CHRONIC PAIN – Physiology and approach to management

John Mathew, Associate Professor, Department of Rheumatology, Christian Medical College, Vellore

Summary: Chronic pain is defined as a long standing pain that lasts 3 months or more. There are various pathological mechanisms that convert a painful stimulus into a chronic pain process. The quality of daily life in a person is significantly affected in those suffering chronic pain and treatment regimens should include measures to address psychological and psychiatric issues as well. Neupathic pain is often difficult to treat with conventional medications or with any single mode of therapy. A step-wise multimodal therapeutic approach is more effective in treating neupathic pain than using analgesics alone. This article describes the approach to chronic pain management and includes a short discussion on Fibromyalgia.

Introduction

Chronic pain and its management is an issue that is important to physicians in a wide variety of settings – from the primary to tertiary care level. Chronic pain has a psychological impact on the person, which needs to be acknowledged and addressed. While approaching a person suffering from chronic pain a detailed history, objective assessment of the pain and physical examination are important in identifying and managing the problem. An understanding of the pathophysiology behind the mechanism of chronic pain and the various therapeutic modalities available will help a physician make well-informed decisions while approaching this problem.

Definition of chronic pain:

Chronic pain may be defined as persistent pain that lasts beyond the ordinary duration of time needed for the body to heal following an insult or injury. The commonly used duration to term a long-standing pain as chronic pain is 3 months. The definitions according to two international associations are given below.

1. The International Association for the Study of Pain (IASP)
   Pain without apparent biologic value that has persisted beyond the normal tissue healing time (usually 3 months)

2. The American Society of Anesthesiologists
   Pain of any etiology not directly related to neoplastic involvement, extending in duration beyond the expected temporal boundary of tissue injury and normal healing adversely affecting the function or well-being of the individual.

Impact of chronic pain

The consequences of chronic pain are varied, affecting different aspects of a patient’s life. It can result in functional impairment and disability, psychological distress (anxiety, depression), and sleep deprivation. Chronic pain disrupts activities of daily living and negatively impacts personal relationships in a significant number of patients. Management of the pain becomes difficult if the physician is not aware of or does not address these issues. For this reason, it is important to approach the problem with a good clinical history and examination backed by knowledge of the mechanisms involved and the treatment modalities available.

Types of pain

Pain may be divided broadly into two types -

1. Nociceptive pain — Nociceptive pain is the perception of nociceptive input, usually due to tissue damage (eg., postoperative pain). A nociceptor is a nerve fiber preferentially sensitive to a noxious stimulus. If the pain persists even after the nociceptive stimulus has ceased, it results in chronic pain. Nociceptive pain could be of various types - musculoskeletal pain, inflammatory pain (eg. inflammatory arthropathies, postoperative pain, tissue injury, infection) or mechanical/compressive pain (eg., low back pain, neck pain, visceral pain from expanding tumor masses).

2. Neuropathic pain - Neuropathic pain is a maladaptive response to a stimulus due to damage to the nervous system which results in a complex, chronic pain state. With neuropathic pain, the nerve fibres themselves may be damaged.
or dysfunctional and these damaged nerve fibres send incorrect signals to other pain centres. This results in pain that may be ill-localised and associated with sensory symptoms like paresthesia, allodynia, dysesthesia etc.

The types of neuropathic pain are -
• **Peripheral neuropathic pain** (eg, painful diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, radicular pain, post-surgical chronic neuropathic pain, and neuropathic cancer pain (such as, chemotherapy-induced neuropathy, neuropathy secondary to tumour antigens, or caused by direct invasion or compression of neural structures)
• **Central pain** (Eg. phantom limb pain, pain from spinal cord injuries, and post-stroke pain).

