle collision [85]. Low back pain is a common injury with prolonged recovery. Biopsychosocial factors, such as the type of compensation system that exists, affect the incidence and prognosis [6].

Chronic psychiatric disease is more common in patients with chronic whiplash-associated disorder than in others. The dominant psychiatric diagnosis, before and after the injury, is depression. Psychiatric morbidity may be a patient-

related risk factor for chronic symptoms after a whiplash injury and seems to be associated with psychiatric vulnerability [7].

Depressive symptomatology after whiplash is common, occurs early, and often persists or becomes recurrent [8].

The incidence of widespread pain disorders (fibromyalgia) increases after cervical spinal injury [8,9].

Chronic whiplash-associated disorders are characterized by mechanical hyperalgesia over the cervical spine and by widespread hypersensitivity to mechanical pressure and thermal stimuli; this finding was independent of state of anxiety and may represent changes in central pain-processing mechanisms [9].

The patients with whiplash-associated disorders may demonstrate symptoms well beyond the neck, including fatigue, dizziness, paresthesias, headaches, spinal pain, nausea, and jaw pain [1].

3.4. Complex Regional Pain Syndromes

Background. Complex regional pain syndrome (CRPS) may develop as a disproportionate consequence of a trauma affecting the limbs without nerve injury (CRPS I, or reflex sympathetic dystrophy [RSD]) or with obvious nerve lesions (CRPS II, or causalgia). (See images below)



A 29-year-old woman with reflex sympathetic dystrophy in the right foot demonstrates discoloration of the skin and marked allodynia [14].

This photo shows the same patient as in the above image, following a right lumbar sympathetic block. Marked increase in the temperature of the right foot is noted, with more than 50% pain relief [14].





A 68-year-old woman with complex regional pain syndrome type II (causalgia) [13].

A 36-year-old woman with right arm reflex sympathetic dystrophy and dystonic posture (movement disorder) [13].



- In the 17th Century, Ambroise Pare presented the earliest description of RSD as severe burning pain following peripheral nerve injury. Pare, a surgeon, treated King Charles IX for smallpox by inducing bleeding with a lancet applied to the arm. After this treatment, the king suffered from persistent pain, muscle contracture, and inability to flex or extend his arm.
- In 1864, Mitchell coined the term causalgia, which means burning pain, to describe persistent symptoms following gunshot wounds to peripheral nerves during the American Civil War.
- In 1900, Sudeck described radiographic spotty osteopenia.
- In 1916, Leriche focused on the sympathetic nervous system.
- In 1943, Livingston expanded the Leriche vicious circle theory that includes the following:
 - Abnormally firing, self-sustaining loops in the dorsal horn
 - Provoked by a small irritation focus in small nerve endings of major nerve trunks
 - Activating central projecting fibers, giving rise to pain
- In 1946, Evans used the term RSD, believing that sympathetic hyperactivity is involved somehow in the abnormal activity in the periphery.

- In 1993, the International Association for the Study of Pain (IASP) held a Special Consensus Conference addressing diagnosis and terminology (endorsing the term CRPS).
- In 1995, Paice wrote that, even after 130 years, there was still no general agreement on what to call RSD, what causes it, or how best to treat it [1].

Pathophysiology. CRPS is a relatively common disabling disorder of unknown pathophysiology [2]. RSD is a variable symptom complex that probably results from multiple causes arising through different pathophysiologic mechanisms. Changes in the peripheral and central somatosensory, autonomic, and motor processing and a pathologic interaction of sympathetic and afferent systems are described as underlying mechanisms.

- Several hypotheses exist regarding the mechanism of sympathetically mediated pain and describe central and peripheral components: a complete functional loss of cutaneous sympathetic vasoconstrictor activity in an early stage of RSD/CRPS I, with recovery [3]. This autonomic dysfunction originates in the central nervous system (CNS).
- The role of spinal component to microcirculatory abnormalities at stage 1 of RSD, which appeared to manifest itself through a neural antidromic mechanism [4]. This spinal component may be evoked by traumatic excitation of a peripheral nerve on the affected side.
- The role of positive feedback circuit, consisting of primary afferent neuron, spinal cord neurons, sympathetic neurons, and a pathologic sympathetic coupling.
- The cause of vascular abnormalities is unknown, and debate still surrounds the question of whether the sympathetic nervous system (SNS) is involved in the generation of these changes.
- In patients with acute RSD, immunoglobulin G labeled with indium-111 (^{111}In) is concentrated in the affected extremity.
- A study with ^{31}P (phosphorus) nuclear magnetic resonance (NMR) spectroscopy showed an impairment of high-energy phosphate metabolism,

which explains why these patients are unable, rather than unwilling, to exercise.

- Electron microscope studies of skeletal muscle biopsies showed reduced mitochondrial enzyme activity, vesiculation of mitochondria, disintegration of myofibrils, abnormal depositions of lipofuscin, swelling of endothelial layers, and thickening of the basal membrane, which are all signs of oxidative stress. Oxygen consumption is reduced in limbs affected by RSD, and reduction of pain following treatment with oral vasodilators has been described.
- After a partial nerve lesion, excessive antidromic activation of undamaged afferent C fibers and neuropeptide release, leading to acute vasodilation within the innervation territory of the affected nerve, were demonstrated.
- The frequency of the presence of human lymphocyte antigen-DQ1 (HLA-DQ1) was increased significantly in RSD compared with control frequencies. This association provides an indication of an organic basis.
- The autoantibodies against nervous system structures have been described in these patients [5].

Epidemiology. United States. Limited information is available. Actual incidence is unknown, as CRPS is often misdiagnosed. Some sources report, the incidence of causalgia (CRPS II) following injury to a peripheral nerve is 1-5%. The incidence of RSD (CRPS I) is 1-2% after various fractures and 2-5% after peripheral nerve injury.

Mortality/Morbidity. RSD has significant morbidity, so raising awareness of this disease is important.

Sex: RSD is reported more commonly in women. [6]

Age. RSD may appear in every age group, but, as widely reported, it is less common in children aged less than 10 years [6].

History. The typical clinical picture of CRPS consists of disproportionate extremity pain, swelling, and autonomic (sympathetic) and motor symptoms.

The condition can affect the upper or lower extremities, but it is slightly more common in the upper extremities.

- Pain:
 - Pain is reported in more than 90% of patients.
 - worsening of pain after exercising the affected limb.
- Edema:
 - Vascular abnormalities (often abnormal vasodilation and skin warming in the early phase and vasoconstriction in later stages) are characteristic symptoms of RSD/CRPS I.
 - Typically, patients with CRPS I exhibit a warm and vasodilated affected extremity in the early stages and cold and pale skin in the later stages.
- Alteration in motor function:
 - The abnormal motor symptoms that are reported most classically in RSD include the following: inability to initiate movement; weakness (in 95% of patients); tremor (in 49%); muscle spasms (25%); dystonia of the affected limb.
- Alteration in sensory function, including hypoesthesia, hyperesthesia, and allodynia, may occur.
- Psychological disturbances may include anxiety, hopelessness, and/or depression.

Physical examination. The common characteristic features of RSD (CRPS I) are spontaneous pain, hyperalgesia, impairment of motor function, swelling, changes in sweating, and vascular abnormalities in a single extremity. An overt nerve injury is not detectable:

- Various sensory symptoms have been observed.
 - Allodynia (mechanical and thermal)
 - Hyperalgesia (mechanical and thermal)
 - Hyperpathia
 - Hypoesthesia
 - Hypothermesthesia

- Proprioception and anesthesia dolorosa (sensibility to touch is absent, while severe pain is present in the anesthetic area)
- Dissociated sensory pattern (on rare occasions)
 - Discoloration of the skin (in 91% of cases), altered skin temperature (in 92%), edema (in 69%), and limited active range of motion (AROM) (in 88%).
 - Hyperhidrosis (in more than 50% of cases) with warm or cold skin temperature.
 - Dystrophic changes may present in skin, subcutaneous tissue, muscles, and bone.
 - Changes in the growth pattern of hair or nails on the affected limb.
- Complex regional pain syndrome:
 - There are 2 types of CRPS, namely CRPS I (RSD) and CRPS II (causalgia). These 2 types are differentiated mainly based upon whether the inciting incident included a definable nerve injury.
 - CRPS I (RSD) occurs after initial noxious event other than a nerve injury.
 - CRPS II (causalgia) occurs after nerve injury.
 - Features common to CRPS types I and II include the following:
 - Pain, whether spontaneous or evoked, may include allodynia (painful response to a stimulus that is not usually painful) and/or hyperalgesia (exaggerated response to a stimulus that is usually only mildly painful).
 - Pain that is disproportionate to the inciting event (eg, years of severe pain after an ankle sprain)
 - Regional pain that is not limited to a single peripheral nerve distribution
 - Evidence of autonomic dysregulation (eg, edema, alteration in blood flow, hyperhidrosis)
 - Diagnosis is excluded if another condition could account for the degree of pain and dysfunction.
 - Typically, CRPS I is subdivided into the following 3 phases:
 - Acute stage - Usually warm phase of 2-3 months
 - Dystrophic phase - Vasomotor instability for several months

- Atrophic phase - Usually cold extremity with atrophic changes
 - These stages may be variable and often are not clear cut.
- Causes.** Various insults that may lead to RSD include the following:
- Trauma (eg, sprain, dislocations, fractures, surgery, burns, crash injury)
 - Neurologic disorders (eg, stroke, tumor, syringomyelia)
 - Herpes zoster infection
 - Myocardial infarction
 - Musculoskeletal disorder (shoulder rotator cuff injury)
 - Malignancy
 - Spontaneous/idiopathic

In 65% of cases, RSD is followed trauma (mostly a fracture); in 19% of cases, it followed an operation; and in 2% of cases, it followed an inflammatory process [6]. In 4% of cases, onset of symptoms followed various other precipitating factors, such as injection, intravenous infusion, or cerebrovascular accident. In 10% of cases, no precipitant could be identified. CRPS II (causalgia) has been reported after automated laser discectomy and cervical epidural injection. The migraine may be a risk factor for the condition and may also be associated with an increased severity of CRPS [8].

Workup

Laboratory Studies

- No diagnostic criteria have been accepted uniformly for RSD, and no single special investigation has been proven sensitive and specific enough for diagnosing RSD.
- As required, routine and specific blood tests should be performed to identify precipitating causes. The exact tests vary according to the body region involved, as well as according to the findings related to the history and physical examination.

Imaging Studies

- Radiographic films may show patchy periarticular demineralization within 3-6 weeks. The extent of osteoporosis is more than expected from disuse alone, and it is a common abnormality revealed on radiographs.

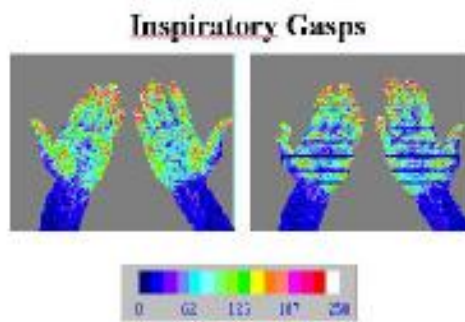
- Three-phase bone scan:
 - may be helpful in revealing findings typical for the diagnosis of RSD and in excluding other conditions that could cause the patient's symptoms. A false-negative bone scan is fairly common.
 - A diagnostic sensitivity is only 44% [9], particularly in the early phase (<20 weeks) of the syndrome.
 - The scintigraphic abnormalities were reported in up to 60% of RSD patients and may be useful in arriving at the diagnosis of RSD, as well as in predicting which patients are likely to respond to systemic steroid therapy [10].
 - Abnormally increased activity must be diffuse, not focal.
 - The most suggestive and sensitive findings on bone scan include diffuse increased activity, with juxta-articular accentuation uptake on the delayed images (phase 3).
 - Phases 1 and 2 are less sensitive and specific for RSD.
- Imaging studies have shown to not be reliable screening tests in the differentiation between normal posttraumatic changes and those changes seen in CRPS due to a low positive predictive value (17-60%) and a moderate negative predictive value (79-86%) [11].

Other Tests

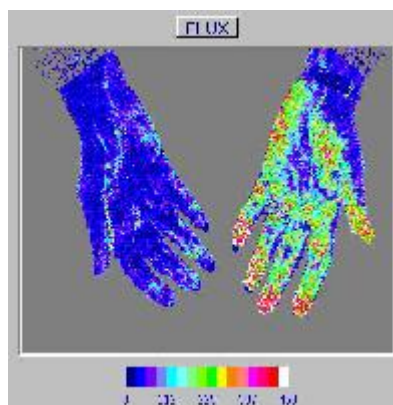
- Skin temperature is simple, but important, to record during examination of the patient with RSD. Skin temperature is measured by (1) tactile perception, (2) surface thermistors, and (3) hand-held infrared thermometers:
 - Vascular changes in RSD:
 - Hyperemic phase: increase in the temperature of the skin early in the course of RSD
 - Cold limb: decrease in the temperature of the skin later in the course of RSD
 - Thermography demonstrates limb temperature differences quantitatively, but it is nonspecific. It may be useful in situations in which sensitivity and specificity are equally important; an asymmetry cutoff of 0,6°C appears optimal [12]. If specificity is more important, a cutoff of 0,8°C or 1,0°C may be considered.

- Sudomotor function testing: abnormalities in resting sweat output, in resting skin temperature, and in a quantitative sudomotor axon reflex test predicted the diagnosis of CRPS I with 98% specificity [13]:
 - Sweat test: the sympathetic skin response (SSR) provides useful information on sudomotor dysfunction in patients with RSD; however, it is not possible yet to determine the final value of SSR for the diagnosis of RSD.
 - Quantitative sudomotor axon reflex test (QSART)
 - Chemical sweat test: this uses agents such as ninhydrin, cobalt blue, or starch iodine.
 - Testing sweat output: the stimulated sweat output is greater and is prolonged when sympathetic hyperfunction is present.
- Electrodiagnostic studies:
 - Results of electromyography (EMG) and nerve conduction studies (NCS) typically are within the reference range in RSD. In fact, if the EMG and nerve studies identify a nerve lesion, the condition is not by definition CRPS I but may instead be CRPS II.
 - Single-fiber EMG examination also shows no definite abnormalities.
 - The electrodiagnostic studies may be normal because C-fiber abnormalities cannot be well detected.
 - Patients with allodynia (demonstrating, for example, extreme pain even when clothing touches the involved limb or when a breeze blows across it) may have a difficult time tolerating EMG and NCS.
- Quantitative sensory testing (QST) quantified perception thresholds objectively.
 - QST uses very precise, reproducible stimuli, allowing comparison of symptomatic areas with asymptomatic areas, comparison with age-matched and sex-matched controls, and changes with time or treatment. This provides the physician with information about the severity and progression of the sensory dysfunction.

