TABLE 85-10 Genes with Minor Alleles Shown to Contribute to Differences in Pain

GCH1	Tegeder et al 2006[130]
COMT (catechol-*O*-methyltransferase)	Zubieta et al 2003[121]
MC1R (melanocortin-1 receptor)	Mogil et al 2003[123]
TRPV1 (transient receptor potential cation channel, subfamily V, member 1)	Kim et al 2004[126]
TRPA1 (transient receptor potential cation channel, subfamily A, member 1)	Kim et al 2006[125]
OPRM1 (m-opioid receptor)	Fillingim et al 2005[127]
ORRD1 (d-opioid receptor)	Kim et al 2004[126]
FAAH (fatty-acid amide hydrolase)	Kim et al 2006[125]
$Na_V1.7$ (voltage-gated sodium channel 1.7)	Reiman et al 2010[128]

autonomic neuropathy (HSAN), which is distinguished by the presence of peripheral neuropathy. Two of five types are due to mutations in genes encoding the NGF β protein and the NGF receptor (TRKA).[120]

Gene association studies have identified several genes that may modulate pain. For example, polymorphisms in catechol-*O*-methyltransferase (COMT) have been found to be associated with pain on injection of hypertonic saline and in pain originating from the temporomandibular joint.[121,122] Other such studies have linked polymorphisms in the melanocortin-1 receptor (MCR1) to μ-opioid-induced analgesia[123] and in the κ-opioid receptor 1 (OPRM1) to morphine sensitivity (**Table 85-10**).[124-127] Given the known importance of $Na_V1.7$ in pain insensitivity and hypersensitivity, a search for polymorphisms in $Na_V1.7$ revealed an allele with a frequency of approximately 10% of that associated with increased pain perception, and Nav1.7 was found to impede sodium channel slow inactivation.[128] Such polymorphisms in $Na_V1.7$ may underlie common variation in pain thresholds.[129]

Other approaches have used animal models to identify genes. Utilizing single nucleotide polymorphism analysis, the enzyme guanosine triphosphate cyclohydrolase (GCH1) was found to be increased in peripheral sensory neurons following axonal injury in mice.[130] By investigating haplotypes in humans, researchers identified a pain protective haplotype (frequency 15.4%), for which homozygotes have reduced postsurgical pain and lower pain thresholds.

Another approach started with identifying mutant flies that exhibited thermal analgesia.[131] This screen identified the mouse equivalent of *CACNA2D3*, the α2δ3 calcium channel subunit. Intriguingly, this gene is very close to the α2δ1 subunit, the target of the neuropathic pain medications gabapentin and pregabalin. Knockout of the gene in mice yielded a robust reduction in thermal and inflammatory pain models. Finally, specific human polymorphisms in *CACNA2D3* associated with both acute and chronic pain reduction phenotypes in human cohorts.

A third strategy was based on examination of mouse strain-dependent differences in tactile hypersensitivity. A genomewide analysis led to identification of pore variants in the purinergic receptor P2XR7 that were responsible for differences in the pain assays.[132] Consistent with the importance of P2XR7, a pain protective P2XR7 haplotype was found in two separate human pain cohorts. A similar approach, but correlating mechanical allodynia in different strains with expression array profiles in DRG neurons, resulted in identification of the *Chrna6*, the nicotinic α6 subunit.[133] Haplotypes in this gene as well have been linked to human pain phenotypes in repeat cohorts.

HUMAN NOCICEPTORS

While much work has focused on animal models of human pain, an alternative is to try to work directly with human nociceptors. This strategy has the advantage of working directly with human tissue, potentially helping to overcome limits of animal models. Two types of approaches exist. Recent studies have obtained post-mortem primary human DRG neurons and have been able to characterize the physiology of the human nociceptors.[134] An alternative approach has taken advantage of stem cell technology to derive nociceptor neurons that recapitulate the functional assortment of nociceptor-specific receptors and channels, as well as sensitization to inflammatory mediators.[135]

CONCLUSION AND FUTURE DIRECTIONS

Nociception and pain perception are critical components of the nervous system that, when functioning properly, serve to protect an organism from injury. Multiple types of nociceptive inputs are processed through both segregated and convergent pathways, and are amplified and expanded during periods of prolonged pain. We now understand that chronic pain results from changes in gene expression and in neuronal and supporting cell architecture primarily within the central nervous system. Simply stated, chronic pain results from changes in the spinal cord and brain that promote both sensitization of the nociceptive system and the continued and augmented sensation of pain. Through better understanding of the precise molecular mechanisms of how chronic pain develops and the genetic factors that predispose particular individuals to pain, tantalizing new targets for analgesics have been identified. In the future, pain treatments will be tailored to the specific underlying mechanisms responsible for pain in particular diseases and in individual patients.

KEY REFERENCES

- Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell*. 2009;139(2):267-284.
- Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annu Rev Neurosci*. 2009;32:1-32.
- Perl ER. Ideas about pain, a historical view. *Nat Rev Neurosci*. 2007; 8(1):71-80.
- Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152(3 Suppl):S2-S15.

REFERENCES

Complete references are available online at www.LongneckerAnesthesiology.com.

CHAPTER 86

Common Pain Syndromes

Michael A. Fishman
Scott G. Pritzlaff
Jordan L. Newmark

KEY POINTS

1. Most common pain syndromes involve peripheral and central processes. Treatment should target both, in an interdisciplinary, biopsychosocial fashion.
2. Low back pain and neck pain are among the leading causes of disability worldwide. Accurate diagnosis and early, interdisciplinary treatment are critical for successful care.
3. Headache disorders rarely represent sinister intracranial pathology. The International Headache Society Guidelines can aid in the diagnosis of various headache disorders.
4. Treatment of many headache disorders entails preventive and abortive strategies. Sound preventive measures are important to optimize outcomes.
5. More than half of all cluster headache sufferers report suicidal ideation. Inquiring about suicidal ideation, contracting patients for safety, and referring them for mental healthcare is very important.

6. Giant cell arteritis should be promptly diagnosed and treated to prevent blindness.
7. Myofascial pain syndrome can occur primarily, or secondarily to another condition. The pathognomonic feature is the myofascial trigger point.
8. Peripheral nerve injury can result in mild to intractable pain due to compression, stretch injury, or transection. Lesion localization may lead to directed treatment with targeted nerve blocks, surgical release, and other measures.
9. Phantom sensation occurs in almost all amputees. Its incidence peaks approximately 1 month after amputation.
10. New American College of Rheumatology diagnostic criteria for fibromyalgia no longer require performance of a tender point count. It now includes somatic symptoms, in addition to widespread pain index symptom severity.
11. The main goals of the treatment for complex regional pain syndrome are analgesia, physical rehabilitation, functional recovery of the affected limb, and return to work.

INTRODUCTION TO COMMON PAIN SYNDROMES

In clinical practice, it is common to encounter patients with a variety of pain syndromes. Mechanistically, many common pain syndromes involve peripheral and central mechanisms, which are explained in detail in other chapters. Treatment often entails an interdisciplinary, biopsychosocial approach. This chapter will provide a concise, updated review of common pain conditions and their management.

BACK AND NECK PAIN

Low back pain is one of the most common symptoms that prompts patients to seek medical care and is the leading cause of disability both in the United States and worldwide.[1,2] The one-year prevalence of low back pain globally is estimated to be about 38%, with age-related prevalence increasing until the 60-65-year age group.[3] Direct and indirect costs associated with low back pain exceed $100 billion annually in the United States.[4]

Neck pain is the sixth leading cause of disability in the United States and the fourth most common globally.[2,5] The estimated one-year prevalence is approximately 25% overall and found to be higher in women, high-income countries, and urban areas.[6]

Pain emanating from the back or neck can be attributed to degeneration and/or inflammation of the neuraxial structures, including the bony spine and its articulations (facet joints, sacroiliac joints), intervertebral disks, ligaments, paraspinal musculature, and neural structures. A combination of etiologies is common and it may be difficult to delineate the pain generator. **Table 86-1** summarizes the most common etiologies of back and neck pain.[7]

Obtaining an adequate history and physical examination is crucial for reaching the correct diagnosis and implementing a successful treatment plan. Clinicians should be vigilant to look for "red flag" signs or symptoms, as these could suggest serious disease such as epidural infection, epidural hemorrhage, cauda equina syndrome, spinal cord compression, spine metastasis, and aortic aneurysm. **Table 86-2** summarizes some of these common warning signs. This chapter discusses only the more common back and neck pain syndromes.

DISKOGENIC PAIN

Diskogenic pain is believed to occur as a result of three main causes, including disk infection, torsion injury, and internal disk disruption (IDD).[8] For the purposes of this chapter, we will focus on the latter two mechanical pain generators. Torsion injury results from forced rotation of the zygapophyseal joint leading to tears in the disk.[8] IDD results from damage to the annular lamellae, dehydration of the nucleus pulposus, and resultant inflammation. In this setting, concomitant nociceptive nerve ingrowth into the disk is thought to cause decreased pain threshold (sensitization) to mechanical loading.[4]

Diagnosis Diagnosis of diskogenic pain is primarily clinical via the history and physical examination. Patients may report an inciting injury or event associated with a "popping" sensation in the back or neck. They report the pain as a deep axial ache that radiates to the shoulders and scapular areas (cervical disks) and to the buttocks and posterior thighs (lumbar disks). The pain is worsened by mechanical loading maneuvers such as sitting, standing, and particularly forward flexion. Predisposing factors include smoking, obesity, and occupational risk factors (prolonged sitting, repetitive lifting, or vibration exposure). Bending radiographs should be obtained to screen for other abnormalities, including spondylolisthesis, fracture, or other pathology. The severity of disc degeneration and/or annular tears can be seen on MRI or CT; however, these findings do not necessarily correlate with the patient's pain.[4,8] The gold standard diagnostic tool is *provocative diskography*, in which the intervertebral disk is percutaneously accessed with a needle under fluoroscopic guidance and then pressurized with a manometer in an attempt to reproduce the patient's pain complaint. However, the risk/benefit ratio of diskography has been called into question in several studies, due to a high false-positive rate, risk of infection, and accelerated disk degeneration.[4,8,9] As such, provocative diskography should be reserved to guide therapy in patients who are planning on surgical or other intervertebral intervention.

Treatment Treatment of diskogenic pain is initially conservative, followed by injections and ablative techniques. Refractory cases may require

TABLE 86-1 Common Causes of Back and Neck Pain

- Vertebral bodies
  - Fractures
  - Neoplastic lesions
    - Primary
    - Metastatic
  - Metabolic derangements
    - Osteoporosis
    - Paget disease
    - Osteitis fibrosa
    - Hyperthyroidism
    - Cushing syndrome
  - Infections
    - Osteomyelitis
- Intravertebral disks
  - Structural lesions
    - Degeneration and herniation
    - Chondromalacia
  - Infections
    - Diskitis
- Ligaments
  - Acute strain
  - Involvement with other conditions
- Muscle structures
  - Primary myofascial pain
  - Secondary myofascial pain
- Joints
  - Facets joints (zygapophysial or "Z" joints)
    - Osteoarthritis
    - Mechanical arthropathy
    - Synovial impingement
    - Meniscoid entrapment
- Sacroiliac joints
  - Mechanical arthropathy
    - Pregnancy
  - Degenerative and inflammatory
    - Osteoarthritis
    - Ankylosing spondylitis
    - Psoriatic arthritis
    - Reiter syndrome
    - Chronic inflammatory bowel disease
- Nerve roots (and dorsal root ganglia)
  - Compressive lesions
  - Neuroradiculopathies
- Meninges
  - Arachnoiditis
  - Scar tissue
- Epidural space
  - Hematoma
  - Infection (abscess)
- Multifactorial
  - Structural
    - Spine instability
    - Kyphosis
    - Scoliosis
    - Spondylolithiasis
  - Degenerative
    - Spinal stenosis
    - Spondylosis
    - Trauma
    - Infection
  - Psychosocial
  - Referred pain

TABLE 86-2 Red Flag/Warning Signs of Neck and Back Pain

Age > 50 years	Progressive neurological deficit
Recent trauma	Refractory pain despite
Fever	History of malignancy
Unexplained weight loss	History of chronic steroid use
Saddle anesthesia	Substance abuse
Urinary/bowel dysfunction	

therapy. Conservative therapy includes physical therapy, weight reduction, and NSAIDs. A systematic review of interventional management of diskogenic back pain found few high-quality studies evaluating interventions, including intradiscal methylene blue injection, steroid injection, ramus communicans ablation, intradiskal electrothermal therapy, and biaculoplasty.[4] Overall, these modalities were found to be superior to sham, but long-term outcomes studies are lacking. A meta-analysis of five randomized controlled trials (RCTs) comparing lumbar fusion versus conservative management found a moderate, nonsignificant benefit for the fusion group in terms of functional outcomes at 1 and 2 years of follow-up.[10] Further prospective studies for interventional and surgical treatment of diskogenic pain are needed.

RADICULAR PAIN

Radicular pain originates as a result of irritation of a nerve root due to a herniated nucleus pulposus or degenerative neuroforaminal narrowing. The most commonly affected levels in the lower back are L4-L5 and L5-S1 and C5-C6 and C6-7 in the neck, although any level can be involved.

Diagnosis Diagnosis begins with history and physical exam. Patients may report sensory and/or motor disturbances that are typically unilateral, but may be bilateral. Physical examination typically reveals decreased sensation, weakness, and/or diminished reflexes in the appropriate nerve distribution(s). Neural tension testing by straight leg raise or femoral stretch testing is positive when pain and paresthesias are reproduced in the patient's typical dermatomal distribution. MR imaging provides information on the corresponding anatomy and can help guide intervention. EMG/NCS can also confirm the diagnosis as well as the chronicity and severity of the injury.

