REVIEWS

Pain management in elderly: A challenge to practicing clinicians

Dominic Gerard Benjamin^{1*}

¹Consultant Geriatrician & Geriatric Diabetic Specialist, Bangalore Baptist Hospital, Bangalore, Karnataka, India

Abstract

Persistent pain, which prolongs beyond the normal healing time, is the most common cause of disability in elderly patients and its management needs a multidisciplinary approach. Pain assessment is often challenging in such patients due to the existence of co-morbid illness and cognitive impairment in some cases.

Keywords: Persistent pain, chronic pain, cognitive impairment, NSAIDs , neuropathic pain, opioids

Introduction

Pain is the most common cause for consulting a clinician for community dwellers and in elderly patients. It is associated with substantial morbidities and disabilities. Epidemiological studies indicate that the prevalence of pain among community dwellers varies between 25%-56%, and the prevalence of back pain among older adults is between 21%-49%. Musculoskeletal pain (back pain and arthritis), neuropathic pain secondary to diabetes mellitus, and postherpetic neuralgia have been identified as the primary causes of pain in elderly subjects, and phantom limb and claudication as the secondary causes in small proportion of individuals. Cancer pain secondary to metastasis/local invasion is also a common cause for severe pain. Pain is also common in institutionalized adults. More than 50% of individuals suffer from chronic pain.

Several competing theories on pain have been proposed in the past. One such theory has categorized the pain as two different entities: pain as an emotion and as a specific sensation.¹ Recent research and advances in medicine have contributed to further enhance our knowledge on pain perception, and also to develop newer pain management strategies. Specificity theory on pain has gained wider recognition during the early part of the 19th century. Unfortunately, there is a tendency among clinicians to view pain dualistically, especially for chronic pain. Specificity theory of pain has theorized that painspecific nerves from various parts of the body project to the brain via the spinal cord.² In the early part of the 20th century, there was a growing concept of central summation of pain i.e. the sensory inputs from noxious stimuli (nociceptors) converge both spatially (across areas of the body) and temporally (over time). The famous theories proposed on pain include: summation theory proposed by Livingstone, pattern theory by Weddell, and sensory interaction theory by Noordendos.³⁻⁵ In the 1960's, based on Noordendos theory, the Gate control theory of pain was formulated.⁶ This theory described a 'gating' mechanism in the substantia gelatinosa area of the spinal cord. This mehcanism modulates the balance between small diameter nerve fibres (facilitate pain) and large diameter fibers (inhibit pain). This relative balance determine the activity of a group of nerves transmitting pain signals in the spinal cord. Gate control theory has proposed the following three dimensions for pain:

- Sensory: Discriminative dimension involving localization, quality, and intensity of the painful stimuli
- Cognitive: Evaluative dimension, appraisal of the meaning, and anticipation of what might occur
- Affective: Motivational dimension, includes emotional response and the motivation to avoid harm⁷

The neuromatrix theory of pain proposed by Melzack hypothesized that the pain process involves the interaction of endocrine, endogenous, opioid, and autonomic nervous systems.⁸ This theory integrates various brain processes

involved in pain. Based on the observations related to phantom limb pain, the theory proposes that matrix of nerve cells in the brain creates a sense of 'self' in the individual.

Pain is truly a subjective phenomenon. Hence, its assessment requires careful and detailed interaction between the patient and healthcare professional. The major challenge in accurate pain assessment in older adults is the underreporting of pain. This might be possible because they are stoic or want to be perceived as 'good patients'. Additionally, the presentation of concurrent illnesses and multiple problems makes pain evaluation more difficult. Pain assessment can be a formidable challenge in patients with cognitive impairment. Assessment of behavioral signs is the preferred method to assess pain in individuals with cognitive impairment. Moreover, there are relatively few validated scales for pain evaluation in older individuals. The verbal and visual analogue scales used in younger individuals do not have the same degree of validation in elderly.

