Chapter

What Do We Need to Consider for Pain Management?

Srini Chary

Abstract

Chronic pain in palliative care is viewed as an illness but remains as a subjective symptom. Hence, we must consider genetics, pain experience, coping skills, epigenetic effects, mental health, social determinants of health, interventions, and molecular biology. Acute pain transitions to chronic pain in some individuals following an injury, and there is poor evidence to stop such change. Acute, Chronic, and mixed pain can occur in patients with trauma, cancer, organ failure due to primary illness and other co-morbidities. The response to interventions may include biopsychosocial, non-pharmacological, surgery, radiation, chemotherapy, interventional radiology, pharmacological and depending upon survivorship, consider what is appropriate with peer reviewed medical evidence. Neurobiology is important in relation to physical and psychological issues; it affects an expression of pain. Manageable pain and relief are considered as being Human Right. Lack of adequate knowledge and treatment resources are common for care providers and patients. Cancer and noncancer pain ought to consider collaborating with interdisciplinary palliative approach, palliative care, and end of life care along with acute, chronic, and mixed pain management. Cancer patients with survivorship is increasing and risk management with chemicals, noncancer individuals appear similar. Barriers include health professional education, lack of treatment resources, medical, economic, ethical, and legal reasons. Pain management as an illness, care providers considers patient and family centered approach, useful to the community.

Keywords: pain taxonomy, genetics, epigenetic effects, biopsychosocial, molecular biology, interventions

1. Introduction

As a care provider, we must consider up to date pain management skills beneficial to individual patient. Valuing, dignity and hope along with better therapeutic relationship with the patient, allows us to return home happier at the end of the day. Relief of pain is not effective; health care professionals feel uncomfortable and complain around the world.

In 1967, the world's first purpose-built, St Christopher's Hospice in south London, England by Dame Cicely Saunders, who was a nurse, social worker and became a physician for "end of life care and clinical research" in the United Kingdom. Dr. Robert Twycross and from Canada Dr. Balfour Mount had worked with Dame Cicely Saunders and Dr. Mount came up with a term "Palliative Care" in 1973 which within a short time, the entire world accepted.

World Health Organization (WHO) present definition comprises: "Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."

More recently "Palliative Approach, Palliative Care and End of Life Care" has been accepted internationally as well as also "Early, Integrated, Collaborative and Inter-professional Care". Advanced care planning, goals of care, and good communication with relevant language and words reduce distress of patient and family (**Figure 1**).

Now palliative care has patients with palliative approach, palliative care, end of life care and survivorship with cancer or organ failure. Dr. Pippa Hawley explained the value of a visual "Bow Tie Model" as a disease management and palliative care triangles can be adopted for cancer and non-cancer interventions [1].

At the end of last century, pain management and scientific research had improved but chronic pain and palliative care specialists with present knowledge were limited in Canada and other parts of the world.

The Gold Standards Framework from the UK has prognostic indicators; general, cancer, and organ failure trajectories, which are important and useful to consider, before treatment plan [2].

In 2007, Boulanger et al., did a study whether chronic non-cancer pain has improved, though more patients were receiving medical analgesics, the changes were minor and could be better in Canada [3].

Genetics play a major role with physical, psychological health or illness and our knowledge and management is improving [4, 5]. Nutrition has a role in pain management and requires learning care providers, patients, and families [6].

Optimal pain management requires history, physical examination, investigations, and appropriate interventions. In the past four to five years "opioid crisis" increased deaths due to the use of illicit fentanyl [7]. "Pain crisis" is an experience of a patient relating to pain and requires immediate interventions, whereas "opioid crisis" relates to substance use disorder or an error with medication or illicit drug use.

IASP, pain and palliative care societies across the world are encouraging physicians and interprofessional team members to consider interventions for pain management, clinical research and in the past three decades, several peer reviewed manuscripts have been published for pain management with such evidence and knowledge, can reduce pain in an individual and community can prosper.

