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Review Article

CHRONIC PAIN, ITS MANAGEMENT AND PSYCHOLOGICAL ISSUES: A REVIEW

MONALISA JENA[1]*, SWATI MISHRA[1], SARITA PRADHAN[2], SWETALINA JENA[3], SUDHANSU SEKHAR MISHRA[1]

[1]Department of Pharmacology, IMS & SUM Hospital, Siksha 'O' Anusandhan University, Bhubaneswar, Odisha, India. [2]Department of Pathology, IMS & SUM Hospital, Siksha 'O' Anusandhan University, Bhubaneswar, Odisha, India. [3]Department of Microbiology, V.S.S Medical College & Hospital, Burla, Odisha, India. Email: drmonalisajena@gmail.com

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ABSTRACT

Chronic pain is one of the most prevalent, disabling conditions both in clinical and psychological aspects and yet often remains inadequately treated due to cost reasons. Moreover, chronic pain commonly occurs in conjunction with depression, anxiety and somatoform disorders. Chronic and recurrent pain not associated with a disease is very common in childhood and adolescence, but there are very less studies and analysis has been done on chronic pain epidemiology and management. As pain is the important factor influencing quality of life and also the reason for which a person seek the advice of physician even require hospitalization that is why this systematic review highlights the different types of chronic pain, epidemiology, pathophysiology, and management of chronic pain along with psychological issues associated with it.

Keywords: Pain, Psychological aspects, Epidemiology, Somatoform disorders.

INTRODUCTION

Pain is considered as chronic when it lasts for more than 3-6 months [1,2] or that extends beyond the expected period of healing without a fixed duration [2]. The most common symptoms reported in general population and general medical practice is a pain [3-5]. Medications for pain are the second most common group of drugs prescribed after cardiac, renal drugs in the United States [6]. It is the most common reason for absenteeism from workplace [7]. Prevalence of persistent pain is more common seen in psychiatric patients, mood disorders and ultimately leads to depressive state [8,9]. It is a strong predictor of depression and *viz*. [10]. Persistent and chronic pain is a major international health problem [11] prompting World Health Organization to campaign against pain [12].

Some terms related to pain should be known to us while studying about pain.

1. Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage
2. Allodynia: Pain due to a stimulus which does not normally provoke pain
3. Dysesthesia: An unpleasant abnormal sensation, whether spontaneous or evoked
4. Hyperalgesia: An increased response to a stimulus which is normally painful
5. Anesthesia dolorosa: Pain in an area or region that is anesthetic
6. Nociceptor: A receptor preferentially sensitive to a noxious stimulus or to a stimulus that would become noxious if prolonged
7. Neuropathic pain (NP): Pain initiated or caused by a primary lesion or dysfunction in the nervous system.

This review contains various aspects of chronic pain briefly so that a person studying about chronic pain can gather a brief knowledge about every aspects of chronic pain at a glance. It includes definition, classification, epidemiology, pathophysiology of chronic pain, and different classes of drugs in its management, recent trends and methods in the management of chronic pain.

BRIEF REVIEW

Classification

Chronic pain is broadly divided as nociceptive pain caused due to activation of nociceptors and NP caused by damage or malfunction of the nervous system (Fig. 1) [13].

Types of chronic pain: (Prototypical diseases)

1. General somatic pain (pain from the outer body): Fibromyalgia (FM) and chronic back pain
2. Visceral pain (pain from the internal organs): Pain from indigestion or constipation, chronic pancreatitis or chronic active hepatitis, visceral pain from gallstones or appendicitis
3. Bone pain: Pain from bone cancer, osteoporosis, spinal fractures, osteomyelitis or arthritis, muscle spasm
4. NP (pain arising in nerves leading from head, face, trunk or extremities to spinal cord): Sciatica, ruptured discs in the spine or infections (shingles), diseases causing peripheral neuropathy (diabetes and AIDS), the arm or leg that has been lost feels like it's still present, and hurts severely ("phantom limb pain"), Herpes zoster (shingles)
5. Circulatory problems: Poor circulation is often a cause of chronic pain usually caused by tobacco use, diabetes or various autoimmune diseases such as lupus or rheumatoid arthritis. Another common cause of poor circulation is complex regional pain syndrome (CRPS) which is a problem of both circulation and nerve transmission. The narrowing of blood vessels prevents enough oxygen and nourishment to the part of affected body. It can be treated by sympathectomy or with non-opioid medication, either with or without surgery, is needed
6. Headaches: Migraine, tension and cluster headaches. It can also result from sinusitis, trigeminal neuralgia and giant cell arteritis or brain tumors.