The presentation of common diseases is also found to be altered in elderly. They may present with painless myocardial infarction, painless acute abdominal emergency, and several other common emergencies with atypical presentation. This is partly due to the alteration in pain sensors, secondary to age-related changes (Table 1). Clinicans should be aware that concurrent illness and sensory impairments may mask pain complaints in elderly patients.

Pain can be quite variable in description, character, and intensity in older adults. It can be categorized as acute

and chronic based on the duration of pain, and nociceptive and neuropathic based on the underlying mechanisms. Acute pain is defined by a distinct onset, obvious cause, and short duration. It is often associated with autonomic activity including tachycardia, diaphoresis, and changes in blood pressure. Acute pain usually indicates acute injury or disease. Chronic pain is usually defined as those persisting beyond 3 months. The newer term 'persistent pain' is preferred over 'chronic pain', as the latter is often associated with negative stereotypes.

Persistent pain can often be unparallel to the observed injury and associated with prolonged functional impairment (both physical and psychological). Autonomic signs may be absent. Many elderly patients manifest 'vicious cycle' of pain. It is a concept that relates to maladaptive and the downward functional spiraling of many individuals with persistent pain. It is also associated with deconditioning, psychological disorders (mood swings and catastrophization), and progressive functional impairments - cycle of worsening pain and progressive disability.

It is imperative to identify the underlying mechanism of pain for effective management of pain. Nociceptive pain arising from tissue injury, inflammation or mechanical deformation responds well to common analgesic medications. Neuropathic pain, resulting from pathological process, arises from peripheral or central nervous system, e.g. diabetic neuropathy, postherpetic neuralgia, and phantom limb pain. Neuropathic pain syndrome is often persistent and difficult to treat.

Pain associated with cancer may result from the tumor

Pain components	Age-related changes			
Pain receptors	 50% decrease in Pacini's corpuscles 10-30% decrease in Messiner's corpuscles/Merkel's disk 			
Peripheral nerves	 Myelinated nerves show decreased density, increased abnormal degenerating fibres, and slow velocity conduction Unmyelinated nerves show decrease in the number of large fibres and substance P 			
Central nervous system	 Loss of dorsal horn neurons with altered inhibition and hyperalgesia Loss of neurons in cortex midbrain and brain stem 			

Table 1: Effect of age-related changes on different pain components noted in elderly

itself or can be a consequence of therapy (e.g., surgery, chemo or radiation therapy). In view of multiple etiologies associated with neoplasia, advanced cancer pain is a typical example of a mixed pain state.

Dysfunctional pain is a group of pain syndromes characterized by amplification of pain signaling, in the absence of either inflammation or injury (as in nociceptive pain) or damage to the nervous system (as in neuropathic pain). These conditions include pain states such as fibromyalgia, irritable bowel syndrome, and interstitial cystitis. The precise pathophysiologic mechanisms of pain in these disorders are unclear, although they share some features of neuropathic pain.

Pain assessment

The measurement of pain intensity is an essential element in the broader pain assessment. Besides the utility of such scales in the research world, the most effective applicability of such scales is in the temporal measure of effectiveness of the ongoing treatments.

A variety of pain scales are used to categorize and quantify the magnitude of pain. Pain scales can be grouped into multi and unidimensional scales. Multidimensional scales provide more in depth measurement and evaluation of pain eg. McGill pain questionnaire, Wisconsin brief pain inventory, geriatric pain measure, and neuropathic pain scale. Since the unidimensional scales usually measure only the pain intensity, they are easy to use and require little time or training, eg. visual analog scale, present pain intensity scale, Faces diagram, Sloan Kettering pain card, and verbal 0-10 scale.

Cognitive impairment, dementia, delirium, and stroke can present substantial challenges to pain assessment. Individuals with mild cognitive impairment are no less valid than those with normal cognitive impairment. The Discomfort Scale for Patients with Dementia of the Alzheimer Type (DS-DAT) is difficult to validate because, it is generated based on the impressions of nursing staff caring for demented patients. The series of items considered for DS-DAT include: negative vocalization, noisy breathing, frightened facial expression, sad vs. content facial expression, frown, tense vs. relaxed body language, and fidgeting. As the name indicates, the DS-DAT is a discomfort scale and may not assess the pain directly. It is unclear whether distress, discomfort, or pain is being assessed. Behavioural methods of pain assessment may be valid in the presence or absence of pain, but they do not assess the intensity of pain. Certain facial expressions are common with intense pain, but they are not necessarily graded responses.