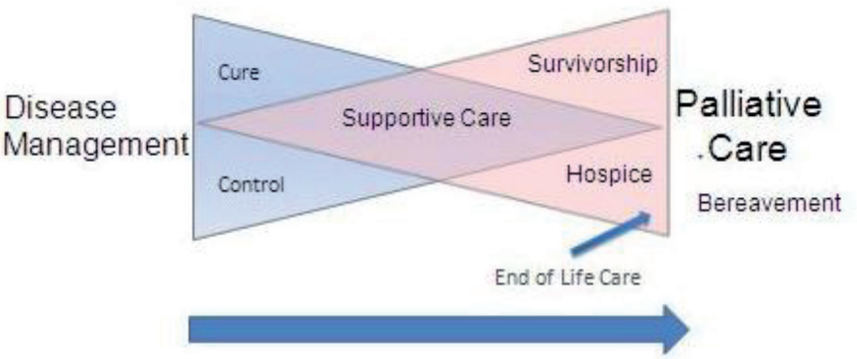

Figure 1.
Bow Tie Model: Bow Tie Model: Palliative care is an interdisciplinary coordination at the time of diagnosis and the timelines can vary in an individual head towards survivorship with cure or illness is controlled and requires supportive care or some individuals can be at the end of life.

2. Optimal pain management

International Association for the study of pain (IASP) has revised, 1979 definition of pain in 2020 considering concepts, challenges and compromises and stated "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" and is relevant for pain management [8].

Pain perception and expression is associated with molecular biology which includes transmission of signals from an injury, transmitting through spinothalamic tract to thalamus in the brain, in nanoseconds, the signals move to limbic system. Alteration in the limbic system, changes in neurotransmitters, tissue receptors lead to high expression of pain, anxiety, frustration, and major depression.

2.1 Acute pain

Acute pain like "stubbed toe or a needlestick" disappears in a few minutes secondary to the antinociceptive nervous system triggered and the pain stimuli release endorphins within the brain, and enkephalins in the brain stem, which block the transmission of pain signals at different levels and the ion channels are functioning.

However, the acute pain secondary to cell injury caused by pressure, heat, chemicals, or physical stimulus; damaged cells release lysosomes which causes inflammation within hours and magnifies the pain signals through the release of signaling chemicals such as prostaglandins, arachidonic acid and leukotrienes in the nervous system and involves glutamate at low levels. Ion channels may not function appropriately thus endorphins may not be active [9].

Acute nerve injury associated with acute neuropathic pain, e.g., broken bone, amputation.

2.2 Chronic pain

Acute, nociceptive, and inflammatory pain can transition to chronic pain, if the pain persists more than 3 months in an individual. In this period of transition, the ion channel function may not be normal, and endorphins may not be active.

Following an acute injury; infection, crush or nerve injury, degeneration of tissues, micro, macro vascular insufficiency, and cancer the recovery is low, and healing is slower, leading to chronic pain associated with poor quality of life.

Palliative and end of life care, some patients who are dependent, frail and require extensive nursing care may have pain crisis along with delirium. Identifying the difference between the symptoms, pain and delirium, using appropriate pharmacological interventions are useful. Refractory symptoms like delirium, respiratory distress, seizures may need palliative sedation. Patients with pain and agitation may require analgesic and intermittent or palliative sedation [10].

2.3 Cancer and pain

Advanced cancer trajectory leads to end of life, pain crisis or delirium and other co-morbidities need to be considered. However, if patient responds to intervention, almost 50% of them are in survivorship and not end of life, requiring long-term pain and symptom management. Cancer pain is often a "mixed pain" as inflammation around primary or metastasis is common [11].