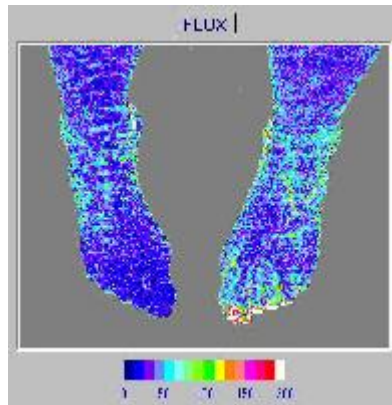
- The standard QST involves determination of vibrotactile detection thresholds (an Ab-fiber – mediated sensation), cool detection thresholds (an Ad-fiber), and warm thermal thresholds (a C-fiber) in appropriate areas. Heat and cold pain thresholds also are obtained with the patient's permission and with the patient controlling the amount of stimulus applied.
- Laser Doppler imaging (see images below):
 - Laser Doppler imaging, with appropriate stressors, provides a simple, fast, noninvasive, and painless method for the study of segmental autonomic function. This study provides excellent spatial information, eliminates many sources of artifact, and can be used to rapidly and repeatedly test skin autonomic reflexes bilaterally.



Normal laser Doppler study of the upper extremities [12].



Laser Doppler study of the upper extremities in a patient with right hand reflex sympathetic dystrophy [12].



Laser Doppler study of the lower extremities in a 25-year-old woman with reflex sympathetic dystrophy in the right foot [12].

- Along with baseline images, mild stressors (inspiratory gasp, cold pressor positional dependency) are used to quantify skin vasoconstrictor reflexes.
- When the patient performs inspiratory gasp repeatedly during laser Doppler image acquisition, the transient capillary flow decreases are displayed easily and dramatically (as dark bands) in the pseudocolor image.
- Diagnostic sympathetic ganglion block: response to such blocks is more indicative of sympathetically maintained pain, which includes other etiologies in addition to CRPS.

Treatment & Management

Rehabilitation Program. Physical Therapy. It is extremely important for patients with RSD to undergo a steady progression from gentle weight bearing to progressive, active weight bearing [14]. Gradual desensitization to increasing sensory stimuli also plays an important role. The altered processing in the CNS is typically reset by a gradual increase in normalized sensation.

Physical therapy (PT), in association with occupational therapy (OT), plays an important role in functional restoration. The goal is to increase strength and flexibility gradually, beginning with gentle gliding exercises.

Occupational Therapy. The occupational therapists are very important for initiating gentle, active measurements and preliminary desensitization techniques with patients who have RSD [16].

Occupational therapists usually are responsible for introducing and maintaining a stress-loading program for patients with CRPS. This program involves active compression and distraction exercises that provide stimuli to the affected extremity without joint motion.

Recreational Therapy can help the patient with chronic pain to take part in pleasurable activities that help to decrease pain. The patient finds enjoyment and socialization in previously lost or new recreational activities. Usually, patients with chronic pain are depressed. Recreational therapists may play an important role in the treatment process and enable the patient to become active.

Vocational therapy should be recommended and initiated early for all appropriate patients. Vocational therapy can provide work capacities and targeted work hardening, and the patient may return to gainful employment.

Medical Issues/Complications

Therapeutic strategies include pharmacologic pain relief, sympatholytic interventions, and rehabilitation.

- All treatments should focus primarily on functional restoration. Use of drugs, sympathetic blocks, and psychotherapy helps to achieve good pain control during PT.
- Early intervention is important (the recognition of symptoms in stage I or early in stage II). Physicians should be alert to signs and symptoms of RSD.
- The time between the start of RSD and clinic attendance may vary from several days to years.
- Identifying any underlying disease (eg, fracture, sprain, radiculopathy) and tailoring specific management are important.
- The pain improvement after release and anterior transposition of the nerve [17].
- Sympathetic or somatic block, if performed, should be integrated into a good rehabilitation program.

Surgical Intervention

- Sympathetic blocks:

- For the upper extremity, a stellate (cervicothoracic) ganglion block is recommended (Bupivacaine is preferred over lidocaine because of its longer half-life). Not all patients experience pain relief after blocks.
- Percutaneous lumbar sympathetic plexus catheter placement usually provides short-term pain relief in most patients and may have some long-term effect.
- Bier block (intravenous regional block) with lidocaine and ketorolac resulted in only short-term pain reduction in patients with CRPS of the lower extremity [18].
- Somatic block, consisting of continuous epidural infusion with different variants of brachial plexus blocks, includes an axillary, supraclavicular, or infraclavicular approach that may be useful.
- Dorsal column stimulator:
 - Localized extremity pain may be relieved by a dorsal column stimulator.
 - A spinal cord stimulator (SCS) can be an effective treatment for the pain of RSD, including recurrent pain after ablative sympathectomy.
 - The low morbidity associated with this procedure and its efficacy in patients with refractory pain related to RSD suggest that SCS is superior to ablative sympathectomy in the management of RSD [19].
 - Careful evaluation is recommended before patient selection.
- Intrathecal infusion: careful selection of patients is needed:
 - An intrathecal (IT) Baclofen pump may be useful for treatment of dystonia in patients with RSD [20].
 - Morphine pump: Intrathecal opioids should be considered carefully for chronic pain of nonmalignant origin.
 - Intrathecal bupivacaine infusion may alleviate the refractory pain, but it does not affect other associated symptoms or the natural course of CRPS I [21].
- Sympathectomy:
 - denervation with radio frequency or a cryoprobe could provide long-term relief.

- Endoscopic cervicothoracic sympathectomy could be an effective minimally invasive therapy for upper extremity RSD.
- Chemical sympathectomy.
- Amputations: Dielissen and colleagues reviewed cases of 28 patients with RSD who had amputations for intractable pain or recurrent infection, or to improve residual function [22].

Consultations. In CRPS the high incidence of personality pathology may represent an exaggeration of maladaptive personality traits and coping styles resulting from chronic, intense pain [23]. Such pathology can be addressed with the help of the following:

- An evaluation by a psychologist is appropriate to identify the stressor and to gather information about the distress of the patient. The evaluation should consist of a structural clinical interview and a personality measure (eg, Minnesota Multiphasic Personality Scale, Hopelessness Index).
- Psychotherapist
- Biofeedback and counseling

Other Treatment

- Transcutaneous electrical nerve stimulation (TENS) can provide good relief for RSD when the condition is limited to the distribution of 1 major nerve [24].
- Ultrasonography.
- Superficial hot packs.
- Vitamin C (a daily dose of 500 mg for 50 days) seems to reduce the prevalence of CRPS after wrist fracture [25].
- Improvements in pain and bone density following intravenous administration of pamidronate, alendronate, or clodronate have been described in a few patients.

Medication Summary. Multiple classes of medications have been tried for patients with CRPS, often with variable results [25].

Analgesic drug therapy for CRPS can be divided into the following categories:

1. Opioid analgesics
2. Nonopioid analgesics (eg, NSAIDs, acetaminophen)

3. Tricyclic antidepressants: Amitriptyline, Imipramine, Doxepin, Clomipramine, Nortriptyline
4. Selective serotonin reuptake inhibitor (SSRI) antidepressants: Paroxetine, Fluoxetine, Sertraline, Escitalopram
5. Other antidepressants: Nefazodone, Venlafaxine, Duloxetine, Bupropion
6. Anticonvulsants
7. Nonsteroidal anti-inflammatory drugs

Further Inpatient Care. Hospitalization usually is not required for patients with RSD, but it depends on how invasive the treatment choice is for pain control and the severity of the case. Sometimes, a short hospitalization is necessary for individuals who need a continuous nerve block. Patients with RSD also may have other associated orthopedic conditions that may be amenable to surgery and that require further inpatient care.

Further Outpatient Care. Patients with RSD generally are treated on an outpatient basis and require a variety of health care professionals to optimally manage their condition.

Deterrence. Recognition of RSD at the early stage is very important to achieve the best result and to prevent spread and progression toward the chronic stage (which is usually more difficult to treat).

Complications:

- Chronic edema (occasionally chronic lymphedema)
- Chronic relapsing infections and ulcers resistant to treatment
- Brown-gray, scaly pigmentations of the skin
- Recurrent, unexplained, spontaneous hematomas
- Dystonia, tremor, and other movement disorders
- Clubbing of fingers or toes and hourglass nails
- Depression and other psychiatric disorders

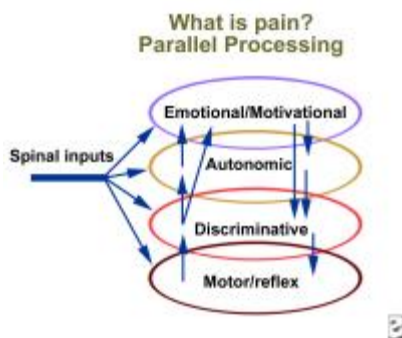
Prognosis: in comparison with adults, children are less disabled from and have more favorable prognoses with RSD [2].

4.5. Fibromyalgia

Fibromyalgia is a disorder of chronic, widespread pain and tenderness. It typically presents in young or middle-aged women but can affect patients of either sex and at any age.

Signs and symptoms. Fibromyalgia is a syndrome that consists of the following signs and symptoms [3]:

- Persistent (≥ 3 mo) widespread pain (pain/tenderness on both sides of the body, above and below the waist, and includes the axial spine [usually the paraspinus, scapular, and trapezius muscles])
- Stiffness
- Fatigue; disrupted and unrefreshing sleep
- Cognitive difficulties
- Multiple other unexplained symptoms, anxiety and/or depression, and functional impairment of activities of daily living (ADLs)



A neurophysiologist's view of pain.

Courtesy of Alan R. Light, PhD [6].

Background. Fibromyalgia was once often dismissed by physicians and the public as a psychological disorder or "wastebasket" diagnosis because of an absence of objective findings on physical examination and usual laboratory and imaging evaluations. Basic and clinical investigations have clarified the neurophysiologic bases for fibromyalgia and led to its current classification as a central sensitivity syndrome (CSS) [4, 5].

Fibromyalgia can now be considered a neurosensory disorder characterized in part by abnormalities in pain processing by the central nervous system (CNS) [6].

At a clinical level, fibromyalgia is much more than widespread pain. It overlaps substantially with other central sensitivity syndromes, such as the following:

- Chronic fatigue syndrome
- Irritable bowel syndrome
- Chronic pelvic pain syndrome/primary dysmenorrhea
- Temporomandibular joint pain
- Tension-type headaches/migraine
- Posttraumatic stress disorder (PTSD)
- Multiple chemical sensitivity
- Periodic limb movement disorder/restless legs syndrome
- Interstitial cystitis

Fibromyalgia also overlaps with other regional pain syndromes and mood and anxiety disorders. The diagnostic label attached to a particular case may be determined largely by the first specialist that the patient sees. For example, a rheumatologist might diagnosis fibromyalgia, whereas a gastroenterologist may diagnose irritable bowel syndrome or an infectious disease specialist may diagnose chronic fatigue syndrome.

Fibromyalgia coexists in unusually high frequency with certain illnesses characterized by systemic inflammation, such as rheumatoid arthritis (RA) [7], systemic lupus erythematosus (SLE) [8], and chronic hepatitis C infection [9], among others. In such cases, both disorders must be recognized and treated for optimum therapeutic outcome, as treatment of one will not necessarily improve the other.

Even as evidence-based medicine supplies a growing array of tools for the management of fibromyalgia, the art of medicine retains a central role. To successfully care for patients with fibromyalgia, the physician must demonstrate compassion as well as skill. Taking a careful history, listening to the patient's concerns, and performing a thorough examination are the foundation for diagnosing and treating fibromyalgia.

Management of fibromyalgia begins with a detailed history and a thorough physical and laboratory examination.

The physician should inform the patient that no cure exists for fibromyalgia but that education, lifestyle changes, and proper treatment can help the individual to regain control and achieve significant improvement. The overall approach for chronic pain in fibromyalgia involves a multifaceted treatment plan that incorporates various adjuvant medicines, aerobic exercise, and psychological and behavioral approaches to reduce distress and promote self-efficacy and self-management.

Historical background. Fibromyalgia was not defined until the late 20th century.

The American College of Rheumatology (ACR) sponsored a multicenter study to develop classification criteria; the results were published in 1990 [10]. To improve diagnosis, new fibromyalgia diagnostic criteria were provisionally accepted by the ACR in 2010 [12].

Despite this progress, the typical patient with fibromyalgia has seen an average of 15 physicians and has had the condition for approximately 5 years before receiving a correct diagnosis. More than 50% of cases are misdiagnosed, and many patients undergo unnecessary surgery or endure costly treatments that provide little benefit.

Nomenclature. The syndrome was renamed fibromyalgia by Yunus et al in their seminal 1981 article derived from the Latin root *fibro* (fibrous tissue) and the Greek roots *myo* (muscles) and *algos* (pain) [17].

Epidemiology. Cases of fibromyalgia have been reported by researchers from around the world. Fibromyalgia exhibits no race predilection.

In the United States, chronic pain and fatigue are extremely prevalent in the general population [60, 73, 74], especially among women and persons of lower socioeconomic status. The prevalence of regional pain is 20%; widespread pain, 11%; and chronic fatigue, approximately 20%.

Fibromyalgia is the second most common disorder that rheumatologists encounter, seen in 15% of evaluated patients. Approximately 8% of patients cared for in primary care clinics have fibromyalgia.

The prevalence of fibromyalgia in the US general population was 2% (3.5% in women and 0.5% in men) [6].

Using data from 5 countries (France, Germany, Italy, Portugal, and Spain), the prevalence of fibromyalgia in Europe at 4,7% [7,8]. Prevalence was estimated to be 5.8% in women and 3.5% in men.

Race-related differences in incidence. In the U.S., African-American women have a higher prevalence of fibromyalgia than white women [3]. Increased body pain and tenderness are associated with decreased socioeconomic status, so this may be an important influence on racial differences.

Sex-related differences in incidence. Fibromyalgia is far more common in women than in men, with a female-to-male ratio of approximately 9:1. Males with fibromyalgia tend to have lower health perception and more physical limitations than females. Females with fibromyalgia have greater pain sensitivity [1] and may exhibit greater life interference due to pain. Among the mechanisms that may contribute to increased pain sensitivity in women are the following [3,4]:

- Differences in primary afferent input to the CNS, with developmental and menstrual cycle–dependent enhancement;
- Developmental and phasic gonadal-hormonal modulation of pain regulatory systems, stress-induced analgesia, and opioid receptors;
- Higher levels of trait and state anxiety;
- Increased prevalence of depression;
- Use of maladaptive coping strategies;
- Increased behavioral activity in response to pain.

Age-related differences in incidence. Although usually considered a disorder of women aged 20-50 years, fibromyalgia can occur at any age and in persons of either sex. The prevalence of fibromyalgia increases with age, and the peak prevalence is not seen in women until age 60-70 years [6,13].

Pathophysiology. Fibromyalgia is currently understood to be a disorder of central pain processing or a syndrome of central sensitivity. This syndrome is a diffuse problem of sensory “volume control” such that patients have a lower threshold of pain and of other stimuli, such as heat, noise, and strong odors. The patients may have hypersensitivity because of neurobiologic changes that affect the perception of pain or because of expectancy or hypervigilance, which may be related to psychological factors [18].

Although the pathogenesis of fibromyalgia is not completely understood, research shows biochemical, metabolic, and immunoregulatory abnormalities.