Pain management

Pain is one of the most apprehensive and pervasive symptoms noted among elderly subjects. It is often under reported and inadequately treated in elderly subjects, despite the availability of effective pain killers.¹⁶⁻¹⁸ One among the various reasons could be cultural. Especially in the eastern culture, pain and suffering are accepted and tolerated or many a times older adults think this is part of ageing. Doctors tend to ignore pain and concentrate more on the chronic diseases, individuals with persistent pain are negatively stereotyped.

There is convincing evidence to suggest an association between the presence of musculoskeletal pain and physical disability.¹⁰ The most common cause of chronic non-cancer pain among elderly is musculoskeletal pain due to arthritis, myofascial pain etc. The prevalence of pain noted in adults over 65 years is around 19-25%.¹¹⁻ ¹³ The significant proportion of individuals, residing in the care home, experience pain due to arthritis (24%) and previous fracture (14%).¹⁴ Some studies have shown higher prevalence of arthritis (about 70%) in care home residents.¹⁵ Due to the high prevalence of pain, the Americian pain society has designated pain as the 'fifth vital sign', which should be documented during every outpatient and inpatient admission.¹⁹

It is very important to set goals of pain management at the initial consultation itself in individuals suffering from persistent pain. Complete elimination of pain is not possible in majority of patients. The patient should be informed that the key management goal is to achieve pain control and not complete elimination of pain. This may help the patient to set realistic expectations. The nonpharmacotherapies may help individuals experiencing persistent pain to cope with some element of pain and avoid the physical and psychological comorbidities such as physical deconditioning and depression. Patients or their caregivers should maintain a daily pain log for recording the pain intensity, medications and side effects, response to treatment, and activities associated with pain. It is imperative for patients to obtain a sense of control over pain. High self-efficacy decreases the risk of associated sequelae. A study by Turner et al. has showed that, among retirement community residents, higher self-efficacy measures for the management of pain were associated with reduced disability and depression, and better pain coping strategies.

Non-pharmacological strategies

American Geriatrics Society has putforth a clinical practice guideline for the management of chronic pain in older populations in 1998 and it was revised in 2002.20 Majority of the clinicans follow the WHO stepladder guidelines.²¹ A wide number of non-pharmacological therapies are used alone or in combination with appropriate pharmacological treatment to manage pain of musculoskeletal origin and to address the sensorimotor dysfunction in patients with musculoskeletal disorders. These can be broadly categorized as electrotherapy modalities (e.g. transcutaneous electrical nerve stimulation [TENS]), acupuncture, thermal modalities (e.g. moist heat, ultrasound), manual therapies (e.g. manipulation or massage), and exercise. Increasingly, physiotherapists are adopting evidence-based approach with proven effectiveness for patient management.

TENS: It is one of the most commonly used electrotherapy modalities. It is usually used as a self-administered therapy in which the patient is given initial instructions on safe and appropriate use of the TENS device and the treatment can be followed according to a predefined schedule. TENS is administered as high frequency (>50Hz), low frequency (<10 Hz), or burst TENS (bursts of high-frequency stimulation administered at a much lower frequency). It is generally used for treating musculoskeletal pain, neuropathic pain, acute or chronic pain, and postoperative pain.²²⁻²⁵ Clinical trials have yielded mixed results on its efficacy. Marchand et al. have showed that high-frequency TENS treatment significantly reduced the affective component of pain.²⁶ In contrast, controlled trials and more recent meta-analysis have concluded that TENS is not effective in the treatment of chronic low back pain.²⁷⁻²⁹ Although the evidence is not conclusive, it is still used to treat musculoskeletal pain in elderly patients.