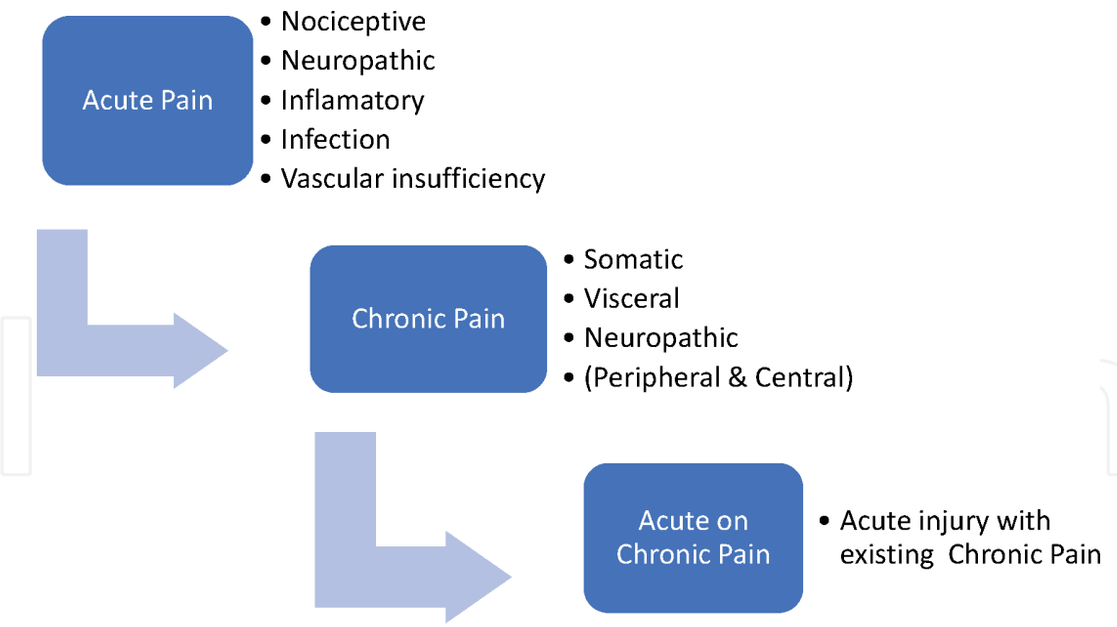

Figure 2.
Pain classification: acute, chronic, and acute on chronic pain.

2.4 Tissue injury, organ failure, comorbidities, and pain

Soft tissue or bone in the elderly have more issues like arthritis, tissue injury and healing can be poor giving rise to the pain. Acute or Chronic kidney disease (AKI or CKD) with comorbidities require pain management and most opioids are excreted through kidney and opioid toxicity is common. Diabetes is associated with neuropathy, likely microvascular insufficiency [12] (**Figure 2**).

2.5 Taxonomy

Nociceptive pain, neuropathic pain and nociplastic pain have been approved by IASP in 2019 and International Classification of Diseases (ICD-11), which the

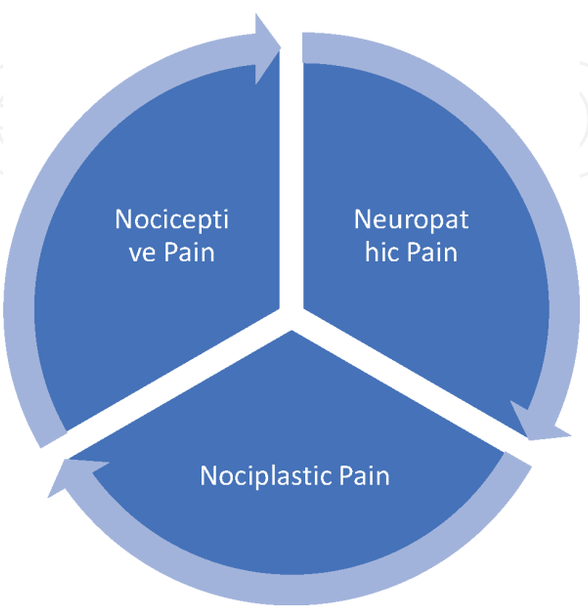

Figure 3.
Taxonomy change in 2019, IASP added "Nociplastic Pain" relating to neuroplasticity and future application of research.

