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Neuropathic Pain

- I. Definition
 - A. Know the current definition of neuropathic pain (Merskey and Bogduk 1994) and reasons for growing criticism against it (Hansson 2002; Backonja 2003).
 - 1. Recognize that neuropathic pain is a consequence of injury or disease affecting the somatosensory system.
 - 2. Know that the patient with neuropathic pain may have concomitant non-neuropathic pain.
- II. Epidemiology of common neuropathic pain syndromes (MacDonald et al. 2000)
 - A. Know that painful peripheral neuropathy is a common complication in HIV/AIDS, diabetes, alcoholism, and vasculitis (Ziegler et al. 1992; Schmader 2002; Schiffito et al. 2002; Koike et al. 2003; Daousi et al. 2004; Wolfe and Trivedi 2004).
 - B. Know that 4 out of 5 patients with idiopathic polyneuropathy and 1 in 3 patients with Guillain Barré syndrome have neuropathic pain (Moulin et al. 1997; Forsberg et al. 2004; Wolfe and Trivedi 2004).
 - C. Know that peripheral neuropathic pain is common after surgical procedures (MacRae 2001), including herniorrhaphy (Poobalan et al. 2001; Neumeyer et al. 2004), thoracotomy (Perttunen et al. 1999, Gotoda et al. 2001), and mastectomy (Wallace et al. 1996; Smith et al. 1999), as well as during treatment with chemotherapeutic agents (Quasthoff and Hartung 2002).
 - D. Know that patients with stroke, spinal cord injury, multiple sclerosis, and syringomyelia frequently develop neuropathic pain, whereas patients with central nervous system tumors or infection rarely do so (Österberg et al. 1994; Andersen et al. 1995; Cohodarevic et al. 2000; Siddall et al. 2003).
 - E. Know that population studies show carpal tunnel syndrome to be very common in certain occupations and in people engaged in repetitive manual work (Atroshi et al. 2003).
 - F. Know that the annual incidence of herpes zoster is around 2–4 cases per 1000 population and that the risk of contracting it increases with age (Schmader 2002).
- III. Etiology
 - A. Know the common causes for neural damage and subsequent pain, i.e., metabolic disease, infection, ischemia, injury, entrapment, connective tissue disease, acquired immunodeficiency, malignancy, drugs, and toxins (Woolf and Mannion 1999; Dworkin 2002; Gonzales et al. 2003; Sommer 2003).
 - B. Know that neuropathic pain may develop without any identifiable cause (e.g., intercostal neuralgia, idiopathic polyneuropathy).
 - C. Know that painful neuropathy may be the first manifestation of a systemic disease.
- IV. Clinical characteristics of neuropathic pain (Jensen et al. 2001; Dworkin 2002; Hansson 2002)
 - A. Know the common symptoms associated with neuropathic pain, e.g., burning pain, electric shock-like pain, pain paroxysms, dysesthesia, and paresthesia (Jensen et al. 2001; Dworkin 2002; Hansson 2002; Sommer 2003). Be aware that aching pain is common in polyneuropathy (Otto et al. 2003) and central pain (Hansson 2002).

- B. Know that questionnaires have been developed to differentiate neuropathic pain from non-neuropathic pain, e.g., the LANSS Pain Scale (Bennett 2001) and the Neuropathic Pain Questionnaire (Krause and Backonja 2003) or to measure various characteristics, e.g., the Neuropathic Pain Scale (Galer and Jensen 1997) and the Neuropathic Pain Inventory (Bouhassira et al. 2004).
 - C. Know the common signs associated with neuropathic pain, including positive (mechanical and thermal allodynia and hyperalgesia, temporal and spatial summation), negative (sensory loss, weakness, and muscle atrophy), and other signs (neuroma signs, referred sensation, swelling, skin flare and discoloration, hyperhidrosis, hypohidrosis, and trophic changes) (Bowsher 1996; Baron 2000; Jensen et al. 2001; Jänig and Baron 2003).