Acupuncture: It is administered via insertion of needles into designated acupuncture points, and subsequently the points are stimulated either using electrical current or manual manipulation. Manual acupuncture produces a short-term improvement in pain and function in patients with osteoarthritis of the knee, and similar results have been observed for osteoarthritis of the cervical spine and temporomandibular joint disorders.³⁰⁻³²

Superficial heat: The use of heat to relieve pain of musculoskeletal origin is common. Heat can be superficially applied using moist hot packs, infrared light, paraffin wax and hot water bath immersion. The most common method used for treating musculoskeletal conditions is moist hot packs. Moist hot packs are applied over the area of pain for 20-30 minutes to heat the superficial tissues. This method helps in increasing skin and joint temperature and blood flow, and decreasing joint stiffness.^{33, 34}

Ultrasound: As a therapeutic modality for relieving pain, it is applied through the skin overlying the painful area. Many studies assessing the efficacy of ultrasound on musculoskeletal pain have reported mixed findings.³⁵⁻³⁷

Pharmacological approach

Three step-WHO analgesic ladder provides the most universally accepted approach to manage pain. The first step of the ladder, which deals with management of mild pain, recommends the use of non-opioid drugs with or without adjuvants. The subsequent two steps deal with management of mild to moderate and moderate to severe pain that may require addition of opioid medications to control pain (Fig.1).

Musculoskeletal pain

The current practice is to commence with a full dose of paracetamol one gram 4 times daily and continue the medication if the pain relief is good (>50%) (Fig. 1). If the pain relief is poor (<50%), nonsteroidal anti-inflammatory drugs (NSAIDs) should be administered under close monitoring. The commonly used NSAIDs are listed in table 2.

Non-opioids confer many advantages including ease of use and availability, low cost, and their effectiveness against wide range of musculoskeletal ailments. Disadvantages of NSAIDs include short-term side effects (commonly gastrointestinal bleeding, acute renal impairment, worsening of hypertension, increase acidity) and long-term effects such as chronic renal failure and cardiovascular events. NSAIDs have a dose ceiling effect and they could be used alone for mild pain. For moderate pain we need to add adjuvants or opioids.

Adjuvants that can be used for mild to moderate pain

Fig. 1: Algorithm depicting the use of pain relievers



Table. 2: Pharmacologic characteristics of commonly used NSAIDS

Class	Generic name	Onset of action	Dosing schedule	Recommended dose	Routes of administration
P-phenol derivatives	Paracetamol	10-60 min	q4-6h	4 gm	PO, IV
Salicylates	Aspirin	2 hrs	q4-6h	2.4 gm	PO/PR
Propionic acid	lbuprofen Naproxen	30-60 min 1hr	q4-8h q6-12h	1.2 gm 1.2 gm	PO/IV PO
Acetic acid	Etodolac Indomethacin Diclofenac	2-4 hrs 30 min 30-60 min	q6-8h q8-12h q8h	600 mg 100 mg 150 mg	PO PO, PR, PV PO
Enolic acid	Piroxicam Meloxicam	1 hr 4-5 hrs	Daily Daily	20 mg 7.5 mg	PO PO
Selective COX2-inhibitors	Celecoxib	3 hrs	Daily-q12h	200 mg	PO

First-line drugs

- Gabapentin 100-300 mg tid, increase by 300-400 mg increments every 5-7 d to 3600 mg qd, divided in 3-4 doses
- Pregabalin 50 mg tid, increase to 100 mg tid, consider further titration upto 200 mg tid. Tricyclic antidepressants 10-25 mg at night, increase by 10-25 mg increments every 7 d to 100-150 mg.
- SNRI-duloxetine 30-60 mg qd, increase by 30-60 mg increments up to 120 mg a day
- Tramadol 50 mg qd or bid, increase by 50 mg increments every 5-7 d to a maximum of 100 mg qid

Second-line drugs

- Carbamazepine 100-200 mg qd or bid, increase by 100-200 mg every 7 d to 600 mg qd in divided doses
- Venlafaxine XR 75 mg qd, increase by 75 mg increments every 7 d to 150-225 mg qd
- Opiate analgesics of varying doses, initiate with short-acting agent qid, as needed. After 1-2 wk, replace with longer-acting agent on a qd or bid schedule.