World Health Organization adopted in the same year. These combined efforts have potential benefits for both research and patient care [13] (**Figure 3**).

Neuroplasticity is the change in neuronal pathways and synapses that occurs due to certain factors: behavior, environment, and neural process. Chronic pain has been related to central excitation, wind-up theory and IASP approved Neuroplastic pain; as the brain learning or neuroplasticity and alteration in the function of anatomy for future research an appropriate term [14, 15].

Epigenetic effects, including major depression in an individual related to negative experience associated with poor coping and neuroplasticity secondary to changes in gene–environment, psychosocial environment leading to lower levels of neurotrophic factors altering structural and functional aspects of brain. Such epigenetic effects can be generational [16–17].

3. Principles of pain management

Pain management should include biopsychosocial assessment, pain severity, pain descriptors and planning physical, psychological, spiritual rehabilitation, invasive therapies, and pharmacological interventions for patients with acute, chronic, neuropathic and nociplastic pain. Patients in pain crisis and agitated often require pharmacotherapy initially to manage pain and following that nonpharmacological interventions have a value and can reduce or stop medications.

Acute pain may require anti-inflammatory medications, steroids and opioids, depending upon the extent of injury for a short period, which could be hours to days, which needs to be explained to the patient and family.

Chronic pain is associated with goal setting. If patient's opioid use disorder risk is high by using "opioid Risk Tool" questionnaire, before opioids are being used requires boundary setting, along with written patient agreement document, for opioid therapy [18].

Patients with life expectancy few hours, days or weeks may need more pharmacological interventions, as other interventions non-pharmacological to improve symptoms, may need longer time to respond (**Figure 4**).

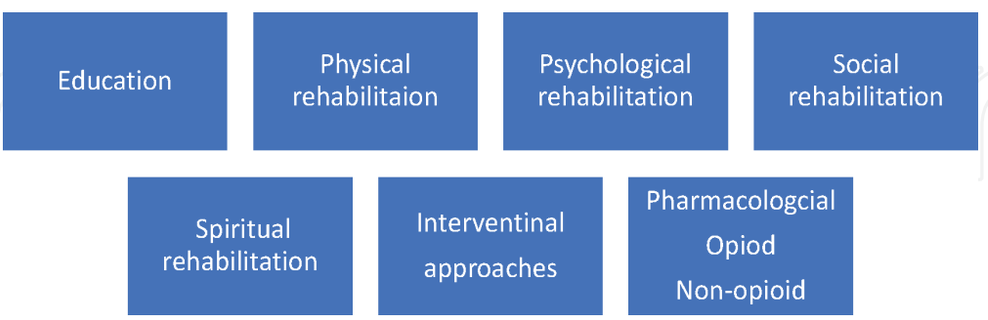

Figure 4.
Pain management includes variety of approaches, which require to improve patient's suffering.

3.1 Education

Individuals with chronic pain, and suffering may benefit with explanation of their pain, which is a subjective symptom along with interventional plan which should include in such education. Such education either individual, or group education, depending upon the choice of the patient. Education can be verbal, written or online [19].

3.2 Physical medicine approach

Somatic, myofascial nociceptive pain can respond to exercise, passive physical modalities (TENS, laser, ultrasound, and massage) along with stretching has value in chronic back, neck and shoulder pain. Elderly, chronic pain, neuropathic, psychosocial and cancer pain patients/individuals may require interprofessional management [20, 21].

3.3 Psychosocial approach

Chronic pain in some patients is associated with alteration in the function and anatomy of limbic system in the brain and prefrontal system is not comfortable.

Cognitive-behavioral therapy (CBT) for chronic pain management has been used widely. Dennis Turk first described in 1983 education, skill acquisition, cognitive and behavioral rehearsal, generalization, and maintenance, and in review 2008 CBT, self-management skills and other suggestions [22].