Treatment Treatment of radicular pain is typically conservative, with physical therapy, NSAIDs, and antineuropathic agents such as gabapentinoids and/or TCAs. Epidural steroid injections have been shown to provide short-term pain relief in patients with acute radicular pain.[11] Multiple approaches to deliver epidural steroids have been described, and the transforaminal or parasagittal interlaminar approaches may have some advantage over the interlaminar approach.[12,13] No validated predictors of response to epidural steroid injections exist. A recent study by McCormick et al reported that greater baseline pain, lack of worsening pain with walking, and a positive femoral stretch test predicted a greater likelihood of pain reduction with transforaminal epidural steroid for lumbosacral radicular pain within 1-4 weeks.[14] Surgical intervention may be required for refractory pain, especially if neurologic deficits are present. Microdiskectomy is the gold standard treatment for uncomplicated herniated nucleus pulposus.

SPINAL STENOSIS

Spinal stenosis results from narrowing of the central canal, lateral recesses, or neural foramina due to age-related degenerative changes, including osteophyte formation, facet hypertrophy, ligamentum flavum hypertrophy, and diffuse broad-based disk bulge. Its occurrence in the cervical spine is referred to as *cervical spondylosis*. Anatomical and radiographic definitions do not correlate to the presence or severity of symptoms. Stenosis in the cervical or thoracic regions can cause nerve root and/or spinal cord compression, resulting in axial, radicular, and/or myelopathic pain and sensorimotor compromise.[15]

Diagnosis There is no gold standard diagnostic tool for spinal stenosis, and as such the diagnosis is based on correlation of the history and physical examination with diagnostic imaging.[16] Patients typically present with insidious onset of neurogenic claudication, reported as numbness, weakness, and pain radiating from the axial spine to the buttocks and legs (lumbar stenosis) or periscapular areas and arms (cervical stenosis). Prolonged standing or walking typically exacerbates the pain in lumbar stenosis, which is typically described as radiating leg or thigh pain.[16] Classically, patients note symptomatic improvement with sitting or with forward flexion ("shopping cart" sign), as this increases the anteroposterior diameter of the central canal. Cervical stenosis patients report loss of fine motor control (ie, difficulty in picking up a coin), frequent falls, a wide-based stance, and gait incoordination.[15] Magnetic resonance imaging (MRI) provides accurate information regarding the bony and soft tissue contributions to canal stenosis, as well as intrinsic cord pathology.[15] It behooves the clinician to rule out other causes of these symptoms, including peripheral neuropathy, vascular claudication, and neoplasms, as well as hip pathology.

Treatment Treatment of spinal stenosis should begin with conservative measures, including physical therapy, NSAIDs, and antineuropathic agents. Epidural steroid injections have been shown to provide little if any benefit in a recent multicenter RCT;[17] however, some notable pain physicians have called the results of this trial into question.[18] Current evidence for functional improvements in terms of increased walking ability is limited for both surgical and nonsurgical treatment.[19] Surgical intervention should be reserved for cases with rapid neurologic progression, cervical myelopathy, or cauda equina syndrome, or in patients who have failed nonoperative management.

FACET ARTHROPATHY

The facet, or zygapophyseal, joints are true synovial joints whose main function is to limit rotation and resist compression during lordosis. Facet joint pain results from conditions that increase the load on them, such as arthritis, decreased disk space, and increased lordosis (as in obesity). The medial branch of the dorsal ramus from the level above and the same level innervate the facet joints. These medial branches also contribute to overlapping innervation of the multifidus muscle. It is estimated that the facet joints can be implicated as the pain generator in low back pain in 15-45% of cases.[20]

Diagnosis Diagnosis of facet joint pain should be suspected in patients presenting gradual-onset, axial low back pain without radicular symptoms. However, patients may report referred pain to the paraspinal, gluteal, and thigh regions. Physical examination reveals ipsilateral reproduction of pain with hyperextension and lateral rotation of the spine, dubbed "facet-loading maneuvers." Neural tension signs should not be present. If obtained, imaging is notable for arthritic hypertrophy of the facet joints, loss of the joint space, and edema of the joint. Diagnostic blocks of the aforementioned medial branches are positive if the familiar pain is relieved during the local anesthetic phase.

Treatment Treatment is initially conservative, and consists of oral analgesics, weight loss, and physical therapy. There is good evidence that radiofrequency ablation of the medial branches results in short- and long-term relief of back and neck pain originating from the facet joints.[21]

SACROILIAC ARTHROPATHY

The sacroiliac joint connects the sacrum to the iliac bones. It is subject to degenerative and inflammatory arthritides as well as mechanical dysfunction.

Diagnosis The history may reveal a precipitating injury, such as a fall, lifting a heavy object, or turning. The pain is a unilateral ache that radiates to the buttock, groin, and thigh areas. It rarely goes below the knee. The pain is worsened by loading the joint, as occurs during prolonged sitting, standing, or bending. There is tenderness over the joint area, and the pain typically is reproduced by the FABER (flexion, abduction, and external rotation of the hip) test. Intraarticular local anesthetic block can help confirm the diagnosis.

Treatment Treatment with NSAIDs and physical therapy can be helpful. Fluoroscopy-guided intraarticular steroid injection has been the mainstay of treatment in clinical practice. Lateral branch blocks as well as cooled and conventional radiofrequency ablation of the lateral branches have been reported useful.[21]

HEADACHE AND OROFACIAL PAIN DISORDERS

Headache disorders are among the most common pain disorders throughout the world. The 2010 *Global Burden of Disease Survey* revealed that for tension headache and migraine alone, the global proportion of population prevalence was approximately 21% and 15%, respectively.[22] This translated to the second and third most prevalent medical disorders worldwide.[22] Furthermore, migraine was found to be the eighth leading cause of years lived with disability worldwide.[22] The reader is referred to **Figure 86-1** for the global ranking and causes of years living in disability.

Ranking legend
1–10 11–20 21–30
31–50 51–90 91–176

Cause	Global	High-income Asia Pacific	Western Europe	Australasia	High-income North America	Central Europe	Southern Latin America	Eastern Europe	East Asia	Tropical Latin America	Central Latin America	Southeast Asia	Central Asia	Andean Latin America	North Africa and Middle East	Caribbean	South Asia	Oceania	Southern sub-Saharan Africa	Eastern sub-Saharan Africa	Central sub-Saharan Africa	Western sub-Saharan Africa
Low back pain	1	1	1	1	1	1	1	1	1	1	2	2	2	2	1	4	1	2	4	3	3	2
Major depressive disorder	2	4	2	2	2	2	2	2	2	2	1	1	1	1	2	2	3	1	2	2	2	3
Iron-deficiency anemia	3	26	48	22	88	14	11	10	15	6	6	3	3	3	3	3	2	3	3	1	1	1
Neck pain	4	3	4	3	4	4	3	3	3	3	3	6	5	5	6	8	7	8	6	6	7	5
Chronic obstructive pulmonary disease	5	21	9	10	6	10	8	11	8	12	18	4	8	10	8	16	4	9	5	5	5	7
Other musculoskeletal disorders	6	2	5	4	3	5	4	4	4	8	4	8	7	6	7	12	8	10	8	9	10	11
Anxiety disorders	7	8	6	6	5	6	5	12	12	4	5	7	4	4	4	6	6	7	7	4	6	9
Migraine	8	11	8	8	15	8	13	8	17	7	8	5	6	8	11	10	5	12	10	25	12	8
Diabetes mellitus	9	7	7	11	8	7	12	5	5	13	7	12	9	17	5	5	11	4	18	27	29	23
Falls	10	5	3	5	12	3	7	9	7	16	21	11	11	16	12	11	12	15	20	26	24	26
Osteoarthritis	11	6	13	15	10	9	14	7	6	11	10	17	12	12	10	14	19	14	17	19	26	20
Drug use disorders	12	12	11	9	7	16	6	17	18	9	11	10	14	11	9	13	9	16	12	16	21	21
Other hearing loss	13	13	18	19	20	12	15	14	11	15	15	9	15	14	17	18	10	19	14	10	18	13
Asthma	14	15	12	7	11	21	10	25	39	5	12	18	21	7	13	9	15	11	9	8	8	12
Alcohol use disorders	15	16	17	17	16	18	9	6	9	10	16	20	10	9	35	17	14	13	11	30	33	40
Schizophrenia	16	17	21	13	9	13	16	16	10	14	13	13	16	15	15	19	17	18	16	21	23	19
Road injury	17	19	14	14	27	11	19	15	13	22	22	15	13	19	14	15	13	17	21	24	22	25
Bipolar affective disorder	18	20	19	20	19	19	17	19	14	17	14	16	17	18	16	20	16	20	19	18	25	22
Dysthymia	19	22	20	21	21	20	20	20	16	20	19	19	19	22	19	22	20	23	22	20	31	27
Epilepsy	20	32	33	44	32	25	23	28	31	18	9	21	20	13	20	25	26	24	15	13	17	14
Ischaemic heart disease	21	18	15	18	17	15	22	13	19	21	25	28	18	31	22	27	31	29	34	41	48	37
Eczema	22	24	26	23	25	22	24	24	22	23	17	23	22	20	21	21	22	22	23	17	20	24
Diarrhoeal diseases	23	30	31	31	29	41	27	37	24	25	20	24	25	21	18	23	23	25	25	14	14	15
Alzheimer's disease and other dementias	24	10	10	12	14	17	18	18	26	28	31	40	30	33	41	30	50	69	48	64	67	64
Benign prostatic hyperplasia	25	9	16	16	13	23	25	29	20	31	36	34	42	36	29	36	45	51	47	61	56	57
Tuberculosis	26	38	83	93	102	56	56	34	42	42	56	14	24	27	24	24	18	6	13	22	16	32
Neonatal encephalopathy*	27	62	66	58	55	44	45	45	29	29	30	30	29	30	31	37	24	30	28	15	27	18
Other vision loss	28	27	22	25	26	27	26	27	33	19	24	26	26	23	26	26	34	26	26	34	39	45
Refraction and accommodation disorders	29	74	60	68	75	24	63	21	37	64	51	32	32	41	28	60	21	36	39	35	37	35
Conduct disorder	30	39	42	38	37	38	32	44	30	27	23	31	27	24	25	32	29	27	30	23	30	29
Periodontal disease	31	31	29	26	35	28	21	23	23	24	27	29	28	28	38	46	40	73	45	33	47	50
Cataracts	32	60	46	67	65	30	52	32	49	49	35	25	40	26	33	44	25	52	58	51	66	52
Thalassaemias	33	41	36	37	46	40	47	48	28	38	50	22	33	54	27	68	32	28	42	49	72	51
Dental caries	34	64	59	71	67	29	50	33	25	37	34	33	31	34	32	40	28	34	32	38	38	36
Edentulism	35	28	27	27	28	26	28	22	41	26	33	45	35	29	36	31	37	59	44	55	57	68
HIV/AIDS	36	131	76	89	50	99	62	31	88	61	52	56	76	68	95	34	55	33	1	11	19	16
Cerebrovascular disease	38	14	23	29	18	34	38	26	27	41	53	42	49	64	68	43	61	70	78	94	85	82
Chronic kidney diseases	39	25	25	30	23	33	30	39	38	32	26	37	47	44	46	54	63	66	62	71	74	71
Malaria	41	154	152	146	147	152	158	149	148	101	116	44	158	111	94	93	57	21	74	12	4	4
Iodine deficiency	42	66	45	53	82	37	79	36	59	56	73	51	23	56	23	38	33	31	24	29	15	38
Rheumatoid arthritis	43	23	24	24	24	31	31	35	45	34	40	58	37	38	53	42	58	62	54	63	63	61
Sickle cell disorders	45	51	32	66	22	80	78	100	114	30	29	123	93	81	50	28	52	101	94	44	9	10
Hookworm disease	49	141	163	159	161	162	76	163	32	40	28	27	133	63	89	63	46	5	29	40	34	49
Schistosomiasis	52	163	163	159	161	162	167	163	122	82	152	147	167	169	54	98	171	167	27	7	11	6
Lymphatic filariasis	53	163	163	159	161	162	167	163	171	136	162	62	167	169	128	147	27	63	79	31	58	17
Exposure to forces of nature	62	86	79	77	79	60	65	30	67	76	74	66	59	55	55	1	73	65	68	72	69	66
Food-borne trematodiases	70	69	153	159	161	162	167	137	21	171	170	64	148	25	102	169	163	167	170	154	172	173
Adverse effects of medical treatment	79	63	65	59	53	76	60	41	82	97	86	85	86	83	76	7	91	89	88	93	91	89
Onchocerciasis	97	163	163	159	161	162	167	163	171	171	170	170	167	169	171	169	171	167	170	58	13	43

FIGURE 86-1. Leading causes of years lived with disability. (*Source: Global Burden of Disease Survey* 2010.[22])

The International Headache Society (IHS), in preparation for the World Health Organization's (WHO) 11th edition of the *International Classification of Diseases* (ICD-11), has recently released its 3rd edition (beta version) of the *International Classification of Headache Disorders* (ICHD-3β).[23] The ICHD-3β is a very valuable resource for diagnosing various headache disorders and will be utilized for the discussion of specific headache conditions below. The reader is referred to **Table 86-3** for a structured classification of headache disorders.

