Pain

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Introduction:

Pain in the general population:

In 2019, the CDC identified 20.4% of adults had chronic pain (now known as persistent pain) and 7.4% of adults had persistent pain that frequently limited life or work activities (referred to as high impact persistent pain) in the past 3 months\(^1\). Non-Hispanic white adults (23.6%) were more likely to have persistent pain compared with non-Hispanic black (19.3%), Hispanic (13.0%), and non-Hispanic Asian (6.8%) adults\(^1\). Chronic pain frequently limits life or work activities, is among the most common reason adults seek medical care, and is associated with decreased quality of life, opioid dependence, and poor mental health\(^1\). Chronic pain is the most common reason patients see a provider, accounting for 40% of all visits in primary care\(^2\). Pain remains a significant public health burden costing $635 billion annually\(^3\). The National Institutes of Health’s recommendations in its National Pain Strategy, released in March 2016, is that “chronic pain is a bio-psychosocial condition that often requires integrated, multimodal, and interdisciplinary treatment, all components of which should be evidence-based”\(^4\).

Persistent and acute pain in both the pediatric and adult population is often unrecognized and undertreated\(^5,6\). On the opposite end of the lifespan, older patients are known to be at risk for poor pain management due to inadequate assessment, interference of many medications, interactions of drugs, and multiple co-morbidities\(^7\).

Pain has a bio-psycho-social impact. Those who suffer from pain are not the only ones who bear the burden. Society as a whole suffers when a person experiences pain, including those with an inherited bleeding disorder (IBD). When a person experiences pain and is disabled due to pain, even for a short period of time, family, friends, schools, employers, and many others are affected. Although direct costs can be measured in missed days from work or school, decrease in productivity, a persons’ quality of life suffers often leading to dysfunction within family and social life\(^8\).

Frequently, HTC nurses are the first point of contact when a patient presents with pain and thus are in a unique position to be able to assist with the person experiencing pain. Nurses are invaluable in the initial and on-going assessment, education, evaluation, and reassessment of the patient, their social support system, level of functioning, and the overall treatment plan. Hemophilia nurses can be strong patient advocates in an area where advocacy is greatly needed.
Incidence of pain in the bleeding disorders community

In recent years, pain has become better documented in this population. Twelve to 76% of persons with a bleeding disorder reported pain regardless of hemophilia severity\(^9-15\). At least 14% of persons with hemophilia (PWH) who utilize prophylaxis continue to report pain\(^13\). Dr. Manco-Johnson in 2016, reported that PWH who utilize prophylaxis report ongoing pain, whether primary prophylaxis (10%) or continuous prophylaxis (22 %)\(^16\). Between 40-60% PWH report that their pain is not well controlled\(^15\). PWH report pain interference with activities of daily living: \(\leq 30\) years (21%); 31-40 years (27%); \(> 40\) years (31%)\(^13\). Thirteen to 25 year old PWH report initial use of pain medications for chronic pain at 11.5 years\(^17\). In exploring the pain experience in young adults, age 13-25 years, non-whites were more likely to report higher levels of pain and lower physical scores\(^18\).

The relationship between pain, depression, and anxiety is well established in the literature in the general population, and is prevalent in persons with a bleeding disorder (PWBD). It has been reported 20% to 60% of PWBD have been diagnosed with depression\(^11,13,19-24\). Potential for depression is greatest with lack of social support and employment\(^19\). PWH who are depressed are less likely to complete high school or treat prophylactically with their hemophilia treatment regimen\(^20\). In addition, those who are depressed will be more likely to report joint pain or have range of motion limitation\(^21\), lack social support, or be unemployed\(^24\).

PWH report anxiety from 14-67\%\(^11,13,22,24,26\). Higher anxiety scores and reported anxiety diagnosis was found among children and adolescents with hemophilia\(^27\). The Hero B study noted that women with Hemophilia B reported greater depression scores than their male counterparts (42% VS 14%) as well as greater anxiety scores (43% vs. 15%). Post-traumatic stress disorder (PTSD) is now becoming an area of interest and research as a result of ongoing pain issues within the bleeding disorders population.

In summary an association between pain, depression, and anxiety are evident which can affect treatment adherence and quality of life issues. As nurses are the frequently the first point of contact for many patients, they are in a unique position to recognize and address these issues.