Vulnerable populations with pain require social and financial rehabilitation along with multidisciplinary engagement.

3.4 Spiritual approach

Spiritual awakening as non-medical approach: meditation seems to benefit self-management skills, emotional improvement, and empowerment. Physical pain and discomfort in an individual may improve, whether neurotransmitters alter to benefit emotions.

3.5 Interventional approaches

3.5.1 Surgery

For patients with a reversible pain diagnosis due to fracture, obstruction, perforation and other causes, surgical intervention is possible and beneficial. Chronic pain improves with deep brain or spinal stimulation, which requires surgery [23].

3.5.2 Radiation therapy

Primary cancer and metastasis either curative or palliative- the intention is to reduce acute or chronic pain. It is a local therapy and initial fractions may increase pain due to inflammation. Systemic injection of radionuclide was used few decades ago for bone metastasis, but at present it is used for thyroid cancer as a primary therapy only [24].

3.5.3 Chemo and immune therapy

Patients with cancer pain receiving chemotherapy, initially the pain may increase due to necrotic tumor and inflammation. After two or three cycles of chemotherapy the tumor may reduce in size and pain may improve along with other symptoms.

3.5.4 Interventional radiology (IR)

Lately nerve mapping is better and anatomically using local anesthetic, steroids or other medications can reduce or stop pain for a few weeks. IR can be used for

palliative bone/musculoskeletal and neuropathic pain in the form of cryoablation, microwave thermal ablation, plasma medicated radiofrequency ablation. Vertebroplasty and kyphoplasty along with stent therapy is possible [25].

Sympathetic blockade, stellate ganglion, coeliac and splanchnic plexus, and lumbar plexus block is possible to reduce sympathetically medicated pain and symptoms.

3.5.5 Neuraxial therapy

Palliative and end of life care when the pain is not manageable epidural and spinal analgesia using local anesthetic, opioid, alpha-2 agonist, and other pharmaceuticals to control pain is available [26].

3.5.6 Pharmacological

Non-opioid analgesics such as anti-inflammatory; acetaminophen, NSAIDs and Cox-2 inhibitors are used for acute pain but less effective with chronic pain including neuropathic or nociplastic pain. Such medications are associated with adverse effects and a therapeutic trial is useful in an individual and testing appropriate dose is useful and not harmful.

3.6 Adjuvants, co-analgesics: systemic and topical

Antidepressants and anticonvulsants have been used as systemic adjuvants for chronic pain and neuropathic pain. Number needed to treat (NNT) and number needed to harm (NNH) was adapted from Finnerup et al. in 2005 and 2007. Topical adjuvants include lidocaine patch and capsaicin and ointment and topical formulation with certain local anesthetic, amitriptyline, ketamine, gabapentin, and clonidine have been reported as beneficial for localized pain which is neuropathic in nature [27, 28].

3.6.1 Opioid analgesics

Chronic pain management requires opioids, we need to consider pain diagnosis, risk/benefit of use of opioid in an individual, mental health and behavior. Opioid risk tool has been useful to note the risk and if it is high, consider goals and boundaries, verbal or written signed documents to encourage patient's better behavior [18] (**Table 1**).

Goal setting—Chronic pain—opioids
Restful sleep at night
Brain activity sharp in the daytime
Affect, being better than neutral
Pain reduction by >30%
Improved activity and function
Physical, psychological rehabilitation
Plan for reduction of opioids—if pain improved

Table 1.
Opioid use requires goal setting and needs to be shared with the patient, the first time and reminded on follow-up.

Boundary setting—high risk—opioids
Strict boundary setting is essential
Treatment agreements—(verbal/signed)
Urine drug testing (UDT)
Interval/contingency dispensing

Table 2.
High risk in a patient with opioids or substance and opioid use disorder likely, consider boundary setting and improving behaviour.