Clinically, patients may present with concerns surrounding the possibility of intracranial disease, such as tumors. However, this actually occurs in only a very small percentage of cases, approximately 0.5%.[24] A thorough history and physical exam should always be conducted, with attention to sinister signs and/or symptoms that could represent a life-threatening pathology. For example, patients with a stable headache disorder presenting with an acute change in their symptoms, along with neck pain, stiffness and fever, may need to be worked up for meningitis with a lumbar puncture (LP) and/or neuroimaging. In the absence of sinister signs and/or symptoms, CT or MRI typically is not necessary, unless a change in headache pattern occurs, or the patient experiences changes in neurologic status (eg, seizures, focal neurologic signs).[25]

TABLE 86-3 Headache Classification

Primary headaches
Migraine
Tension-type headache
Trigeminal autonomic cephalalgias
Other primary headache disorders
Secondary headaches
Headache attributed to trauma or injury to the head and/or neck
Headache attributed to cranial or cervical vascular disorder
Headache attributed to nonvascular intracranial disorder
Headache attributed to a substance or withdrawal from it
Headache attributed to infection
Headache attributed to disorder of homeostasis
Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure
Headache attributed to psychiatric disorder
Painful cranial neuropathies, other facial pains and other headaches
Painful cranial neuropathies and other facial pains
Other headache disorders

Source: Adopted from ICHD-3β[2]

COMMON PRIMARY HEADACHES

Migraine Migraine headache is divided into two major subtypes: migraine without aura and migraine with aura. Although each will be discussed separately, both share overlapping features. Furthermore, it is common for patients to report a family history of migraine and should be asked during the clinical interview.

Migraine without Aura Migraine headache presents with episodes lasting 4-72 hours. It is described as unilateral and pulsating with a moderate to severe intensity, and is often provoked by physical activity. Important features are the presence of nausea with or without vomiting, as well as possible photophobia and phonophobia. Less commonly, migraine episodes can present with cutaneous allodynia, cranial autonomic symptoms, or a temporal relationship with menstruation. **Table 86-4** outlines the ICHD-3β diagnostic criteria.[23] Numerous mechanisms are being actively investigated, including the role of cortical spreading depression and other cortically based processes, balance of neurotransmitter and receptor systems such as the 5-hydroxytryptamine (5-HT) system, and pain circuitry sensitization.[23]

TABLE 86-4 Migraine without Aura (ICHD-3β Diagnostic Criteria)

Diagnostic criteria:

A. At least five attacks[1] fulfilling criteria B–D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)[2,3]
C. Headache has at least two of the following four characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. One or a few migraine attacks may be difficult to distinguish from symptomatic migraine-like attacks. Furthermore, the nature of a single or a few attacks may be difficult to understand. Therefore, at least five attacks are required. Individuals who otherwise meet criteria for 1.1 *Migraine without aura* but have had fewer than five attacks, should be coded 1.5.1 *Probable migraine without aura*.
2. When the patient falls asleep during a migraine attack and wakes up without it, duration of the attack is reckoned until the time of awakening.
3. In children and adolescents (aged under 18 years), attacks may last 2-72 hours (the evidence for untreated durations of less than 2 hours in children has not been substantiated).

TABLE 86-5 Migraine with Aura (ICHD-3β Diagnostic Criteria[23])

Description:

Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
   1. Visual
   2. Sensory
   3. Speech and/or language
   4. Motor
   5. Brainstem
   6. Retinal
C. At least two of the following four characteristics:
   1. At least one aura symptoms spreads gradually over ≥ 5 minutes, and/or two or more symptoms occur in succession.
   2. Each individual aura symptoms lasts 5-60 minutes[1]
   3. At least one aura symptoms is unilateral[2]
   4. The aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

Notes:

1. When, for example, three symptoms occur during an aura, the acceptable maximal duration is 3x60 minutes. Motor symptoms may last up to 72 hours.
2. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

Migraine with Aura Migraine headaches with an aura component are noted to present with recurrent, short lived (eg, minutes), focal neurological symptoms that usually occur before, or occasionally during, a painful migraine episode. Over 90% of auras are visual in nature. Less common auras include perceived unilateral sensory changes, speech disturbance, or motor weakness. **Table 86-5** outlines the ICHD-3β diagnostic criteria.[23] Mechanistically, it is currently assumed that cortical spreading depression, likely secondary to decreases in local cerebral blood flow, plays an important role.

Migraine Complications A number of complications may potentially occur secondary to a migraine headache disorders. The reader is referred to **Table 86-6** for a list of such complications.

Migraine Treatment Treatment is often divided into preventive strategies to reduce the number of headache days as well as symptom severity, and abortive therapy to treat acute attacks. Interdisciplinary treatment encompassing medication optimization, lifestyle modification, patient education, and pain psychology is the ideal treatment paradigm. **Table 86-7** (see also **Figure 86-2**) outlines various treatment modalities.

TENSION-TYPE HEADACHE

Tension-type headache (TTH) is a very commonly encountered primary headache disorder. According to the ICHD-3β, the lifetime prevalence

TABLE 86-6 Migraine Headache Complications

Status migrainosus—debilitating episode lasting >72 hours
Persistent aura without infarction—aura lasting ~1 week with negative neuroimaging
Migrainous infarction—aura associated with ischemic brain lesion in relevant region by neuroimaging
Migraine aura-triggered seizure—seizure provoked by migraine with aura

TABLE 86-7 Migraine Headache Treatment Strategies

Preventive strategies

Medications—antiepileptics (eg, topirmate), calcium channel blockers (eg, verapamil), β-blockers (eg, propranolol), tricyclic antidepressants (eg, nortriptyline), gabapentinoids (eg, gabapentin)

Interventions—onabotulinumtoxin A via phase III research

Evaluating Migraine Prophylaxis Therapy (PREEMPT) *protocol*[26, 27]—see Figure 86-2 for location of injection sites

Lifestyle—avoidance of triggers, regularly scheduled sleeping, mealtimes, and daily cardiovascular exercise[28]

Patient education[29]

Pain psychology (eg, biofeedback)

Abortive strategies

Medications—triptans (eg, rizatriptan), NSAIDs (eg, diclofenac powdered solution),[30] corticosteroids (eg, dexamethasone),[31] ergot alkaloids (eg, dihydroergotamine), opioids (eg, hydromorphone)[a]

[a]Opioids should be used with caution, as chronic utilization may lead to tolerance, dependence, and/or medication overuse headaches.

TABLE 86-8 ICHD-3β TTH Diagnostic Criteria[23, 32]

Tension-type headache has three key forms:

1. Infrequent episodic: at least 10 episodes occurring on <1 day per month
2. Frequent episodic: at least 10 episodes occurring on ≥1 day but <15 days per month for equal to or more than 3 months
3. Chronic: headache occurring on ≥15 days per month for more than 3 months

Tension-type headache must have each of the following characteristics:

A. At least 10 attacks fulfilling criteria B–E

B. Headaches lasting from 30 min to 7 days (for infrequent and frequent ETTH only) or from hours to continuous (for CTTH only)

C. At least 2 of the following 4 characteristics:
   1. Bilateral location
   2. Pressing or tightening (non-pulsating) quality
   3. Mild or moderate intensity
   4. Not aggravated by routine physical activity

D. Both of the following characteristics:
   1. No nausea or vomiting[a]
   2. No more than one of photophobia or phonophobia

E. Not attributed to another disorder

CTTH chronic tension-type headache, *ETTH* episodic tension-type headache

[a]The diagnostic criteria for CTTH allow for no more than one of the three features of mild nausea, photophobia or phonophobia

of TTH ranges from approximately 30-78%, depending on the study.[23] The exact etiological factors and mechanisms surrounding TTH are still under active investigation; however, a combination of peripheral and central pain mechanisms likely play a key role. Pericranial tenderness induced by palpation is a hallmark feature of TTH, especially over the frontal, temporal and masseter muscles, among others. According to prior ICHD versions, it may be difficult to distinguish TTH from mild migraine without aura. In response to this, the ICHD-3β diagnostic criteria has been updated to include several TTH subtypes, with stricter criteria to allow for higher-quality research in this domain. **Table 86-8** outlines the TTH diagnostic criteria. **Table 86-9** summarizes treatment for TTH.

The following types of headache are TTH subtypes:[23]

- Infrequent episodic tension-type headache
- Frequent episodic tension-type headache
- Chronic tension-type headache
- Probable tension-type headache

TRIGEMINAL AUTONOMIC CEPHALALGIAS

Trigeminal autonomic cephalalgias (TACs) represent a family of headache disorders that are typically unilateral in nature, and associated with ipsilateral trigeminal parasympathetic, and secondary cranial sympathetic activation. Here, common subtypes will be discussed separately. **Table 86-10** presents the family of TAC subtypes.

Cluster Headache Cluster headaches are located in unilateral, periorbital regions and are of severe pain intensity. Ipsilateral, autonomic findings are present during episodes.

Episodes last 15-180 minutes, occurring as often as 8 times per day, or as infrequently as 1 every 48 hours. Patients may experience *cluster periods* where these headaches occur more frequently from weeks to months, followed by a remission period of months to years. Demographically, patients are generally 20-40 years of age, and men are affected 3 times as often as women.[23] Furthermore, a large number of cluster headache sufferers report a history of smoking tobacco.[35] The effect of smoking cessation on cluster headache is controversial.[35] Alcohol is a well-described trigger for cluster headache and should be avoided, especially during cluster periods.[35]

An important aspect of cluster headache is its link to suicidal ideation (SI). More than half of those with cluster headache report SI,

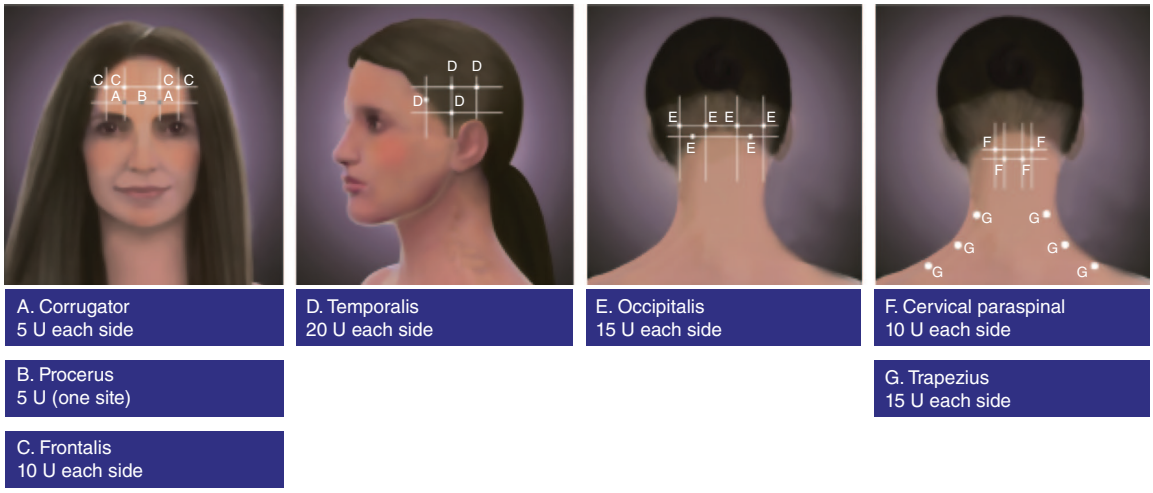

FIGURE 86-2. Location of injection sites for the PREEMPT protocol.[27]

TABLE 86-9 TTH Treatment Modalities

Acute treatment
NSAIDs[32]
Aspirin[32]
Acetaminophen[32]
Caffeine, in moderation[32]
Prophylactic treatment
Tricyclic antidepressants[32, 33]
Mirtazapine[33]
Tizanidine[32]
Nonpharmacologic treatment
Trigger-point injections[34]
Manual therapy[33]
Biofeedback[32, 33]
Cognitive behavioral therapy[33]
Acupuncture[33]
Transcutaneous electrical nerve stimulation (TENS)[33]

while about half engage in self-harm during episodes.[35] Asking patients with cluster headache about SI, obtaining a safety contract, and referring them for mental healthcare is an important management strategy. **Table 86-11** outlines the ICHD-3β diagnostic criteria for cluster headache.[23] **Table 86-12** presents treatment modalities.

Indomethacin-Responsive TACs Paroxysmal hemicrania and hemicrania continua are primary headaches within the TAC family that are "absolutely responsive" to indomethacin treatment. Therefore, symptom resolution with indomethacin provides important diagnostic information for both the patient and the treating physician. The ICHD-3β diagnostic criteria for paroxysmal hemicrania and hemicrania continua are provided in **Tables 86-13 and 86-14**, respectively.[23]

COMMON SECONDARY HEADACHES

Headache Attributed to Low-Cerebrospinal-Fluid (CSF) Pressure Low-CSF-pressure headaches are commonly encountered by the practicing anesthesiologist, especially in the context of CSF leakage after neuraxial procedures. Low-CSF-pressure headaches are often orthostatic in nature, and can present with a number of other symptoms including neck pain, nausea, dizziness, or tinnitus/hearing changes. Symptoms are generally worse while in the upright position, and improved when laying horizontal. The ICHD-3β diagnostic criteria are provided in **Table 86-15**.

Postdural puncture headache (PDPH) represents a subset of low-CSF-pressure headaches. PDPHs occur within 5 days of a neuraxial procedure, during which time the dura mater was either intentionally or accidently punctured, leading to leakage of CSF from the dural sac. Symptoms are similar to that of low CSF pressure headache. According to the ICHD-3β, independent risk factors for PDPH include female gender, age 31-50 years, previous history of PDPH, and needle orientation with the bevel perpendicular to the neuraxial structures.[23]

Both CSF fistula headache and headache attributed to spontaneous intracranial hypotension are additional subsets of low-CSF-pressure headaches. These also present in a similar fashion, and mechanistically share the same pathophysiology. Additionally, there is growing evidence that mixed connective tissue diseases may be correlated with spontaneous intracranial hypotension, perhaps due tissue friability or poor tissue

TABLE 86-10 ICHD-3β TAC Subtypes[23]

Cluster headache
Paroxysmal hemicrania
Short-lasting unilateral neuralgiform headache attacks
Hemicrania continua
Probable trigeminal autonomic cephalalgia

TABLE 86-11 ICHD-3β Diagnostic Criteria for Cluster Headache[23]

Diagnostic criteria:

A. At least five attacks fulfilling criteria B–D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal plan lasting 15–180 minutes (when untreated)[1]
C. Either or both of the following:
   1. At least one of the following symptoms or signs, ipsilateral to the headache:
      a) Conjunctival injection and/or lacrimation
      b) Nasal congestion and/or rhinorrhoea
      c) Eyelid oedema
      d) Forehead and facial sweating
      e) Forehead and facial flushing
      f) Sensation of fullness in the ear
      g) Miosis and/or ptosis
   2. A sense of restlessness or agitation
D. Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active
E. Not better accounted for by another ICHD-3 diagnosis.