 - D. Know that simple bedside tests alone have low power of distinguishing neuropathic pain from non-neuropathic pain (Rasmussen et al. 2004).
- V. Pathological changes in the nervous system
- A. Know the pathological changes that occur in the affected nerve(s), e.g., Wallerian degeneration, sprouting, formation of end-neuromas and neuromas-in-continuity, and compression-induced atrophy (Devor and Seltzer 1999; Burnett and Zager 2004).
 - B. Know the pathological changes that occur in the central nervous system following disease or injury, such as necrosis, apoptosis, gliosis, demyelination, and cavitation, and know that late effects may occur, e.g., syrinx formation following spinal cord injury (Profyris et al. 2004).
- VI. Pathophysiological mechanisms in the peripheral nerve fibers for neuropathic pain (Devor and Seltzer 1999; Woolf and Mannion 1999; Woolf 2004)
- A. Changes in the peripheral afferents.
 - 1. Know that injury causes ectopic discharges at the site of injury, at the neuroma, and at the dorsal root ganglion.
 - 2. Know that increased activity is also seen in neighboring uninjured C fibers (Wu et al. 2001).
 - 3. Know that upregulation of several sodium channels, downregulation of potassium channels, and reduction in threshold in TRP transducer ion channels have a major role in the generation and maintenance of increased activity.
 - 4. Know that sensitization of a subgroup of mechanoinsensitive C fibers may contribute to hyperalgesia (Orstavik et al. 2003).
 - 5. Know that A fibers may undergo phenotype switch, and start expressing brain-derived neurotrophic factor (BDNF) and substance P.
 - 6. Be familiar with the role of inflammatory mediators, e.g., cytokines, prostaglandins, and serotonin, in the maintenance of peripheral sensitization.
 - 7. Know that hypersensitivity of adrenergic receptors in injured terminals may make them excessively sensitive to the effects of circulating norepinephrine.
 - B. Central changes following peripheral nerve injury or disease (Woolf and Mannion 1999; Ji et al. 2003).
 - 1. Understand the concept of central sensitization and know that several forms of central sensitization occur (both dependent on and independent of nociceptor activity).
 - 2. Appreciate that increased and prolonged ectopic activity in peripheral nociceptors (and in non-nociceptors following phenotype switch) promotes increased synaptic efficacy in the dorsal horn and increased responsiveness of dorsal horn neurons and expansion of their receptive fields.
 - 3. Appreciate that central sensitization explains many features of neuropathic pain, including referral outside the injured nerve's territory and touch-evoked pain.
 - 4. Be aware that central sensitization-like phenomena occur in the rostroventral medulla, amygdala, anterior cingulate cortex, and trigeminal brainstem complex.

5. Be aware of reports of increased sprouting of central terminals of injured fibers within the dorsal horn, and know that conclusive evidence is still lacking.
- C. Be familiar with the significance of activation in spinal astrocytes and microglia in chronic neuropathic pain (Watkins et al. 2001).
 - D. Be aware of increased spontaneous activity in the thalamus as the result of injury to the peripheral and central nervous systems, and understand its relation to pain (Lenz et al. 2000; Nandi et al. 2003).
 - E. Be aware of the structural and functional neuroplastic changes that occur at the subcortical and cortical level following injury to the peripheral or central nervous system and contribute to perception of pain (Flor 2002, 2003; Wall et al. 2002).
 - F. Be aware of the evidence suggesting disruption of spinal inhibition involving, e.g., GABAergic and cannabinoid mechanisms (Drew et al. 2004).
 - G. Be aware of the mechanisms of descending modulation of spinal nociceptive processing, and know that this phenomenon has both inhibitory and facilitatory components (Porreca et al. 2002).
- VII. Investigations (Cruccu et al. 2004)
- A. Know the common bedside tests used to assess positive and negative signs (Cruccu et al. 2004).
 - B. Know the advantages and limitations of conventional neurophysiological tests, e.g., that nerve conduction studies will show level of pathology but cannot detect abnormal C-fiber or A-delta-fiber function (Treede 2003).