Pathophysiology

At the site of injury special nerve cell endings called nociceptors, respond to various stimuli such as heat, pressure and inflammation, sending a rapid signal responsible for the release of chemical mediators that amplify the pain signal. This whole process is called nociception. On a day-to-day basis pain subsides after the recovery from tissue injury, such as a burn, a cut or even a broken bone. However, when the pain does not subside even after healing of cause is known as chronic or persistent pain. In this case, the individual may experience one or more of the following: Spontaneous pain (pain for no apparent reason), hyperpathia (more pain than would be expected after a painful event), hyperalgesia (increased intensity of pain to a further noxious stimulus), secondary hyperalgesia (spreading of sensitivity or pain to nearby, uninjured tissue), and allodynia (sensation of pain from a normally innocuous stimulus) [17].

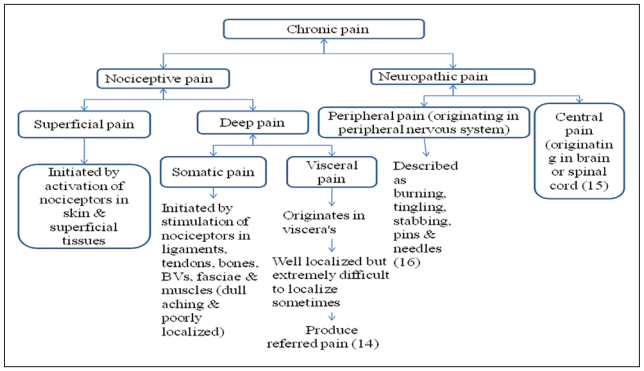

Fig. 1: ???

Under persistent activation nociceptive transmission to the dorsal horn may induce a pain which in turn induces pathological changes that lower the threshold for pain signals. It may also generate non-nociceptive nerve fibers to respond to pain signals and transmit the signals. The type of nerve fibers that propagates the pain signals are the C-fibers as they have a slow conductivity giving rise to a painful sensation that persists over a long time [18] which is difficult to reverse or eradicate once established [19]. In some chronic pain, the cause may be genetic which interfere with neuronal differentiation, leading to a permanent reduction in the threshold for pain [20].

Epidemiology

It includes brief knowledge about chronic pain in different age groups, sexes and in pregnant ladies. Chronic pain is an epidemic worldwide with 1.5 billion people feeling its effects. Various studies found that the prevalence of chronic pain was very high and consumes a large amount of healthcare resources of the world.

Chronic and recurrent pain is prevalent in children and adolescents and affects women at higher rate than men [21] and prevalence increases with age. Psychological issues are also closely related to this chronic persistent pain including anxiety, depression, low self-esteem, even suicidal tendency [21]. It is important for clinician to give a vigilant look on the problem of pain and long-term consequences of pain in children which has increased over the last several decades [22,23]. There is always an underlying fear regarding use of drugs during pregnancy even some pregnant women prefer suffering from pain rather using pain medications. Such women are at higher risk of under or no treatment and associated with more anxiety, depression even hypertension risk and ends in unhealthy pregnancy [24,25]. Pain is a common complaint of elderly individuals [26] which is a great challenge for primary care physician. The elderly are more prone for arthritis, bone and joint disorders, cancer and other chronic disorders associated pain [27]. They are often either untreated or undertreated for pain which can have a negative impact on the health and quality of life resulting in psychological problems [28].

What are the symptoms of chronic pain?

The symptoms of chronic pain include:

- Mild to severe pain that does not go away
- Pain that may be shooting, burning, aching, or electrical
- Feeling of discomfort, soreness, tightness, or stiffness.

Pain is not a symptom that exists alone but associated with other problems such as:

- Fatigue, sleeplessness, withdrawal from activity and increased need to rest
- Weakened immune system, changes in mood including hopelessness, fear, depression, irritability, anxiety, and stress and disability.

Management

Complete remission of chronic pain for a longer period is difficult, but the aim should be improving quality of life by decreasing the pain even for some while [29]. Pain management is the branch of medicine dealing with the approach to the relief of pain and improvement in the quality of life [30]. Acute pain usually resolves with the efforts of one doctor; however, the management of chronic pain frequently requires the coordinated efforts of a team [31]. Psychological treatments including cognitive behavioral therapy and acceptance and commitment therapy [32].