Note:

1. During part (but less than half) of the time-course of 3.1 *Cluster headache*, attacks may be less severe and/or of shorter or longer duration.

TABLE 86-12 Treatment for Cluster Headache

Acute treatment
Oxygen 7-12 L/minute;[36] increase to 15 L/minute if no response
Triptans: zolmitriptan intranasal, sumatriptan intranasal or subcutaneous[37]
Intranasal lidocaine, 1 cm^3
Preventive treatment
Verapamil,[38] methysergide,[38] lithium,[38] glucocorticoids[39,40]
Avoidance of alcohol during cluster periods
Considering smoking cessation
Suicidal ideation (SI) and patient safety
Ask about SI and harm to self; obtain safety contract and provide referral to mental health provider

TABLE 86-13 ICHD-3β Diagnostic Criteria for Paroxysmal Hemicrania[23]

Diagnostic criteria:

A. At least 20 attacks fulfilling criteria B-E
B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 2-30 minutes
C. At least one of the following symptoms or signs, ipsilateral to the pain:
   1. Conjunctival injection and/or lacrimation
   2. Nasal congestion and/or rhinorrhoea
   3. Eyelid oedeme
   4. Forehead and facial sweating
   5. Forehead and facial flushing
   6. Sensation of fullness in the ear
   7. Miosis and/or ptosis
D. Attacks have a frequency above five per day for more than half of the time
E. Attacks are prevented absolutely by therapeutic doses of indomethacin[1]
F. Not better accounted for by another ICHD-3 diagnosis.

Note:

1. In an adult, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased if necessary up to 225 mg daily. The dose by injection is 100-200 mg. Smaller maintenance doses are often employed.

TABLE 86-14 ICHD-3β Diagnostic Criteria for Hemicrania Continua[23]

Diagnostic criteria:

A. Unilateral headache fulfilling criteria B-D
B. Present for > 3 months, with exacerbations of moderate or greater intensity.
C. Either or both of the following:
   1. At least one of the following symptoms or signs, ipsilateral to the headache:
      a) Conjunctival injection and/or lacrimation
      b) Nasal congestion and/or rhinorrhoea
      c) Eyelid oedeme
      d) Forehead and facial sweating
      e) Forehead and facial flushing
      f) Sensation of fullness in the ear
      g) Miosis and/or ptosis
   2. A sense of restlessness or agitation, or aggravation of the pain by movement
D. Responds absolutely to therapeutic doses of indomethacin[1]
E. Not better accounted for by another ICHD-3 diagnosis.

Note:

1. In an adult, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased if necessary up to 225 mg daily. The dose by injection is 100-200 mg. Smaller maintenance doses are often employed.

healing.[41, 42] **Table 86-16** outlines diagnostic and treatment modalities to be considered for low-CSF-pressure headaches.

Severe cases of low- CSF pressure headache can lead to changes in mental status, obtundation, subdural hematoma, and death. Aggressive management of these cases should be pursued to prevent these complications.

The practicing anesthesiologist is often consulted in cases of low-CSF-pressure headache for autologous epidural blood patch placement. Although rare, it should be noted that unrecognized injection of whole blood into the intrathecal space during epidural blood patch placement may lead to complications such as arachnoiditis.[44,45] Epidural blood patch placement with fluoroscopic guidance and use of contrast agents demonstrating needle placement in the epidural space may help prevent intrathecal injection of blood, and should be considered.

Medication Overuse Headache Medication overuse headache (MOH) is a headache condition commonly encountered by clinicians. It is estimated that 1-3% of the general population suffers from MOH.[46] It is often unclear whether overuse of medication is the primary or secondary cause of the condition. The ICHD-3β subtypes are as follows:

- Ergotamine-overuse headache
- Triptan-overuse headache
- Simple analgesic–overuse headache; acetaminophen, nonsteroidal anti-inflammatory
- Opioid-overuse headache
- Combination analgesic-overuse headache
- Medication-overuse headache attributed to multiple drug classes not individually overused
- Medication-overuse headache attributed to unverified overuse of multiple drug classes
- Medication-overuse headache attributed to other medication

Table 86-I7 outlines the ICHD-3β diagnostic criteria for MOH.[23]

TABLE 86-15 ICHD-3β Criteria for Low-CSF-Pressure Headache[23]

Diagnostic criteria:

A. Any headache fulfilling criterion C
B. Low CSF pressure (< 60 mm CSF) and/or evidence of CSF leakage on imaging
C. Headache has developed in temporal relation to the low CSF pressure or CSF leakage, or led to its discovery
D. Not better accounted for by another ICHD-3 diagnosis.

TABLE 86-16 Diagnostic and Treatment Modalities for Low-CSF-Pressure Headaches[43]

Diagnostic tests
Brain MRI
Lumbar puncture with opening pressure measurement
Myelography
Cisternography
Treatment modalities
Expectant management and reassurance for 5 days[23]
Medications: tylenol, caffeine, butalbital, opioids
Liberal IV and/or PO hydration
Autologous epidural blood patch
Intrathecal saline infusion
Surgical repair of dural sac

Management of MOH entails discontinuation of acute or abortive medication, and considering the addition of a preventative agent, such as topiramate.[46] However, further research is needed to determine the optimal approach.[46]

COMMON CRANIAL NEUROPATHIES

Trigeminal Neuralgia (TGN) The trigeminal nerve, which is the fifth cranial nerve (CNV), arises from the pons and segments into three major sensory branches: ophthalmic (V1), maxillary (V2), and mandibular (V3). These three branches converge proximally at the Gasserian ganglion. Understanding the structure of the trigeminal nerve is important for diagnosing and treating facial pain conditions related to the trigeminal system.

Trigeminal neuralgia is a common facial pain disorder that presents with unilateral, episodic attacks of pain that are described as electrical in nature, and located over one or more divisions of the trigeminal nerve. Episodes may be induced by nonpainful stimuli. Occasionally, there is a moderately intense, constant pain between episodes. In some cases, autonomic symptoms such as ipsilateral eye lacrimation or injection of the sclera may be present. Episodic symptoms are likely caused by compression of the trigeminal complex by an arterial vessel, while persistent symptoms may be caused by central sensitization.[23] An MRI should be

TABLE 86-17 ICHD-3β Diagnostic Criteria for MOH

Diagnostic criteria:

A. Headache occurring on ≥ 15 days per month in a patient with a pre-existing headache disorder
B. Regular overuse for > 3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache[1]
C. Not better accounted for by another ICHD-3 diagnosis.

Note:

1. Patients should be coded for one or more subtypes of 8.2 *Medication-overuse headache* according to the specific medication(s) overused and the criteria for each below. For example, a patient who fulfils the criteria for 8.2.2 *Tripton-overuse headache* and the criteria for one of the subforms of 8.2.3 *Simple analgesic-overuse headache* should receive both these codes. The exception occurs when patients overuse combination-analgesic medications, who are coded 8.2.5 *Combination-analgesic-overuse headache* and not according to each constituent of the combination-analgesic medication.

   Patients who use multiple drugs for acute or symptomatic treatment of headache may do so in a manner that constitutes overuse even though no individual drug or class of drug is overused; such patients should be coded 8.2.6 *Medication-overuse headache attributed to multiple drug classes not individually overused*.

   Patients who are clearly overusing multiple drugs for acute or symptomatic treatment of headache but cannot give an adequate account of their names and/or quantities are coded 8.2.7 *Medication-overuse headache attributed to unverified overuse of multiple drug classes* until better information is available. In almost all cases, this neccessitates diary follow-up.

TABLE 86-18 Interventional Procedures for Trigeminal Neuralgia

Fluoroscopic guided Gasserian[a] or distal branch intervention[b]
Hartel technique
Mandibular notch approach
CT-guided Gasserian[a] or distal branch intervention[b]
γ-Knife radiosurgery[47]

[a]Patients should be warned prior to Gasserian interventions that corneal anesthesia and subsequent eye injury is a possibility.

[b]Interventions may include diagnostic nerve block with local anesthetic, or nerve ablation with balloon compression, glycerol rhizotomy, or radiofrequency thermocoagulation.[48]

obtained to establish whether the presence of a blood vessel is causing trigeminal nerve compression.

Treatment of TGN includes medications, interventional procedures, and decompressive neurosurgery. Sodium channel blockers are first-line medications, especially carbamazepine and oxcarbazepine. When prescribing carbamazepine, patients' complete blood counts (CBC) should be routinely checked to monitor for the development of agranulocytosis. While treating with oxcarbazepine, one should regularly check serum sodium levels for hyponatremia. Numerous interventional procedures have been described and are summarized in **Table 86-18**. From a surgical perspective, trigeminal decompression should be considered.

Painful Trigeminal Neuropathy *Trigeminal neuropathy* is pain over the distribution of one or more divisions of the trigeminal nerve secondary to nerve injury. **Table 86-19** summarizes the ICHD-3β classification for the various painful trigeminal neuropathies.[23] Definitive treatment should try to target the underlying cause of the trigeminal nerve injury. Additional treatment modalities are listed above, under the TGN section of this chapter. General nerve injury related pain and treatment is included in later portions of this chapter.

TEMPOROMANDIBULAR DISORDERS

Temporomandibular disorders (TMDs) are a common set of orofacial, musculoskeletal conditions that afflict 5-12% of the US population, with costs exceeding $4 billion annually.[49] Patients typically present with pain over the temporomandibular joint (TMJ) or muscles of mastication. This may be associated with temporal headaches, ear pain, tinnitus, clicking/popping of the TMJ, or locking of the jaw. The exact etiology of TMD is controversial; however, it appears to represent a multifaceted, biopsychosocial phenomenon.[50] A number of gene polymorphisms are also thought to play an important role in some patients with TMD.[50]

Regarding formal diagnosis, the *Diagnostic Criteria for Temporomandibular Disorders* (DC/TMD) contains a physical component (axis I) as well as psychosocial and disability component (axis II), both of which were recently updated by the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group.[49] In total, 38 various axis I disorders exist, consisting of 12 types within four categories: myalgia, arthralgia, intraarticular disorders, and headache secondary to TMD. A review of the updated International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group provides additional information to assist with diagnosis and ICD coding.[49]

First-line treatment should include reversible, conservative modalities.[50] This includes patient education, self-management techniques, physiotherapy, acupuncture, cognitive behavioral therapy, and splints/mouth guards. Medication options include NSAIDs, gabapentinoids, tricyclic antidepressants, and low-dose benzodiazepines. Botulinum toxin trigger-point injections may be helpful; however, additional research is needed to support this treatment.[50] Irreversible treatment methods such as orthodontics, occlusal equilibration, and surgery are seldom recommended.[50]

TABLE 86-19 ICHD-3β Painful Trigeminal Neuropathies[23]

Painful trigeminal neuropathy attributed to acute herpes zoster
Postherpetic trigeminal neuropathy
Painful posttraumatic trigeminal neuropathy
Painful trigeminal neuropathy attributed to multiple sclerosis plaque
Painful trigeminal neuropathy attributed to space-occupying lesion
Painful trigeminal neuropathy attributed to other disorder

GIANT CELL ARTERITIS

Giant cell arteritis, also referred to as *temporal arteritis*, is a vascular headache caused by granulomatous inflammation of large and medium-sized cranial vessels that originate directly from the aortic arch. The pathophysiological mechanisms are unknown. Demographically, those affected are typically older than 50 years of age. Patients present with a new-onset headache, a swollen or tender area of discomfort over the temporal artery, visual changes, fatigue, malaise, or jaw complaints.[51] Diagnostic testing may reveal an elevated erythrocyte sedimentation rate, elevated C-reactive protein, and positive temporal artery biopsy. Treatment includes a several-week course of oral steroids with prednisone. It is important to note that prompt diagnosis and treatment is essential to prevent blindness secondary to anterior ischemic optic neuritis.[51]

MUSCULOSKELETAL PAIN SYNDROMES

Musculoskeletal (MSK) disorders are highly prevalent worldwide, and bear with them significant biopsychosocial and economic impacts. The 2010 *Global Burden of Disease* survey studied the contribution of MSK disorders to disability in 187 countries and 21 regions of the world. The five major defined conditions in the study were: osteoarthritis (OA), rheumatoid arthritis (RA), gout, low back pain (LBP), and neck pain (NP).[1,5,52-56] Overall, MSK disorders accounted for 21.3% of years lived with disability (YLDs) globally, second only to mental and behavioral disorders (see **Figure 86-3**).[52] In the United States, the direct cost of treating an individual patient with an MSK disease has risen from $4800 per year between the years 1996 and 1998, to $7800/year between 2009 and 2011.[57] The aggregate total direct and indirect costs for all patients with an MSK disease are estimated at $873.8 billion per year in 2011, representing 5.7% of the US gross domestic product (GDP).[57] Effective diagnosis and treatment of MSK disorders with a goal of increased function is paramount to reducing the overall burden of this group of diseases on our healthcare system and economy.

MYOFASCIAL PAIN SYNDROME

Myofascial pain syndrome (MPS) is a common cause of soft tissue pain. MPS can occur primarily, or can present as a reactive component to other conditions, such as a radiculopathy. The pathognomonic feature of MPS is the myofascial trigger point (TrP), a localized, tender, and firm or taut region within muscles or their fascia.[58] Palpation of the TrP causes a sharp contraction, known as the *local twitch response* (LTR).[59] Other clinical features include autonomic activation (vasoactivity, piloerection) or referred pain to distant sites.[59] The pathophysiology is hypothesized to be due to a traumatic/microtraumatic event causing tonic local contraction of muscle fibers, that eventually causes shortening of sarcomeres.[58] Persistence in this state causes local hypoxia with release of vasoactive mediators.[58] Patients with MPS can also develop central sensitization, a state of increased pain perception resulting from increased gain of the painful signals (see other chapters of this text for a detailed discussion of central sensitization).