 - C. Know the advantages and limitations of quantitative sensory testing (Shy et al. 2003; Chong and Cros 2004).
 - D. Know the advantages and limitations of laser-evoked potentials (Treede 2003; Truini et al. 2004).
 - E. Be aware of the use of structural magnetic resonance imaging and know that it has diagnostic value in sciatica and trigeminal neuralgia and may be useful in selected cases of nerve injury or entrapment (Meaney 1995; Akimoto et al. 2002; Koltzenburg and Bendzsus 2004).
 - F. Be aware of the potential of functional brain imaging in assessment of neuropathic pain.
 - G. Be aware that skin punch biopsies are useful in the diagnosis of small-fiber neuropathies (Griffin et al. 2001).
- VIII. Know the following common neuropathic pain syndromes, including their clinical features, supporting laboratory and radiographic findings, differential diagnosis, natural course, and proposed pathology.
- A. Painful focal neuropathies (including mononeuropathies, plexopathies, and radiculopathies).
 1. Syndromes related to compression of peripheral nerves or nerve roots, e.g., lumbar and cervical radiculopathies, carpal and tarsal tunnel syndrome, and meralgia paresthetica (Stewart 2000).
 2. Syndromes related to inflammation of peripheral nerves (e.g., acute herpes zoster and Guillain-Barré syndrome (Moulin et al. 1997; Haanpää et al. 1999).
 3. Syndromes related to ischemia/infarction of peripheral nerves, e.g., diabetic or vasculitic mononeuropathies (Griffin 2001; Dyck and Vindebank 2002).
 4. Syndromes associated with nerve injury, with or without neuroma formation, e.g., stump pain, postmastectomy pain, postherniorrhaphy pain (Macrae 2001).
 5. Common syndromes with unknown etiology (e.g., intercostal neuralgia).
 - B. Painful polyneuropathies (including acute-onset and slow-onset distal symmetrical polyneuropathies)
 1. HIV (Schiffito et al. 2002; Luciano et al. 2003).

2. Mixed small- and large-diameter-fiber polyneuropathies, e.g., diabetic, vasculitic, toxic, inflammatory, and paraneoplastic (Otto et al. 2003; Sommer 2003; Wolfe and Trivedi 2004).
 3. Small-fiber neuropathies, e.g., idiopathic, Fabry's disease, amyloid, acute-onset diabetic neuropathy (Luciano et al. 2002; Lacomis 2003).
- C. Postherpetic neuralgia (Watson 2003).
- D. Trigeminal neuralgia and other cranial neuralgias (Nurmikko and Eldridge 2001).
- E. Phantom limb pain (Flor 2002).
- F. Brachial plexus avulsion (Wynn Parry 1980).
- G. Central post-stroke pain (Bowsher 1996; Gonzales and Casey 2003).
- H. Other common central pain syndromes, e.g., spinal cord injury, spinal cord tumor, tethered cord syndrome, multiple sclerosis, syringomyelia (Gonzales and Casey 2003; Finnerup and Jensen 2004).
- I. Cancer-associated neuropathic pain, e.g., tumor invasion of nerve and plexus, epidural metastases, post-radiation syndromes, and drug-induced neuropathies.
- J. Complex regional pain syndrome (CRPS) type II (Jänig and Baron 2003).

IX. Therapeutic interventions applied in neuropathic pain

- A. Know the common pharmacological approaches used for neuropathic pain of all types.
1. Be aware of the multiple coexisting mechanisms in many neuropathic pain conditions and the advantages and disadvantages of combination therapy.
 2. Be aware of the limitations of controlled clinical trials, and familiar with methods for assessing the quality of publications (Jadad and McQuay 1993).
 3. Know specific agents and syndromes where data from controlled clinical trials have established efficacy (Sindrup and Jensen 1999; Dworkin et al. 2003a).
 - a. Tricyclic antidepressants (McQuay et al. 1996).
 - b. Serotonin-norepinephrine reuptake inhibitors (SNRIs), e.g., venlafaxine and duloxetine (Sindrup et al. 2003; Rowbotham et al. 2004).