### Table 1: Causes of chronic pain according to the system involved

<table>
<thead>
<tr>
<th>Musculoskeletal disorders</th>
<th>Neurologic disorders</th>
<th>Reproductive disorders (uterine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Osteoarthritis/ degenerative joint disease/spondylosis</td>
<td>• Brachial plexus traction injury</td>
<td>• Adenomyosis</td>
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<tr>
<td>• Rheumatoid arthritis</td>
<td>• Cervical radiculopathy</td>
<td>• Chronic endometritis</td>
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<tr>
<td>• Lyme disease</td>
<td>• Thoracic outlet syndrome</td>
<td>• Atypical dysmenorrhea or ovulatory pain</td>
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<tr>
<td>• Reiter syndrome</td>
<td>• Spinal stenosis</td>
<td>• Cervical stenosis</td>
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<tr>
<td>• Disk herniation/facet osteoarthropathy</td>
<td>• Arachnoiditis</td>
<td>• Endometrial or cervical polyps</td>
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<tr>
<td>• Fractures/compression fracture of lumbar vertebrae</td>
<td>• Polymyositis</td>
<td>• Leiomyomata</td>
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<tr>
<td>• Faulty or poor posture</td>
<td>• Cutaneous nerve entrapment in surgical scar</td>
<td>• Symptomatic pelvic relaxation (genital prolapse)</td>
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<tr>
<td>• Fibromyalgia</td>
<td>• Postherpetic neuralgia (shingles)</td>
<td>• An intrauterine contraceptive device can also be associated with chronic pain.</td>
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<tr>
<td>• Mechanical low back pain</td>
<td>• Neuralgia (eg, iliohypogastric, ilioinguinal, or genitofemoral nerves)</td>
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<tr>
<td>• Chronic coccygeal pain</td>
<td>• Polyneuropathies</td>
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<tr>
<td>• Muscular strains and sprains</td>
<td>• Polyradiculoneuropathies</td>
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<tr>
<td>• Piriformis syndrome</td>
<td>• Mononeuritis multiplex</td>
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<tr>
<td>• Hernias (eg, obturator, sciatic, inguinal, femoral, spigelian, perineal, umbilical)</td>
<td>• Chronic daily headaches</td>
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<tr>
<td>• Abdominal wall myofascial pain (trigger points)</td>
<td>• Muscle tension headaches</td>
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<tr>
<td>• Chronic overuse syndromes (eg, tendonitis, bursitis)</td>
<td>• Migraine headaches</td>
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<tr>
<th>Urologic disorders</th>
<th>GI disorders</th>
<th>Extraterine reproductive disorders</th>
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<tbody>
<tr>
<td>• Bladder neoplasm</td>
<td>• Chronic visceral pain syndrome</td>
<td>• Endometriosis</td>
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<tr>
<td>• Chronic urinary tract infection</td>
<td>• Gastroesophageal reflux</td>
<td>• Adhesions</td>
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<tr>
<td>• Recurrent cystitis</td>
<td>• Peptic ulcer disease</td>
<td>• Adnexal cysts</td>
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<tr>
<td>• Recurrent urethritis</td>
<td>• Pancreatitis</td>
<td>• Chronic ectopic pregnancy</td>
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<tr>
<td>• Urolithiasis</td>
<td>• Chronic intermittent bowel obstruction</td>
<td>• Chlamydial endometritis or salpingitis</td>
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<tr>
<td>• Urethral diverticulum</td>
<td>• Colitis</td>
<td>• Endosalpingiosis</td>
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<tr>
<td>• Chronic urethral syndrome</td>
<td>• Chronic constipation</td>
<td>• Ovarian retention syndrome (residual ovary syndrome)</td>
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<td>• Urethral carbuncle</td>
<td>• Diverticular disease</td>
<td>• Ovarian remnant syndrome</td>
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<td>• Prostatitis</td>
<td>• Irritable bowel disease</td>
<td>• Ovarian dystrophy or ovulatory pain</td>
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<tr>
<td>• Urethral stricture</td>
<td>• Irritable bowel syndrome</td>
<td>• Pelvic congestion syndrome</td>
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<td>• Testicular torsion</td>
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<td>• Postoperative peritoneal cysts</td>
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<tr>
<td>• Peyronie disease</td>
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<td>• Residual accessory ovary</td>
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<tr>
<th>Psychological disorders</th>
<th>Other</th>
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<tr>
<td>• Bipolar personality disorders</td>
<td>• Cardiovascular disease (eg, angina)</td>
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<tr>
<td>• Depression</td>
<td>• Peripheral vascular disease</td>
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<tr>
<td>• Porphyria</td>
<td>Chemotherapeutic, radiation, or surgical complications</td>
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<td>• Sleep disturbances</td>
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Physiology of pain

An understanding of the physiology of pain and the pathways involved helps in identifying the targets for therapy and approach to a patient with chronic pain. The physiologic processes associated with pain are i) Transduction, ii) Transmission, iii) Modulation and iv) Perception

1. **Transduction** refers to the conversion of a noxious stimulus (thermal, mechanical, or chemical) into electrical activity in the peripheral terminals of nociceptor sensory fibers.