Diagnosis of MPS is made clinically, relying on pertinent elements of the medical history and physical examination. Patients should be asked to complete a pain diagram, which should illustrate localized areas of pain that may be superimposed on widespread pain in the setting of central sensitization. The timing of MPS can be acute, chronic, or acute on chronic. The quality of pain is typically reported as dull, deep, aching and can be well or poorly localized with and without radiation. MPS can mimic other conditions, including radicular and visceral pain (ie, TrPs in the abdominal wall or down the leg). In the absence of consensus diagnostic criteria, it is generally accepted that the diagnosis of MPS can be made by palpation of the taut band within the muscle and causing exquisite tenderness that reproduces the patient's spontaneous pain complaint.[58,59] Palpation should be performed perpendicular to the

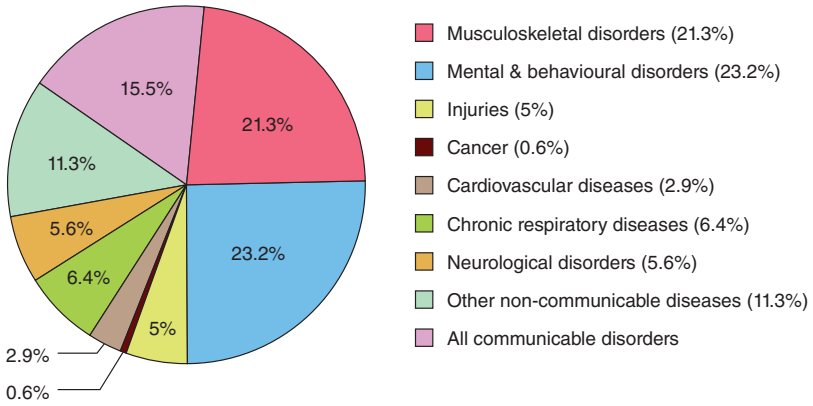

FIGURE 86-3. Burden of disability due to musculoskeletal disorders. The 2010 Global Burden of Disease (GBD) study studied the contribution of MSK disorders to disability in 187 countries and 21 regions of the world. Musculoskeletal disorders accounted for 21.3% of years lived with disability, second only to mental and behavioral disorders.[52]

direction of the muscle fiber in question, as taut bands are universally oriented in the same direction.[59] Ideally, the muscle should be grasped between the fingers in a pincer grip and then rolled through the palpating fingers to appreciate the presence of any taut TrPs. Pressure applied to the TrP itself can elicit an LTR.

Myofascial TrPs can serve as peripheral pain generators to precipitate or exacerbate other conditions, presumably by facilitating global nociceptive transmission. Specifically, TrPs have been associated with headache disorders, fibromyalgia, and visceral pain syndromes.[58]

Treatment of MPS focuses on the deactivation of the TrPs themselves as well as addressing any causative factors. It is critical to be mindful that TrPs may be an insidious harbinger to other pathology, such as radiculopathy, and should not curtail any further diagnostic maneuvers as indicated by history and physical. In the absence of concerning pathology, eliminating TrPs to break the cycle enhancing chronic pain and to restore normal tone and function of the affected muscles is the overarching goal.

TrP injections (TPIs) have been widely used to facilitate this process and are the gold standard for the treatment of MPS.[60] They are relatively safe when performed by clinicians with appropriate training. In 2009, Scott and colleagues reviewed all published systematic reviews or randomized controlled trials (RCTs) and noted that TPIs relieved symptoms of MPS in multiple studies, but were no better than other less invasive treatments such as laser and ultrasound.[60] TPIs with botulinum toxin were not more effective than saline or lidocaine, whereas all were more effective than dry needling alone.[60] However, relying on TPIs as sole treatment is not recommended – they should be used in conjunction with postinjection stretching or exercise therapy as part of a comprehensive, multidisciplinary pain management regimen.

OSTEOARTHRITIS

Osteoarthritis (OA) is the most common joint disorder, is one of the most common chronic diseases in the elderly, and is a leading cause of disability. In the United States, it is estimated that one-third of people over the age of 65 have OA.[61] Costs of OA are estimated at $10 billion per year in the United States, mostly due to absenteeism and hip or knee arthroplasty.[61] Obesity is the most significant independent predictor of both incidence and progression of OA as well as the need for surgery.[61] The risk for development of OA is increased by high-impact repetitive activities, smoking, and osteoporosis.

Osteoarthritis typically involves multiple joints, and those most commonly involved are the metatarsophalangeal (MTP) joint of the great toe (hallux valgus or "bunion"), proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints of the fingers, and carpometacarpal (CMC) joint of the thumb, hips, knees, and both lumbar and cervical spines. Other joints, even major weight-bearing joints such as the ankle, are regularly spared unless they are involved in secondary forms of OA. It is unclear what the specific pain generator for OA is, and this may vary between individuals, which would explain variability in response to therapies. **Figure 86-4** illustrates possible pain generators based on immunohistochemical staining for substance P in nerve fibers.[62]

Diagnosis of OA is typically made clinically, and pain is typically the presenting feature. The classic presentation is a middle-aged or elderly patient with mechanical joint pain and morning stiffness that improves with activity.[63] If there is any need for clarity, it is helpful to obtain blood tests and imaging to rule out other causes of pain, such as inflammatory, infectious, or crystalline arthritides. Radiographic findings include joint space narrowing, osteophytes, subchondral cysts, and bony sclerosis.[63]

Treatment of OA has been the focus of more than a dozen societal guidelines. In 2012, the Chronic Osteoarthritis Management Initiative (COAMI) of the US Bone and Joint Initiative performed a systematic review of recommendations and guidelines in the literature and identified five main areas of treatment:[64]

1. Education and self-management (joint protection, stretching)
2. Exercise and weight loss (low-impact aerobic exercise)
3. Assistive devices (walking aids or assist devices to improve ADLs)

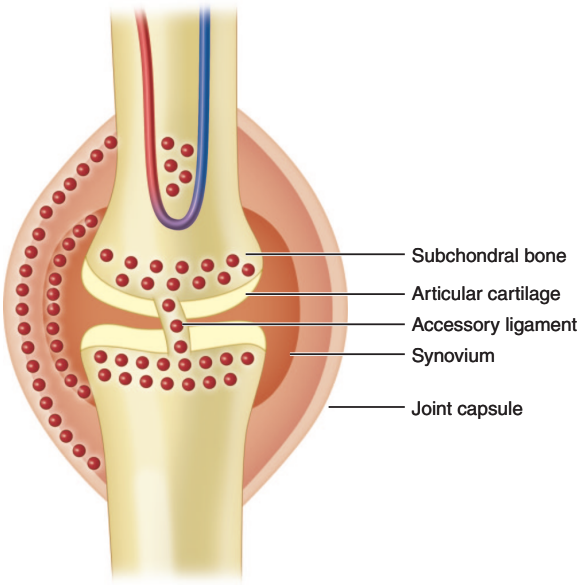

FIGURE 86-4. Diagram of generic synovial joint structures. Red dots illustrate possible pain generators derived from immunohistochemical staining of substance P in nerve fibers. Question marks indicate the possibility of a vascular (ischemic or vasospastic) pain generator.[62]

4. Alternative and complementary approaches (thermal modalities)
5. Surgical interventions (joint replacement)

Pharmacologic treatment of OA focuses on a stepwise analgesic approach to symptom management. Acetaminophen is generally agreed on as first-line therapy. Second-line agents include oral nonsteroidal anti-inflammatory drugs (NSAIDs) as well as topical treatment with NSAIDs or capsaicin.[64] Refractory cases can be treated with tramadol, duloxetine, or stronger opioids.[64,65]

Interventional treatment of OA ranges from fluoroscopic- or ultrasound-guided joint denervation procedures to intraarticular injections. Intraarticular knee and hip corticosteroid injections are recommended broadly in societal guidelines.[64] There is evidence supporting clinical benefits of intraarticular hyaluronic acid (HA) or platelet-rich plasma (PRP) injections for OA.[66,67] High-quality RCTs comparing these two therapies are lacking, and it is unclear which is more efficacious.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic multisystem disease with inflammatory polyarthritis of symmetric distribution affecting the peripheral joints of the hands (sparing DIP joints), feet, wrists, elbows, shoulders, hips, knees, and ankles. The cervical spine is generally the only axial skeleton affected by RA.

Rheumatoid arthritis manifests in constitutional symptoms of fatigue, low-grade fever, weight loss, and morning stiffness. Synovitis (inflammation of the synovium) is the hallmark of RA. It produces pain, swelling, and tenderness of the joints. RA is characterized by a waxing-and-waning course with relapses and remissions. Pain in RA is multifactorial. In the early stages, it is secondary to inflammation. At later stages, the damaging effects of erosion of cartilage and bone also cause pain. RA can be accompanied by FM. RA complications can also result in pain such as vertebral body fractures, compression of the median nerves by synovial tissue in the carpel tunnel, rheumatoid vasculitis, cervical spine instability at the C1-C2 level, and septic arthritis. Pain often persists in RA despite optimal control of inflammation, suggesting that the mechanisms of pain progression diverge from the inflammatory process of the disease (see **Figure 86-5**).[68]

Diagnosis is based on the history and physical examination and is supported by the presence of rheumatoid factor, which is present in 80% of patients with RA. Radiographically, soft-tissue swelling, juxtaarticular osteopenia, symmetric space narrowing, and bony erosions are seen.

Treatment of RA relies on direct-acting analgesics, anti-inflammatory drugs, and disease-modifying antirheumatic drugs (DMARDs). The 2013 update of the European League Against Rheumatism recommendations states that therapy with DMARDs should be started as soon as the diagnosis of RA is made, with a treatment goal of remission or low disease activity.[69] A multitude of DMARDs exist across a variety of classes, including synthetic chemical compounds and biological agents, a detailed discussion of which is beyond the scope of this text. Therapies in development include biologic and synthetic agents with a variety of targets, including interleukin 6 (IL6), IL17, B-cell-depleting agents, and Janus kinase (JAK) inhibitors.[70]

Management of RA and monitoring of DMARD therapy should be done primarily by a rheumatologist. The goal of the pain practitioner is to support those physicians with symptom management and to identify undiagnosed patients to ensure that they are appropriately referred. It is also important for the anesthesiologist to be aware that these patients are often on immunosuppressant medications and/or glucocorticoids.

When pain is unresponsive to treatment, therapeutic and prophylactic surgical options should be pursued, including synovectomy, arthroplasty, joint fusions, and joint replacement. Opioids might be the only option to provide adequate analgesia in advanced cases refractory to treatment or when contraindications to other modalities exist.

OTHER ARTHRITIDES

Multiple other arthritic syndromes may have pain as a cardinal feature. They include spondyloarthropathies, gout, and pseudogout. Arthritis can also accompany other systemic diseases, such as systemic lupus erythematosus, scleroderma, polymyalgia rheumatica, giant cell arteritis, Reiter syndrome, and inflammatory bowel disease.

Treatment should always focus on treating the underlying condition. NSAIDs usually provide acceptable analgesia. Opioids may be required for more severe cases.

Bursitis *Bursae* are small fluid-filled sacs with a synovial lining that act as a cushion to reduce friction between two tissue layers or between tissue and bone. Inflammation of a bursa is termed *bursitis*, a common cause of musculoskeletal pain that can affect any of the more than 140 bursae in the human body.[71] Septic bursitis (SB) must be distinguished from nonseptic bursitis (NSB), as this will dictate the treatment pathway. SB may present with signs of the *systemic inflammatory response syndrome* (SIRS) in addition to local findings of skin lesion and warmth

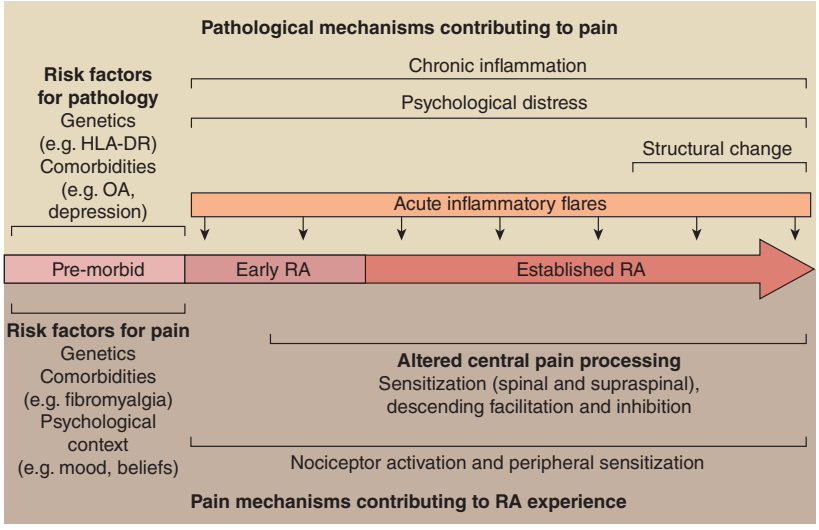

FIGURE 86-5. Schematic representation of the natural history of pain secondary to rheumatoid arthritis (RA). Multiple mechanisms are responsible for pain pathogenesis at different timepoints in the disease. Green shading represents pathological changes (ie, joint destruction, psychopathology), purple shading represents alterations in pain processing, and red shading represents acute on chronic pain flares. Pain pathophysiology in any setting is complex and causes changes across multiple systems, which is represented here in the setting of RA. Genetic variation may predispose individuals to develop pain and associated comorbidities, such as depression.[68]

over the bursa itself.[71] In this setting, the bursa should be aspirated for gram stain and culture. Two-thirds of cases are NSB, 80% of patients are male, and the cause is typically posttraumatic or secondary to overuse.[71] The most common types of bursitis involve the elbow (olecranon), knee (prepatellar), hip (trochanteric), and heel (retrocalcaneal).[72]

Diagnosis Bursitis must be differentiated from other musculoskeletal pain generators, including tendonitis, arthritis, fracture, ligamentous injury, and tumor.[72] In the absence of concerning vital signs, history elements, or skin lesions suggesting SB, it is a clinical diagnosis based on the presence of unilateral swelling and tenderness to palpation. A skin surface temperature difference of >2.2°C predicts the presence of SB with 100% sensitivity and 94% specificity.[71,72]

Treatment Treatment of NSB is generally conservative with NSAIDs and PRICE (protection, rest, ice/immobilization, compression, and elevation) therapy with or without needle drainage of the bursa. Intrabursal steroid injection with methylprednisolone has been shown to result in a more rapid decrease in swelling and decrease need for aspiration when compared to NSAID or placebo in NSB.[71] Treatment of SB is the same with the added administration of targeted antibiotic therapy. Refractory cases may require surgical bursectomy.