Pain. The pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [19].

Neurophysiologically, the pain experience derives from a complex sensation-perception interaction involving the simultaneous parallel processing of nociceptive input from the spinal cord to multiple regions of the brain (see the image below).

In addition to strictly sensory-discriminative elements of nociception and afferent input from somatic reflexes, major contributions from pathways and regions of the brain that are associated with emotional, motivational, and cognitive aspects of pain are evident and help determine the subjective intensity of pain. The 2 principal effectors of the stress response, the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic nervous system (SNS), are also activated.

Although normally adaptive, the stress response may become maladaptive in patients with chronic pain and fatigue syndromes such as fibromyalgia [20, 21, 22, 23]. Negative emotions (eg, depression and anxiety) and other negative psychological factors (eg, loss of control, unpredictability in one's environment) and certain cognitive aspects (eg, negative beliefs and attributions, catastrophizing) can all function as stressors with actions in these systems.

In some patients with fibromyalgia, such negative emotional, motivational, and cognitive stressors may dominate the clinical picture, potentially leading to a self-sustaining neuroendocrine cascade that contributes to flu-like symptoms, depressed mood, fatigue, myalgias, cognitive difficulties, and poor sleep.

The important biologic elements here include proinflammatory cytokines, the HPA axis, other neuroendocrine axes, and the autonomic nervous system. Growth hormone abnormalities are also thought to contribute to symptoms in fibromyalgia [25].

A number of abnormalities in pain processing have been demonstrated in fibromyalgia [1,13]. Among them are the following:

- Excess excitatory (pronociceptive) neurotransmitters (eg, substance P, glutamate levels in the insula)
- Low levels of inhibitory neurotransmitters (eg, serotonin and norepinephrine) in descending antinociceptive pathways in the spinal cord
- Maintained enhancement of temporal summation of second pain
- Altered endogenous opioid analgesic activity in several brain regions known to play a role in pain modulation
- Dopamine dysregulation

Fibromyalgia is a polygenic syndrome with multiple different underlying genetic polymorphisms; genetic testing to tailor therapy and to predict response to therapy will soon become available.

The biochemical changes seen in the CNS, the low levels of serotonin, the four-fold increase in nerve growth factor, and the elevated levels of substance P all lead to a whole-body hypersensitivity to pain and suggest that fibromyalgia may be a condition of central sensitization or of abnormal central processing of nociceptive pain input [5].

Central processes. Plasticity in the function of N-methyl-D-aspartate (NMDA) subtype glutamate receptors is necessary for central sensitization to occur. Increased sensitivity of central NMDA receptors were implicated in earlier

studies as playing a primary role in fibromyalgia. However, subsequent evidence has suggested that suppression of the normal activity of dopamine-releasing neurons in the limbic system is the primary pathology in fibromyalgia. Increasing evidence indicates that fibromyalgia may represent a dysregulation of dopaminergic neurotransmission.

Serotonin. Many studies have linked serotonin, a neurotransmitter, to sleep, pain perception, headaches, and mood disorders. Lower-than-normal levels of serotonin have been observed in patients with fibromyalgia. A low platelet serotonin value is believed to be the cause of the low serum levels, which have been correlated with painful symptoms.

Low serotonin levels in the CNS are thought to result from low levels of tryptophan (the amino acid precursor to serotonin) and 5-hydroxyindole acetic acid (a metabolic by-product) in the cerebrospinal fluid (CSF) [3,5].

Substance P is a neurotransmitter that is released when axons are stimulated. Elevated levels of substance P increase the sensitivity of nerves to pain or heighten awareness of pain [3,6]. These elevated levels cause fairly normal stimuli to result in exaggerated nociception.

Some authors believe that neither elevated substance P levels nor low serotonin levels alone can be the primary cause. Instead, the dual dysfunction may be responsible for fibromyalgia.

Adenosine triphosphate. Researchers have found low levels of adenosine triphosphate (ATP) in red blood cells of patients with fibromyalgia. It has been suggested that low platelet serotonin levels can be explained if platelet ATP levels are also low. ATP is necessary to move and then hold serotonin in platelets.

Dysfunction of the hypothalamic-pituitary-adrenal axis. Studies of the neuroendocrine aspects of fibromyalgia have found dysfunction of the HPA axis [3,7]. The HPA axis is a critical component of the stress-adaptation response. The sequence of HPA action is that corticotropin-releasing hormone (CRH) from the hypothalamus stimulates the anterior pituitary to release adrenocorticotropic

hormone (ACTH). In turn, ACTH stimulates the adrenal cortex to produce glucocorticoids (eg, cortisol).

Some authors have noted that 5 main measurable neuroendocrine abnormalities are associated with dysfunction of the HPA axis [3,8]. These are as follows:

- Low free cortisol levels in 24-hour urine samples
- Loss of the normal circadian rhythm, with an elevated evening cortisol level (when it should be at its lowest level)
- Insulin-induced hypoglycemia associated with an overproduction of ACTH
- Low levels of growth hormone
- Stimulated ACTH secretion leading to insufficient adrenal release of glucocorticoids

Circadian regulation and the stress-induced stimulation of the HPA axis are, in part, regulated by serotonin. Perturbations in serotonin metabolism (as well as premorbid abnormalities of the HPA axis) may explain the abnormalities of the HPA axis in fibromyalgia. Dysfunction of the HPA axis may exaggerate the effects of abnormal serotonin metabolism. Hypoactivity of the HPA axis may cause low central serotonin levels.

Growth hormone, produced during delta sleep, is involved in tissue repair. Therefore, disrupted stage 4 (delta) sleep associated with fibromyalgia may account for low levels of growth hormone. Growth hormone stimulates the production of insulin-like growth factor I (IGF-I) in the liver. Most patients with fibromyalgia have low levels of IGF-I and that low levels are specific and sensitive for fibromyalgia [3,9].

Nerve growth factor was found to be 4 times higher in the CSF of patients with fibromyalgia than it was in the CSF of individuals without the condition. Nerve growth factor enhances the production of substance P in afferent neurons, increasing an individual's sensitivity to or awareness of pain. Nerve growth factor also may play a role in spreading or redistributing perceived pain signals.

Cognitive impairment. Fibromyalgia is associated with a decline in short-term, working, episodic, semantic (predominantly verbal), and procedural (skills) memory. Imaging modalities such as single-photon emission computed tomography (SPECT) scanning have helped to define decreased blood flow in the right and left caudate nuclei and thalami.

Functional magnetic resonance imaging (fMRI) can show brain activity by depicting increased blood flow to areas actively engaged in a task. Increased blood flow and, hence, increased oxygenation have different magnetic properties. These properties can be detected and measured using fMRI.

In a study of persons performing a task requiring memory (alphabetization), persons with fibromyalgia performed almost as well as controls, but fMRI showed that more brain areas were activated during the memory task in persons with fibromyalgia than in controls, because the task was harder for the patients to perform [4].

Patients with fibromyalgia had lower activation in the inhibition and attention networks but increased activation in other areas. The inhibition and pain perception may use overlapping networks, which may cause resources to be unavailable for other processes when they are taken up by pain processing [1].

Cognitive dysfunction has been linked to CNS imbalances. Abnormal levels of such neurotransmitters as substance P, serotonin, dopamine, norepinephrine, and epinephrine may cause cognitive dysfunction. Neuroendocrine imbalance of the HPA axis may play a role. Another possible cause of cognitive dysfunction is the distracting quality of pain in fibromyalgia. Cognitive performance of patients with fibromyalgia is correlated with their reported level of pain.

Brain damage from the effects of stress hormones may be involved in the cognitive dysfunction in fibromyalgia. The water retention and glial cell abnormalities are causes of cognitive dysfunction in fibromyalgia.

Sleep disruption is considered an integral feature of fibromyalgia. About 70% of patients recognize a connection between poor sleep and increased pain,

along with feeling unrefreshed, fatigued, and emotionally distressed [2, 4]. The patients with fibromyalgia have disordered sleep physiology.

Many neurohormones, antibodies, and other molecules are synthesized during sleep; therefore, when sleep is disrupted, biochemical abnormalities can occur, leading to multisystem disturbances.

Sleep can be divided into 2 main parts: nonrapid eye movement (NREM) and rapid eye movement (REM), which alternate cyclically through the night, always starting with NREM sleep. In each successive cycle through the night, NREM sleep decreases, and REM sleep increases. Each cycle, NREM plus REM, lasts about 90 minutes.

NREM is divided into 4 stages:

- Stage 1 is initial drowsiness
- Stage 2 is light sleep
- Stages 3 and 4 are progressively deeper levels of sleep.

In stages 3 and 4, an electroencephalogram (EEG) will show delta waves, which are high-amplitude (>75 mV) waves that move slowly (0,5-2 Hz). Much of the body's regulatory work, as well as the synthesis of many substances (eg, antibodies, growth hormone, other neurochemicals), occurs during NREM sleep.

REM sleep has a low-voltage, mixed-frequency pattern on EEGs and is considered dream sleep. In this stage, the body has a complete loss of muscle tone, known as flaccid paralysis, and it cannot move. During this part of sleep, consolidation of memories may occur, but disagreement still exists as to what takes place with regard to memory during REM sleep. During waking hours, the brain generates alpha waves with a frequency of 7,5-11 Hz.

The disordered sleep physiology in fibromyalgia has been identified as a sleep anomaly of alpha-wave intrusion, which occurs during NREM stage 4 sleep. It is believed to be linked to the numerous metabolic disturbances associated with fibromyalgia, including abnormal levels of neurotransmitters (serotonin, substance P) and neuroendocrine and immune substances (growth hormone, cortisol, interleukin-1). These metabolic imbalances are thought to be responsible through

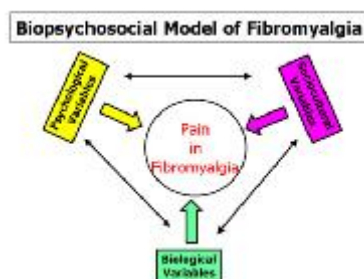
impairment of tissue repair and disturbance of the immunoregulatory role of sleep for the increased symptoms associated with this sleep disorder of alpha-wave intrusion.

Most alpha-wave intrusions occur during the first few hours of sleep, decreasing throughout the night to normal levels by early morning. This hypothesis correlates well with patients' frequent reporting that their best sleep is obtained in the early morning hours, just before arising.

Many fibromyalgia patients also have primary sleep disorders that can reduce sleep quality, such as obstructive sleep apnea, restless legs syndrome, or periodic limb movement disorder. All patients should be screened for the presence of primary sleep disorders before assuming that reduced sleep quality is due to fibromyalgia.

Etiology of fibromyalgia is multifactorial and includes both environmental and genetic factors. The causes of fibromyalgia have not yet been fully clarified. Fibromyalgia pain can now be classified as a neurosensory disorder (with the identification of central sensitization and abnormal central nociceptive processing in affected patients).

Engel's biopsychosocial model of chronic illness (ie, health status and outcomes in chronic illness are influenced by the interaction of biologic, psychological, and sociologic factors) provides a useful way to conceptualize fibromyalgia [4]. The model is pictured in the image below.



Biopsychosocial model of fibromyalgia [6].

Biologic variables. Certain biologic variables contribute to the development and persistence of fibromyalgia, although none, as a single element, explains all facets of fibromyalgia. Certain variables (eg, physical trauma, exposure to toxins)

have been widely incriminated by the public, particularly in medicolegal settings, but are actually of little significance in the etiology of fibromyalgia.

Inheritance. The extremely important genetic contribution to fibromyalgia and related central sensitivity syndromes was first suggested by family studies [4,6]. For example, altered serotonin metabolism has been linked to a genotype of the promoter region of the serotonin transporter gene [49]. Single-nucleotide polymorphisms in the genes for catecholamine-O-methyltransferase (which inactivates catecholamines) and β 2-adrenergic receptors have been linked to increased pain perception [5].

Female sex. Central pain modulatory systems in females are influenced by phasic alterations in reproductive hormone levels. Aversive stimuli and stressful tasks are more likely to evoke SNS, HPA axis, and psychological responses in females than in males [1].

Sleep. Almost all patients with fibromyalgia sleep poorly hence. The intrusion of alpha waves into slow delta wave stage III/IV (deep) sleep was the first objective abnormality observed in fibromyalgia [2]. Although not the proximate cause of fibromyalgia, abnormal sleep affects both limbs of the stress response system and contributes to negative mood and cognitive difficulties.

Stress/neuroendocrine and autonomic dysregulation. Fibromyalgia, chronic fatigue syndrome, regional chronic pain syndromes, and certain emotional disorders that frequently coexist with fibromyalgia all involve central dysregulation of the stress response system [1,2,3]. In these disorders, various forms of stress function as initiators or perpetuators of functional alterations in the corticotropin-releasing hormone (CRH) neuron, with associated effects on the HPA axis, other neuroendocrine axes, and the SNS.

The extremely high prevalence of stress-related disorders in society may reflect maladaptation of the stress response system in the face of the almost universal stress and consequent distress that characterizes modern life.

Other variables. While most patients begin to experience symptoms between the ages of 20 and 50 years, the prevalence of the syndrome increases with age. The highest prevalence occurs between ages 60 and 79 years [13].

Physical deconditioning is also an important variable. Disrupting stage 4 sleep in sedentary healthy controls elicited the appearance of musculoskeletal and mood symptoms similar to those seen in fibromyalgia patients [12].

While considered unlikely to be sole triggers, infection may also contribute to exacerbation of symptoms via cytokine vagus nerve stimulation of the corticotropin-releasing hormone neuron/stress response system in bidirectional brain-immune system communication [9].

Variables with an uncertain relationship to the development of fibromyalgia include the following:

- Decreased collagen cross-linking
- Hypermobility
- Chiari malformation
- Environmental chemicals

Psychological variables. The cognitive-behavioral variables can be pivotal in the development and maintenance of persistent pain and functional disability [3,4]. The repertoire of operant cognitive-behavioral variables in adults has antecedents in earlier life (eg, childhood abuse, parental alcoholism, learned behaviors from living as children with dysfunctional or chronically ill parents).

Negative beliefs (eg, self-blame for the mysterious enduring pain) are associated with a range of adverse consequences, as follows:

- Increased subjective pain intensity
- Reduced compliance with treatment
- Low self-esteem
- Somatization
- Psychological distress

In patients with chronic pain, the expected degree of tolerance to stimuli or activities that evoke pain or fatigue predicts actual tolerance. Expected danger (damage) predicts avoidance.

Self-assessed inability to work, helplessness, low perceived control over pain, and maladaptive coping all affect pain severity and the overall impact of fibromyalgia. Thus, some patients with fibromyalgia perceive that they are using excessive effort during formal exercise testing of muscle, even though their actual muscle function is electrophysiologically normal.

Similarly, the discordance between self-reported disability versus observed functional disability can be high in some patients with fibromyalgia. In contrast, such discordance is generally low or absent in patients with other rheumatic diseases, such as ankylosing spondylitis and rheumatoid arthritis.