2. **Transmission** refers to the passage of action potentials from the peripheral terminal along axons to the central terminal of nociceptors in the central nervous system. Conduction is the synaptic transfer of input from one neuron to another (from spinal cord to thalamus to sensory cortex of cerebrum).

   Pain sensation begins in the periphery of the nervous system. Pain stimuli are sensed by specialized nociceptors that are the nerve terminals of the primary afferent fibers. The pain signal is then transmitted to the dorsal horn of the spinal column and then transmitted to the central nervous system (CNS) where it is processed and interpreted in the somatosensory cerebral cortex. Only a small fraction of the sensory input that enters the spinal cord is transmitted via action potentials from the neurons in the dorsal horn to the thalamus and to the cortex – otherwise one would be overloaded with nociceptive stimuli.

   Multiple ascending pathways may be involved in relaying nociceptive information to the brain. Of these, the spinothalamic pathway is the major route by which pain and temperature information ascend to the cerebral cortex. Most of the nociceptive specific neurons project contralaterally within the spinal cord and ascend within the anterolateral quadrant, forming the spinothalamic tract which synapses in the thalamus. Neurons from the thalamus project to multiple brain areas in the primary and secondary somatosensory cortex, cingulate cortex, prefrontal cortex, insular cortex, amygdala, and the cerebellum.

3. **Modulation** refers to the alteration (e.g., augmentation or suppression) of sensory input.

4. **Perception** refers to the "decoding"/interpretation of afferent input in somatosensory and association regions of the brain that gives rise to the individual's specific sensory experience.

**Signal transfer in the spinal cord**

The signal transfer from neurons in the dorsal horn of the spinal cord that project to the brain is mediated either through direct monosynaptic contact or through interneurons which may be either excitatory or inhibitory. Counter-irritation and low-threshold afferent inputs (TENS or spinal cord stimulation) is a therapy that activates these inhibitory mechanisms. The effect is generally small and short lasting.
**Box 1: Mechanisms promoting chronic pain**

There are a number of mechanisms that result in a painful stimulus becoming chronic. Understanding the mechanism involved in chronic pain at the molecular and cellular level helps us in our efforts to develop therapeutic measures that target these mechanisms. It also helps us to tailor individual therapy for patients.

Some of the mechanisms that result in the conversion of a painful stimulus to a chronic pain are 1) peripheral sensitization, 2) central sensitization, 3) ectopic excitability, 4) structural reorganization/phenotypic switch of neurons, 5) primary sensory degeneration and 6) disinhibition.

1. **Peripheral sensitization**
   Tissue inflammation results in cell breakdown and the release of cytokines, chemokines and other factors which the nociceptive receptors are exposed to. These cytokines recruit inflammatory cells at the site of inflammation. Cytokines like IL-1 Beta can activate nociceptors to generate action potentials and induce pain hypersensitivity or they may act as nociceptor sensitisers (decrease the threshold of nociceptor stimulation).
   Tissue damage, inflammation and sympathetic stimulation thus result in a sort of ‘sensitising soup’ of cytokines and other pro-inflammatory agents that increase transduction sensitivity or reduce stimulation thresholds.

2. **Central sensitization**
   This process amplifies the synaptic transfer from the nociceptor terminal to dorsal horn neurons. Initially the process is activity dependant, i.e., more the painful stimulus, more the pain. Later, as more and more painful stimuli reach the synaptic level, transcriptional changes occur in the molecular machinery of the dorsal horn neuron. As a result, previously sub-threshold synaptic inputs to nociceptive neurons now generate an augmented action potential output. So even subtle stimuli which may not be nociceptive may now result in pain.
   The glutamate-activated N-methyl-D-aspartic acid (NMDA) receptor is integral to this central sensitization process.

3. **Ectopic excitability**
   Damaged nociceptive neurons and the cytokines released result in the neurons producing ectopic action potentials. This leads to sensory inflow even in the absence of a peripheral stimulus.

4. **Structural reorganization/phenotypic switch**
   Normally nerve fibers carrying nociceptive pain stimuli synapse in Lamina I or II of the dorsal horn of the spinal cord. A chronic barrage of pain stimuli beyond a particular level can cause neuronal damage and reorganization of the laminar structure. This results in nociceptive nerve fibers synapsing with deeper laminae while other sensory stimuli synapse with the superficial laminae. This results in normally non-painful stimuli (touch, pressure etc.) being perceived as painful.