Tendinopathy *Tendinopathy* is a clinical syndrome that is typically associated with overuse tendon injury, but may also be seen in the setting of other medical conditions. Repetitive strain causes production of inflammatory mediators and microrupture of collagen fibers. Impaired healing may occur in the setting of hypoxia, which then leads to microvessel angiogenesis into the tendon. Concomitant pathological ingrowth of sensory nerve fibers along with microvasculature can occur, causing a previously insensate (nonpainful) tendon to become a painful tendon structure as nociceptive and inflammatory mediators act on these sensory nerves.[73]

Diagnosis Diagnosis is based on history and physical examination. Patients present with pain, swelling, and impaired functional performance. The most commonly involved tendons are the Achilles, patellar, rotator cuff, and extensor carpi radialis brevis tendons. The most common sites of pain are at the tendon insertion sites and the surrounding bursae, as these are the most vascular and densely innervated locations.[73]

Treatment Treatment is largely conservative, with initial recommendations to include exercise focusing on eccentric loading maneuvers. Physical therapy is critical to ensure that quality exercises are performed, and helps to increase compliance and facilitate recovery. Adjuvant biophysical therapies may also be pursued, including extracorporeal shock wave therapy (may initiate healing of failed tendon repair), injection therapies with blood products or steroids (good short-term, limited long-term effects). Surgery aimed at removal of calcifications or abnormal neoinnervation has had some promising results, but RCT data are lacking.[73]

NEUROPATHIC PAIN

Neuropathic pain is a pathologic pain that results from sustained transmission of pain signals in the absence of ongoing tissue injury or activation of pain-sensitive afferent peripheral nerves. Neural injury or dysfunction at any point along the somatosensory system from the peripheral nerve endings to the brain can cause neuropathic pain. Multiple mechanisms (peripheral and central) are responsible for sustaining neuropathic pain. Although its role is less identified than in nociceptive pain conditions, primary sensitization of nociceptive nerve endings might be a factor contributing to sustaining neuropathic pain. Damaged nerve fibers, especially neuromas, may generate ectopic action potentials, which contribute to neuropathic pain. When input from peripheral nociceptors into the dorsal horn of the spinal cord decreases, as encountered in deafferentation conditions such as shingles and after amputation, the dorsal horn neurons become hyperexcitable and may even develop spontaneous activity. In addition, the reduction of peripheral sensory input leads to ephaptic sprouting of the neurons neighboring the affected central neurons, resulting in magnification of the perceived pain field. Central sensitization, as outlined, also plays a major role in neuropathic pain. Because the inhibitory interneurons normally are excited by peripheral input, attenuation of this input will decrease inhibition and amplify the pain signal. In general, the inhibitory circuits of pain signal are downregulated at the level of both the spinal cord and the brain. At the level of the brain, different sites are involved in the processing of pain signal, and the somatosensory pain homunculus is not quite preserved. The initial neural injury and subsequent evolving mechanisms explain the complexity of clinical features encountered in neuropathic pain syndromes.

Some clinical features are common among neuropathic syndromes, whereas others are unique to specific syndromes. Patients usually have different types of pain. A stimulus-independent pain is a spontaneous pain experienced by patients without sensory stimulation. It consists of a background constant pain, intermittent exacerbations, and brief episodes of other symptoms. The pain usually is burning, aching, crushing, gnawing, lancinating, shooting, electrical, or lightning in quality, and associated with painful numbness and paresthesias (dysesthesias). The stimulus-evoked pain includes a variety of signs, such as hyperalgesia, mechanical and thermal allodynia, and hyperpathia. A list of common neuropathic pain syndromes can be found in **Table 86-20**.[7]

TABLE 86-20 Common Neuropathic Pain Syndromes[7]

Peripheral Neuropathic Pain
Acute and chronic inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)
Alcoholic polyneuropathy
Chemotherapy-induced polyneuropathy
Complex regional pain syndrome (CRPS)
Congenital painful neuropathies
Entrapment neuropathies (eg, carpel tunnel syndrome)
Hereditary painful neuropathies
HIV neuropathy
Iatrogenic neuralgias (eg, postmastectomy or postthoracotomy pain)
Idiopathic sensory neuropathy
Compression neuropathy (ie, by tumor)
Nutritional deficency-related neuropathies
Painful diabetic neuropathy
Paraneoplastic neuropathy
Phantom limb pain
Postherpetic neuralgia
Postradiation myelopathy/plexopathy
Radiculopathy syndromes (cervical, thoracic, lumbosacral)
Toxic exposure-related neuropathies
Cranial neuralgias (eg, trigeminal, glossopharyngeal)
Posttraumatic neuralgias
Central Neuropathic Pain
Compressive myelopathy (eg, spinal stenosis, tumor)
HIV myelopathy
Multiple sclerosis-related pain
Parkinson disease-related pain
Postischemic myelopathy
Postradiation myelopathy
Poststroke pain
Posttraumatic spinal cord injury pain
Syringomyelia

PERIPHERAL NERVE INJURY AND ENTRAPMENT

Peripheral nerve injury can result in mild symptoms to disabling, intractable pain. The main causes of nerve injury are traumatic, iatrogenic, and anatomic entrapment. Mechanistically, nerve injury occurs due to compression, stretch injury, or transection. The extent of nerve injury is divided into three categories based on degree of damage to neural structures.[74]

Neurapraxia is the mildest form, involving typically a blunt, compression, or stretch injury affecting the myelin sheath without damaging the

nerve itself. Conduction is intact both proximal and distal to, but delayed or absent at, the site of injury. The result is temporary sensorimotor deficits distal to that site that resolve over several weeks. *Axonotmesis* results from focal demyelination and axonal damage leading to *wallerian degeneration*, a process in which the axon distal to the site of injury breaks down to make way for eventual axonal regeneration. This occurs in the first week after injury, and leads to absence of downstream conduction with sensorimotor deficits. Axonal regeneration and end-organ reinnervation are required for recovery, which is length-dependent and may occur spontaneously or require surgery. *Neurotmesis* is the most severe form of injury, resulting from complete transection of all neural structures, including the axon and its connective tissue. Without intact connective tissue elements, there can be no organized regeneration and surgical intervention is required.[74]

Compression injuries most commonly occur at anatomic locations where nerves traverse tissue or fascial planes through narrow openings. Compression injuries typically result in neurapraxia. Traumatic or iatrogenic injuries may occur anywhere and can cause any of the aforementioned types of injury. For the purpose of this text, we will focus on representative nerve entrapment syndromes, but the anesthesiologist should be aware of the more severe injuries as they may be present on entering the operating room due to trauma, or caused perioperatively by surgical manipulation, patient positioning, regional anesthesia, or vascular cannulation.

APPROACH TO SUSPECTED NERVE ENTRAPMENT OR INJURY

Diagnosis of suspected nerve entrapment or injury begins with the history and physical examination. In addition to a general medical history, the OPQRST (onset, provoking/palliating factors, quality, radiation, severity, and timing) of the pain complaint should be obtained whenever pain is the presenting complaint. It is helpful to elicit specific inciting events in the case of nerve injury, such as trauma or medical/surgical procedure history. In the case of nerve entrapment, an employment and activity history should be obtained to identify predisposing factors such as repetitive strain injury. Physical examination should include a neurologic examination including motor, sensory, and reflex testing. An appropriate examination of the spine should be performed to distinguish between central and peripheral etiologies.

A proposed clinical triad for the diagnosis of nerve compression includes weakness or sensory disturbance distal to the site of compression, pain with compression or positive Tinel's sign, and a positive scratch collapse test at the site of compression.[75,76] **Table 86-21** lists common physical diagnosis maneuvers for nerve compression and injury.

Diagnostic testing for peripheral nerve entrapment or injury includes electrodiagnostic studies (nerve conduction study and electromyography) as well as imaging studies. Nerve conduction studies (NCSs) evaluate the speed of conduction of an impulse through a nerve, whereas electromyography (EMG) uses needles to measure muscle response to a neural impulse. Imaging studies may include plain radiographs to rule out fractures or bony abnormalities. Recent advances in high-resolution magnetic resonance neurography (MR-neurography) and high-resolution ultrasound (HRU) have improved the ability to localize lesions.[77] MR-neurography exploits increases in the weighted nerve T2 signal after injury, resulting in a hyperintense appearance of injured nerves or fascicles.[77]

Treatment of nerve entrapment or injury should begin at the time of clinical suspicion and begin with conservative management, including activity modification, physical therapy, and splinting (when appropriate). Empiric treatment with anti-inflammatory and antineuropathic medications (ie, gabapentinoids or TCAs) has a role in symptom management. However, diagnostic efforts should focus on definitive therapy for patients who fail to respond to conservative management or who manifest significant pain or disability (ie, complex regional pain syndrome). Lesion localization has implications in terms of directed treatment, including targeted nerve blocks, surgical release, and other surgical techniques, including nerve transfer and pulsed radiofrequency neuromodulation (pRF).

COMMON NERVE ENTRAPMENT SYNDROMES

Carpal tunnel syndrome is the most common painful mononeuropathy, resulting from compression of the median nerve as it passes in between the carpal bones and flexor retinaculum at the wrist. Predisposing factors include fractures, ganglion cysts, synovial disorders, arthritides, ergonomic stressors, repetitive use, pregnancy, obesity, renal insufficiency, diabetes, and acromegaly. Patients report paresthesias and/or dysesthesias over the median nerve distribution of the hand from the thumb to the lateral half of the fourth digit with sparing of the thenar eminence and radial palm. On exam, thenar muscle weakness and atrophy may be present; Tinel's sign and Phalen's test can help to confirm the diagnosis. First-line treatment consists of wrist splinting, with steroid injection reserved as a temporizing measure for symptomatic relief in patients with an immediate need to return to exacerbating activities. Carpal tunnel release surgery is indicated for patients who fail conservative management or who present with moderate-severe sensorimotor symptoms.[78]

Cubital tunnel syndrome is the second most common upper extremity mononeuropathy, resulting from compression of the ulnar nerve as it passes between the medial epicondyle and the olecranon while travelling underneath the aponeurosis formed between those two structures. Predisposing factors include external trauma, ergonomic compression, ganglion cysts, and supracondylar spurs. Patients report paresthesias in

TABLE 86-21 Physical Diagnosis Maneuvers for Nerve Compression and Injury

Maneuver	Condition	Technique	Positive Result
Modified Adson's maneuver	TOS	90° abduction and external rotation of the upper extremity while palpating radial pulse	Reproduction of pain and paresthesia within 60 seconds, ± loss of radial pulse
DF-EV test	TTS	Ankle placed in maximal passive EV and DF while all MTP joints dorsiflexed and held for 10 seconds	Induced or increased pain and paresthesia; increased likelihood of Tinel's over tarsal tunnel
Durkan's test	CTS	Examiner compresses carpal tunnel for 30 seconds	Pain or paresthesia in median nerve distribution within 30 seconds
Phalen's maneuver	CTS	Wrists held in complete forced flexion by pushing dorsal surfaces of hands together for 60 seconds	Reproduces pain and/or paresthesias in median nerve distribution
Scratch collapse test	Nerve compression	(1) Test sustained shoulder external rotation; (2) scratch skin at site of suspected nerve compromise; (3) retest external rotation resistance	Loss of external rotation resistance and collapse of arms (stimulation of skin at compromised nerve site leads to inhibition of voluntary muscle activity)
Summation: (1) spatial; (2) temporal	Nerve injury	(1) Gently glide finger over distribution of suspected nerve injury; (2) gently tap finger over distribution of suspected nerve injury	Reproduction or intensification of baseline pain state
Tinel's sign	Nerve compression	Percussion over nerve at suspected site of compression	Paresthesias in nerve distribution distal to site
ULTT	TOS, neural tension	(1) Arms abducted to 90° with elbows extended; (2) dorsiflex wrists; (3) tilt head to side with ear to shoulder…modifications can be made to target specific nerves	Each move increases tension on brachial plexus contralateral to head tilt

Abbreviations: CTS = carpal tunnel syndrome; DF-EV = dorsiflexion-eversion test; MTP = metatarsophalangeal; TOS = thoracic outlet syndrome; TTS = tarsal tunnel syndrome; ULTT = upper limb tension test.

the fourth and fifth digits and ulnar distribution hand muscle weakness. On exam, the ulnar nerve may be noted to be tender or enlarged at the medial epicondyle; Tinel's sign or compression testing can reproduce or aggravate the patient's typical symptoms. First line treatment is conservative, including extension splinting at night and ergonomic modifications to reduce leaning on and/or pad the elbow.[78]