SPECIFIC MEDICATIONS

Non-opioid analgesics

Non-steroidal anti-inflammatory drugs (NSAIDs) which are effective in the treatment of pain (aspirin, cyclooxygenase-2 [COX-2] inhibitors, etc.) have anti-inflammatory, analgesic and antipyretic effects [33]. The most common complication of these group of drugs is gastrointestinal problems and increasing incidence of cardiovascular risk which recommended acetaminophen, non-acetylated salicylates and short-term opioids instead of COX-2 inhibitors in patients with coronary artery disease by the American Heart Association [34] Even acetaminophen is a slightly weaker analgesic than NSAIDs [35], it is considered as first line drug because of its favorable safety profile and low cost. Acetaminophen is associated with asymptomatic elevations of aminotransferase levels at dosages of 4 g/day even in healthy adults, but the clinical significance is uncertain [36].

Tramadol

It exerts an analgesic effect through binding to the mu opioid receptor (opioid effect) and weakly inhibits the reuptake of serotonin and norepinephrine (non-opioid effect), as tricyclic antidepressants (TCAs). It has proven effective in osteoarthritis (OA), FM and NP. The problem associated with its use is the psychological dependence (craving) when discontinuing the drug [37]. Some other side effects are seizure (caution with history of seizures and those taking a tricyclic or selective serotonin reuptake inhibitors (SSRI) antidepressant, a monoamine oxidase inhibitor, an antipsychotic drug, or other opioids) [38]. Dose reduction is recommended in older adult (>75 years) and in those with renal impairment or cirrhosis (max daily dose shouldn't exceed 400 mg).

Opioid analgesics

Study of Furlan *et al*. [39] showed opioids use in chronic non-cancer pain. Propoxyphene and dextropropoxyphene are no longer recommended due to its low therapeutic window and less potency than codeine. It accumulates with repeated doses, causing respiratory depression, sedation and cognitive impairment, particularly in elderly patients or those consuming alcohol. Opioid therapy compared to placebo resulted in higher nausea, constipation, drowsiness, dizziness and vomiting [40]. Endocrinological abnormalities such as hypogonadism and erectile dysfunction may be associated with opioid therapy [41]. In women, opioid use has been associated with amenorrhea and decreased sex hormone levels [42]. Risk factors for opioid abuse in chronic pain are young age, male sex, past alcohol or cocaine abuse, previous drug conviction, and mental illness, pain in multiple regions and after motor vehicle accidents [43].

Antidepressants

TCAs and SSRIs: TCAs such as amitriptyline, imipramine, clomipramine, desipramine, and nortriptyline were commonly used in the treatment of multiple pain conditions showing analgesic effect in chronic pain conditions [44] such as diabetic neuropathy, postherpetic neuralgia, tension headache, migraine, atypical facial pain, FM and low back pain, but not in painful HIV sensory neuropathy [45], spinal cord injury [46], and cisplatin-induced neuropathy [47]. Analgesic effect is independent of effect on mood and dose is less than typical antidepressant doses. Advantages of TCAs include low cost whereas disadvantages are sedation, constipation, dry mouth, postural hypotension, arrhythmias; falls in older adult patients and death in overdose. The main contraindications to its use are significant cardiac arrhythmias, prostatic hypertrophy, and narrow-angle glaucoma. Some studies concluded that SSRIs (fluoxetine, paroxetine, and citalopram) have a

relatively weak effect in ameliorating chronic pain [48]. SSRIs are also safer in cases of overdose. In elderly patients, Fluoxetine should be avoided due to its extensive half-life.

Serotonin–norepinephrine reuptake inhibitors: Duloxetine and venlafaxine have proven superior to placebo in diabetic peripheral neuropathy [49,50]. It is also approved in FM by FDA [51]. This agent is of interest because of its action similar to TCAs and similar structure to tramadol [52]. Venlafaxine is effective in postherpetic neuralgia, painful polyneuropathy, headache, NP, atypical facial pain and radicular back pain [53]. Venlafaxine was not superior to imipramine as a higher number of patients withdrew it due to side effects with venlafaxine in comparison to imipramine. Higher incidence of dry mouth and sweating with Imipramine and tiredness with venlafaxine is seen. The most common side effects are nausea, dyspepsia, sweating, somnolence, and insomnia. In elderly patients, an increase in blood pressure is seen, so it should be monitored.