5. **Primary sensory degeneration**
   The interpretation of pain by the cortex of the brain is altered by changes in neurotrophic factors, compensatory local changes in the surrounding neurons or dorsal root ganglion/dorsal horn of the spinal cord and changes in related glia. This results in abnormal sensations.

6. **Disinhibition**
   GABA blockade recruits previously absent Aβ fiber inputs to lamina II cells, effectively uncovering a previously silent synaptic pathway.

   Partial nerve injury results in selective loss of GABAergic inhibitory synaptic currents due to apoptosis in GABAergic inhibitory interneurons.

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**Figure 2: Laminae of spinal cord grey matter**

APPRAOH TO A PATIENT WITH CHRONIC PAIN

A good history and physical examination are important in evaluation of chronic pain. This is directed towards trying to get an etiological diagnosis of the pain if possible. It is also essential in making a management plan.

History
Clinical history is perhaps the most important aspect in the approach to chronic pain, especially in neuropathic pain and conditions like fibromyalgia because physical examination and investigations often do not provide further information. The different aspects of history in pain are described further, below.

Physical examination
A complete physical examination, including a neurological assessment should be done. Relevant parts of the physical examination according to the possible cause should be done in detail. Eg., joint examination in articular pain, pelvic examination in women with pelvic pain.

Diagnostic tests
Directed testing should be done when a specific cause of pain is suggested by the history and physical examination. Interventional diagnostic procedures such as diagnostic joint block (i.e. ., facet and sacroiliac) and diagnostic nerve block (e.g., peripheral or sympathetic, celiac plexus and hypogastric) may be useful.

Pain history –

1. Characteristics of the pain - Characterisation of pain like site of pain, intensity of pain, quality of pain (sharp, dull, colicky, throbbing etc.), onset of pain and its profile, exacerbating and relieving factors need to be enquired. Neuropathic pain is often challenging to manage because of the wide variety of etiologies, symptoms and underlying mechanisms (see box 1 for possible mechanisms). It may also be difficult to accurately localize the pain or the organ system involved in many cases. The pain may be described as shooting, stabbing, like an electric shock, burning, tingling, tight, numb, prickling, itching and a sensation of pins and needles. Symptoms of dysesthesia, allodynia, hyperalgesia, anaesthesia dolorosa (pain felt in an anaesthetic [numb] area or region), and sensory gain or loss may also be described. (See box 2)

<table>
<thead>
<tr>
<th>Box 2: Sensory abnormalities in neuropathic pain⁹</th>
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<tbody>
<tr>
<td>Paraesthesia - tingling sensation</td>
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<tr>
<td>Hyperalgesia - increased response to painful stimuli</td>
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<tr>
<td>Allodynia - pain due to a stimulus which does not normally produce pain</td>
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<tr>
<td>Hyperpathia - an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold. (This often explosive reaction is associated with continuing pain after cessation of the stimulus.)</td>
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<tr>
<td>Dysesthesia - an unpleasant abnormal sensation, whether spontaneous or evoked</td>
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</table>

IASP- Pain taxonomy³
The International Association for the Study of Pain (IASP) has proposed a taxonomy for pain based on the various aspects of pain (referred to as axis). This taxonomy is useful in characterizing the type of pain that a person suffers from. Clinical history and examination should ideally be aimed at determining the axes of this taxonomy.

The five axes in this taxonomy are
• Axis I: Anatomic regions – Which anatomic region is affected?
• Axis II: Organ systems – Which organ system is involved?
• Axis III: Temporal characteristics, pattern of occurrence – duration and temporal/spatial pattern of pain.
• Axis IV: Intensity, time since onset of pain
• Axis V: Etiology – possible cause of the pain.
2. **Associated symptoms** – other symptoms along with the pain gives clues to the organ of origin. Symptoms associated with pain like joint swelling, stiffness or restriction, muscle cramps or spasms, neuropathic symptoms would be helpful.