 - c. Gabapentin and pregabalin (Mellekers et al. 2001, Dworkin et al. 2003b).
 - d. Other antiepileptic drugs, e.g., carbamazepine in trigeminal neuralgia and lamotrigine in diabetic and HIV neuropathy (Eisenberg et al. 2001; Simpson et al. 2003).
 - e. Opioids (Kalso et al. 2004).
 - f. Topical treatments, e.g., capsaicin, lidocaine patch (Meier et al. 2003; Mason et al. 2005).
 - g. Tramadol (Dühmke et al. 2004).
 - h. Cannabinoids in multiple sclerosis (Svendsen et al. 2004, Rog et al. 2005).
 - i. Bupropion (Schemenuck et al. 2001).
 - j. Dextromethorphan (Sang et al. 2002).
 4. Know agents which may have efficacy but data are insufficient or conflicting (e.g., selective serotonin reuptake inhibitors [SSRIs], adenosine, i.v. ketamine).
 5. Be aware of data suggesting lack of effect of drugs in certain neuropathic pains, e.g., amitriptyline in HIV neuropathy (Kieburtz et al. 1998), dextromethorphan in postherpetic neuralgia (Sang et al. 2002), topiramate in diabetic neuropathy (Thienel et al. 2005), riluzole in peripheral neuropathic pain (Galer et al. 2000), and sodium valproate in spinal cord injury (Drewes et al. 1994).
 6. Be aware of the lack of evidence supporting the use of nonsteroidal anti-inflammatory drugs in neuropathic pain.
 7. Know the contraindications, side effects, and interactions of drugs commonly used in neuropathic pain, and how to minimize the risk of adverse effects.
 8. Know the indications and contraindications for prescribing strong opioids in neuropathic pain.

9. Know the drugs traditionally used in the treatment of sympathetically mediated pain and be aware of the limited data in support of their use (e.g., corticosteroids, phenoxybenzamine, prazosin, guanethidine, and clonidine).
- B. Know the data supporting intrathecal and epidural administration of drugs (ziconotide, morphine, clonidine, and bupivacaine) in selected cases (Bennett et al. 2000).
 1. Be aware of the indications and contraindications for drug delivery systems.
 2. Be aware of risks and complications (e.g., infection, overdosing, granuloma formation, catheter migration).
 - C. Know the limited role of regional approaches in the management of chronic neuropathic pain other than in syndromes in which pain is thought to be primarily sympathetically mediated (Abram 2000). Know that published evidence supporting the use of chemical sympathectomy in neuropathic pain is virtually absent (Mailis and Furlan 2001). Be aware of the indications, techniques, and potential complications of sympathetic blockade.
 - D. Know the role of surgical approaches to pain management in patients with neuropathic pain.
 1. Be aware of the role of peripheral procedures in selected patients with specific pain syndromes, e.g., decompression of entrapped peripheral nerves, microvascular decompression in trigeminal neuralgia, or controlled gangliolysis in trigeminal neuralgia (Stewart 2000; Nurmikko and Eldridge 2001).
 2. Be aware of the conflicting reports regarding surgical procedures in the treatment of post-injury neuromas.
 3. Be aware of extremely limited data supporting the use of neurolytic procedures in peripheral neuropathic pain (e.g., cryosurgery, phenol).
 4. Be aware of the data suggesting efficacy of dorsal root entry zone lesions in selected patients with specific pain syndromes, e.g., avulsion of the brachial plexus, or pain following spinal cord injury (Sindou et al. 2001).
 - E. Be familiar with neurostimulation in the management of neuropathic pain.
 1. Be aware of the limited data published on the efficacy of transcutaneous electrical nerve stimulation and other similar electric stimulation methods.
 2. Be aware that there are insufficient data supporting the efficacy of acupuncture in the management of neuropathic pain to warrant any conclusions.