Certain data support a hypervigilance model of pain in patients with fibromyalgia [2]. Heightened sensitivity to pain results at least in part to increased attention to external stimuli and a preoccupation with pain sensations.

Perceived self-efficacy is the level of confidence that the patient requires to control pain effectively. People with low self-efficacy beliefs anticipate failure and stop using effective coping strategies. Higher coping self-efficacy is associated with less negative mood and less pain.

Self-efficacy may be a significant determinant of pain itself, particularly with respect to its emotional arousal and unpleasant effects. The maladaptive coping strategies, such as catastrophizing about pain, worsen the pain experience, especially with respect to the development of depression. In persons with high catastrophizing, pain perception is augmented by increased activity in response to painful stimuli in brain areas involved in the following [6]:

- Anticipation of pain (medial frontal cortex, cerebellum)
- Attention to pain (dorsal anterior cingulate gyrus, dorsolateral prefrontal cortex)
- Emotional aspects of pain (claustrum, closely connected to the amygdala)

Lifetime psychiatric comorbidity is common in individuals with fibromyalgia, including the following [5, 6]:

- Mood disorders (bipolar disorder, major depressive disorder)
- Anxiety disorders (generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, PTSD, social phobia)
- Eating disorders
- Substance use disorders

Pressure-pain thresholds (degree of tenderness with application of pressure) correlate with psychological comorbidity in patients with fibromyalgia, as follows [6,7]:

- Low tenderness is associated with moderate depression/anxiety, moderate catastrophizing, and moderate control over pain.
- High tenderness is associated with high depression/anxiety, high catastrophizing, and low control over pain.
- Extremely high tenderness is associated with normal levels of depression/anxiety, very low catastrophizing, and highest control over pain.

People who are healthy and people who have fibromyalgia but no depression exhibit increased rCBF only in the somatosensory cortices and the anterior insula, whereas people with fibromyalgia and depression also show increased rCBF in the amygdala and contralateral anterior insula, which are involved in affective pain processing [8].

However, chronic pain is not simply a manifestation of depression. Despite common reports of pain and other somatic symptoms, patients with pure major depression, compared with patients with fibromyalgia, actually have fewer tender points, increased pain thresholds, and more stoic responses to pain stimuli [69]. In addition, negative emotions such as sadness and anger have been shown to be general risk factors for pain amplification independent of a diagnosis of fibromyalgia [24].

Personality traits have the largest effect on the cognitive processes by which people attach meanings and implications to their pain [24].

Most common is a perfectionism-compulsiveness personality, characterized by a rigid belief system in the need to be perfect, high underlying anxiety, and an unawareness of feelings and emotions. Another common personality style is the self-sacrificing type, characterized by a tendency to put everyone else's needs before one's own.

Pain behaviors can be important perpetrators of illness through reinforcement of the responses that patients with fibromyalgia induce as a means to get attention, to obtain medication, or to avoid work or activity. This can lead to limitation of physical and social activity, dependence on narcotics and alcohol, and unemployment.

Environmental and sociocultural variables. Multiple experiences and forces in a person's environment and social culture influence the pain experience, either positively (eg, high job satisfaction in a person who strains his or her back at work) or negatively (eg, physician who medicalizes a minor injury by diagnostic waffling and inappropriate diagnostic testing) [3,4]. Environmental and sociocultural variables include the following:

- Psychosocial experiences during childhood
- Spousal and family support
- Ethnologic factors
- Focus on definable causes
- Media hype
- Primary and secondary gain

Developmental variables include the psychosocial experiences during childhood (eg, school stress, role models, unhappy families, abuse) that shape the cognitive, affective, and behavioral aspects of pain in adults. Two thirds of patients with chronic pain have first-degree relatives with chronic pain, one third have a family member with an affective illness, and one third have a family member with alcohol abuse.

Childhood physical, emotional, or sexual abuse appears to be a common antecedent of anxiety, somatization, and chronic pain in many adults [7].

Spousal and family support can either mitigate or adversely affect the various dimensions of chronic pain.

Job satisfaction and a healthy work environment lessen the emotional distress associated with chronic pain. Conversely, job dissatisfaction strongly predicts the progression of acute back pain to chronic low back pain.

Pain tolerance may be profoundly influenced by culture. The prevalence of widespread chronic pain is zero in Pima Indians but is approximately 10% in white populations on both sides of the Atlantic.

Prognosis. Fibromyalgia is a chronic relapsing condition (averages 10 outpatient visits per year and 1 hospitalization every 3 years). Chronic pain and fatigue in fibromyalgia increases the risk for metabolic syndrome.

Entirely reversing the allodynia and hyperalgesia in patients with fibromyalgia may be impossible. Nevertheless, symptoms can be significantly improved in many patients, particularly if ongoing stressors are relieved and self-efficacy for pain control can be achieved.

The treatment goal that responds least to therapy is improvement in daily functioning.

Dysfunctional patients have high levels of pain and anxiety, major impairment in daily functioning, and, quite often, opioid dependence. These patients have a very poor prognosis.

Other patient characteristics associated with guarded prognosis include the following:

- High levels of distress
- Long-standing fibromyalgia
- Major psychiatric disease or severe depression and anxiety that responds poorly to treatment
- An ingrained pattern of work avoidance
- Marked functional impairment despite multidisciplinary approaches to treatment
- Opioid or alcohol dependence

Fibromyalgia is not a life-threatening, deforming, or progressive disease. Without proper diagnosis and treatment, however, a patient with fibromyalgia may have the illusion of disease progression (caused by sleep deprivation and physical deconditioning).

The fibromyalgia has a significant negative impact on the quality of social and economic functions in patients' lives: 15% of the people with fibromyalgia are receiving disability benefits, disability rates as high as 44% in fibromyalgia patients have been reported.

Diagnosis. Fibromyalgia is a diagnosis of exclusion and patients must be thoroughly evaluated for the presence of other disorders that could be the cause of symptoms before a diagnosis of fibromyalgia is made. The clinical assessment may reveal objective evidence for a discrete or comorbid illness, such as the following:

- Hypothyroidism
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Polymyalgia rheumatic
- Other inflammatory or autoimmune disorders
- Serious cardiac conditions in those with chest pain, dyspnea, and palpitations

Laboratory testing include the following:

- Complete blood count with differential
- Metabolic panel
- Urinalysis
- Thyroid-stimulating hormone level
- 25-hydroxy vitamin D level
- Vitamin B12 level
- Iron studies, including iron level, total iron binding capacity, percent saturation, and serum ferritin level
- Magnesium level
- Erythrocyte sedimentation rate

- Antipolymer antibody assay: May provide conclusive evidence for a subgroup of people with fibromyalgia; about 50% of fibromyalgia patients have antipolymer antibodies

The 2010 ACR diagnostic criteria require physicians to evaluate patients by questioning to determine scores on a widespread pain index (WPI) and a symptom severity (SS) scale.

The WPI quantifies the extent of bodily pain on a 0-19 scale by asking patients if they have had pain or tenderness in 19 different body regions (shoulder girdle, hip, jaw, upper arm, upper leg, lower arm, and lower leg on each side of the body, as well as upper back, lower back, chest, neck, and abdomen) over the past week, with each painful or tender region scoring one point.

The SS scale quantifies symptom severity on a 0-12 scale by scoring problems with fatigue, cognitive dysfunction and unrefreshed sleep over the past week each on a scale.

Physical Examination. The goal of the physical examination is to confirm the diagnosis, rule out concomitant systemic diseases, and recognize common coexisting conditions. Except for painful tender points and, perhaps, signs of deconditioning, physical examination findings are typically normal in fibromyalgia patients. The tender-point examination should be performed first during the physical examination, because other aspects of the examination may influence sensitivity of tender points.

Performance of the tender-point examination can be improved by using the manual tender-point survey (MTPS) method [14].

The MTPS consists of standardized components including:

- 1) location of the tender-point sites,
- 2) patient and examiner positioning,
- 3) order of tender-point examination,
- 4) pressure application technique,

5) pain severity rating scores in which fibromyalgia patients rate pain severity upon digital palpation of each tender point on a verbal 11-point numerical rating scale from 0 (no pain) to 10 (worst pain).



Tender points in fibromyalgia.

A pain severity score of at least 2 required to count a tender point as positive. Eighteen tender points are palpated at standard locations arranged symmetrically on the body, along with 3 control points [14].

The thumb pad of the examiner's dominant hand is used to apply pressure to each evaluation site one at a time during the tender-point examination. This allows the examiner to use important tactile cues and is as reliable as the use of a dolorimeter. The procedure is as follows: First, visually locate the evaluation site. Then, with the thumb pad, press perpendicularly into the evaluation site with gradually increased pressure for 4 seconds until a pressure of 4 kg is reached, roughly enough force to blanch the examiner's nail bed. Each tender-point site should be palpated only once to avoid sensitization. The patient is asked to respond with a "yes" or "no" if he or she has pain at the site being examined. If the patient's response is "yes," the individual is asked to rate the pain on a scale of 0 (no pain) to 10 (worst pain), and record each response.

Pain scores from each of the 18 tender-point sites can be averaged to yield a Fibromyalgia Intensity Score (FIS) that varies from 0-10, with higher scores indicating more severe tenderness. The FIS can be monitored over time to evaluate response to therapy.

Site locations. The standard 18 fibromyalgia tender points exist as 9 pairs (in addition to 3 control sites), 4 on the anterior of the body and 5 on the posterior of the body [10]. The sites are as follows:

- 1 control site - Forehead

- 2 and 3 diagnostic sites - Occiput at the nuchal ridge
- 4 and 5 diagnostic sites - Trapezius
- 6 and 7 diagnostic sites - Supraspinatus
- 8 and 9 diagnostic sites - Gluteal
- 10 and 11 diagnostic sites - Low cervical
- 12 and 13 diagnostic sites - Second rib
- 14 and 15 diagnostic sites - Lateral epicondyle
- 16, control site - Distal middle third of the right forearm
- 17 control site - Nail of the left thumb
- 18 and 19 diagnostic sites - Greater trochanter
- 20 and 21 diagnostic sites - Medial knee

The American College of Rheumatology (ACR) specifies the location of tender points on the anterior body as follows:

- At the fifth through seventh inter-transverse spaces of the cervical spine
- In the pectoral muscle, at the second costochondral junctions
- Approximately 3 finger breadths (2 cm) below the lateral epicondyle
- At the medial fat pad, proximal to the joint line

The ACR specifies the location of tender points on the posterior body as follows:

- At the upper border of the shoulder in the trapezius muscle, midway from the neck to the shoulder joint
- At the craniomedial border of the scapula, at the origin of the supraspinatus
- In the upper outer quadrant of the gluteus medius
- Just posterior to the prominence of the greater trochanter at the piriformis insertion

Other evaluations. After completing the tender-point examination, the physician should include neurologic, joint, and musculoskeletal evaluations. Note the presence of swelling, deformities, and erythema. Examine the patient's gait, joint range of motion (ROM), and posture for structural asymmetry and skeletal deficiencies. Palpate the soft tissues for tone or spasm.

Pressure algometry



Pressure algometer (dolorimeter) is useful device for rough quantitation of pain perception and pain tolerance is a pressure algometer, or dolorimeter.

Normal values are 4 kg/cm² or greater.

It can also serve as a useful tool for educating the patient regarding the nature of altered central nociceptive processing, allodynia (pain with stimuli that should not cause pain, such as gentle touching) and hyperalgesia (amplification of pain experienced from peripheral stimuli that are expected to be painful) [13].

Potential **complications** of fibromyalgia include the following:

- Extreme allodynia with high levels of distress
- Opioid or alcohol dependence
- Marked functional impairment
- Severe depression and anxiety
- Obesity and physical deconditioning
- Metabolic syndrome

Diagnostic Considerations. Although no basis for many of the multiple symptoms of patients with fibromyalgia will be found upon physical examination or laboratory testing, the physician must remain alert for organic illness (eg, colon carcinoma in a patient with irritable bowel syndrome).

The clinical assessment may reveal objective evidence for a discrete illness, such as hypothyroidism, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), polymyalgia rheumatica, or another inflammatory or autoimmune disorder. Such findings do not exclude comorbid fibromyalgia. Indeed, approximately 25% of patients with RA and approximately 50% of patients with SLE also have fibromyalgia, and the provision of optimum care in such cases impels recognition and treatment of both illnesses.

It is important to recognize that treatment of an autoimmune disorder in a patient with comorbid fibromyalgia usually does not improve fibromyalgia symptoms. Recognition and treatment of fibromyalgia in these patients is vitally important to avoid overtreatment with immunosuppressives that can result when providers falsely assume symptoms are caused by the autoimmune condition. Other problems to consider in the differential diagnosis of fibromyalgia include the following:

- Atypical chest pain
- Chronic fatigue syndrome
- Multiple chemical sensitivity
- Sick building syndrome
- Vulvodynia
- Vulvar vestibulitis

Because complaints of chest pain, shortness of breath, and palpitations are common, serious cardiac problems should be considered and may require extensive evaluation. Many symptoms in patients with fibromyalgia can be related to mitral valve prolapse syndrome.

Approach Considerations. Patients with fibromyalgia do not have characteristic or consistent abnormalities on laboratory testing. However, routine laboratory and imaging studies are important to help rule out diseases with similar manifestations and to assist in diagnosis of certain inflammatory diseases that frequently coexist with fibromyalgia. In addition to complete blood cell (CBC) count and differential count, basic metabolic panel, and urinalysis, the following limited evaluation is reasonable.

- Thyroid-stimulating hormone: Hypothyroidism shares many clinical features with fibromyalgia, especially diffuse muscle pain and fatigue
- 25-Hydroxy vitamin D level: Low levels can cause muscle pain and tenderness
- Vitamin B-12 level: Very low levels can cause pain and fatigue

- Iron studies including iron, total iron binding capacity, percent saturation, and serum ferritin: Low levels can cause fatigue and can lead to poor sleep and depressive symptoms; for patients with restless legs syndrome, percent saturation should be maintained above 20% and serum ferritin should be kept above 50 ng/mL
- Magnesium: Low levels can lead to muscle spasms, which are common in fibromyalgia patients; magnesium supplementation can also improve symptoms in some fibromyalgia patients; recommended magnesium levels in fibromyalgia patients are at least 2 mEq/L

The erythrocyte sedimentation rate (ESR) is often recommended as a routine laboratory test in fibromyalgia patients to rule out the presence of inflammatory disorders that may mimic symptoms. While the ESR is usually normal in patients with fibromyalgia, it is a nonspecific measure of inflammation and mild elevations may not be meaningful. The upper limit of normal for the ESR in women is half their age (eg, a level of 40 in an 80-year-old women is normal), and in men is half their age minus 10. The ESR can also be mildly elevated in obese patients. However, a high ESR may be indicative of an inflammatory disorder or occult malignancy that should be thoroughly evaluated.

Routine antinuclear antibody (ANA) or rheumatoid factor (RF) testing is not recommended unless patients have signs or symptoms concerning for systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA). A low-titer positive ANA or RF level is common in the general population, so these findings may be of no clinical significance in a fibromyalgia patient.