3. **Impact of the pain** – The impact of pain on various aspects mentioned below gives an estimate of the severity of the pain and is useful in assessing response to therapy during follow up.
   a. Activities of daily living
   b. Social and recreational functioning
   c. Mood, affect, and anxiety
   d. Relationships
   e. Occupation
   f. Sleep
   g. Exercise

4. **Pain intensity scales** (see box 3)

5. **Previous evaluation** and/or treatment

6. **Psychiatric illness** - Underlying psychiatric comorbidities must be sought and identified (like depression, anxiety, posttraumatic stress disorder, substance abuse, other psychiatric disorders). If present, the treatment of these conditions can significantly improve pain relief.

7. **Patient perceptions** and psychological factors – Look for and address psychological symptoms secondary to pain such as anxiety, sleep disturbance, loss of appetite, lack of energy and diminished physical activity.

**Referral**

**Indications for referral to a multi-disciplinary care / tertiary care:**
- significant disability or loss of functioning are observed
- when there is an escalating need for analgesics

**Box 3. Assessment of pain - Pain intensity scales**

It is important to quantify the intensity of pain as objectively as possible. Pain is a relative sensation, the perception of which differs according to the psychological make-up of the person and is not easily conveyed to a physician. An objective measure is therefore useful to quantify the degree of pain. The pain intensity scales that can help us in this regard include:
- verbal scale – no pain/mild/moderate/severe/ unbearable pain
- numerical rating scale (NRS) – grade pain on a scale of 1 - 10
- visual analog scale (VAS) – Indicate severity of pain on a visual analogue scale (Figure 3)

An important aspect to be noted is that pain intensity scales cannot be used to compare the intensity of pain between patients. These scales should only be used to compare the same patient’s pain over a time period (Eg. Pain today and pain after two months).

![Visual analogue scale](image)

**Figure 3: Visual analogue scale**
TREATMENT OPTIONS:

The treatment of chronic pain is complicated and often difficult with just one mode of therapy (e.g. pharmacological). Multimodal therapy using different interventions at the same time usually provides greater benefit in the long term. The approach should also include interventions to address the overall impact of pain on the patient (psychological, relational etc.) and periodic follow-up evaluations should be developed and implemented as part of the overall treatment strategy. The options available for management of chronic pain are detailed in the discussion below with a brief description of the pharmacological treatment.

1. pharmacologic
2. physical medicine (heat, cold, exercise)
3. behavioral medicine
4. neuromodulation
5. interventional
6. surgical approaches

Pharmacologic treatment

Pharmacological therapy is the most easily available intervention in a peripheral clinic. However the efficacy of pain relief is enhanced if treatment with medications is combined with other interventions like physiotherapy or neuromodulation (multimodal therapy). The pharmacological options include:

- Non-opioid analgesic agents (e.g., aspirin, acetaminophen, NSAIDs, COX-2 Inhibitors)
- Tramadol
- Opioids
- Antidepressants - (tricyclic anti-depressants (TCA) and serotonin-norepinephrine reuptake inhibitors (SNRIs))
- Antiepileptic drugs - gabapentin, pregabalin, and other anticonvulsants
- Muscle relaxants
- Topical analgesic agents

These medications can be used either singly or in combinations. The approach to pharmacological treatment is best done in a systematic step-wise manner. As a guide, the WHO pain ladder (Box 4) and an algorithm for the management of neuropathic pain (Fig. 4) are given below.

Box 4. WHO analgesic ladder

This is the pain management recommendation for cancer related pain which can be used for non-cancer chronic pain as well.

Adjuvants include medications to relieve associated symptoms like anxiety, psychiatric symptoms and sleeplessness.

The important features of the WHO ladder are:

1. Oral administration of analgesics is preferred.
2. Analgesics should be given at regular interval (when indicated) - Analgesics given for moderate to severe pain are given on a fixed dose schedule around the clock and not on an “as needed” or “prn” basis. This allows for more consistent pain relief since patients do not have to "play catch-up" with the previous dose that has largely worn off. Patients given scheduled analgesics are more comfortable and use less medication overall.
3. Analgesics should be prescribed according to pain intensity as evaluated by a scale of intensity of pain.
4. Dosing of pain medication should be adapted to the individual based on factors such as body weight, renal and hepatic function and need.