 3. Be aware of the data supporting the use of peripheral nerve stimulation in selected neuropathic syndromes (Eisenberg et al. 2004; Johnson and Burchiel 2004).
 4. Be aware of the emerging data supporting the use of spinal cord stimulation in the management of selected neuropathic pain conditions (Quigley et al. 2003; Mailis-Gagnon et al. 2004).
 5. Be aware of the data suggesting benefit from motor cortex stimulation in selected neuropathic pains.
 6. Be aware of the data suggesting benefit from deep brain stimulation in selected patients with neuropathic pain.
 - F. Know the utility of rehabilitation to neuropathic pain management.
 1. Understand the fundamental importance of physical therapy in treatment for some neuropathic disorders (e.g., CRPS).
 2. Know the analgesic potential of orthoses and prostheses in selected patients with particular pain syndromes (e.g., a prosthesis for a patient with stump pain and phantom pain).
 3. Have knowledge of a multidisciplinary approach to the patient with pain and related disabilities secondary to neuropathic lesion, and understand the importance of maintained function as a goal equal in importance to the goal of pain relief.

G. Recognize the need for behavioral and psychological approaches to neuropathic pain.

1. Know that depression and anxiety are commonly associated with neuropathic pain and may need specific therapy.
2. Know that sleep disturbance is common in neuropathic pain.
3. Know that quality of life is severely reduced in chronic neuropathic pain.
4. Be aware of the efficacy of cognitive-behavioral pain management programs in neuropathic pain.

REFERENCES

- Abram SE. Neural blockade for neuropathic pain. *Clin J Pain* 2000; 16(2 Suppl):S56–61.
- Akimoto H, Nagaoka T, Nariai T, et al. Preoperative evaluation of neurovascular compression in patients with trigeminal neuralgia by use of three-dimensional reconstruction from two types of high-resolution magnetic resonance imaging. *Neurosurgery* 2002; 51:956–961.
- Andersen G, Vestergaard K, Ingeman-Nielsen M, Jensen TS. Incidence of post-stroke pain. *Pain* 1995; 61:187–193.
- Atroshi I, Gummesson C, Johnsson R, McCabe SJ, Ornstein E. Severe carpal tunnel syndrome potentially needing surgical treatment in a general population. *J Hand Surg [Am]* 2003; 28:639–644.
- Backonja M-M. Defining neuropathic pain. *Anesth Analg* 2003; 97:785–790.
- Baron R. Peripheral neuropathic pain: from mechanisms to symptoms. *Clin J Pain* 2000; 16(2 Suppl):S12–20.
- Bennett G, Deer T, Du Pen S, et al. Future directions in the management of pain by intraspinal drug delivery. *J Pain Symptom Manage* 2000; 20:S44–50.
- Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain* 2001; 92:147–157.
- Bouhassira D, Attal N, Fermanian J, et al. Development and validation of the Neuropathic Pain Symptom Inventory. *Pain* 2004; 108:248–257.
- Bowsher D. Central pain: clinical and physiological characteristics. *J Neurol Neurosurg Psychiatry* 1996; 61:62–69.
- Burnett MG, Zager EL. Pathophysiology of peripheral nerve injury: a brief review. *Neurosurg Focus* 2004; 16(5):E1.
- Chong PST, Cros DP. Technology literature review: quantitative sensory testing. *Muscle Nerve* 2004; 29:734–747.
- Cohodarevic T, Mailis A, Montanera W. Syringomyelia: pain, sensory abnormalities and neuroimaging. *J Pain* 2000; 1:54–66.
- Cruccu G, Anand P, Attal N, et al. EFNS Guidelines on neuropathic pain assessment. *Eur J Neurol* 2004; 11:153–162.
- Daousi C, MacFarlane IA, Woodward A, et al. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. *Diabet Med* 2004; 21:976–982.
- Devor M, Seltzer Z. Pathophysiology of damaged nerves in relation to chronic pain. In: Wall PD, Melzack R (Eds). *Textbook of Pain*. Edinburgh: Churchill Livingstone, 1999, pp 129–144.