Tarsal tunnel syndrome is the most common site of tibial nerve entrapment, resulting from compression as the nerve courses under the flexor retinaculum at the level of the medial malleolus. Predisposing factors include ankle trauma, ganglion cysts, and foot deformities. Patients report numbness and pain in the sole of the foot that spares the heel. Examination may reveal a Tinel's sign at the tarsal tunnel. Initial treatment is conservative, but may also include steroid injections into the tarsal tunnel or surgical release.[79]

Peroneal neuropathy is the most common mononeuropathy in the lower extremity, resulting from injury or compression of the common peroneal nerve as it courses around the fibular head superficially. The most common mechanisms of injury are trauma in addition to external compression from prolonged squatting or kneeling, or patient positioning in the healthcare environment. Patients present with a foot drop due to weakness of the dorsiflexors and evertors of the ankle and sensory loss along the anterolateral shin and dorsum of the foot. A Tinel's sign may be present at the fibular head.[79]

Meralgia paresthetica is an entrapment mononeuropathy of the lateral femoral cutaneous nerve (LFCN), resulting from compression as it passes under the inguinal ligament near the anterior superior iliac spine (ASIS).[79] Predisposing factors include external compression (tight waistbands, seat belts, tool belts), obesity, pregnancy, and rapid weight changes. The nerve is also commonly injured during surgical procedures involving incisions in the area, including inguinal hernia repair, cesarean section, renal transplantation, and hip surgery. Patients report pain, and/or paresthesias or dysesthesias over the anterolateral thigh. Examination reveals a pure sensory loss in the LFCN distribution as well as a Tinel's sign at the ASIS. Ultrasound-guided nerve blocks can be both diagnostic and therapeutic, and anesthesiologists are often called on to assist in this treatment modality.[80] Cases of sustained relief have been reported with pulsed radiofrequency neuromodulation of the LFCN.[81,82]

Painful neuromas occur as a result of impaired nerve regeneration after a traumatic or iatrogenic injury such as a surgical incision. Neuromatous-type pain is mediated by C- and A-delta nociceptive fibers that abnormally sprout after an injury, at which time they acquire the ability to fire spontaneously and/or can be stimulated by sympathetic afferents.[83] The clinical diagnosis of a neuroma can be made when there is pain in the region of a scar and associated abnormal sensorium in the distribution of the involved peripheral nerve. There is frequently a painful, hyperalgesic, or allodynic response to focal areas of scar palpation. Tinel's sign and a positive scratch-collapse test may also be present. Treatment involves desensitization therapy, diagnostic nerve blocks, scar injections, anti-neuropathic pain medications, and referral to peripheral nerve surgeons for consideration of scar revision, nerve graft, or nerve release.[83]

PAINFUL PERIPHERAL NEUROPATHIES

A wide variety of etiologies lead to peripheral neuropathies. It is important to realize that not all neuropathies are painful, as is the case with most of the inherited neuropathies. Some patients with neuropathy have chronic pain due to other conditions, and their pain should not be immediately attributed to the concomitant nonpainful neuropathy. The distribution of neuropathy can be generalized and symmetric (polyneuropathy), such as diabetic and alcoholic polyneuropathy; multifocal (mononeuropathy multiplex), such as collagen vascular disease–related neuropathies; or focal (mononeuropathy), as seen in trauma and entrapment neuropathies. Polyneuropathy usually is symmetric and starts in a distal-to-proximal gradient in a "glove and stocking" distribution. Mononeuropathy multiplex affects multiple peripheral nerves arbitrarily and sometimes can be difficult to differentiate from polyneuropathy. Mononeuropathy follows the distribution of the affected nerve. Neuropathies may result from injury to the axons (axonal neuropathies), to myelin (demyelinating neuropathies), or mixed lesions. Most of the neuropathies encountered in pain medicine practice are axonal neuropathy types. Acute (AIDP) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are examples of demyelinating neuropathies usually seen in pain practice. There are many causes of painful peripheral neuropathies, many of which are idiopathic. However, HIV-related and diabetic neuropathies are among the more common disease-associated neuropathies.

Acute herpes zoster (shingles) is the most common cause of sensory neuropathy. It results from reactivation of the dormant varicella-zoster virus (VZV) in the cranial nerve, dorsal root and autonomic ganglionic neurons or satellite cells, followed by transmission of the virus particles to the nerve endings proximally and distally. The annual incidence of shingles in the United States is 3.2 cases per 1000. The risk of acute herpes zoster is higher among patients with HIV infection or cancer and particularly among children with leukemia and transplant recipients. Dermatomal distribution and vesicular rash are the hallmarks of acute herpes zoster. The most affected nerves follow this order: thoracic spinal roots, ophthalmic division of the trigeminal nerve (V1), maxillary division of the trigeminal nerve (V2), cervical spinal roots, and sacral spinal roots. The earliest clinical features of acute herpes zoster noticed by patients are dermatomal dysesthesias associated with pruritus. This could be accompanied or followed shortly by the appearance of the typical rash, which matures through different stages until it crusts and heals. The pain worsens with progression and consists of dysesthesias, burning, and shooting pain. It tends to resolve spontaneously as the crust falls off, a process that takes 4-5 weeks.[84]

Postherpetic neuralgia (PHN) is persistent pain 120 days after the onset of rash of herpes zoster. Risk factors for PHN include the following:[85]

1. Age: 40% of patients over 50 years and 75% of patients over 75 years develop PHN following resolution of rash.
2. Prodrome of pain prior to rash onset.
3. Degree of spread of the rash. Increased risk with extension beyond a single dermatome.
4. Severity of pain during the acute attack.

Patients report constant or paroxysmal pain that is in the same dermatomal distribution as their shingles. The quality of the pain is described as burning, itching, or stabbing. The intensity of the pain can be severe, and can lead to significant biopsychosocial impact, especially in the elderly. There is limited evidence to suggest that antiviral treatment during the acute herpes zoster infection can reduce the severity of PHN.[85,86] A retrospective review by Pica et al noted that patients treated initially with antivirals had a 2.6% incidence of PHN compared to 18.6% of untreated patients at 12 months.[87] However, a 2014 Cochrane review could not substantiate that antiviral treatment reduces the incidence of PHN.[86]

Treatment of PHN begins with simple analgesics such as acetaminophen or mild opoioids. Antineuropathic medications in the form of tricyclic antidepressants (ie, nortriptyline) and/or anticonvulsants in the form of gabapentinoids are most likely to confer benefit and may be synergistic.[85,88] Topical lidocaine has a limited role in the treatment of PHN, according to a 2014 Cochrane Review in which six studies were evaluated and the rate of response was modest at best.[89] A 2013 meta-analysis by Mou et al evaluated the efficacy of the 8% capsaicin patch (Qutenza) in the treatment of PHN and found modest results, with 44% of patients reporting a 30% reduction in pain and 11% reporting complete relief 2-12 weeks after treatment.[90] Spinal cord stimulation has been shown to decrease pain and increase function in 82% of patients in a prospective case series involving 28 patients.[91]

CENTRAL PAIN

Central pain is a "deafferentation" pain that can result from any lesion found in the CNS.[92] Virtually any type of lesion can produce this type of pain, including demyelinating, vascular, infectious, inflammatory, and traumatic. Pain onset may be delayed by several months after the initial insult, reflecting the slow degeneration process within the CNS. Pain usually correlates to the anatomic site of the causative lesion. The pain features are those of neuropathic pain.

Brain-based central pain results from a variety of etiologies. Thalamic pain (Dejerine-Roussy syndrome) is the prototype of central pain, but lesions in the brainstem and other sites also can produce central pain. Strokes are the most common cause, with pain reported to occur in ≤8% of poststroke patients.[93] Other etiologies include multiple sclerosis, Parkinson's disease, brain abscess, encephalitis, and tumors.

Spinal-cord-based central pain is a common complication of spinal cord injuries. Trauma is the most common etiology.[94] Iatrogenic, inflammatory, demyelinating, vascular, neoplastic, and congenital lesions are other possible causes. The most common level of injury associated with pain is cauda equina followed by the central cord injuries. Syringomyelia and syringobulbia can occur as delayed consequences of trauma or congenital malformations and produce neuropathic pain of segmental pattern.

Multiple sclerosis (MS) is very common cause of non-trauma-related central pain. This disease is characterized by demyelination and axonal degeneration. Pain is an predominant symptom of MS, reported in 44-80% of patients.[95] Symptoms including dysesthetic limb pain and painful spasms have a high prevalence in this population.

The clinical presentation of central pain varies widely depending on the etiology and patient. It is often difficult to describe a "typical presentation." Central pain is often described as an idiosyncratic pain state; patients with apparently identical lesions may or may not go on to develop chronic pain.[96] Patients suffering from central pain may describe a pain that acquires many different forms – sometimes simultaneously. Whereas the most common descriptors are adjectives such as "burning," "lancinating," and "aching"; others describe their pain more like "throbbing," "pulling," or "icy." Some patients report the onset of pain contralateral to the CNS lesion to be immediate; however, most report the onset to be within a month.[97]

Central pain is one of the most difficult pain states to effectively treat. Pregabalin and lamotrigine have shown encouraging results.[98-100] Some evidence exists for the benefit of tricyclic antidepressant (TCAs).[101] Other agents used for neuropathic pain, such as antiepileptic drugs (AEDs) and opioids, have been used, but no sound evidence supports their efficacy. In addition to medication, neuromodulation methods including motor cortex stimulation (MCS) have also been shown to be successful in patient with refractory central neurogenic pain. MCS has shown durable pain relief in patients with thalamic pain.[102]

FIBROMYALGIA

Fibromyalgia (FM) is a multisymptomatic syndrome defined by the core feature of chronic, widespread pain. It is thought to be a condition of disordered central afferent processing. FM is a common entity that affects women more than men and increases steadily with age. The major symptoms of FM including multifocal pain, fatigue, sleep disturbances, and cognitive or memory problems. Although classically it has not been considered a central pain syndrome, FM has increasingly been classified under this category. The core symptoms seen in individuals with FM as well as many other closely related "central" pain syndromes are multifocal pain, fatigue severe enough to limit daily activities, sleep disturbances, cognitive or memory problems, and, in many cases, psychological distress.[103]

Although a definitive causal relation has not been established, FM usually is precipitated by trauma, stress, infections, or other factors. It commonly accompanies a wide range of medical conditions, including rheumatoid arthritis (RA), low back pain, systemic lupus erythematosus, Sjögren syndrome, osteoarthritis (OA), inflammatory bowel disease, irritable bowel syndrome, headache, mood disorders, restless legs syndrome, and sleep disturbance, particularly stage 4. Research shows that certain individuals might have vulnerability to FM because of past life events or a complex genetic component interacting with environmental insults.[104,105]

Patients typically present with chronic, widespread stiffness and pain that is described as a constant dull ache worsened by muscle overactivity. FM is usually associated with a constellation of symptoms such as easy fatigability, nonrestorative sleep, cognitive dysfunction, depression, and somatic complaints other than musculoskeletal pain.[104]

The diagnosis of FM is usually based on the recommendations of the American College of Rheumatology (ACR) classification criteria. The diagnostic criteria for FM published in 1990 require chronic widespread pain plus a certain number of tender points to make the diagnosis. According to this definition, FM was an almost exclusively female disease because women have many more tender points than do men. The new diagnostic criteria for FM published in 2010 and 2011 no longer require performing a tender point count to make the diagnosis and instead ask about the constellation of nonpain somatic symptoms that are typically present in addition to widespread pain (eg, fatigue, sleep disturbance, memory, and mood problems).[106] By using either of these criteria, substantially more men are diagnosed, with a female:male ratio of approximately 2:1 (instead of 9:1 with the 1990 criteria).[107] This female:male ratio is similar to those seen for almost all chronic pain conditions. The new diagnostic criteria for fibromyalgia combine the widespread pain index (WPI) with the symptom severity (SS) scale score.[108] **Table 86-22** lists the 2010 ACR diagnostic criteria.

Treatment of FM should be interdisciplinary in nature and consist of psychological techniques, physical therapy, especially aquatic-based exercises, treatment of comorbid mental health and associated sleep concerns, and pharmacologic therapies. Multiple medications have proven effective for the management of pain in FM and are now approved by the Food and Drug Administration (FDA). These are pregabalin, duloxetine,

TABLE 86-22 2010 American College of Rheumatology Fibromyalgia Diagnostic Criteria

A patient satisfies diagnostic criteria for fibromyalgia if the following three conditions are met:

1. **Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3–6 and SS scale score ≥9.**
2. **Symptoms have been present at a similar level for at least 3 months.**
3. **The patient does not have a disorder that would otherwise explain the pain.**

WPI: Note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19.

Shoulder girdle, left/right	Chest
Upper arm, left/right	Abdomen
Lower arm, left/right	Upper back
Hip (buttock, trochanter), left/right	Lower back
Upper leg, left/right	Neck
Lower leg, left/right	
Jaw, left/right	

SS scale score
- Fatigue
- Waking unrefreshed
- Cognitive symptoms

For the each of the three symptoms above, indicate the level of severity over the past week using the following scale:
0 = no problem
1 = slight or mild problems, generally mild or intermittent
2 = moderate, considerable problems, often present and/or at a moderate level
3 = severe: pervasive, continuous, life-disturbing problems

Considering somatic symptoms in general, indicate whether the patient has[a]
0 = no symptoms
1 = few symptoms
2 = a moderate number of symptoms
3 = a great deal of symptoms

The SS scale score is the sum of the severity of the three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12.

[a]Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

and milnacipran.[109-112] Tricyclic antidepressants (TCAs) have also been shown effective in FM and have the added benefit improving sleep. NSAIDs have varying degrees of success. Naltrexone hydrochloride, an opioid antagonist, has more recently has been used as a treatment for fibromyalgia. This drug has been found to reduce proinflammatory cytokines and neurotoxic superoxides in the central nervous system microglia cells. In recent studies, naltrexone has show great promise in treating fibromyalgia symptoms with minimal side effects.[113,114] Tramadol, a dual-reuptake inhibitor of norepinephrine and serotonin with weak opioid receptor affinity, may be useful. Strong opioid receptor agonists have not been shown to be effective. Most FM patients tend to have a chronic course, with exacerbations, remissions, and fluctuating symptoms.