Anticonvulsants

Anticonvulsants have been used in the management of pain since the 1960s along with antidepressants due to their ability to reduce neuronal excitability [54]. They are useful for chronic NP (gabapentin and pregabalin: Neuromodulators). They inhibit the release of excitatory neurotransmitters important in pain. Gabapentin is useful in NP, cancer-related neuropathy, phantom limb pain, spinal cord injury, Guillain–Barre syndrome [55]. Carbamazepine is used in trigeminal neuralgia [56]. Gabapentin and pregabalin should be considered the first-line anticonvulsants for NP other than trigeminal neuralgia. Gabapentin is now available in a generic formulation, making it less costly than pregabalin. Gabapentin was well tolerated showing mild to moderate dizziness and somnolence in the initiation phase [57]. Additional side effects include ataxia and confusion. Conversely, pregabalin has a simpler dosing schedule (twice daily compared to 3-4 times daily), simpler dose titration and an additional FDA indication (FM) and well tolerated with the most common side effects are dizziness and somnolence. Carbamazepine's primary mechanism is through sodium channel blockade useful in analgesic effects in trigeminal neuralgia, diabetic neuropathy and migraine prophylaxis, also in glossopharyngeal neuralgia, paroxysmal pain in multiple sclerosis, post-sympathectomy pain, cancer and post-traumatic neuralgia [58]. Other anticonvulsants used are lamotrigine, oxcarbazepine, topiramate, etc.

Other pharmacological agents

Skeletal muscle relaxants

They are FDA approved for either spasticity (baclofen, dantrolene, and tizanidine) or musculoskeletal conditions (carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol and orphenadrine) [59]. Cyclobenzaprine is the best studied muscle relaxant in musculoskeletal disorders for FM, as well as muscle spasms with fewer side effects. Muscle relaxants have a limited role in the treatment of chronic pain, except for cyclobenzaprine as one option in treating FM.

Topical analgesics

A potential advantage of topical agents is avoidance of systemic side effects. Disadvantages are localized areas skin reactions. Topical analgesics (lidocaine, capsaicin, and salicylate) have a limited role in treating localized mild to moderate neuropathic or osteoarthritic pain, either as an adjunct to other medications, or as an alternative to oral medications. Lidocaine 5% patch has an FDA indication for postherpetic neuralgia. Capsaicin is an alkaloid derived from chili peppers; used in NP and musculoskeletal conditions [60]. The main disadvantage of capsaicin is burning sensation. Topical salicylate has proven superior to placebo in both acute pain and chronic pain [61]. A recent randomized controlled trial (RCT) suggests topical ibuprofen may also be beneficial for knee OA [62].

Neuroleptics

As a general rule, neuroleptics are not analgesic and should be avoided for the treatment of pain. Methotrimeprazine has been demonstrated to exhibit analgesic properties in cancer pain [63], and pimozide was found to demonstrate better efficacy than carbamazepine in one RCT for trigeminal neuralgia [64]. These are associated with unpleasant extrapyramidal side effects and irreversible tardive dyskinesia. In previous studies, it was found that the addition of fluphenazine to amitriptyline did not confer any additional analgesia in the treatment of postherpetic neuralgia [65].

Clonidine

In humans, various studies indicated an analgesic effect of epidural clonidine in the treatment of arachnoiditis [66], reflex sympathetic dystrophy (CRPS Type 1), [67] and cancer pain [68]. Another study showed comparison of the effects of epidural clonidine, lignocaine and the combination demonstrated equivalent analgesia between clonidine and the local anesthetic in patients with low back and leg pain and NP [66]. The evidence indicates that both epidural and systemic clonidine (given intravenous or transdermally) is analgesic, but use is limited by sedation and postural hypotension.

Recent trends

Acupuncture is effective for the treatment of chronic pain. It is the insertion and stimulation of needles at specific points on the body to facilitate recovery from pain. Although initially developed as part of traditional Chinese medicine, some acupuncturists with medical qualifications said acupuncture in physiologic terms, without reference to premodern concepts [69]. An estimated 3 million American adults receive acupuncture treatment each year with chronic pain as the most common presentation [70]. It is known to have physiologic effects as analgesia [71,72], but without accepted mechanism which makes it highly controversial. Although data indicate that acupuncture is more than a placebo, suggesting that factors in addition to specific effects of needling are important contributors to therapeutic effects [73].