- Dyck PJ, Vindebank AJ. Diabetic and nondiabetic lumbosacral radiculoplexus neuropathies: new insights into pathophysiology and treatment. *Muscle Nerve* 2002; 25:477–491.
- Dworkin RH. An overview of neuropathic pain: syndromes, symptoms, signs and several mechanisms. *Clin J Pain* 2002; 18:343–349.
- Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain. Diagnosis, mechanisms, and treatment recommendations. *Arch Neurol* 2003a; 60:1524–1534.
- Dworkin RH, Corbin AE, Young JP Jr, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology* 2003b; 60:1274–1283.
- Eisenberg E, Lurie Y, Braker C, Daoud D, Ishay A. Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study. *Neurology* 2001; 57:505–509.
- Eisenberg E, Waisbrod H, Gerbershagen HU. Long-term peripheral nerve stimulation for painful nerve injuries. *Clin J Pain* 2004; 20:143–146.
- Finnerup NB, Jensen TS. Spinal cord injury pain—mechanisms and treatment. *Eur J Neurology* 2004; 11:73–82.
- Flor H. Phantom-limb pain. Characteristics, causes and treatment. *Lancet Neurol* 2002; 1:182–189.
- Flor H. Remapping somatosensory cortex after injury. *Adv Neurol* 2003; 93:195–204.
- Forsberg A, Press R, Einarsson U. Impairment in Guillain-Barré syndrome during first two years after onset: a prospective study. *J Neurol Sci* 2004; 227:131–138.
- Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale. *Neurology* 1997; 48:332–338.
- Galer BS, Twilling U, Harle J, et al. Lack of efficacy of riluzole in the treatment of peripheral neuropathic pain conditions. *Neurology* 2000; 55:971–975.
- Gonzales GR, Casey KL. Central pain syndromes. In: Jensen TS, Wilson PR, Rice ACR (Eds). *Clinical Pain Management: Chronic Pain*. London: Arnold, 2003, pp 403–416.
- Griffin JW. Vasculitic neuropathies. *Rheum Dis Clin North Am* 2001; 27:751–760.
- Griffin JW, McArthur JC, Polydefkis M. Assessment of cutaneous innervation by skin biopsies. *Curr Opin Neurol* 2001; 14:655–659.

- Gotoda Y, Kambara N, Sakai T, et al. The morbidity, time course, and predictive factors for persistent post-thoracotomy pain. *Eur J Pain* 2001; 5:89–96.
- Haanpää M, Laippala P, Nurmi T. Pain and somatosensory dysfunction in acute herpes zoster. *Clin J Pain* 1999; 15:78–84.
- Hansson P. Neuropathic pain: clinical characteristics and diagnostic workup. *Eur J Pain* 2002; 6(Suppl A):47–50.
- Jänig W, Baron R. Complex regional pain syndrome: mystery explained? *Lancet Neurol* 2003; 2:687–695.
- Jensen TS, Gottrup H, Sindrup SH, Bach FW. The clinical picture of neuropathic pain. *Eur J Pharmacol* 2001; 429:1–11.
- Ji R-R, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP. Do pain and memory share similar mechanisms? *Trends Neurosci* 2003; 26:696–705.
- Johnson MD, Burchiel KJ. Peripheral stimulation for treatment of trigeminal postherpetic neuralgia and trigeminal posttraumatic neuropathic pain: a pilot study. *Neurosurgery* 2004; 55:135–141.
- Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain* 2004; 112:372–380.
- Kiebertz K, Simpson D, Yiannoutsos C, et al. A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. *Neurology* 1998; 51(6):1682–1688.
- Koike H, Iijima M, Sgiura M, et al. Alcoholic neuropathy is clinicopathologically distinct from thiamine-deficiency neuropathy. *Ann Neurol* 2003; 54:19–29.
- Koltzenburg M, Bendszus M. Imaging of peripheral nerve lesions. *Curr Opin Neurol* 2004; 17:621–626.