Multidisciplinary team management to pain

A multidisciplinary team approach to pain management is the standard of practice and requires the patient be an active participant\(^8\). The team of health care providers can work directly with the person in pain using a variety of measurements, interventions, and strategies for self-management to provide a patient centered treatment plan that is unique for the patient in pain. Team members consist of a group of medical specialists from different disciplines with an emphasis on pain management and can include; physicians, nurses, advance practice nurses, social workers, psychologists, counselors, behavioral therapists, physical therapists, case managers, occupational therapists, and other health professionals as needed. With this multidisciplinary team approach, pain can be addressed physically, psychologically, as well as socially. The
objective of pain management in the individual with pain is a joint effort to determine the unique strategies that will help in management of pain.

A multimodal approach to pain is typically encouraged where there is the use of different classes of drugs with varying mechanisms of action to produce a synergistic effect while minimizing dosing and potential side effects as well as maximizing efficacy. The multimodal approach also includes utilization of alternative modalities of therapy such as non-pharmacologic strategies. This chapter will review all potential modalities for pain management in persons with bleeding disorders (PWBD).

Pain in persons with bleeding disorders

Pain can be experienced by any person with a bleeding disorder whether male or female. Pain can be the result of an acute joint bleed or muscle trauma, IV access for treatment, or dysmenorrhagia experienced by females. Even at a young age, persons with hemophilia can experience pain, whether it is pain from a bleeding event, or even pain or discomfort from treatment requiring IV access. Persistent pain can be the result of damaged joints from repeated bleeding episodes. Persons with bleeding disorders frequently experience acute pain concurrently with persistent pain, and thus are unusual in their presentation compared to the general population. The associated pain may accumulate after years of hemarthrosis, especially if a PWH has an inhibitor which can make bleed management increasingly challenging. Over time, these repeated joint bleeds can lead to persistent daily pain due to resulting end stage joint disease.

Overall, pain is an undertreated phenomenon. This is true within the general population as well. Nurses can assist with assuring that patients receive the best care possible, including pain management. Inadequate treatment of pain has many bio-psych-social as well as financial ramifications. As stated by B.E. Cole in Clinical Pain Management; “The failure to relieve pain is a national tragedy. Many barriers are described for why this happens but none excuses the failure to relieve pain. While practitioner, patient, and system-related barriers may increase the challenge for relieving pain; all barriers can be overcome and relief provided”.

Acute and Persistent Pain

Definition of Pain

“an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of damage. Pain is always subjective. It is an unpleasant and is an emotional experience”.

Acute pain

- Pain that has lasted less than 3 months
- Cause is often obvious, such as a surgical intervention, trauma, IV access for infusions
- Generally results from disease, inflammation, or injury to tissues
- Onset is quick
• May be accompanied by anxiety or emotional distress
• Cause can be usually be diagnosed and treated where pain will then diminish as healing occurs
• Usually analgesic medications can be reduced in a short period and the patient will return to his/her baseline pain status
• Self-limiting; in certain instances, can lead to persistent ongoing pain

Persistent Pain
• Severe discomfort that can extend past 6 months
• Causes may be unclear
• Treatment is focused on pain reduction, increased function, and improved quality of life
• Can be classified as a disease process itself
• Can be worsened by environmental and psychological factors
• May co-exist with other persistent pain conditions as well as depression and anxiety
• May not see the actual injury or physical responses (changes in heart rate, blood pressure, grimacing or crying out)
• Maintenance of daily function is important
• Considered non-life threatening

Pain secondary to hemophilia can often start early in a child’s life initially presenting as an acute pain episode from bleeding into a muscle or joint as well as a result of the procedure associated with bleed management (IV infusions). Pain in a bleeding joint is the result of pressure against the synovial lining and adjacent tissue as blood collects in the affected joint as well as inflammation caused by trapped blood. Repeated bleeding into the same joint can result in the development of a target joint and progression to hemophilia arthropathy (destruction of bone), which may cause significant persistent pain. In some instances, a different type of pain emerges that persists long after bleeding episodes have subsided and appears to be neurogenic in nature where patients may describe this pain as a burning sensation.

PATHOPHYSIOLOGY OF PAIN

Pain pathway

• The science of pain is a complex process
• Painful stimuli are transmitted from the pain of injury through nerves to the spinal cord and ultimately the brain. However, as the process occurs, there are other complex set of processes that modulate the individual pain experience.