Topical applicants

- Capsaicin 0.075% apply tid or qid, can be considered as the first-line or as an adjunctive therapy
- Lidocaine 5% patches

are tricyclic antidepressants (eg. amitriptyline and SNRIduloxetine) and anticonvulsants (eg. gabapentin and pregabalin). Low-dose diazepam and baclofen may be beneficial in cases with increased spasm.

Opioids

Opioid has been the cornerstone in the management of cancer-related pain. There is enough literature evidence substantiating the effectiveness of opioids and its derivatives in treating persistent pain due to non-cancer, and neuralgic and postoperative pain.

The most commonly used opioids and their derivatives are morphine, oxynorm, oxycodiene, codiene, tramadol, tapentadol, buprenorphine, and fentanyl. A landmark paper published by Portenoy *et al.* (1986) has concluded that the long-term use of opioid effectively relieves the pain, but its effect on improving physicial and social life is ambiguous.³⁸ However, the major limitation of opioids use is their side effects, eg. confusion, constipation, sedation, nausea, vomiting, and respiratory depression. Although sedation is a common complaint in opioid naive patients, the effect is transient. Since constipation is the common and persistent side effect of opioid, it is recemmended to commence stool softeners and increase hydration.

Opioids can worsen the cognitive function in individuals with underlying cognitive dysfunction. Studies by Zancy and Haythornthwaite *et al.* have substantiated the association between long-term opioid use and cognitive impairment.^{39, 40} Fear of addiction is another major barrier to long-term opioid use. The risk of addiction is minimal in individuals with no prior history of substance abuse.

Neuropathic pain

Neuropathic pain is defined as the pain resulting directly from a lesion or disease affecting the somatosensory system.⁴¹ The injury or dysfunction may involve peripheral or central nervous system structures. Poorly controlled neuropathic pain is associated with mood and sleep disturbance, and impaired ability to work and participate in social/recreational activities.⁴² The pathophysiologic basis of neuropathic pain is complex and not fully understood. Peripheral mechanisms include altered sensitivity and activation of 'c' nociceptor terminals, resulting in ectopic discharges in damaged or regenerating fibers, recruitment of silent nociceptors, spontaneous discharges in more proximal segments of the sensory nerve, including the dorsal root ganglion.^{43, 44}

Pharmacologic agents should be initiated at low doses, and titrated using small increments over several weeks, until an adequate clinical response or intolerable side effects is noted. Agents with sedating profiles should be started as a single bedtime dose. The therapeutic agents used for treating neuropathic pain are briefed in table 3. SNRI may cause hyponatremia at very low dose, hence repeating the electrolytes in 2-3 days is mandatory after starting the treatment. Many a times, the pain relief is partial, usually these agents work well as combination therapy. Failure of one particular class of drugs does not necessarily predict failure of another class of agents.

Management of common painful conditions in elderly

Low back pain

Specific etiology cannot be established in most of the patients with low back pain. Imaging and referral to an appropriate specialist is essential in elderly subjects with a history of cancer, unexplained weight loss, duration of pain greater than one month, night time pain or unresponsiveness to previous therapies, spinal infection and fever, history of injection drug use, or recent skin/ urinary infection. Neurological involvement as suggested by sciatica symptoms, and pseudo caludication suggestive of lumbar spinal stenosis should be referred to orthopedicians. Individuals presenting with cauda equina symptoms should be considered as a surgical emergency.

Most studies on various treatments for low back pain, especially for chronic low back pain, have reported limited efficacy. Even the most commonly prescribed treatments, such as medications, exercise, and manipulation have shown limited improvement. Reassuring and counselling the patients will help to counter negative thoughts and to cope with the ailment. Educating the patients on ergonomics, proper lifting techniques, and exercise has been found to be useful in reducing the disability. NSAIDs at regular interval have been proven to be useful for relieving low back pain. However, these medications should be used with utmost caution in elderly patients. Small dose of muscle relaxant (e.g.diazepam and baclofen) will help in reducing muscle spasm. There is no definitive evidence to prove the effectiness of tricyclic antidepressants and opiate in relieving chronic low back pain. Lignocaine patch has been found to be useful.