Ultrasound procedures in pain [74]

It has emerged to become one of the principle tools used in the performance of chronic pain interventions. It allows identification of target structures, visualization of needle placement and observation of therapeutic medication in real time. Utilization of it instead of fluoroscopy spares healthcare providers and patients the risk of radiation exposure. It is still in its relatively early stages and additional studies are required to further evaluate the efficacy and limitations of its use.

Intrathecal drug delivery systems [75]

It is an effective therapy for chronic pain intractable to medical management but underutilized due to high-complexity and limited reimbursement. The clinical utility remains limited by lack of prospective RCTs, lack of physician knowledge on the pharmacodynamics and pharmacokinetics of it.

Non-invasive brain stimulation techniques

It is a technique that can guide brain plasticity and suitable to treat chronic pain that is associated with substantial reorganization of central nervous system activity. Studies from the 1950s investigated the use of this therapeutic method for the treatment of chronic pain.

Recent developments

Non-invasive brain stimulation – e.g. repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) using new parameters of stimulation have shown better results. These studies explored alternative sites of stimulation, such as the secondary somatosensory cortex (rather than primary motor cortex) for treatment of chronic visceral pain and new parameters of stimulation, such as repeated sessions of tDCS with 2 mA for the treatment of chronic central pain. It is in its preliminary stage. Other parameters of stimulation need to be further explored such as theta burst stimulation and the combination of tDCS and rTMS. The duration of effects is

another important issue; so, maintenance therapy regimens, as well as the development of portable stimulators, need to be investigated [76].

Change of approach in management of pain in elderly [77]

Many elderly people suffer from chronic pain, but it is regularly under-treated, partly because managing these patients is often complex due to patient's unwillingness to complain, atypical pain presentations, multiple morbidities, and cognitive defects. In accordance with biopsychosocial model of pain, a multidisciplinary approach to pain management is recommended, with pharmacotherapy, psychological support, physical rehabilitation, and interventional procedures available. Defective organ function and other physiological changes require lower initial doses of analgesics with less frequent dosing intervals, and the physician must be aware of all medications that the patient is taking, in order to avoid drug/drug interactions. Non-adherence to treatment is common and various strategies can be employed to improve it; involving the elderly patient's caregivers and family, using medication systems such as pill-boxes, or even sending text messages.

Effect of non-pharmacological approach in chronic pain management [78]

Pain perception is affected by sensory (physical being and activities), cognitive (thoughts), or emotional (feelings) factors which are the main target for non-pharmacological treatment modalities. Massage therapy is used for chronic headache, backache or shoulder pain by stimulating A-δ nerve fibers to inhibit pain transmission, improve circulation and enhance sleep quality. Sensory and procedural information coupled with behavioral techniques can be used to distract children away from pain by decreasing fear and anxiety. These also include psychological therapy, art and expression therapy, support therapy, and hypnosis. Specific techniques include breathing techniques, guided imagery, progressive muscle relaxation, biofeedback, cognitive behavioral training (CBT), and music therapy, promoting a positive attitude, overcoming depression, feeling reassured that pain is not harmful, taking control of one's chronic pain and life, and stress management. CBT has been suggested as interventions for migraine headache. Psychological factors related to adjustment to living with chronic pain, such as pain-related anxiety and fear, and helplessness tend to increase perceived pain, psychological distress, and physical disability, while factors that promoted self-efficacy, pain-coping strategies, readiness to change, and acceptance, tend to decrease perceived pain, distress, and disability. It is evident that a non-pharmacological approach to reduce chronic pain can help children to cope better in the presence of painful procedures or interventions which may provide useful adjunctive therapies that assist children to cope emotionally, mentally, and physically.

Cognitive and behavioral therapy [79]

CBT is the "gold standard" psychological treatment for individuals with a wide range of pain problems with lack of risks associated with chronic pain medications, surgeries, and interventional procedures. It benefits for pain in comorbid conditions such as diabetes and cardiovascular disease. Unfortunately, most individuals with chronic pain never receive CBT. Increased knowledge about CBT can help guide these efforts. Refinement and use of accurate prognostic tools, with care stratified on the basis of psychosocial risk factors, also hold much promise.