1. Transduction:
   a. A process where afferent nerve endings (A-beta, A-delta and C fibers in the skin and tissue) participate in translating noxious stimuli into nociceptive impulses
   b. A-beta fibers (myelinated, large diameter) respond mostly to light touch and movement such as vibration
c. A-delta fibers (fast, myelinated, small diameter) and C-fibers (slower, unmyelinated) respond to painful (noxious) stimuli
d. Any fiber that responds to pain (noxious) stimulation is classified as a pain fiber, also known as a nociceptor

2. Transmission
a. Movement of impulses from the nerves to the brain (sent through dorsal horn of the spinal cord and then along sensory tracts to the brain)
b. The primary afferent nerves (mostly A-delta and C fibers) in the periphery send and receive chemical and electrical signals to their counterparts in the spinal column
c. The intensity and quality of pain is determined by the somatosensory cortex (sensory aspect of pain)
d. The emotional response is determined by the frontal cortex and the limbic system

3. Modulation
a. This is the process of dampening or amplifying the pain signal
b. Probably takes place at multiple levels but primarily in the dorsal horn of the spinal cord
c. The dorsal horn is rich in opioid receptors (mu, delta, and kappa)
d. Modulation can be activated by many modalities including the use of opioids (endogenous and non-endogenous), neurotransmitters such as serotonin and norepinephrine, electrical stimulation, stress, and suggestion.
e. The major ascending tract, the spinothalamic tract (STT) ultimately divides the 2 different pathways as it approaches the thalamus, lending to the sensory/discriminative aspects of pain perception and/or the affective/motivational aspects of pain perception.

4. Perception
a. The conscious awareness and subjective experience of pain
b. Results from the interaction of transduction, transmission, modulation, psychological and other characteristics of the individual

GATE CONTROL THEORY

- A model of pain modulation that ties all four of the above steps together
- Initially proposed by Melzack and Wall in 1965.
- Proposed the existence of an internal capacity to diminish or intensify the degree of perceived pain through the adjustment of incoming impulses at a neurological gate located in the spinal cord
- The integration of these inputs (sensory neurons, segmental spinal cord level and the brain) differentiates between types of fibers carrying pain signals, determining whether the gate will be opened or closed
- The “gate” can be manipulated by psychological variables (emotions, thoughts, distraction, and stress reaction), pharmacologic measures (altering transduction, transmission, and modulation) or psychological intervention
- Gate control theory is often used to explain phantom or persistent pain
NORMAL PAIN (NOCICEPTIVE PAIN)

1. Classified as somatic (bone, joint, muscle, skin or connective tissue) or visceral (organs, such as GI tract) pain
2. Nociception
   a. When pain receptors (nociceptors) are damaged or irritated they transmit the signal of pain to the brain
   b. Nociceptive pain is usually time limited in that as the tissue heals the pain resolves (does not include arthritic pain)
   c. Often described as well localized, constant, aching, and throbbing in quality
   d. Usually responds well to anti-inflammatory (NSAIDs), acetaminophen, or opioids

ABNORMAL PAIN

“Pain that occurs in the context of a nociceptive system that has been altered by tissue damage or other processes” 31.

1. Inflammatory pain
   • Sensation resulting from injury to a somatic tissue (i.e. skin, muscle, bone) customarily followed by an inflammatory reaction (i.e. acute injury)
   • The inflammatory response releases substances that cause “sensitization” of the peripheral pain fibers (nociceptors). Often these pain fibers will develop a lower threshold for firing resulting in more frequent firing than when in a normal state. When this occurs, even normally non-noxious stimuli (i.e. light touch or contact with clothing) will cause pain
   • After tissue healing, the pain generally resolves
   • However, in states of ongoing inflammation or injury, such as hemophiliac joint bleed, where inflammation may resolve but leave permanent anatomic alternations (i.e. joint damage produced by hemarthropathy) persistent pain may result even though inflammation disappears or becomes unnoticeable
2. Central sensitization
   • The consequence of continual or frequent and excessive pain signals from the periphery can overwhelm the central nervous system; often referred to as “wind-up”
   • This bombardment of pain signals cause long-term changes in the central nervous system leading to persistent amplification of those pain signals.
   • Central sensitization is one suggested mechanism where abnormally harmless stimulus produces pain
3. Allodynia
   • The phenomenon of normally harmless/painless stimuli (i.e. light touch) process pain
4. Hyperalgesia
   • Exaggerated response to a normally painful stimuli
   • Distinction between primary and secondary is important when deciding on treatment
• To effectively treat central sensitization pain, hypersensitivity must be addressed during the clinical assessment of the patient. Therapy that targets the mechanisms of hypersensitivity, if present, rather than mechanisms of nociception, need to be used to try to alleviate symptoms
  
a) Primary hyperalgesia
    - Occurs at the site of injury
    - Characterized by a lower pain threshold, spontaneous pain and increased sensitivity
    - Usually features thermal and mechanical hypersensitivity

b) Secondary hyperalgesia
    - Hyperalgesia occurring outside the area originally injured
    - Thought usually to be a consequence of central sensitization

c) Neuropathic pain
    - Pain due to damaged or dysfunctional nerves
    - The pathophysiology of neuropathic pain can have both peripheral and central mechanisms that generate abnormal signals with abnormal excitability.