Osteoarthritis

Osteoarthritis (OA) is one of the common causes of joint pain and disability in elderly. The treatment of OA is directed towards reducing the symptoms and the prevention of disability. There are no proven pharmacological therapies to prevent the progression of joint damage due to OA. The management of OA includes a combination of nonpharmacologic approaches such as exercise and patient education; pharmacological therapies including oral, topical, and intraarticular medications, and surgical interventions including total joint arthroplasty.

Management should be individualized based on the patient's expectations, their level of function and activity, the joints involved, the severity of disease, occupational and avocational needs/interests, and the nature of any co-existing medical problems. Goal of treatment is to control pain, minimize disability, and improve their quality of life.

Non-pharmacological therapy, which is generally initiated before the commencement of pharmacological treatment includes regular exercise programme, weight reduction, and education. Pharmacological agents are used in individuals who are symptomatic and have failed to respond to non-pharmacological treatment. The choice of medication depends on the severity of disease and inflammatory reaction in the joints. It is prudent to start with paracetamol and then add small dose NSAIDs (naproxen 250 mg twice daily) under regular monitoring. It is recommended to add topical analgesic and lignocaine patch for treating severe pain. Intra-articular injections can be used in individuals with persistent symptoms in one or few affected joints, even after pharmacological treatment, or in whom NSAIDs are contraindicated. There is insufficient evidence to use glucosamine or chondroitin compounds for the treatment of OA. Surgical management is essential if the chronic disabiling symptoms persist even after non-pharmacological treatment.

Chronic headache

Episodic tension-type of headache is the most common cause of recurrent chronic headache in elderly. It is imperative to rule out red flag symptoms based on patient history and primary diagnostic tool. The red flag symptoms are history suggestive of systemic illness (weight loss, cancer, and persistent fever), neurological symptoms (confusion, meningism, and focal neurology) and early morning headache. Such patients are at increased risk for secondary types of headache (e.g., giant cell arteritis, trigeminal neuralgia, subdural hematoma, acute herpes zoster and postherpetic neuralgia, and brain tumors) and some types of primary headache (hypnic headache, cough headache, and migraine accompaniments). Full dose paracetamol is effective in symptomatic relief, but treating the underlying cause is necessary to bring about long-term relief.

Fibromyalgia

Treatment of fibromyalgia is directed at reducing the major symptoms, i.e. chronic widespread pain, fatigue, insomnia, and cognitive dysfunction. Treatment should be individualized and multidisciplinary, involving both non-pharmacologic measures and drug therapy. It is paramount that the patient is educated about the disease and the treatment.

Exercise has shown to produce significant benefits for relieving pain and improving function. Low-impact aerobic activities such as fast walking, biking, swimming, or water aerobics are found to be very effective. The type and intensity of the program should be individualized and should be based on patient preference and the presence of any other commodities. Individuals with persisting symptoms, after adequate exercise, will benefit from gradually increasing dose of amitriptyline. If fatigue is the major symptom then duloxetine at low dose is a good option. Some patients present with significant sleep problem, pregabalin is a good drug for such individuals.

Conclusion

Chronic pain in older adults is a complex phenomenon that requires a multifaceted approach incorporating nonpharmacological and pharmacological modalities. Individuals with persistent pain should be ideally dealt in exclusive pain clinic and it should be a multidisciplinary approach involving psychologist, physiotherapist and occupational therapist.

Competing interests

The author declares that he has no competing interests.

Disclosure

None

Citation

Benjamin DG. Pain management in elderly: A challenge to practicing clinicans. IJRCI. 2015;3(S1):SR1.

*Correspondence: Dominic Gerard Benjamin, Consultant Geriatrician & Diabetic Specialist, Bangalore Baptist Hospital, Bangalore, Karnataka, India. dominicbenjamin25@gmail.com

Submitted: 20 May 2015, Accepted: 20 August 2015, Published: 1 October 2015

References

- Descartes R. L'Homme, trans. M.Foster . Lectures on the history of physiology during 16th,17th and 18th centuries. Cambridge: Cambridge university press; 1901.
- Melzack R, Wall PD. The challenge of pain .New York :Penguin Science; 1996.