The use of Opioids in non-cancer chronic pain is a matter of much debate and recent evidence shows that it may not offer much benefit in the long term. (In countries where access to opioids is highly restricted, this may not be a relevant issue.)
Management of neuropathic pain:
The management of neuropathic pain is challenging and a multimodal approach (Eg. Medications and physiotherapy/ neuromodulation) is often more efficacious than a single mode of therapy. An algorithmic approach to the pharmacological treatment of neuropathic pain is given in Figure 4. It is recommended that first line drugs are initiated first along with topical agents. The decision to proceed to the next level must be taken only if a trial of drugs in the present level after a reasonable duration of time proves ineffective in reducing the pain. If second line drugs are ineffective, it is advisable to refer the patient to a specialist center for further pain management. The pharmacological properties of medications (with doses) in the various classes is described in Table 2.
### Table 2: PHARMACOLOGICAL AGENTS for chronic pain

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adult Dose (more than 60 Kg)</th>
<th>Caution</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Paracetamol</strong></td>
<td>0.5–1 g every 4–6 hours to a max. of 4 g daily</td>
<td>Generally safe, use with caution in hepatic insufficiency, Alcohol dependence, chronic alcoholism, chronic malnutrition, or dehydration.</td>
<td>One of the first-line drugs used for nociceptive pain relief. Systemic NSAIDs should be avoided as far as possible. Start with paracetamol and try to stick with this drug. Move on to other NSAIDs only if the maximum dosage is ineffective.</td>
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<tr>
<td>Liver disease/heavy alcohol use – max. 2gm/day</td>
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<td><strong>Amitriptyline</strong></td>
<td>10 mg once daily (at bedtime), increased slowly at intervals of a few days to a week. The maximum effective dose is disputed, but usually 75 mg at night is sufficient.</td>
<td>Doses higher than 75 mg are associated with anticholinergic adverse effects on brain, bladder, bowel and blood pressure. Dry mouth is common.</td>
<td>Commonly used first line agent for neuropathic pain.</td>
</tr>
<tr>
<td><strong>Gabapentin</strong></td>
<td>300 mg once daily on day 1, then increase according to response to a maximum of 300 mg 3 times daily. Higher doses are not recommended.</td>
<td>Avoid abrupt withdrawal; use with caution in elderly, diabetes mellitus, mixed seizures (including absences); history of psychotic illness.</td>
<td>Useful as a first line agent in chronic neuropathic pain. Acts by binding to voltage-gated calcium channels located presynaptically, and may modulate the release of excitatory neurotransmitters which participate in epileptogenesis and nociception.</td>
</tr>
<tr>
<td><strong>Pregabalin</strong></td>
<td>75 mg daily, increased slowly if necessary after 3–7 days to maximum of 300 mg daily in 2 divided doses.</td>
<td>Avoid abrupt withdrawal (taper over at least 1 week); use with caution in severe congestive heart failure, conditions that may precipitate encephalopathy</td>
<td>Useful as a first line agent in chronic neuropathic pain. Binds to alpha2-delta subunit of voltage-gated calcium channels within the CNS, inhibiting excitatory neurotransmitter release.</td>
</tr>
<tr>
<td><strong>Tramadol</strong></td>
<td>Start with 50 mg one to two times per day and titrated as needed to a maximum total daily dose of 400 mg (100 mg 4 times daily)</td>
<td>Common side effects of tramadol include sedation, nausea, constipation, orthostatic hypotension, and decreased seizure threshold. Use with caution in those with increased risk for suicide, particularly in patients who have emotional disturbance, suicidal ideation or attempts in the past, or are addiction-prone.</td>
<td>This is a weak opioid that has some activity at mu receptors. It is useful as a rescue therapy or second line therapy in neuropathic pain. It improves functional outcomes and pain in patients with fibromyalgia. There is very little abuse potential compared with regular Opioids.</td>
</tr>
<tr>
<td><strong>Duloxetine</strong></td>
<td>60 mg once daily; max. 120 mg daily in divided doses <strong>Note:</strong> In diabetic neuropathy, discontinue if inadequate response after 2 months; review treatment at least every 3 months</td>
<td>Avoid if prone to gastritis. May cause sleeplessness, so avoid bedtime dosage Concomitant use of duloxetine with monoamine oxidase inhibitors (MAOIs) intended to treat psychiatric disorders. Wait ≥14 days between discontinuance of MAOI and initiation of duloxetine. Use caution in severe renal impairment, Heavy alcohol use, pregnancy, lactation</td>
<td>Useful in diabetic neuropathy and fibromyalgia Duloxetine is a potent inhibitor of neuronal serotonin and noradrenaline reuptake and a weak inhibitor of dopamine reuptake.</td>
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</table>
Fibromyalgia