Formal sleep studies may be useful in patients whose sleep does not improve with the usual conservative measures (eg, elimination of caffeine, prescription of hypnotics or nighttime tricyclics).

Serum transferrin saturation and serum ferritin screening can be useful for detecting the unusual cases of hemochromatosis in which patients present with diffuse arthralgias and myalgias. Consider screening with serum transferrin saturation and a serum ferritin concentration in patients aged 40-60 years,

especially those with small-joint arthropathy in the hands and/or calcium pyrophosphate dehydrate deposition disease (CPPD).

The antipolymer antibody assay is a blood test (in approximately 50% of patients with fibromyalgia). This biologic marker may provide conclusive evidence for a subgroup of people with fibromyalgia.

There are no histologic abnormalities seen in fibromyalgia syndrome. Earlier belief that fibromyalgia was associated with inflammation in muscle fascia has been disproven.

Carefully assess all possible causal or perpetuating factors. Investigate psychological and sociocultural factors and identify any specific regional sources of ongoing nociceptive pain (eg, degenerative spondylosis, bursitis).

Self-Report Forms. While waiting to see the physician, the patient, in a few minutes, can complete a simple self-report form [9] that incorporates visual analogue scales for pain and fatigue and a global self-assessment of overall status, along with validated scales for physical and psychological health status such as the following:

- Modified Health Assessment Questionnaire
- Fibromyalgia Impact Questionnaire
- Checklist of current symptoms
- Scales for helplessness and cognitive performance
- The Physician Health Questionnaire - 9 for depression
- The Generalized Anxiety Disorder - 7 questionnaire for anxiety
- The Mood Disorder Questionnaire to screen for bipolar disease

Easily adaptable to a busy practice, the use of self-report forms provides information that is invaluable for the psychosocial assessment of pain, both for aiding with diagnosis and monitoring response to therapy.

Psychometric Testing includes the following:

- Minnesota Multiphasic Personality Inventory
- Social Support Questionnaire
- Sickness Impact Profile

- Multidimensional Pain Inventory (MPI)

In multidisciplinary settings, information obtained from these tests is useful for a more comprehensive assessment.

Approach Considerations. The physician should inform the patient that no cure exists for fibromyalgia but that education, lifestyle changes including regular physical activity, and proper medications can help the individual to regain control and achieve significant improvement. When patients with fibromyalgia fully understand the nature of the disease, they are more likely to comply with treatment and to take an active role in managing the disease.

If significant nociceptive pain coexists with the diffuse chronic pain of fibromyalgia, manage it pharmacologically with non-narcotic medications such as antidepressants, anticonvulsants, or muscle relaxers [1,4].

Poor sleep is virtually universal in fibromyalgia and contributes importantly to pain, depression, and fatigue. Accurate diagnosis and pharmacologic and nonpharmacologic management are essential [1,5,7].

Trigger point injections, acupuncture, chiropractic manipulation, and myofascial release are usually well received by patients and can be beneficial, but results are not long lasting and patients may not be able to afford long-term therapy since these are sometimes not covered by insurance.

Managing Flare-ups. Patients should learn to identify the factors that trigger flare-ups (although, on occasion, no trigger can be identified) and what measures to take to decrease their symptoms [1,2]. Tips for avoiding and managing flare-ups include the following:

- Treat infections quickly
- Avoid changes in diet
- Exercise as prescribed (ask patients not to increase their routine without consulting a physician)
- Moderate changes in activity
- Avoid unnecessary life changes
- Treat changes in mood or sleep early and aggressively

- Always start new medications at the lowest possible dose
- Prepare for unavoidable situations that have caused flare-ups in the past (eg, arrange for an increase in sleep medication or for help with housework and child care)
- Encourage patients to pace their activities and know their limits

Management. Models of pain behavior that interrelate biologic, cognitive, emotional, and behavioral variables form the basis for cognitive-behavioral and operant-behavioral approaches to adult pain management. Fibromyalgia in children responds to a combination of psychotherapy, exercise, relaxation techniques, and education. Pharmacotherapy is generally not indicated in children.

Nonpharmacotherapy

- Diet (eg, promote good nutrition, vitamin supplementation, bone health, weight loss)
- Stress management
- Aerobic exercise (eg, low-impact aerobics, walking, water aerobics, stationary bicycle)
- Sleep therapy (eg, education/instruction on sleep hygiene)
- Psychologic/behavioral therapy

Pharmacotherapy. Always combine pharmacologic and nonpharmacologic therapy in the treatment of fibromyalgia. Aggressively treat comorbid depression.

Medications used in the management of fibromyalgia include the following:

- Analgesics (eg, tramadol)
- Antianxiety agents (eg, alprazolam, clonazepam, zolpidem, zaleplon, trazodone, buspirone, temazepam, sodium oxybate)
- Skeletal muscle relaxants (eg, cyclobenzaprine)
- Antidepressants (eg, amitriptyline, duloxetine, milnacipran, venlafaxine, desvenlafaxine)
- Anticonvulsants (eg, pregabalin, gabapentin, tiagabine)
- Alpha-2 agonists (eg, clonidine)

Other agents used in fibromyalgia may include the following:

- Vitamins and minerals
- Malic acid and magnesium combination
- Antioxidants
- Amino acids
- Herbs and supplements

If nonpharmacotherapy fails to improve sleep problems, the following medications may help:

- Antidepressants (eg, trazodone, SSRIs, SNRIs, tricyclic antidepressants)
- Anticonvulsants (eg, clonazepam, gabapentin, tiagabine)
- Nonbenzodiazepine hypnotics (eg, zolpidem, zaleplon, eszopiclone)
- Muscle relaxants (eg, cyclobenzaprine, tizanidine)
- Dopamine agonists (eg, pramipexole)

4. Chronic Pain Syndrome

4.1. Approach Considerations

The decision to perform any laboratory or imaging evaluations is based on the need to confirm the diagnosis and to rule out other potentially life-threatening illnesses. Sometimes certain investigations are needed to provide appropriate and safe medical or surgical treatment. The recommended treatment should be based on clinical findings or changes in examination findings.

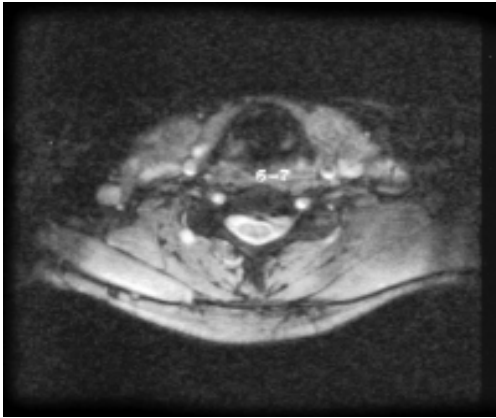
Extreme care should be taken during diagnostic testing for chronic pain syndrome (CPS). Carefully review prior testing to eliminate unnecessary repetition.

Routine complete blood count (CBC), urinalysis, and selected tests for suspected disease are important. Urine or blood toxicology is important for drug detoxification, as well as opioid therapy.

Imaging studies. Imaging studies, including with radiography, magnetic resonance imaging (MRI), and computed tomography (CT) scanning, are important tools in the workup of patients with CPS. (See the images below.)

T1-weighted sagittal magnetic resonance imaging (MRI) scan of the cervical spine in a patient with rheumatoid arthritis shows basilar invagination with cranial migration of an eroded odontoid peg. There is minimal pannus. The tip of the peg indents the medulla, and there is narrowing of the foramen magnum, due to the presence of the peg. Inflammatory fusion of several cervical vertebral bodies is shown [1].





Axial magnetic resonance imaging (MRI) scan of the cervical spine in a patient with cervical radiculopathy. This image reveals a C6-C7 herniated nucleus pulposus [1].

4.2. Treatment & Management

Management of chronic pain in patients with multiple problems is complex [11], usually requiring specific treatment, simultaneous psychological treatment, and physical therapy (PT). A good relationship between the physician and patient should be established.

Treatment of chronic pain syndrome (CPS) must be tailored for each individual patient. The treatment should be aimed at interruption of reinforcement of the pain behavior and modulation of the pain response. The goals of treatment must be realistic and should be focused on restoration of normal function (minimal disability), better quality of life, reduction of use of medication, and prevention of relapse of chronic symptoms.

Psychological interventions, in conjunction with medical intervention, PT, and occupational therapy (OT), increase the effectiveness of the treatment program [14]. Family members are involved in the evaluation and treatment processes. Appropriate caution must be taken during CPS treatment in patients who exhibit any of the following behaviors:

- Poor response to prior appropriate management
- Unusual, unexpected response to prior specific treatment
- Avoidance of school, work, or other social responsibility
- Severe depression
- Severe anxiety disorder

- Excessive pain behavior
- Physician shopping
- Noncompliance with treatment in the past
- Drug abuse or dependence
- Family, marital, or sexual problems
- History of physical or sexual abuse

Inpatient and outpatient care. Hospitalization usually is not required for patients with chronic pain syndrome, but it depends on how invasive the treatment choice is for pain control and on the severity of the case.

5. Physical Therapy

A self-directed or therapist-directed physical therapy (PT) program, individualized to the patient's needs and goals and provided in association with occupational therapy (OT), has an important role in functional restoration for patients with chronic pain syndrome (CPS) [15].

The goal of a PT program is to increase strength and flexibility gradually, beginning with gentle gliding exercises. PT techniques include hot or cold applications, positioning, stretching exercises, traction, massage, ultrasonographic therapy, transcutaneous electrical nerve stimulation (TENS), and manipulations. Heat, massage, and stretching can be used to alleviate excess muscle contraction and pain.

TENS has significant benefit in the treatment of rheumatoid arthritis and osteoarthritis. Electrodes should be applied over or near the area of pain with the dipole parallel to major nerve trunks. TENS application should be avoided near the carotid sinus, during pregnancy, and in patients with demand-type pacemakers. The most common adverse effect of TENS is skin hypersensitivity.

Use of application of heat and cold is encouraged for the treatment of CPS, although the use of cold in neuropathic pain is controversial.

Occupational and Recreational Therapy. Occupational therapy (OT) is very important for initiating gentle, active measurements and preliminary desensitization techniques among patients who have chronic pain, especially regional chronic pain syndrome.

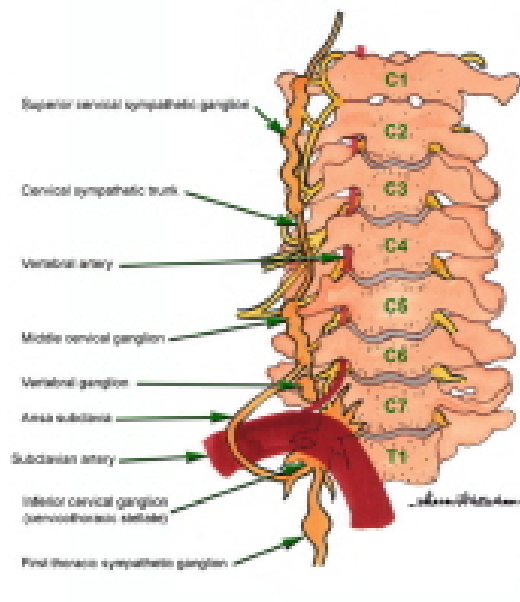
Recreational therapy can help the patient with chronic pain to take part in pleasurable activities that help to decrease pain. Usually, patients with chronic pain are depressed because of intense pain. Recreational therapists may play an important role in the treatment process as they help enable the patient to become active.

Vocational Therapy should be recommended and initiated early for all appropriate patients. It can provide work capacities and targeted work hardening so

that the patient may return to gainful employment, the ultimate functional restoration.

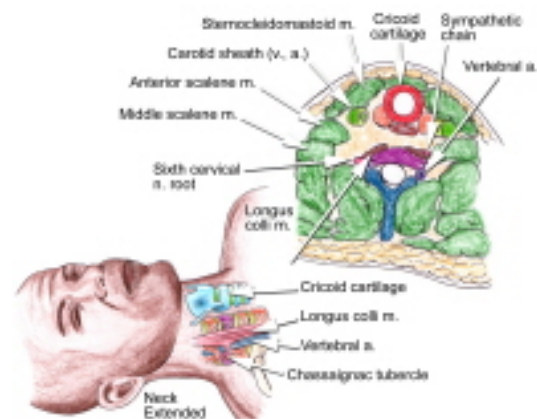
Each patient is evaluated to determine work history, educational background, vocational skills and abilities, and motivation level to return to work. The patient should get help from a vocational counselor regarding legal rights and obligations in each state (eg, workman's compensation).

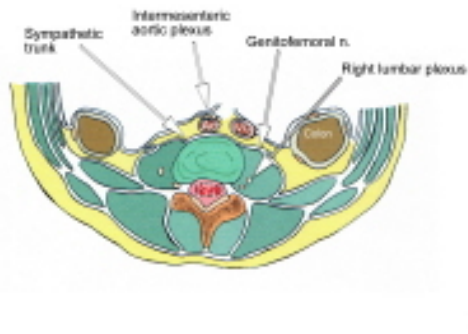
Nerve blocks are used for diagnostic, prognostic, and therapeutic procedures. Sympathetic blocks, including stellate ganglion and lumbar sympathetic blocks, commonly are used and are more effective therapeutic tools for chronic pain.



Schematic anatomical representations, sympathetic chain and stellate ganglion [14].

Stellate block, important anatomical landmarks (surface and cross-sectional views) [14].





Pertinent anatomy for lumbar sympathetic block (cross-sectional view) [14].

Spinal cord stimulation commonly is used to treat neuropathic pain refractory to other forms of treatment. It also is used for patients with a failed back syndrome with radicular pain. Careful evaluation is recommended before patient selection.

Intrathecal morphine pumps, either fully implantable or external, are used to treat chronic pain. Use of these devices should be considered very carefully for pain of nonmalignant origin.

Psychophysiologic Therapy consists of reassurance, counseling, relaxation therapy, stress management programs, and biofeedback techniques. With these treatment modalities, the frequency and severity of chronic pain may be reduced [14].

Biofeedback may be helpful in some patients when combined with medications, while behavioral techniques have been successfully used to treat myofascial and sympathetically mediated pain syndromes.

Relaxation training, including autogenic training and progressive muscle relaxation, commonly is used. This approach is as effective as biofeedback.

6.Chronic Pain Syndrome Medication

Medication Summary. Pharmacotherapy for chronic pain syndrome (CPS) consists of symptomatic abortive therapy (to stop or reduce the severity of the acute exacerbations) and long-term therapy for chronic pain. Initially, pain may respond to simple over-the-counter analgesics, such as paracetamol, ibuprofen, aspirin, or naproxen. If treatment is unsatisfactory, the addition of other modalities or the use of prescription drugs is recommended. If possible, avoid barbiturate or opiate agonists. Also, discourage long-term and excessive use of all symptomatic analgesics because of the risk of dependence and abuse.

Tizanidine may improve the inhibitory function in the central nervous system (CNS) and can provide pain relief. Amitriptyline and nortriptyline are the tricyclic antidepressants (TCAs) most frequently used to treat chronic pain. The selective serotonin reuptake inhibitors (SSRIs) fluoxetine, paroxetine, and sertraline are commonly prescribed by many physicians. Other antidepressants, such as doxepin, desipramine protriptyline, and buspirone, also can be used.