- 3. Livingstone WK. pain mechanism. New York :Macmillan, 1943
- Weddell G. Somesthesis and the clinical senses. Ann Rev Psychol.1955;6:119-36.
- 5. Noordenbos W .Pain. Amesterdam: Elsevier Science Ltd; 1959.
- Melzack R, Wall PD. Pain Mechanisms: A New Theory. Science. 1965 Nov 19;150(3699):971–9.
- Melzack R, Casey KL. Sensory, motivational and central control determinants of pain; a new conceptual model. In: Kenshalo D ed.The Skin Senses. Springfield : Thomas ,1968. p.423-439.
- Melzack R. From the gate to the neuromatrix. Pain. 1999 Aug;Suppl 6:S121–6.
- Gibson SJ, Helme RD. Age differences in pain perception: a review of physiological ,psychological , laboratory and clinical studies.
 In: Budd K and Hamann W (eds). Pain Reviews. London: Edward Arnorld,1995:111-137.
- Scudds RJ, McD Robertson J. Empirical evidence of the association between the presence of musculoskeletal pain and physical disability in community-dwelling senior citizens. Pain. 1998 Apr;75(2-3):229–35.
- Davis MA, Ettinger WH, Neuhaus JM. Sex differences in osteoarthritis of the knee (OAK). The role of obesity. Arthritis Rheum 1986;S16.
- Felson DT. The epidemiology of knee osteoarthritis: results from the Framingham Osteoarthritis Study. Semin Arthritis Rheum. 1990 Dec;20(3 Suppl 1):42–50.
- Solomon L. Clinical features of osteoarthritis. In: Kelley WN, Ruddy S,Harris EDJ, et al, eds. Textbook of rheumatology. Vol 2. 5th Ed. Philadelphia: WB Saunders; 1997:1383–408.
- Cooner E, Amorosi S. The study of pain and older Americans. Study conducted for the National Council on the Aging. Study No 628200. New York: Louis Harris and Associates, 1997.
- Ferrell BA, Ferrell BR, Rivera L. Pain in cognitively impaired nursing home patients. J Pain Symptom Manage. 1995 Nov;10(8):591–8.
- Oncology 1998;12:169–75. R P. Practice guidelines for cancer pain therapy. Issues pertinent to the revision of national guidelines. Oncology (Williston Park). 1998 Nov;12(11A):169–75.
- McCaffery M. Pain control. Barriers to the use of available information. World Health Organization Expert Committee on Cancer Pain Relief and Active Supportive Care. Cancer. 1992 Sep 1;70(5 Suppl):1438–49.
- Bernabei R, Gambassi G, Lapane K, Landi F, Gatsonis C, Dunlop R, et al. Management of pain in elderly patients with cancer. SAGE Study Group. Systematic Assessment of Geriatric Drug Use via Epidemiology. JAMA. 1998 Jun 17;279(23):1877–82.
- Molony SL, Kobayashi M, Holleran EA, Mezey M. Assessing pain as a fifth vital sign in long-term care facilities: Recommendations from the field. J Gerontol Nurs. 2005 Mar;31(3):16–24.
- American Geriatrics Society. AGS Panel on Chronic Pain in Older Persons. The management of chronic pain in older persons. J Am Geriatr Soc 1998;46:635–51.
- WHO | WHO's cancer pain ladder for adults [Internet]. WHO. [cited 2015 Sep 7]. Available from: http://www.who.int/cancer/palliative/ painladder/en/
- 22. Robinson AJ. Transcutaneous electrical nerve stimulation for the control of pain in musculoskeletal disorders. J Orthop Sports Phys Ther. 1996 Oct;24(4):208–26.
- Mannheimer C, Carlsson CA. The analgesic effect of transcutaneous electrical nerve stimulation (TNS) in patients with rheumatoid arthritis. A comparative study of different pulse patterns. Pain. 1979 Jun;6(3):329–34.
- 24. Mannheimer C, Lund S, Carlsson CA. The effect of transcutaneous electrical nerve stimulation (TNS) on joint pain in patients with

rheumatoid arthritis. Scand J Rheumatol. 1978;7(1):13-6.