The three best-studied nonpharmacological therapies are education, cognitive behavioral therapy, and exercise, and all these have strong evidence (level I, A) for use in FM. Another advantage of these treatments is that they can lead to sustained (eg, >1 year) improvements. Access and adherence are the biggest issues with these therapies.[106] Complementary and alternative therapies can also be helpful in managing FM. As in other disorders, there are relatively few controlled trials to advocate their general use. Trigger-point injections, chiropractic manipulation, tai chi, yoga, acupuncture, and myofascial release therapy all have some evidence of efficacy and are among the more commonly used modalities.[115] Transcutaneous electrical nerve stimulation (TENS) has also been shown to be successful in the management of pain and improvement in function in individuals with fibromyalgia.[116]

POSTAMPUTATION PAIN

Postamputation pain (PAP) presents as a heterogeneous group of overlapping pain syndromes. It can be secondary to neuroma, CRPS, somatic pain, and phantom limb pain (PLP). PAP pain syndromes are neuropathic in origin. There exists no consensus on the treatment for PAP.[117]

Stump pain is a chronic sensation of pain at the site of amputation. It also is referred to as *residual limb pain*.[118] It may occur with phantom limb pain or alone. Several factors may account for stump pain and should be evaluated, including surgical trauma, ischemia, local infection, ill-fitting prostheses, or a painful neuroma formation. Treatment should focus on treating the underlying etiology. Treatment of painful neuromas ranges from simple injections to surgical interventions, with varying degrees of success.[119]

Phantom sensation is the perception of the amputated part and occurs in almost all amputees. *Phantom limb pain* (PLP) is the perception of pain distal to the amputation site. It has unclear etiology, but deafferentation of central neurons seems to play a major role in the development of phantom pain. Its incidence peaks approximately 1 month after amputation and gradually improves as the pain "telescopes" toward the stump. The pain results in paroxysms of burning and twisting sensation in the amputated part. Phantom pain should be differentiated from stump pain.

Treatment of phantom pain is challenging. Pharmacologic agents for neuropathic pain should be attempted. TCAs, tramadol, and gabapentin have been shown to be effective.[120,121] Nerve blocks can be tried for more difficult cases. In refractory cases, surgical options (eg, dorsal root entry zone lesions) and more invasive procedures might be the only effective methods for treating the pain.

There has been increasing focus on neuromodulation as a treatment option for PAP. The Neuromodulation Appropriateness Concensus Committee (NACC) believes that postamputation and stump pain are generally considered better indications for conventional spinal cord stimulation, if it is possible to generate paresthesia in the phantom limb. The NACC recommends proceeding with neuromodulation therapies but underscores the necessity of using caution, realizing that the etiology of the pain may vary for the reasons noted and the results may be unpredictable.[117,122]

SYMPATHETICALLY MAINTAINED PAIN AND COMPLEX REGIONAL PAIN SYNDROMES

Sympathetically maintained pain (SMP) is defined as "pain that is maintained by sympathetic efferent innervation or by circulating catecholamines."[123] Thus SMP is not a clinical diagnosis but rather a pathophysiologic mechanism in chronic pain marked by improvement of pain when sympathetic blockade is performed. When the pain does not respond to sympathetic blockade, it is called *sympathetically independent pain* (SIP). SMP is thought to be a major culprit in many chronic pain states, such as peripheral and central neuropathic pain syndromes.[124-126]

The sympathetic nervous system can initiate or maintain pain as sympathetic fibers coexist with primary afferents in peripheral tissues, especially along the vasculature. Symptoms of sympathetically mediated pain include burning or stabbing pain, allodynia and/or trophic disorders.[127]

COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome (CRPS) is considered to be a neuropathic SMP syndrome. The two types of CRPS are type I (previously called *reflex sympathetic dystrophy*) and type II (previously called *causalgia*). CRPS is more common in women than in men, and the incidence reaches its peak in the fifth decade.[128,129] It involves one limb in most cases, and there is a history of noxious traumatic injury with or without nerve involvement.[129,130] There is no correlation between the severity of injury and the severity of the ensuing pain syndrome. Direct injuries to CNS structures have been reported as causative, including spinal cord and brain injuries.[131,132] In CRPS type II particularly, there may be a stretch injury to the nerve, without interruption of the nerve. Multiple risk factors have been postulated to predispose to CRPS, including immobilization, smoking, genetic predisposition, and psychological factors.[133-136]

The exact mechanism of CRPS is not known, but it appears to be a disease of both the CNS and the peripheral nervous system.[137,138] Peripherally, β-adrenergic sensitization of the nociceptive afferent fibers occurs. As a result, nociceptors are activated by release of norepinephrine by sympathetic postganglionic fibers. Release of certain mediators, such as prostaglandins, by sympathetic fibers can further sensitize the nociceptive afferents. If the injury results in myelin loss of the fibers, artificial synapses develop between the affected sensory afferents and sympathetic efferents, a process called *ephaptic transmission*. The dorsal root ganglion is thought to be another site for ephaptic transmission resulting from sprouting of sympathetic postganglionic fibers around sensory neurons. At the level of the dorsal horn of the spinal cord, the wide dynamic range neurons, which are second-order neurons, are activated and sensitized by the active injured C fibers. Sensitized wide dynamic range cells are thought to be activated by other stimuli, such as light touch, explaining the phenomenon of allodynia. At the level of the brain, there is altered sensorimotor processing and increased hyperexcitability.[139,140] Thus CRPS results from interaction between the CNS and the periphery. Central changes are reflected as alterations in somatic sensation (including pain), the motor system, and the peripheral autonomically regulated effector systems (vasculature, sweat glands, inflammatory cells).[137]

In most cases the presenting symptom of CRPS is pain, which most often is burning and does not follow a dermatomal pattern.[128,141] Other common symptoms and signs include decreased range of motion, weakness, hyperpathia, allodynia, hyperalgesia, color change, altered skin temperature, edema, hyperesthesia, hypoesthesia, sweating change, nail or hair changes, and dystonia.[128,142] Although symptoms typically start in a distal limb, CRPS has been reported to start in other regions of the body, such as the head, proximal limbs, and genitalia.[143] Spread of CRPS features proximally or to other regions of the body has been well described.

The diagnosis of CRPS can be made only in the absence of any other diagnosis explaining the findings. Diagnosis of CRPS was originally based the Orlando criteria, endorsed by the International Association for the Study of Pain.[144-146] A modified, updated version called the *Budapest criteria* was subsequently introduced and largely replaced earlier versions.[147,148] The Budapest criteria have a greater specificity and also include motor features of the syndrome.[149] **Table 86-23** lists the Budapest diagnostic criteria for CRPS.

No specific diagnostic test is available for CRPS.[150] Several tests can help confirm the diagnosis or rule out other conditions. Blood tests, including erythrocyte sedimentation rate, blood cell count, and rheumatologic testing, may be necessary to help rule out infection or a rheumatologic condition.[150] When vasomotor features are present, vascular studies can exclude a vascular etiology. NCS and EMG may clarify the presence of nerve injury necessary for the diagnosis of CRPS type II. An important distinction between CRPS type II and peripheral mononeuropathy is that the somatosensory symptoms in CRPS extend beyond the distribution of the

TABLE 86-23 Budapest Criteria for Complex Regional Pain Syndrome

1. Continuing pain that is disproportionate to any inciting event
2. Must report at least one symptom in three of the four following categories:
   Sensory—reports of hyperesthesia and/or allodynia
   Vasomotor—reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   Sudomotor/edema—reports of edema and/or sweating changes and/or sweating asymmetry
   Motor/trophic—reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and or trophic changes (hair, nails, skin)
3. Must display at least one sign at the time of evaluation in 2 or more of the following categories:
   Sensory=—evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
   Vasomotor—evidence of temperature asymmetry and/or skin color changes and/or asymmetry
   Sudomotor/edema—evidence of edema and/or sweating changes and/or sweating asymmetry
   Motor/trophic—evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)
4. No other diagnosis better explains the signs and symptoms

affected nerve.[150] Radiographic studies including magnetic resonance imaging (MRI) often are necessary to exclude bone or soft-tissue pathology as the source of pain. Plain radiographic studies may show findings of bony demineralization, which is not specific to CRPS and could be the result of disuse.[151] A three-phase bone scan of the affected extremity has variable sensitivity and is relatively nonspecific in the diagnosis of CRPS. Classic findings include increased periarticular uptake throughout the three phases (blood pool, blood phase, scan phase).[150] Thermography can assist in confirming thermal dysregulation. Simple measures also can provide this information, using infrared thermometer or skin temperature probes that document the temperature of the normal and the affected limbs. A temperature difference of 0.6°C between limbs is considered significant.[152] Quantitative sudomotor axonal reflex testing evaluates autonomic function by measuring sweat output in response to a cholinergic agent. Although a positive response to a sympathetic block can help in establishing the diagnosis, it is not required to diagnose CRPS.[150]

A pharmacologic sympathetic block can be performed with intravenous infusion of phentolamine. However, the more common approach is performance of a local anesthetic sympathetic trunk block. A lumbar paravertebral sympathetic block is performed for lower limbs, and a cervicothoracic block (stellate ganglion block) or upper thoracic sympathetic block is performed for upper limbs. Evidence of a satisfactory sympathetic block (eg, thermography) in the absence of a somatic nerve block should be demonstrated.[150] If favorable results are achieved by sympathetic blocks, then their continued administration may be useful.

Optimal management of CRPS involves an interdisciplinary approach to therapy focused on functional restoration of the affected limb.[153] The main goals of the treatment are pain control, physical rehabilitation, functional recovery of the affected limb, and return to work. The drugs used in therapy have not been demonstrated to significantly change the overall course of the syndrome and have been used primarily to help patients progress with their rehabilitative program.[154] Rapid initiation of comprehensive treatment is recommended, with advancement to higher levels of intervention if initial therapy shows no benefit in 2 weeks. Simultaneous physical rehabilitation, psychological therapy, and provision of adequate analgesia are key elements in the treatment plan. Multiple physical and occupational therapy measures can be used in the process of rehabilitation, starting with desensitization and stress loading, then gentle active range of motion and stretching to increase flexibility, and eventually normalization of use and general conditioning.[155]

Psychological therapy should focus on educating patients that pain sensations in CRPS type I do not indicate tissue damage, and that reactivation of the affected limb is important. With persistent symptoms, clinical psychological assessment is recommended, eventually followed by cognitive behavioral therapy. Comorbid conditions such as depression, sleep disturbance, anxiety, and generalized physical deconditioning should be treated.

Analgesia is achieved using oral or topical neuropathic pain agents, including TCAs, AEDs, NSAIDs, opioids, and other agents.[156] Corticosteroids may be effective, especially if the inflammatory component is profound.[157] Calcitonin, topical dimethylsulfoxide (DMSO), and α_1-adrenoceptor antagonists (eg, terazosin, phenoxybenzamine) may be helpful. Many other drugs have been anecdotally used, with varied results (including prazosin, clonidine, mexiletine, ketamine, baclofen, bisphosphonates, muscle relaxants, and calcium channel blockers).[158] Infusion therapy with ketamine has a recently gained more attention but there is no high quality evidence available evaluating the efficacy of ketamine for pain. Therefore, there is only weak evidence for the efficacy of ketamine for CRPS, and it cannot be considered a first line option.[159,160]

When symptoms are persistent, patients who had favorable results with diagnostic sympathetic blockade are often offered intravenous regional anesthesia (IVRA). IVRA using phentolamine, guanethidine, reserpine, droperidol, and atropine have been shown to be ineffective.[136] Sympathetic blockade via a local injection may be particularly beneficial if pain and swelling is limiting participation in therapy despite medication. These blocks involve the injection of local anesthetics along the lumbar sympathetic chain (for lower limbs) or stellate ganglion (for upper limbs) under fluoroscopic guidance. A good response includes an increase in temperature in the affected extremity, without a motor or sensory block, reduced pain, decreased allodynia, and improved range of motion.[161] Sympathetic block can be performed with a long acting local anesthetic such as bupivacaine and other agents such as clonidine and corticosteroids may also be added. There is also evidence that suggests that performing sympathetic blocks with botulinum toxin may prolong patient's pain relief as compared to local anesthetic alone.[162]

Patients who have not had good results with sympathetic blockade may require a combined somatic/sympathetic block using indwelling catheters to allow adequate physical therapy and rehabilitation. Epidural catheters also have been used in this fashion.[163] If sympathetic blocks are effective in producing analgesia but duration is limited, neurolysis with either neurolytic injections or radiofrequency-lesioning techniques can be considered.[164] Spinal cord stimulation appears to be an effective treatment, especially for CRPS type I.[117,122,161,165] Spinal analgesia may be an effective treatment of CRPS when other modalities fail.[163,166,167]

KEY REFERENCES

- Friedly JL, Comstock BA, Turner JA, et al. A randomized trial of epidural glucocorticoid injections for spinal stenosis. *N Engl J Med*. 2014;371(1):11-21.
- Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalagia*. 2013; 33(9):629-808.
- Manchikanti L, Abdi S, Atluri S, et al. An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. part II: Guidance and recommendations. *Pain Physician*. 2013;16(2 Suppl):S49-S283.
- Schiffman E et al. Diagnostic criteria for temporomandibular disorders (DC/TMD) for clinical and research applications: recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group. *J Oral Facial Pain Headache*. 2014;28(1):6-27.
- Vos T, Flaxman AD, Naghavi M et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010. A systemic analysis for the global burden of disease study 2010. *Lancet*. 2012;380(9859):2163-2196.

REFERENCES

Complete references are available online at www.LongneckerAnesthesiology.com.