Botulinum toxin type A (BoNT-A) has direct analgesic effects when administered to patients with chronic neuropathic pain (performing actions that are independent of its effect on muscle tone) [19].

A combination of pharmacologic and behavioral intervention were more effective than conventional therapy in the treatment of patients suffering from depression and chronic pain [20].

Antidepressants, Other. These agents increase the synaptic concentration of serotonin and/or norepinephrine in the CNS by inhibiting their reuptake by the presynaptic neuronal membrane.

Amitriptyline is an analgesic for certain chronic and neuropathic pain.

Dosing Forms: Depression. Outpatient: 25 mg PO qHS initially; increase by 25 mg every 5-7 days to 100-200 mg/day (may divide doses throughout day or give at bedtime); if needed, may increase to 300 mg/day.

Inpatient: 100-300 mg PO qDay.

Postherpetic Neuralgia (Off-label): 70 mg PO qDay for at least 3 weeks

Migraine Prophylaxis: 10-25 mg PO qHS; 10-400 mg PO qHS dose range.

Geriatric Dosing. Depression: 10-25 mg PO qHS; may increase by 10-25 mg increments qWeek if needed and as tolerated.

Dosage range: 25-150 mg/day.

Dosing Considerations:

- Avoid; strong anticholinergic and sedative effects; may cause orthostatic hypotension (Beers criteria)
- Consider alternatives; if must use, initiate with lower initial dose

Black Box Warnings: antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults (<24 years) taking antidepressants for major depressive disorders and other psychiatric illnesses; this increase was not seen in patients over age 24 years; a slight decrease in suicidal thinking was seen in adults over age 65 years.

In children and young adults, the risks must be weighed against the benefits of taking antidepressants.

Patients should be monitored closely for changes in behavior, during the initial 1-2 months of therapy and dosage adjustments.

Worsening behavior and suicidal tendencies that are not part of the presenting symptoms may require discontinuation of therapy.

This drug is not approved for use in pediatric patients.

Contraindications: Hypersensitivity, Severe cardiovascular disorder, Narrow-angle glaucoma, Within 14 days of MAOIs (risk of serotonin syndrome), Any drugs or conditions that prolong QT interval, Acute recovery post-MI.

Cautions:

- ✓ Bone marrow suppression reported;
- ✓ May cause sedation and impair mental and physical abilities;
- ✓ May cause orthostatic hypotension;
- ✓ Use caution in patients with cardiovascular disease, diabetes, mania, hepatic and renal impairment, thyroid dysfunction, and seizure disorder;

- ✓ Clinical worsening and suicidal ideation may occur despite medication in adolescents and young adults (18-24 years);
- ✓ Risk of anticholinergic side effects; may cause constipation, urinary retention, blurred vision, and xerostomia;
- ✓ Use caution in patients with urinary retention, open-angle glaucoma, BPH, decreased gastrointestinal motility, or paralytic ileus.

Nortriptyline has demonstrated effectiveness in the treatment of chronic pain. By inhibiting the reuptake of serotonin and/or norepinephrine by the presynaptic neuronal membrane, this drug increases the synaptic concentration of these neurotransmitters in the CNS. Pharmacodynamic effects such as the desensitization of adenylyl cyclase and down-regulation of beta-adrenergic receptors and serotonin receptors also appear to play a role in its action.

Duloxetine is indicated for diabetic peripheral neuropathic pain. It is a potent inhibitor of neuronal serotonin and norepinephrine reuptake.

Venlafaxine inhibits neuronal serotonin and norepinephrine reuptake. In addition, it causes beta-receptor down-regulation. Venlafaxine may decrease neuropathic pain and help with sleep and other mood disorders.

Dosing Forms: Depression. Immediate release: 75 mg/day PO divided q8-12hr initially; may be increased by ≤ 75 mg/day no faster than every 4 days. Up to 225-375 mg/day PO divided q8-12hr.

Extended release: 37,5-75 mg PO once daily initially; may be increased by 75 mg/day every 4 days; not to exceed 225 mg/day.

Generalized Anxiety. Extended release: 37,5-75 mg PO once daily initially; may be increased by 75 mg/day every 4 days; not to exceed 225 mg/day.

Administration: Take with food. If discontinuing therapy after ≥ 7 days, taper dosage.

Dosing Modifications: Mild to severe renal impairment - reduce dosage by 25-50%. Mild to moderate hepatic impairment - reduce dosage by 25-50%

Contraindications. Hypersensitivity.

Coadministration with serotonergic drugs:

- Coadministration with monoamine oxidase inhibitors (MAOIs) increases risk of serotonin syndrome;
- Do not use MAOIs concomitantly within 14 days before initiating venlafaxine or within 7 days after discontinuing venlafaxine;
- Symptoms include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma;

Cautions:

- ✓ Increased intraocular pressure or angle-closure glaucoma
- ✓ Bipolar mania, history of seizures
- ✓ Hepatic or renal impairment
- ✓ Clinical worsening and suicidal ideation may occur despite medication in adolescents and young adults (18-24 years)
- ✓ When discontinuing, taper dosage to avoid flu-like symptoms
- ✓ Risks of sustained hypertension, hyponatremia, abnormal bleeding, and impeded height and weight growth in children

Pharmacology. Mechanism of Action. "Bicyclic" antidepressant; drug is structurally unrelated to SSRIs, MAOIs, and tricyclic antidepressants (TCAs), but it and its metabolite are potent inhibitors of serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake; it does not have MAOI activity or activity for H₁ histaminergic, muscarinic cholinergic, or alpha₂-adrenergic receptors.

Absorption: 92%. Bioavailability: 45%.

Peak plasma time: Immediate release, 2-3 hr; extended release, 5.5-9 hr.

Concentration: Immediate release - 225-290 ng/mL; extended release - 150-260 ng/mL.

Distribution: Protein bound: 27-30%. V_d: Immediate release - 7.5 L/kg.

Metabolism: in liver by CYP2D6. Metabolites: O-desmethylvenlafaxine

Enzymes inhibited: CYP2D6 (weak).

Elimination. Half-life: 5-11 hr (prolonged in renal or hepatic dysfunction)

Dialyzable: No.

Excretion: Urine (87%).

Fluoxetine is an atypical non-tricyclic antidepressant (non-TCA) with potent specific 5HT-uptake inhibition and fewer anticholinergic and cardiovascular adverse effects than TCAs. Consider this drug as an alternative to TCAs.

Dosing Forms: **Major Depressive Disorder:** Initial: 20 mg PO qDay. May consider gradually increasing dose after several weeks by 20 mg/day; not to exceed 80 mg qDay.

Fibromyalgia: 20-80 mg PO qDay. Efficacy may increase with concomitant amitriptyline.

Migraine Prophylaxis: 20-40 mg PO qDay.

Dosing Modifications. Renal impairment - use caution; drug accumulation may occur with severe renal impairment.

Hepatic impairment (cirrhosis) - decreased clearance of parent drug and active metabolite (norfluoxetine); lower or less frequent dose recommended.

Adverse Effects: Headache (20-25%), Nausea (20-25%), Insomnia (15-20%), Anorexia (10-15%), Anxiety (10-15%), Asthenia (10-15%), Diarrhea (10-15%), Nervousness (10-15%), Somnolence (10-15%).

Contraindications: Hypersensitivity. Concomitant pimozide or thioridazine, Breastfeeding, Coadministration with MAOIs.

Cautions:

Clinical worsening and suicidal ideation may occur despite medication in adolescents and young adults (aged 18-24 years).

Risk of serotonin syndrome when used with other strong serotonergic drugs.

Risk of bleeding (GI and other) when used in combination with NSAIDs, aspirin, or drugs affecting coagulation.

Activation of mania/hypomania (screen for bipolar disorder).

Hyponatremia.

Seizures.

May prolong QT interval and cause ventricular arrhythmia, including torsade de pointes.

Mydriasis reported; caution in patients with acute narrow-angle glaucoma.

Hypoglycemia reported; may alter glycemic control in patients with diabetes.

Pregnancy: Conflicting evidence regarding use of SSRIs during pregnancy and increased risk of persistent pulmonary hypertension of the newborn, or PPHN.

Sertraline is an atypical non-TCA with potent specific 5HT-uptake inhibition and fewer anticholinergic and cardiovascular adverse effects than TCAs. Consider it as an alternative to TCAs.

Dosing: tablet 25mg, 50mg, 100mg.

Major Depressive Disorder: Initial: 50 mg PO qDay. May increase by 25 mg at 1-week intervals to no more than 200 mg qDay.

Dosing Modifications: Renal impairment - dose adjustment not necessary. Hepatic impairment - use caution; administer lower or less frequent dosing.

Adverse Effects: Diarrhea (20-25%), Nausea (20-25%), Headache (20-25%), Insomnia (20-25%), Ejaculation disorder (10-15%), Dizziness (10-15%), Dry mouth (10-15%), Fatigue (10-15%), Somnolence (10-15%).

Contraindications: Hypersensitivity.

Concomitant pimozide: Risk of long QT syndrome

Coadministration with serotonergic drugs.

Cautions:

Clinical worsening and suicide ideation may occur despite medication.

Use caution in patients with seizure disorders.

Increases risk of hyponatremia and impairment of cognitive/motor functions in the elderly.

Increases risk of bleeding in patients taking anticoagulants/antiplatelets concomitantly .

Pregnancy. Avoid abrupt withdrawal.

Coadministration with other drugs that enhance the effects of serotonergic neurotransmission (eg, tryptophan, fenfluramine, fentanyl, 5-HT agonists, St. John's Wort) should be undertaken with caution and avoided whenever possible due to the potential for pharmacodynamic interaction.

Pharmacology. Mechanism of Action: Selective serotonin reuptake inhibitor; little or no affinity for alpha-adrenergic histamine or cholinergic receptor
Bioavailability: Absorption increased by food.

Peak plasma time: 4.5-8.4 hr.

Protein bound: 98%.

Metabolized by hepatic cytochrome P450 enzymes. Metabolites: Minimal potency.

Elimination: Half-life: 26 hr.

Dialyzable: No. Excretion: Urine (12-14% unchanged); feces (40-45%)

Paroxetine is an atypical non-TCA with potent specific 5HT-uptake inhibition and fewer anticholinergic and cardiovascular adverse effects than TCAs. Consider it as an alternative to TCAs.

Dosing: Depression. Conventional: 20 mg PO qDay initially; may increase by 10 mg/day qWeek to no more than 50 mg/day.

: 25 mg PO qDay initially; may increase by 12.5 mg/day qWeek to no more than 62.5 mg/day.

Diabetic Neuropathy: 10 mg/day PO initially; may increase to 20-60 mg/day.

Dosing Modifications: Severe renal impairment (CrCl <30 mL/min) - 10 mg PO qDay initially; may titrate; not to exceed 40 mg/day.

Adverse Effects (Based on 40 mg Dose): Nausea (15-24%), Insomnia (11-24%), Dry mouth (9-18%), Headache (17%), Asthenia (10-15%), Constipation (10-15%), Diarrhea (9-12%), Dizziness (6-14%), Ejaculation disorder (10-15%), Tremor (4-11%)

Contraindications: Hypersensitivity.

Coadministration with serotonergic drugs.

Cautions: Clinical worsening and suicidal ideation may occur despite medication in adolescents and young adults (18-24 years).

Use caution in patients with narrow-angle glaucoma, bipolar disorder, seizure disorder, history of suicidal thought/behavior.

Conflicting evidence regarding use of SSRIs during pregnancy and increased risk of persistent pulmonary hypertension of the newborn (see Pregnancy).

Risk of complications such as feeding difficulties, irritability, and respiratory problems reported in neonates exposed to SNRIs/SSRIs late in third trimester.

Risk of cardiovascular defects in infants whose mothers took drug during early pregnancy.

Withdraw gradually.

Use lower starting dose in renal impairment ($\text{CrCl} < 30 \text{ mL/min}$) or severe hepatic impairment.

Increases risk of hyponatremia and impairment of cognitive and motor functions in the elderly.

May impair platelet aggregation especially when used in combination with aspirin or NSAIDs; increases risk of bleeding in patients taking anticoagulants/antiplatelets concomitantly.

Epidemiologic studies on bone fracture risk following exposure to some antidepressants, including SSRIs, have reported an association between antidepressant treatment and fractures; there are multiple possible causes for this observation and it is unknown to what extent fracture risk is directly attributable to SSRI treatment.

Bone fractures reported to be associated with antidepressant use.

Pharmacology. Mechanism of Action. SSRI; little or no affinity for alpha-adrenergic histamine or cholinergic receptor.

Peak plasma time: 5,2-8,1 hr (immediate-release); 6-10 hr (controlled-release).

Peak plasma concentration: 61,7 ng/mL.

Distribution: Protein bound: 93-95%

Metabolism: Hepatic P450 enzyme CYP2D6. Enzymes inhibited: CYP2D6.

Metabolites: Inactive.

Elimination: Half-life: 21 hr. Dialyzable: No.

Excretion: Urine (64%); feces (36%).

Anticonvulsants. Class Summary

Certain antiepileptic drugs (eg, gabapentin and pregabalin) have proven helpful in some cases of neuropathic pain [8]. Pregabalin also demonstrated pain relief in diabetic peripheral neuropathy and postherpetic neuralgia. It may provide benefit in other neuropathic pain as well [23].

A *Cochrane Database of Systematic Reviews* article that looked at 29 studies with a total of 3571 participants with chronic pain conditions concluded that gabapentin provided pain relief in about 30% of patients. Adverse events, although frequent, were mostly tolerable; they included dizziness, somnolence, peripheral edema, and gait disturbance [24].

Other anticonvulsant agents (eg, clonazepam, topiramate, lamotrigine, zonisamide, tiagabine) also have been tried in chronic pain syndrome (CPS).

Gabapentin has anticonvulsant properties and antineuralgic effects; however, its exact mechanism of action is unknown. It is structurally related to GABA but does not interact with GABA receptors.

Dosing: Postherpetic Neuralgia

- Day 1: 300 mg PO qDay
- Day 2: 300 mg PO q12hr
- Day 3: 300 mg PO q8hr
- Maintenance: Subsequently titrate as needed up to 600 mg PO q8hr

Diabetic Neuropathy: 900 mg/day PO initially; may increase gradually q3Days to 1800-3600 mg/day.

Dosing Modifications: Renal impairment:

- CrCl >60 mL/min: 300-1200 mg PO TID
- CrCl 30-60 mL/min: 200-700 mg q12hr
- CrCl 15-29 mL/min: 200-700 mg qDay
- CrCl <15 mL/min: 100-300 mg qDay

- Hemodialysis (CrCl <15 mL/min): Administer supplemental dose (range 125-350 mg) posthemodialysis, after each 4 hr dialysis interval; further dose reduction should be in proportion to CrCl (eg, CrCl of 7.5 mL/min should receive one-half daily posthemodialysis dose).