- Kumar VN, Redford JB. Transcutaneous nerve stimulation in rheumatoid arthritis. Arch Phys Med Rehabil. 1982 Dec;63(12):595–6.
- Marchand S, Charest J, Li J, Chenard JR, Lavignolle B, Laurencelle L. Is TENS purely a placebo effect? A controlled study on chronic low back pain. Pain. 1993 Jul;54(1):99–106.
- Deyo RA, Walsh NE, Martin DC, Schoenfeld LS, Ramamurthy S. A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back pain. N Engl J Med. 1990 Jun 7;322(23):1627–34.
- Milne S, Welch V, Brosseau L, Saginur M, Shea B, Tugwell P, et al. Transcutaneous electrical nerve stimulation (TENS) for chronic low back pain. Cochrane Database Syst Rev. 2001;(2):CD003008.
- Brosseau L, Milne S, Robinson V, Marchand S, Shea B, Wells G, et al. Efficacy of the transcutaneous electrical nerve stimulation for the treatment of chronic low back pain: a meta-analysis. Spine. 2002 Mar 15;27(6):596–603.
- Christensen BV, Iuhl IU, Vilbek H, Bülow HH, Dreijer NC, Rasmussen HF. Acupuncture treatment of severe knee osteoarthrosis. A long-term study. Acta Anaesthesiol Scand. 1992 Aug;36(6):519–25.
- Thomas M, Eriksson SV, Lundeberg T. A comparative study of diazepam and acupuncture in patients with osteoarthritis pain: a placebo controlled study. Am J Chin Med. 1991;19(2):95–100.
- Johansson A, Wenneberg B, Wagersten C, Haraldson T. Acupuncture in treatment of facial muscular pain. Acta Odontol Scand. 1991 Jun;49(3):153–8.
- 33. Oosterveld FGJ, Rasker JJ, Jacobs JWG, et al. The effect of local heat and cold therapy on the intraarticular and skin surface

temperature of the knee. Arthritis Rheum 1992 Feb;35 (2):146-51.

- Reitman C, Esses SI. Conservative options in the management of spinal disorders, Part II. Exercise, education, and manual therapies. Am J Orthop. 1995 Mar;24(3):241–50.
- Downing DS, Weinstein A. Ultrasound therapy of subacromial bursitis. A double blind trial. Phys Ther. 1986 Feb;66(2):194–9.
- Munting E. Ultrasonic therapy for painful shoulders. Physiotherapy. 1978 Jun;64(6):180–137.
- Nwuga VC. Ultrasound in treatment of back pain resulting from prolapsed intervertebral disc. Arch Phys Med Rehabil. 1983 Feb;64(2):88–9.
- Portenoy RK, Foley KM. Chronic use of opioid analgesics in nonmalignant pain: report of 38 cases. Pain. 1986 May;25(2):171–86.
- Zacny JP. Should people taking opioids for medical reasons be allowed to work and drive? Addiction. 1996 Nov;91(11):1581–4.
- Haythornthwaite JA, Menefee LA, Quatrano-Piacentini AL, Pappagallo M. Outcome of chronic opioid therapy for non-cancer pain. J Pain Symptom Manage. 1998 Mar;15(3):185–94.
- Galer BS, Gianas A, Jensen MP. Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life. Diabetes Res Clin Pract. 2000 Feb;47(2):123–8.
- Galer BS, Gianas A, Jensen MP. Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life. Diabetes Res Clin Pract. 2000 Feb;47(2):123–8.
- Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet. 1999 Jun 5;353(9168):1959–64.
- Ochoa J, Torebjörk HE, Culp WJ, Schady W. Abnormal spontaneous activity in single sensory nerve fibers in humans. Muscle Nerve. 1982;5(9S):S74–7.