What activates glia and immune cells?
Pro-inflammatory cytokines
Chemokines
ATP
Neuropeptides
Prostaglandins
Glutamate
Nitric oxide
Endogenous danger signals

Table 3.
Long-term opioid use can activate glia and immune cells causing tolerance, allodynia, and hyperalgesia and considering how to approach pain management.

Opioids use has been common, and morphine was considered as a "gold standard" for pain management few decades ago along with "no ceiling". Initially, morphine was used for acute pain when the pain was excessive and Twycross, once he was able to establish physiological half-life of morphine, suggested every 4 h, and on the clock. In the early 1980s and before, opioids were short-acting oral pills, liquid, and injectable. Long acting opioids through formulation became available in the late 1980s and 1990s. Now tramadol, oxycodone, codeine, hydromorphone, morphine long acting oral medications along with transdermal fentanyl and buprenorphine are available [29] (**Table 2**).

Several animal and clinical studies have shown codeine, oxycodone, morphine, and fentanyl may have benefit relieving pain for short term but when used long term lead to glial and immune cells activation, leading to tolerance, allodynia, and hyperalgesia [30, 31]. Hydromorphone long-term use has similar effect, opioid neurotoxicity with twitching, myoclonus, unrestful night sleep, and minor agitation. Activation of glial cell is associated with N-methyl-D-Aspartate (NMDA) receptor and release of amino acid, glutamate which is neuroexcitatory [30, 31]. None of the above opioids have NMDA antagonism. Methadone and levorphanol have two racemic mixtures opioid with half-life 7–8 h and non-opioid, NMDA antagonist, norepinephrine, and serotonin re-uptake inhibition. Ketamine has NMDA antagonism but adverse effects in relation to tolerance and mental health issues are high [32] (**Table 3**).

3.6.2 Opioid use

For the use of opioids as analgesics we need to consider pharmacokinetics, active metabolites, half-life, and excretion. "Start low and go slow" has been the principle and in pain crisis either opioid toxicity or pain is not responding requires higher

doses. Opioid switch in such states and 20–30% reduction of equianalgesic opioid need to be considered. Breakthrough pain, if it occurs 10% of 24-h dose of the opioid is used as a dose and around half-life such dose is given [33].

The short-term use of opioids may be useful for acute pain, but the long-term use is associated with activation of glial and immune cells with neuroexcitatory chemicals along with tolerance and hyperalgesia [30, 31] (**Figure 5**).

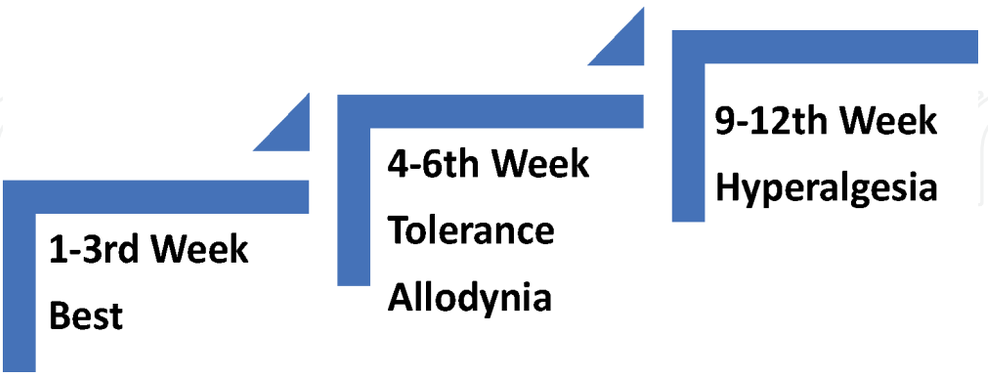

Figure 5.
Animal and clinical studies have shown Codeine, Oxycodone, Morphine, and Fentanyl when used long term, leads to neurotoxicity: Tolerance, allodynia and hyperalgesia and we need to consider better interventions to reduce pain and suffering.