- Krause SJ, Backonja MM. Development of a neuropathic pain questionnaire. *Clin J Pain* 2003; 19:306–314.
- Lenz FA, Lee JI, Garonsik IM, et al. Plasticity of pain-related neuronal activity in the human thalamus. *Prog Brain Res* 2000; 129:259–273.
- Luciano CA, Russell JW, Banerjee TK. Physiological characterization of neuropathy in Fabry's disease. *Muscle Nerve* 2002; 26:622–629.
- Luciano CA, Pardo CA, McArthur JC. Recent developments in the HIV neuropathies. *Curr Opin Neurol* 2003; 16:403–409.
- MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 2000; 123:665–676.
- Macrae WA. Chronic pain after surgery. *Br J Anaesth* 2001; 87:88–98.
- Mailis A, Furlan A. Sympathectomy for neuropathic pain. *Cochrane Database Syst Rev* 2002; 1:CD002918.
- Mailis-Gagnon A, Furlan AD, Sandoval JA, Taylor R. Spinal cord stimulation for chronic pain. *Cochrane Database Syst Rev* 2004; 3:CD003783.
- Meaney JF, Eldridge PR, Dunn LT, et al. Demonstration of neurovascular compression in trigeminal neuralgia with magnetic resonance imaging. Comparison of surgical findings in 52 consecutive operative cases. *J Neurosurg* 1995; 83:799–805.
- Merskey H, Bogduk N (Eds). *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*, 2nd ed. Seattle: IASP Press, 1994.
- Moulin DE, Hagen N, Feasley TE, Amiseh R, Hahn R. Pain in Guillain-Barré syndrome. *Neurology* 1997; 48:328–331.
- Nandi D, Aziz T, Carter H, Stein J. Thalamic field potentials in chronic central pain treated by periventricular gray stimulation: a series of eight cases. *Pain* 2003; 101:97–107.
- Neumayer L, Giobbie-Hunder A, Jonasson O, et al. Open mesh versus laparoscopic mesh repair of inguinal hernia. *N Engl J Med* 2004; 350:1819–1827.
- Nurmikko TJ, Eldridge PR. Trigeminal neuralgia. *Br J Anaesth* 2001; 87:117–132.
- Orstavik K, Weidner C, Schmidt et al. Pathological C-fibers in patients with a chronic painful condition. *Brain* 2003; 126:567–578.
- Österberg A, Boivie J, Holmgren H, Thuomas K-A, Johansson I. The clinical characteristics and sensory abnormalities of patients with central pain caused by multiple sclerosis. In: Gebhart GF, Hammond DL, Jensen TS (Eds). *Proceedings of the 7th World Congress on Pain*, Progress in Pain Research and Management, Vol. 2. Seattle: IASP Press, 1994, pp 789–796.
- Otto M, Bak S, Bach FW, Jensen TS, Sindrup SH. Pain phenomena and possible pain mechanisms in patients with painful polyneuropathy. *Pain* 2003; 101:187–192.
- Perttunen K, Tasmuth T, Kalso E. Chronic pain after thoracic surgery: a follow-up study. *Acta Anaesthesiol Scand* 1999; 43:563–567.
- Poobalan AS, Bruce J, King PM, et al. Chronic pain and quality of life following open inguinal hernia repair. *Br J Surg* 2001; 88:1122–1126.
- Porreca F, Ossipov MH, Gebhart GF. Chronic pain and medullary descending facilitation. *Trends Neurosci* 2002; 25:319–325.
- Profyris C, Cheema SS, Zang D, et al. Degenerative and regenerative mechanisms governing spinal cord injury. *Neurobiol Dis* 2004; 15:415–436.
- Quasthoff S, Hartung P. Chemotherapy-induced peripheral neuropathy. *J Neurol* 2002; 249:9–17.
- Quigley DG, Arnold J, Eldridge PR, et al. Long-term outcome of spinal cord stimulation and hardware complications. *Sterotact Funct Neurosurg* 2003; 81:50–56.