Administration. Reducing the dose, discontinuing the drug, or substituting an alternative medication should be done gradually over a minimum of 1 week.

Adverse Effects: Ataxia (11-15%), Dizziness (16-20%), Fatigue (11-15%), Somnolence (16-20%).

Contraindications: Hypersensitivity.

Cautions: Increased blood CPK levels and rhabdomyolysis reported

Antiepileptic drugs increase risk of suicidal thoughts or behavior in patients taking these drugs for any indication; monitor for emergence or worsening depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

May cause CNS depression, which may impair physical or mental abilities.

May potentiate effects of other sedatives or ethanol when administered concomitantly.

Do not discontinue abruptly; gradually taper over a minimum of 1 week.

Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as multiorgan hypersensitivity.

Pharmacology. Mechanism of Action: structurally related to neurotransmitter GABA, but has no effect on GABA binding, uptake, or degradation; mechanism for analgesic and anticonvulsant activity unknown.

Absorption: Variable from proximal small bowel by L-amino transport system.

Bioavailability: Inversely proportion to dose; 60% (900 mg/day); 47% (1200 mg/day); 34% (2400 mg/day); 33% (3600 mg/day); 27% (4800 mg/day).

Peak plasma time: 2-4 hr.

Peak plasma concentration: 8536 ng/mL.

Distribution: Protein bound: <3%

Metabolism: Gabapentin is not appreciably metabolized in humans.

Not a substrate, inducer, or inhibitor of CYP450 isoenzymes.

Elimination: Half-life: 5-7 hr

- Dialyzable: Yes
- Excretion: Urine

Pregabalin is a structural derivative of GABA; its mechanism of action unknown. Pregabalin binds with high affinity to the alpha2-delta site (a calcium channel subunit), and in vitro, pregabalin reduces the calcium-dependent release of several neurotransmitters, possibly by modulating calcium channel function. The US FDA approved it for the treatment of neuropathic pain associated with diabetic peripheral neuropathy or postherpetic neuralgia and as adjunctive therapy in partial-onset seizures.

Dosing: Diabetic Peripheral Neuropathic Pain. Initial: 50 mg PO q8hr. May increase to 100 mg PO q8hr within 1 week, as needed; not to exceed 600 mg/day

Postherpetic Neuralgia. Initial: 150-300 mg/day PO divided q8-12hr. Maintenance: May increase to 300 mg/day divided q8-12hr after 1 week, as needed

Fibromyalgia. Initial: 150 mg/day PO divided q12hr. Maintenance: May increase to 300-450 mg/day divided q12hr after 1 week, as needed.

Dosing Modifications

Renal impairment (CrCl 30-60 mL/min) - Decrease dose by 50%.

Renal impairment (CrCl 15-30 mL/min).

- If 150 mg/day in normal renal function: Decrease dose to 25-50 mg/day
- If 300 mg/day in normal renal function: Decrease dose to 75 mg/day
- If 450 mg/day in normal renal function: Decrease dose to 100-150 mg/day
- If 600 mg/day in normal renal function: Decrease dose to 150 mg/day

Adverse Effects. Dose-dependent: Dizziness (21%), Somnolence (12%), Peripheral edema (9%), Xerostomia (8%), Asthenia (5%).

Postmarketing Reports: Headache, Nausea, Diarrhea, Gynecomastia and breast enlargement.

Contraindications: Hypersensitivity.

Cautions. Discontinue gradually over at least 1 week.

Monitor for physical dependence and withdrawal symptoms.

Monitor for decreased platelet count and increased creatinine-kinase levels.

Increased risk of angioedema, peripheral edema, dizziness, somnolence, blurred vision, and weight gain.

May impair ability to drive or perform hazardous tasks.

Antiepileptic drugs increase risk of suicidal thoughts or behavior in patients taking these drugs for any indication; monitor for emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pharmacology. Mechanism of Action. Precise mechanism of action unknown but is a GABA analogue that binds to a subunit of voltage-gated calcium channels in CNS; does not affect sodium channels, opiate receptors, or cyclo-oxygenase enzyme activity; interactions with descending noradrenergic and serotonergic pathways originating from the brain stem appear to reduce neuropathic pain transmission from spinal cord.

Bioavailability: >90%. Peak plasma time: 1,5 hr.

Protein bound: None.

Metabolism: Minimal.

Elimination: Half-life: 6.3 hr. Excretion: Urine.

Analgesics. Class Summary

Analgesics are commonly used for many pain syndromes. Pain control is essential to quality patient care. Analgesics ensure patient comfort, promote pulmonary toilet, and have sedating properties, which are beneficial for patients who have sustained traumatic injuries.

Oxycodone - Long-acting opioids may be used in patients with CPS. Start with a small dose and, if appropriate, gradually increase it.

Fentanyl - is a potent narcotic analgesic with a much shorter half-life than morphine sulfate. It is the drug of choice for conscious-sedation analgesia. Fentanyl is ideal for analgesic action of short duration during anesthesia and during

the immediate postoperative period. It is an excellent choice for pain management and sedation of short duration (30-60min).

Fentanyl is easy to titrate and is easily and quickly reversed by naloxone. When the transdermal dosage form is used, most patients achieve pain control with 72-hour dosing intervals; however, some patients require dosing intervals of 48 hours.

Acetaminophen - is the drug of choice for the treatment of pain in patients with documented hypersensitivity to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), with upper GI disease, who are pregnant, or who are taking oral anticoagulants.

Dosing: Analgesia&Fever: immediate-release - 325-650 mg PO/PR q4hr PRN, or 500 mg PO q8hr PRN; extended-release - 1300 mg PO q8hr PRN.

Not to exceed a cumulative dose of 4 g/day of acetaminophen.

Renal Impairment:

CrCl 10-50 mL/minute: Administer q6hr

CrCl <10 mL/minute: Administer q8hr

Other Indications & Uses: Potent analgesic and antipyretic activity with weak anti-inflammatory activity.

Adverse Effects (Frequency Not Defined): Angioedema, Disorientation, Dizziness, Pruritic maculopapular rash, Stevens-Johnson syndrome, Gastrointestinal hemorrhage, Agranulocytosis, Leukopenia, Thrombocytopenia, Hepatotoxicity.

Contraindications: Hypersensitivity.

Hepatitis or hepatic/renal dysfunction, alcoholism.

Repeated administration in patients with anemia or cardiac, pulmonary, or renal disease.

Cautions. Acetaminophen in many other dosage forms and products, check label carefully to avoid overdose.

Risk of hepatotoxicity is higher in alcoholics, chronic high dose, or use of more than one acetaminophen-containing product.

Risk for rare, but serious skin reactions that can be fatal (Stevens-Johnson Syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis).

Pharmacology. Mechanism of Action. Acts on hypothalamus to produce antipyresis. May work peripherally to pain impulse generation; may also inhibit prostaglandin synthesis in CNS.

Pharmacokinetics: Peak Plasma Time: 10-60 min (PO immediate-release); 60-120 min (PO extended-release).

Protein Bound: 10 to 25%.

Metabolism: Liver (microsomal enzyme systems); conjugation (glucuronic/sulfuric acid).

Half-life elimination: 1,25-3 hr.

Excretion: urine (principally as acetaminophen glucuronide with acetaminophen sulfate/mercaptate).

Nonsteroidal Anti-Inflammatory Drugs. Class Summary

NSAIDs have analgesic, anti-inflammatory, and antipyretic activities. Their mechanism of action is not known, but they may inhibit cyclo-oxygenase activity and prostaglandin synthesis. Other mechanisms may exist as well, such as inhibition of leukotriene synthesis, lysosomal enzyme release, lipoxygenase activity, neutrophil aggregation, and various cell membrane functions.

Ibuprofen is the drug of choice for patients with mild to moderate pain. It inhibits inflammatory reactions and pain by decreasing prostaglandin synthesis.

Pain: 200-400 mg PO q4-6hr; not to exceed 1.2 g.

Fever: 400 mg PO q4-6hr PRN or 100-200 mg q4hr as needed; not to exceed 3.2 g/day; patient should hydrate before administration.

Inflammatory Disease: 400-800 mg PO q6-8hr; not to exceed 3.2 g/day.

Osteoarthritis: 300 mg, 400 mg, 600 mg, or 800 mg PO q6-8hr; not to exceed 3200 mg/day. Monitor for gastrointestinal (GI) risks.

Administration: Take with food or 8-12 oz of water to avoid GI effects.

Dosing Modifications: Significantly impaired renal function: Monitor closely; consider reduced dosage if warranted. Severe hepatic impairment: Avoid use.

Adverse Effects: Dizziness (3-9%) , Epigastric pain (3-9%), Heartburn (3-9%), Nausea (3-9%), Rash (3-9%), Tinnitus (3-9%), Edema (1-3%), Fluid retention (1-3%), Headache (1-3%) , Vomiting (1-3%).

Black Box Warnings

Cardiovascular risk

- NSAIDs may increase risk of serious cardiovascular thrombotic events, myocardial infarction (MI), and stroke, which can be fatal
- Risk may increase with duration of use
- Patients with existing cardiovascular disease or risk factors for such disease may be at greater risk
- NSAIDs are contraindicated for perioperative pain in setting of coronary artery bypass graft (CABG) surgery

Gastrointestinal risk:

- NSAIDs increase risk of serious GI adverse events, including bleeding, ulceration, and gastric or intestinal perforation, which can be fatal
- GI adverse events may occur at any time during use and without warning symptoms
- Elderly patients are at greater risk for serious GI events

Contraindications

Absolute:

- Aspirin allergy
- Perioperative pain in setting of coronary artery bypass graft (CABG) surgery
- Preterm infants with untreated proven or suspected infection; bleeding with active intracranial hemorrhage or GI bleed; thrombocytopenia, coagulation defects, proven or necrotizing enterocolitis, significant renal impairment, congenital heart disease where patency of the PDA is necessary for pulmonary or systemic blood flow

Relative:

- Bleeding disorder
- Duodenal/gastric/peptic ulcer
- Stomatitis
- Systemic lupus erythematosus (SLE)
- Ulcerative colitis
- Upper GI disease
- Late pregnancy (may cause premature closure of ductus arteriosus)

Cautions:

Use caution in asthma, congestive heart failure (CHF), hepatic or renal impairment, and hypertension.

Long-term administration of NSAIDs may result in renal papillary necrosis and other renal injury; patients at greatest risk include elderly individuals; those with impaired renal function, hypovolemia, heart failure, liver dysfunction, or salt depletion; and those taking diuretics, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers.

Fever, rash, abdominal pain, nausea, liver dysfunction, and meningitis have occurred in patients with collagen-vascular disease, especially SLE.

Platelet aggregation and adhesion may be decreased; monitor patients with coagulation disorders receiving the therapy.

Risk of hyperkalemia may increase in patients with diabetes, the elderly, renal disease.

Pharmacology. Mechanism of Action. Inhibits synthesis of prostaglandins in body tissues by inhibiting at least 2 cyclo-oxygenase (COX) isoenzymes, COX-1 and COX-2.

May inhibit chemotaxis, alter lymphocyte activity, decrease proinflammatory cytokine activity, and inhibit neutrophil aggregation; these effects may contribute to anti-inflammatory activity.

Absorption. Rapidly absorbed (85%). Bioavailability: 80-100%.

Onset: 30-60 min. Duration: 4-6 hr.

Protein bound: 90-99%.

Rapidly metabolized in liver (primarily by CYP2C9; CYP2C19 substrate) via oxidation to inactive metabolites.

Elimination: Half-life: 2-4 hr (adults); Excretion: Urine (50-60%; <10% unchanged); remainder in feces within 24 hr.

Naproxen sodium. This agent is used for the relief of mild to moderate pain. It inhibits inflammatory reactions and pain by decreasing the activity of cyclo-oxygenase, which results in a decrease in prostaglandin synthesis.

Pain: 500 mg PO initially, then 250 mg PO q6-8hr or 500 mg PO q12hr PRN; not to exceed 1250 mg/day naproxen base on day 1; subsequent daily doses should not exceed 1000 mg naproxen base.

Extended release: 750-1000 mg PO qDay; may temporarily increase to 1500 mg/day if tolerated well and clinically indicated.

Rheumatoid Arthritis, Osteoarthritis, Ankylosing Spondylitis: 500-1000 mg/day PO divided q12hr; may increase to 1500 mg/day if tolerated well for limited time.

Extended release: 750-1000 mg PO qDay; may temporarily increase to 1500 mg/day if tolerated well and clinically indicated.

Migraine: 750 mg PO initially, may give additional 250-500 mg if necessary; not to exceed 1250 mg in 24 hr.

Dosing Considerations: 220 mg of naproxen sodium contains 200 mg of naproxen. Delayed-release formulation not recommended for acute pain. Take with food or 8-12 oz of water to avoid gastrointestinal (GI) effects.

Dosing Modifications: CrCl <30 mL/min: Use not recommended.

Pain:

>2 years - cancer pain: 5-7 mg/kg PO q8-12hr; not to exceed 1000 mg/day

>12 years:

- 500 mg PO initially, then 250 mg PO q6-8hr or 500 mg PO q12hr PRN; not to exceed 1250 mg/day naproxen base on day 1; subsequent daily doses should not exceed 1000 mg naproxen base;

- extended release: 750-1000 mg PO qDay; may temporarily increase to 1500 mg/day if tolerated well and clinically indicated.

Adverse Effects: Abdominal pain (3-9%), Constipation (3-9%), Dizziness (3-9%), Drowsiness (3-9%), Headache (3-9%), Heartburn (3-9%), Nausea (3-9%), Edema (3-9%).

Black Box Warnings

Cardiovascular risk:

- NSAIDs may increase risk of serious cardiovascular thrombotic events, myocardial infarction (MI), and stroke, which can be fatal;
- Risk may increase with duration of use;
- Patients with existing cardiovascular disease or risk factors for such disease may be at greater risk;
- NSAIDs are contraindicated for perioperative pain in setting of coronary artery bypass graft (CABG) surgery

Gastrointestinal risk:

- NSAIDs increase risk of serious GI adverse events, including bleeding, ulceration, and gastric or intestinal perforation, which can be fatal
- GI adverse events may occur at any time during use and without warning symptoms
- Elderly patients are at greater risk for serious GI events

Contraindications

Absolute: Aspirin allergy; perioperative pain in setting of coronary artery bypass graft (CABG) surgery.

Relative: Bleeding disorders, delayed esophageal transit, hepatic disease, peptic ulcer, renal impairment, stomatitis, late pregnancy (may cause premature closure of ductus arteriosus).

Cautions

Use caution in congestive heart failure (CHF), hypertension, renal/hepatic impairment, or aspirin sensitive asthma.

May increase risk of aseptic meningitis, especially in patients with systemic lupus erythematosus and mixed connective tissue disorders.

Prolonged use may increase risk of adverse cardiovascular events.

May cause anaphylactoid reactions, even in patients with no prior exposure to NSAIDs.

Long-term administration of NSAIDs may result in renal papillary necrosis and other renal injury; patients at greatest risk include elderly individuals, those with impaired renal function, hypovolemia, heart failure, liver dysfunction, or salt depletion, and those taking diuretics, angiotensin-converting enzyme inhibitors, or angiotensin-receptor blockers.