Methadone is available as two racemic mixtures; R-methadone is an opioid with lower half-life and S-methadone is NMDA antagonist, Norepinephrine, and serotonin re-uptake inhibitor. Methadone has been used as harm-reduction for opioid use disorder and being used as an analgesic. Rapid titration using German, Morley Makin, Kansas, and Edmonton method in the form of stepped approach to opioid switch is possible [34, 35].

Methadone is also used when neuropathic and nociplastic pain is associated with existing opioid toxicity; twitches, jerks (myoclonus) and neurotoxicity with confusion and delirium. In such state, it is possible to use low dose twice or three times a day and ultra-low dose with slow titration is possible along with existing opioid or co-analgesics can be reduced and stopped gradually if benefit is noted [36]. Patients with mental health issues require higher dose and patients who are comfortable psychologically, pain relief and physical suffering require very low dose of methadone for cancer, acute or chronic kidney disease (**Tables 4**–**6**).

3.6.3 Adverse effects associated with the use of opioids

Nausea, minor hallucinations, and somnolence are common at the start of opioids, if the dose remains the same in a few days often such symptoms fade or require lower dose of opioid or therapeutic intervention for the symptom.

Glia and Immune cells release neuroexcitatory, pain enhancing substances
Arachidonic acid and prostaglandins
Excitatory amino acids (glutamate)
Pro-inflammatory cytokines/chemokines
Nerve growth factors
Reactive oxygen and nitrogen species

Table 4.
Neuroexcitatory chemicals enhance pain and the present and future research has a value to improve pain and suffering.

Opioid pharmacokinetics and use as an analgesic				
Opioid	Half-Life	Active metabolites	Excretion	Start dose
Codeine	3–4 hrs	Morphine	Renal	30 mg Q4h
Oxycodone	2–6 hrs	Oxymorphone	Renal	5 mg Q4h
Morphine	2–4 hrs	M6G, M3G	Renal	1 mg Q4h
Hydromorphone	2–4 hrs	H6G, H3G	Renal	1 mg Q4h
Fentanyl patch	17 hrs	Norfentanyl	Renal	12 mcg/h
Methadone	6–150 hrs	None known	Hepatic	1 mg? Q8h
Buprenorphine patch	37 hrs	B3G, NorB3G	Hepatic	5 mcg/h, Q7days

Opioid use as an analgesic, "start low and go slow" for pain management. Once pain is stable, same long acting opioid can be used to reduce tolerance. Medications Fentanyl patch, Methadone and Buprenorphine patch are long acting, and dose need to be adjusted, taking half-life into consideration.

Table 5.
Opioid use as an analgesic and "start low and go slow" for pain management.

Cancer clinic internal protocol methadone—Calgary					
1–7 days	**7–14 days**	**14–21 days**	**21–28 days**	**28–35 days**	**35–42 days**
1 mg daily	1 mg Q12h	1 mg Q8h	2 mg Q8h	3 mg q8h	5 mg Q8h
2.5 mg daily	2.5 mg Q12h	2.5 mg Q8h	5 mg Q8h	7.5 mg Q8h	10 mg Q8h

At the Tom Baker Cancer Centre, Pain Clinic in Calgary, Canada an Internal Protocol was applied to patients with opioids and pain has not improved. Evidence relating to neurotoxicity, tolerance, allodynia, and hyperalgesia methadone has been used at ultra-low dose and slow titration to relieve pain.

Table 6.
Opioid use as an analgesic and "start low and go slow" for pain management.

Dry mouth and constipation are common and require water sipping and laxatives, respectively.

Respiratory depression can occur with high doses of opioids.

Reduction androgen/testosterone can occur due to long-term use of opioids.

Neurotoxicity can occur associated with infection, renal insufficiency, and other medications; consists of hallucinations, delirium, twitching, jerks (myoclonus) and seizures. Such symptoms require reducing existing opioid, opioid switch, or adjunct medications.