Fibromyalgia is a disorder characterized by widespread chronic musculoskeletal pain accompanied by a constellation of symptoms including fatigue, cognitive dysfunction, sleep difficulties, stiffness, anxiety, and depressed mood. It is believed that fibromyalgia alters and amplifies painful sensations by affecting the way the brain perceives and processes pain signals. The patient complains of chronic pain and a feeling of being unwell continuously. Many experts consider this disease a functional disorder because of the lack of a definite pathology or defining radiological/serological abnormality. However a diagnosis can often be made with a careful approach to the symptoms and signs. Many of the principles for management of neuropathic pain can be used for management of pain due to fibromyalgia.

1) Confirm the diagnosis: Fibromyalgia is not necessarily a diagnosis of exclusion. With a good history and physical examination (showing multiple tender points), we can positively make a diagnosis of fibromyalgia. Radiological and blood investigations may be helpful in ruling out other causes – they are often negative.

Characteristic features of pain\textsuperscript{11,12} which can help in diagnosis of Fibromyalgia are:

\begin{enumerate}
  \item Pain in all four quadrants of the body, above and below the waist, on both sides for at least three months
  \item Associated with somatic complaints including fatigue and sleep, mood (depression), unrefreshed sleep and cognitive disturbance (usually memory).
  \item There may be multiple tender points on physical examination (though this is supportive, it is not essential to the diagnosis).
\end{enumerate}

2) Patient education: Fibromyalgia is a chronic pain disorder and is often accompanied by anxiety and feelings of hopelessness. Explaining the condition is therefore the most important aspect of management because a positive outlook to the illness can significantly affect the response to treatment.

3) Treatment:
\begin{itemize}
  \item Most patients respond to a trial with low-dose tricyclic anti-depressants or selected anti-depressants or anti-convulsants. In our department, Pregabalin is used. If ineffective, an SNRI like duloxetine is added on.
  \item An exercise program along with medicines is very helpful in reducing pain.
  \item Evaluate and treat co-morbid illnesses like mood and sleep disturbances
  \item Patients not responding to above mentioned medications and exercise, the following measures may need to be implemented.
  \begin{itemize}
    \item Speciality referral (management by a team that includes rheumatologist, physiatrist, and other pain management physicians)
    \item Combination of drug therapies
    \item Physical therapy measures
    \item Psychological interventions such as cognitive behavioural therapy
  \end{itemize}
\end{itemize}
Other Interventions for chronic pain

These may be adjuncts to and may be used as part of multimodal therapy along with pharmacological therapy.

1. **Behavioral medicine approaches**: This includes cognitive behavioral therapy, bio-feedback and relaxation therapy, psychotherapy and individual or group counseling. These techniques are aimed at altering the mental perception of pain.

2. **Aerobic exercise** – The natural release of endorphins during exercise can result in significant pain relief and a sense of well-being.

3. **Acupuncture** – Although the mechanism of action is not known, this is effective in some patients.

4. **Physical therapy** (heat/cold application, ultrasonic stimulation etc.)

5. **Electrical neuromodulation** - Neuromodulation with electrical stimulus involves direct stimulation of the nervous system with electrical signals and is a useful adjunctive therapy in the multimodal treatment of chronic pain that does not respond to other treatment options. Some of the options include:

   - **Subcutaneous peripheral nerve field stimulation**: This technique targets small nerve fibres in the subcutaneous tissue, beneath the skin. Subcutaneous peripheral nerve stimulation may be used to treat patients with painful peripheral nerve injuries who have not responded to other therapies.

   - **Spinal cord stimulation**: Spinal cord stimulation may be helpful in the treatment of persistent radicular pain in patients who have not responded to other therapies. It may also be considered for other selected patients (e.g., peripheral neuropathic pain, peripheral vascular disease, or postherpetic neuralgia).

   - **Transcutaneous electrical nerve stimulation (TENS)**

TENS: This is a fairly safe technique which uses low-voltage electric current to relieve pain in a particular region of the body. TENS is useful in management for patients with chronic back pain and may be used for other pain conditions (e.g., neck and phantom limb pain).

References

10. Don L. Goldenberg. Diagnosis and Differential Diagnosis of Fibromyalgia. The American Journal of Medicine, 122(12), Supplement, December 2009, Pages S14–S21