Management of pain during pregnancy [80]

Medications used in therapeutic doses for acute and chronic pain appear to be relatively safe in pregnancy. To minimize fetal risk, initiate drug interventions at the lowest effective dose, especially in late pregnancy, and select analgesics only after careful review of a woman's medical or medication history. Women should avoid using NSAIDs after 32 weeks' gestation, owing to the possibility of antiplatelet or prolonged bleeding effects. Opioids should also be used with caution, especially in higher doses in late pregnancy when the infant should be observed carefully in the neonatal period for any signs of withdrawal (neonatal abstinence syndrome).

Psychological issues

As we have already discussed a lot about chronic pain, now it is concluded that chronic pain is a condition influenced by biological, psychological, and social factors. It should be managed not only by treating its biological causes but also there is requirement of focus on its psychological and social influences and consequences. Development of cognitive and behavioral therapies becomes a good approach by means of CBT. CBT is now a mainstream treatment, alone or in combination with pharmacotherapy or rehabilitation. As postulated by learning theory [81], social and environmental variables (e.g. responses from family) have been shown to be associated with pain behaviors and disability levels [82]. Association of chronic pain with depression, physical disability, and activity and social role limitations were seen in various previous studies [83]. Fear-avoidance (activity avoidance due to fear of increased pain or bodily harm) is a part of psychological issues in chronic pain [83]. The goals of CBT for pain are to reduce pain and psychological distress and to improve physical and role function by helping individuals decrease maladaptive behaviors, increase adaptive behaviors, identify and correct maladaptive thoughts and beliefs, and increase self-efficacy for pain management [84]. Many individuals with chronic pain have mood, anxiety, and sleep disorders [85]. Over the past 40 years, psychologists have played essential roles in the development and evaluation of interventions for reducing pain, suffering, and activity limitations among individuals with chronic pain.

CONCLUSION WITH FUTURE TRENDS

From various studies it has come into limelight that the future trends in the management of chronic pain must be multidisciplinary with medications such as specific individual exercising, regular training in relaxation techniques, group therapy led by a clinical psychologist (1.5 hrs) per week, patient education sessions once a week, two physiotherapy treatments per week (CBT) for pacing strategies, medical training therapy and neurophysiology information given by trained physician. The efficacy of such programs is better than standard medical treatment. Therefore, the set-up of multidisciplinary programs for chronic pain patients appears to be reasonable and patients should be referred to adequately specialized institutions, instead of being sent to various individual medical specialists sequentially. Intensive inpatient programs seem to be more effective for patients with more severe disabilities, which is consistent with the findings of Guzmán *et al*. [86] Future studies should compare different methods, settings and durations of multidisciplinary treatments and examine their connection with patient characteristics in more detail in order to detect differential effects. Further, studies are needed to establish determinants or prognostic indicators of success, and to also define the therapeutic potential for a successful rehabilitation [87].

There are many new agents and new models for persistent pain have allowed researchers to define the pharmacology of analgesia in more detail. We have already learned that more than one systemic agent is often necessary to target relevant mechanisms [54], and that when two agents are used, it is sometimes possible to obtain better analgesia at lower doses and with fewer side effects [88]. In the future, it is probable that treatment protocols will include both systemic and topical agents targeting both central and peripheral mechanisms. Novel neuromodulators targeting sodium and calcium channels, N-Methyl-D-aspartic acid receptor antagonists, purinergic agents, and agents targeting the endocannabinoid system and others are all in development, as well as agents for topical use, and these will provide additional options as analgesics in the future.

Chronic pain involves multiple pathophysiological mechanisms with peripheral and central components. The management of chronic pain requires an interdisciplinary approach.

Pharmacotherapy for pain must take place within an overall management plan that maximizes the patient's involvement in the pursuit of health, even in the face of pain. This review has provided information regarding the major classes of medication used to assist in

the management of chronic pain, including the NSAIDs, acetaminophen, antidepressants and anticonvulsants. The use of chronic opioids has been reviewed, along with an approach to comorbid pain and addiction. Emerging areas, including topical approaches and an introduction to the field of cannabinoids, have also been presented.

Surgical and chemical sympathectomy has been used to treat NP. Important areas for future research include developing a specific diagnostic method for NP; identifying associations between symptoms, signs, and pathology to guide mechanism-based treatment strategies; comparing combination treatments with monotherapy; and conducting pharmacogenomic studies to guide prescribing [89].

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