Methadone and other substrates with enzyme interactions can lead to serotonin syndrome and QT/QTc prolongation.

3.6.4 Use of assessment tools

- Brief pain inventory (BPI) [37].
- The DN4 questionnaire [38, 39].
- Edmonton symptom assessment system revised (ESAS-R) [40].
- Opioid risk tool (ORT) [18].
- Pain disability index (PDI) [41].
- Roland Morris scale [42].

3.6.5 Malignant bowel obstruction (MBO)

Carcinomatosis can occur with cancer, intra-abdominal organs and results in bowel obstruction with pain and cramps. If it is localized surgery is helpful. If the obstruction can be seen by gastrointestinal endoscopy a stent can be inserted with pain and obstruction relief. However, if the obstruction on the bowel being multiple sites dexamethasone and somatostatin analogue is used subcutaneously. Initially injectable opioids are used for pain relief, and if obstruction is relived can reduce and stop opioids but somatostatin analogue may continue [43, 44].

4. Opioids, pain and substance use disorder

Chronic pain in patients with cancer, noncancer injury related, organ failure renal insufficiency, and trauma related individuals if they are at the end of life pain and have substance use disorder (SUD), we need to consider "comfort care" as goals and assist as best as we can.

However, similar patients engaged in survivorship, SUD need to be assessed and mental health/addiction services, need to be collaborated. Some of the patients with SUD or opioid use disorder (OUD) require Mu-agonist therapy using methadone or suboxone.

5. Potential future treatments for pain

We need to consider further research to improve care for individual patient. Chronic pain is considered as an illness with suffering. Several organizations have been working and care providers need to engage in raising questions and proceeding with research investigation.

Investigations and research in relation to genetics, non-opioids like; ion channels, alpha-2-agonists, glia, and immune cells along with non-pharmacological approach physical, psychological, social, spiritual rehabilitation and research in nutrition is worthwhile.

6. Conclusion

Palliative care consists of patients with illness in the early phase and advanced end of life care. Patient's wishes, worries, goals of care, and shared decisions along with subjective symptom like pain need to be considered.

Chronic pain is an illness and remains as a subjective symptom for an individual. Biopsychosocial, spiritual, and medical approach can benefit patient, family, and community. As care providers we ought to be up to date, evidence supported approach to relieve suffering of patient and family. Animal experiments and human clinical research have given care providers knowledge, and application of pain management can be better.

Acute pain often heals within days to weeks, but when the pain persists from an injury for more than three months chronic pain is considered. Central excitatory chemicals in the central nervous system can increase pain expression. Such change allows anxiety, frustration, and mental health issues.

Interventions like interventional, psychological, physical, pharmacological and nutrition have a value to reduce the chronic pain illness, suffering and improve function in an individual.

In the future, a2–Adrenergic agonists, ion-channel modifiers, and nanotechnology using nanoparticles to transport pharmaceuticals to reduce adverse effects and improve efficiency have a value in pain management and being investigated.

Thus, consider individual patient despite common diagnosis, require self-management skills, and endure or improve symptoms using appropriate therapies.

Education of care providers, patients and families is important; avoid stigmatizing an individual with chronic pain, substance use disorder, poor quality of life and mental health issues.

Acknowledgements

I wish to acknowledge and thank Dr. Neil Hagen, Dr. Alexander (John) Clark and Dr. Christopher Spanswick with whom I did learn and practice pain management in Calgary, Alberta, Canada. Thanks to Dr. Pippa Hawley, she allowed me to use the "Bow Tie Model" figure, in this chapter.

I wish to thank International Association for the Study of Pain, Canadian Pain Society, American Academy of Hospice and Palliative Care, Canadian Society of Palliative Care Physicians, and Pallium Foundation of Canada.

Conflict of interest

I do not have any conflict of interest and grateful to continue to work and assist patients, families, and my colleagues. The tables and figures were prepared by me and visual information was created through information from peer-reviewed publications.

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