May cause drowsiness, dizziness, and blurred vision.

Platelet aggregation and adhesion may be decreased; may prolong bleeding time; monitor closely patients with coagulation disorders.

May increase risk of hyperkalemia in the elderly, renal disease, or diabetics, especially when used concomitantly with drugs that increase hyperkalemia.

May cause serious skin reactions including exfoliative dermatitis, toxic epidermal syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis; discontinue therapy at first sign of skin rash.

Pharmacology. Mechanism of Action: Inhibits synthesis of prostaglandins in body tissues by inhibiting at least 2 cyclooxygenase (COX) isoenzymes, COX-1 and COX-2.

May inhibit chemotaxis, alter lymphocyte activity, decrease proinflammatory cytokine activity, and inhibit neutrophil aggregation; these effects may contribute to anti-inflammatory activity.

Absorption. Bioavailability: 95%. Onset: 30-60 min. Duration: < 12 hr
Peak serum time: 1-4 hr (tablets); 2-12 hr (delayed release empty stomach); 4-24 hr (delayed release with food).

Distribution. Protein bound: <99%. Metabolized in liver via conjugation.

Metabolites: 6-Desmethylnaproxen, glucuronide conjugates.

Enzymes inhibited: COX-1, COX-2.

Elimination. Half-life: 12-17 hr. Dialyzable: No value.

Clearance: 0,13 mL/min/kg. Excretion: Urine (95%), feces (<3%).

Diclofenac inhibits prostaglandin synthesis by decreasing COX activity, which, in turn, decreases formation of prostaglandin precursors.

Dosing: Rheumatoid Arthritis, Osteoarthritis: Diclofenac potassium: 50 mg PO q8-12hr. Diclofenac sodium: 50 mg PO q8hr or 75 mg PO q12hr. Extended release: 100 mg PO once daily; may be increased to 100 mg PO q12hr.

Mild-to-Moderate Acute Pain: Immediate-release tab: 100 mg PO once, then 50 mg PO q8hr PRN.

Acute Migraine: Oral solution: 50 mg in 30-60 mL of water, mixed well and drunk immediately. Not for prophylaxis.

Administration: Tablet/capsule - take with food or 8-12 oz of water to avoid GI adverse effects.

Oral solution - do not use liquids other than water to reconstitute; foods decrease effectiveness.

No Interactions Found.

Adverse Effects (Frequency Not Defined): Abdominal distention and flatulence, Abdominal pain or cramps, Constipation, Diarrhea, Dizziness, Dyspepsia, Edema, Fluid retention, Headache, Peptic ulcer or GI bleeding, Rash, Acute hepatitis, Agranulocytosis, Asthma, Leukopenia, Nephrotoxicity.

Black Box Warnings

Cardiovascular risk

- Nonsteroidal anti-inflammatory drugs (NSAIDs) may increase risk of serious cardiovascular thrombotic events, myocardial infarction (MI), and stroke, which can be fatal
- Risk may increase with duration of use
- Patients with existing cardiovascular disease or risk factors for such disease may be at greater risk
- NSAIDs are contraindicated for perioperative pain in setting of coronary artery bypass graft (CABG) surgery

Gastrointestinal risk

- NSAIDs increase risk of serious GI adverse events, including bleeding, ulceration, and gastric or intestinal perforation, which can be fatal
- GI adverse events may occur at any time during use and without warning symptoms
- Elderly patients are at greater risk for serious GI events

Contraindications. Absolute: Hypersensitivity to diclofenac, history of aspirin triad, treatment of perioperative pain associated with CABG.

Cautions

Bronchospasm, cardiac disease, CHF, hepatic porphyria, hypertension, fluid retention, severe renal impairment, smoking, systemic lupus erythematosus.

Platelet aggregation and adhesion may be decreased; may prolong bleeding time.

Use caution in blood dyscrasias, bone marrow depression.

Potential risk for cardiovascular damage and hepatotoxicity.

Use caution in relative: bleeding disorder, peptic ulcer, stomatitis, ulcerative colitis, upper GI disease, hepatic disease, late pregnancy (may cause premature closure of ductus arteriosus).

Long-term administration of NSAIDs may result in renal papillary necrosis and other renal injury; patients at greatest risk include elderly individuals, those with impaired renal function, hypovolemia, heart failure, liver dysfunction, or salt depletion, and those taking diuretics, angiotensin-converting enzyme inhibitors, or angiotensin-receptor blockers.

May cause dizziness blurred vision and neurologic effects that may impair physical and mental abilities.

Risk of serious skin reactions, including Stevens Johnson syndrome and necrotizing enterocolitis.

Pharmacology. Mechanism of Action

Inhibits cyclooxygenase (COX-1 and COX-2), thereby inhibiting prostaglandin synthesis.

May also inhibit neutrophil aggregation/activation, inhibit chemotaxis, decrease proinflammatory cytokine level, and alter lymphocyte activity.

Absorption: ~100% absorbed. Bioavailability: 50-60%.

Peak plasma time: Oral solution, 10-30 min; extended-release tablet, 2-3 hr.

Onset of action: potassium salt faster acting than sodium salt (dissolves in stomach instead of duodenum).

Distribution: Protein bound: 99-99,8%.

Metabolized in liver by hydroxylation and conjugation with glucuronic acid, taurine amide, sulfuric acid, and other biogenic ligands, as well as conjugation of unchanged drug.

Enzymes inhibited: COX-1, COX-2.

Elimination. Half-life: 1,2-2 hr. Excretion: Urine (50-70%), feces (30-35%).

Indomethacin - is thought to be the most effective NSAID for the treatment of ankylosing spondylitis, although no scientific evidence supports this claim. It is used for relief of mild to moderate pain; it inhibits inflammatory reactions and pain by decreasing the activity of COX, which results in a decrease of prostaglandin synthesis.

Dosing: Inflammatory/Rheumatoid Disorders: Immediate release: 25-50 mg PO/PR q8-12hr; not to exceed 200 mg/day.

Extended release: 75-150 mg/day PO in single daily dose or divided q12hr; not to exceed 150 mg/day.

Bursitis/Tendinitis: Immediate-release: 75-150 mg/day PO/PR divided q6-8hr.

Extended-release: 75-150 mg/day PO in single daily dose or divided q12hr.

Pain: (for mild-to-moderate acute pain) 20 mg PO TID or 40 mg PO BID/TID.

Dosing Considerations. Geriatric.

- Monitor renal function (drug is renally excreted); decreased renal function more likely in elderly
- produces most central nervous system (CNS) adverse reactions in elderly

- Lowest dose and frequency recommended

Administration: Take with food or 8-12 oz of water to avoid GI effects

Contraindications

Absolute

- Hypersensitivity
- Aspirin allergy
- History of aspirin triad
- Preoperative pain associated with CABG surgery

Relative

- Bleeding disorder
- Duodenal/gastric/peptic ulcer
- Stomatitis
- Ulcerative colitis
- Upper GI disease
- Late pregnancy (may cause premature closure of ductus arteriosus)

Cautions

Use caution in patients with history of bronchospasm, cardiac disease, CHF, hypertension, hepatic or renal impairment.

Long-term administration of NSAIDs may result in renal papillary necrosis and other renal injury; patients at greatest risk include elderly individuals, those with impaired renal function, hypovolemia, heart failure, liver dysfunction, or salt depletion, and those taking diuretics, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers.

Prolonged use may cause corneal deposits and retinal disturbances; discontinue if visual changes observed.

Risk of aggravation of psychiatric disturbances, epilepsy, fluid retention, or Parkinson disease.

Reduction in cerebral blood flow associated with rapid IV infusion.

Serious skin adverse events (eg, exfoliative dermatitis, Stevens-Johnson Syndrome).

Pharmacology. Mechanism of Action. Inhibits synthesis of prostaglandins in body tissues by inhibiting at least 2 cyclo-oxygenase (COX) isoenzymes, COX-1 and COX-2.

May inhibit chemotaxis, alter lymphocyte activity, decrease proinflammatory cytokine activity, and inhibit neutrophil aggregation; these effects may contribute to anti-inflammatory activity.

Absorption. Bioavailability: ~100%. Onset: 30 min. Duration: 4-6 hr.
Peak plasma time: 0,5-2 hr.

Distribution: Protein bound: 99%.

Metabolized in liver. Enzymes inhibited: COX-1, COX-2 .

Elimination. Half-life: 4,5 hr (prolonged in neonates).

Excretion: Urine (60%), feces (>33%).

Ketoprofen - is used for relief of mild to moderate pain and inflammation. Small dosages are indicated initially in small patients, elderly patients, and patients with renal or liver disease. Doses higher than 75 mg do not increase the therapeutic effects. Administer high doses with caution, and closely observe the patient's response.

Dosing: Pain Management: Immediate-release: 25-50 mg PO q6-8hr as necessary.

Extended-release: 200 mg PO qDay; not recommended for acute pain.

Rheumatoid Arthritis or Osteoarthritis: Immediate-release: 75 mg PO q8hr or 50 mg PO q6hr. Extended-release: 200 mg PO qDay.

Administration: Take with food or 8-12 oz water to avoid GI effects.

Adverse Effects: Increased liver function test (up to 15%), Dyspepsia (12%), Dizziness (3-9%), Headache (3-9%), Impaired renal function disorder (3-9%), Upper GI ulcers, 3-6 mth treatment; 2-4%, 1 yo treatment), Nausea (>3%) , Diarrhea (>3%), Abdominal pain (>3%), Constipation (>3%), Flatulence (>3%), Rash (1-3%).

Contraindications. Absolute: ASA allergy.

Relative: Bleeding disorders, hepatic disease, peptic ulcer, stomatitis, ulcerative colitis, upper GI disease, late pregnancy.

Cautions

Asthma (bronchial), cardiac disease, CHF, HTN, renal impairment, SLE.

Long-term administration of NSAIDs may result in renal papillary necrosis and other renal injury; patients at greatest risk include the elderly, or those with impaired renal function, hypovolemia, heart failure, liver dysfunction, salt depletion, and individuals taking diuretics, ACE inhibitors, or ARBs.

Pharmacology. Mechanism of Action. Inhibits synthesis of prostaglandins in body tissues by inhibiting at least cyclooxygenase-1 (COX-1) and -2 (COX-2) May inhibit chemotaxis, may alter lymphocyte activity, decrease proinflammatory cytokine activity, and may inhibit neutrophil aggregation. These effects may contribute to its anti-inflammatory activity.

Pharmacokinetics. Bioavailability: 90%.

Duration: 6 hr (immediate release). Onset: <30 min (immediate release).

Peak Plasma Time: 0,5-2 hr (immediate release).

Protein Bound: 99%.

Metabolism: Liver.

Dialyzable: Yes.

Enzymes inhibited: Cyclooxygenase.

Half-life: 2-4 hr (immediate release); 3-7,5 hr (ER).

Excretion: Urine 50-90% as glucuronide conjugates; feces 1-8%.

Patient Education. The patient and family should have a good understanding about the multifactorial nature of chronic pain and the benefits of a multidisciplinary comprehensive management plan [11].

The patient should avoid uncomfortable stressful positions and bad posture. In addition, regular exercise, good sleeping habits, and balanced meals are helpful in maintaining good health. The patient may also benefit from instruction in biofeedback and relaxation techniques.

Tasks for final control of eventual level

1. Physician's tactics in the detection of patients with acute coronary syndrome:
 - A. Immediate hospitalization in specialized intensive care unit of cardiology department.**
 - B. Confinement to bed and outpatient treatment.
 - C. Planned hospitalization in therapeutic department.
 - D. Tactics determined after routine examination of the patient.
 - E. Only patients with ECG changes are hospitalized.

2. Patient of 72 years old complained of severe pain in the right lower limb, inability to walk because of the pain. He was sick during 2 days. Physical examination: right lower extremity was cold by touch, pale skin, all kinds of sensitivity was reduced. No pulsation of arteries of the right lower limb, the left lower limb - weakened. Diagnosis: obliterate atherosclerosis of the lower extremities during 15 years. Your preliminary diagnosis is?
 - A. Acute ileofemoral venous thrombosis
 - B. Right-side Leriche syndrome;
 - C. Acute ileofemoral arterial thrombosis**
 - D. Ileofemoral abdominal aortic aneurysm.
 - E. Lymphostasis

3. The healthy man of 28 years felt acute pain in the left half of the chest, hypopnea, heart pain, palpitations, dry hoarse cough. Physical examination: acrocyanosis, restriction of respiratory excursions, percussion - left tympanic, auscultation - diminished breath sounds. What is most informative diagnostic method?
 - A. X-ray;**
 - B. Bronchoscopy;
 - C. Computer tomography;

- D. Angiography;
 - E. Plain radiography of the chest.
4. The family doctor was appealed to the 12 week's pregnant woman. She complains to stabbing abdominal pain, intensive uterine bleeding. Which doctor should be appealed?
- A. Hospitalized to the gynecological department;**
 - B. Call the obstetrician - gynecologist;
 - C. Hospitalized to the maternity hospital;
 - D. Hospitalized to the surgical department;
 - E. Haemostatic therapy.
5. The routine examination for every patient with suspected cervical spondylosis is
- A. Plain cervical radiography**
 - B. Computer tomography
 - C. MRI tomography
 - D. Ultrasound examination
 - E. Physical examination
6. The myofascial pain is termed as:
- A. Pain attributed to cervical nerves injuries
 - B. Pain attributed to muscle
 - C. Pain attributed to surrounding fascia of muscle
 - D. Pain attributed to muscle and its surrounding fascia**
 - E. Pain attributed to cervical trauma
7. Various neuromuscular, reproductive, gastrointestinal (GI), and urologic disorders may cause or contribute to chronic pain
- A. Various psychiatric disorders
 - B. Various surgical disorders

C. Various neuromuscular, reproductive, gastrointestinal (GI), and urologic disorders

D. Various neuromuscular disorders

E. Various neuromuscular and rheumatologic disorders

8. Pharmacotherapy of cervical spondylosis is the goal to reduce morbidity and prevent complications. It is including:

A. Corticosteroids, Muscle relaxants, injection

B. Nonsteroidal anti-inflammatory drugs

C. Nonsteroidal anti-inflammatory drugs, Corticosteroids, Muscle relaxants, Antidepressants

D. Nonsteroidal anti-inflammatory drugs and Corticosteroids

E. physical therapy, nonsteroidal anti-inflammatory drugs

9. NSAIDs may increase risk of serious events, such as:

A. risk of stroke

B. serious cardiovascular thrombotic events, myocardial infarction (MI), and stroke

C. risk of serious gastrointestinal adverse events, including bleeding, ulceration, gastric or intestinal perforation

D. risk of serious gastrointestinal adverse events, including gastric or intestinal perforation

E. all of mentioned above

10. Diagnostic criterion for chronic pain is the duration of pain:

A. 14 days

B. 1 month

C. 10 days

D. 1 year

E. 3 months

RECOMMENDED LITERATURE

A. Main

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