- Rasmussen PV, Sindrup SH, Jensen TS, Bach FW. Symptoms and signs in patients with suspected neuropathic pain. *Pain* 2004; 110(1–2):461–469.
- Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy. *Pain* 2004; 110:697–706.
- Sang CN, Booher S, Gilron I, Parada S, Max MB. Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia: efficacy and dose-response trials. *Anesthesiology* 2002; 96:1053–1061.
- Schiffito G, McDermott M, McArthur JC, et al. Incidence of and risk factors for HIV associated distal sensory polyneuropathy. *Neurology* 2002; 58:1764–1768.

- Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. *Clin J Pain* 2002; 18:350–354.
- Schemenuck MR, Sherman S, Davis B. Double-blind, randomized trial of bupropion SR for the treatment of neuropathic pain. *Neurology* 2001; 57:1583–1588.
- Shy ME, Frohmann EM, So YT, et al. Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2003; 60:898–904.
- Siddall PJ, McClelland JM, Rutkowski SB, Cousins MJ. A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain* 2003; 103:249–257.
- Simpson DM, McArthur JC, Olney M, et al. Lamotrigine for HIV-associated painful sensory neuropathies: a placebo-controlled trial. *Neurology* 2003; 60:1508–1514.
- Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999; 83:389–400.
- Sindrup SH, Bach FW, Madsen C, Gran LE, Jensen TS. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. *Neurology* 2003; 60:1284–1249.
- Sindou M, Martens P, Wael M. Microsurgical DREZotomy for pain due to spinal cord and/or cauda equina injuries: long-term results in a series of 44 patients. *Pain* 2001; 92:159–171.
- Smith WCS, Bourne D, Squair J, Phillips DO, Chamber AW. A retrospective study of post mastectomy pain syndrome. *Pain* 1999; 83:91–95.
- Sommer C. Painful neuropathies. *Curr Opin Neurol* 2003; 16:623–628.
- Stewart JD. *Focal Peripheral Neuropathies*, 3rd ed. Philadelphia: Lippincott William & Wilkins, 2000.
- Svensen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 2004; 329:253.
- Thienel U, Neto W, Schwabe SK, Vijapurkar U. Topiramate in painful diabetic polyneuropathy: findings from three double-blind, placebo-controlled trials. *Acta Neurol Scand* 2005; in press.
- Treede RD. Neurophysiological studies of pain pathways in peripheral and central nervous system disorders. *J Neurol* 2003; 250:1152–1161.
- Truini A, Romanelli A, Galeotti F, Iannetti GD, Cruccu G. Laser evoked potentials for assessing sensory neuropathy in human patients. *Neurosci Lett* 2004; 361:25–28.
- Wallace MS, Wallace AM, Lee J, Dobke MK. Pain after breast surgery: a survey of 282 women. *Pain* 1996; 66:195–205.
- Watkins LR, Milligan ED, Maier SF. Spinal cord glia: new players in pain. *Pain* 2001; 93:201–205.
- Watson CPN. Postherpetic neuralgia. In: Jensen TS, Wilson PR, Rice ASC (Eds). *Chronic Pain: Clinical Pain Management*. London: Arnold, 2003, pp 451–458.
- Wolfe GI, Trivedi JA. Painful neuropathy and its nonsurgical treatment. *Muscle Nerve* 2004; 30:3–19.
- Woolf CJ. Dissecting out mechanisms responsible for peripheral neuropathic pain: implications for diagnosis and therapy. *Life Sci* 2004; 74:2605–2610.
- Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms and management. *Lancet* 1999; 353:1959–1964.
- Wu G, Ringkamp M, Hartke TV, et al. Early onset of spontaneous activity in uninjured C-fiber nociceptors after injury to neighboring nerve fibers. *J Neurosci* 2001; 21:RC140(1–5).
- Wynn Parry CB. Pain in avulsion lesions of the brachial plexus. *Pain* 1980; 9:41–53.
- Ziegler D, Gries FA, Spuler M, Lessmann F. The epidemiology of diabetic neuropathy. *J Diabet Complications* 1992; 6:49–57.