d) Dysfunctional pain
    - Pain and abnormal sensitivity not associated with noxious stimulus, tissue damage, inflammation, or identifiable lesion to the nervous system
    - May include fibromyalgia, tension-type headaches, migraines, irritable bowel syndrome
    - Individuals with these syndromes share a number of common characteristics, including hyper-vigilance to sensory stimuli, exaggerated experience of a diverse array of sensory stimuli, high prevalence of associated conditions and in some cases abnormal biomarkers (i.e. high substance P levels in the spinal fluid)

e) Referred pain
    - The perception of pain in a body part in which it did not originate
    - The mechanism of referred pain is thought to be a convergence of primary afferent fibers from different locations onto the same spinal cord neurons. The spinal nerves serve both deep tissue structures as well as skin structures leading to mis-location of the perception of the pain signal.

Research continues to evolve on the differentiation of the different types of pain and response to treatment associated with specific type of pain. All of these factors are considerations when treating pain in persons with bleeding disorders.

PAIN ASSESSMENT

Goals of Therapy
The first step in pain assessment in the bleeding disorder patient is to identify the *mutually* agreed upon goal between the patient and provider, which should include:

a) Increase function  
b) Minimize side effects

**A “functional pain goal” is based on achieving an activity or quality of life issue.** This provides a clear direction as to the planned desired improvement. Keep in mind, if a person with hemophilia has been experiencing persistent pain for many years, a goal of “no pain” or 0/10 on a numeric pain rating scale is not a realistic goal. The goal should include a reduction of the current pain level, or preferably, improvement in the level of functioning.  

**Measurable outcomes** are necessary to provide a clear goal:

- Suggested measureable outcomes (goals) can include:
  - Pain intensity decreased
  - Reduction of medications as pain improves
  - Improved sleep
  - Improved functional activities
  - Increased involvement in social activities

It is important to use a pain scale that works for the individual patient and use it consistently. Some patients find that a numeric rating scale (0-10) reduction can be visualized, whereas others may find a decrease in the percentage (%) of pain may be easier to visualize.

Development of measurable goals can be incorporate the “SMART” mnemonic:

- S = Specific
- M = Measurable
- A = Achievable
- R = Realistic/relevant
- T = Time specific

**BARRIERS**

- Barriers to effective pain management should be explored as potential barriers can affect goal achievement.  
- The Patient Medication Assessment questionnaire (PMAQ) barrier assessment can assist in identification of where barriers may occur.  
- Identification of potential barriers can provide an opportunity for increased education with the patient in the arena of pain management.  
- In the appendix, Table 1. provides a list of potential barriers experienced by patients, providers, as well as institutions and/or pharmacies.

**ADHERENCE**

**Definition:** “attachment or commitment to a person, cause, or belief” such as adherence to a defined plan of care.
Patients can completely adhere to a treatment plan or partially adhere to the plan. This can be related to dose of a treatment, frequency of the treatment, and/or timing of the treatment. As nurses it is important to ask the right questions regarding how their pain may be managed related to many of the issues reviewed here. There are many dimensions of adherence that can affect a patient’s management of pain which can include:

- Social & economic
- Health care system
- Condition related
- Therapy related
- Patient related

**ASSESSMENT**

- The first and best assessment is the patient’s reported level of pain followed by potential causes of pain; pain behaviors, surrogate report, and response to analgesic trial\(^{35}\) (see Appendix; Diagram 1.)
- There are 7 steps to an appropriate assessment to ensure that adequate information is collected which include\(^{40}\) (see Appendix: Diagram 2)
  a) Location of pain; have patient point to the area
  b) Description of pain – use of patients own words to describe the pain
  c) Intensity; use of pain rating scales and/or affect towards functional pain goal
  d) Duration: how long does the pain last
  e) Alleviating/aggravating factors: what makes the pain better, what makes it worse, what previous treatments have been trialed and work/don’t work
  f) Associative factors; what other symptoms are noted; i.e. nausea, depression, anxiety
  g) Impact of pain on quality of life: i.e. ability to sleep, work, socialization, sexual activity, hobbies, activities of daily living

This is an ongoing process of assessment and re-assessment.

- There are several assessment tools available that can be helpful in determining the level of pain and function of a patient. A non-exhaustive list is included in Table 2 in the appendix with links provided.\(^{40-55}\) Diagram 4 in the appendix provides visual examples of pain tools.
- The Pain, Functional Impairment, and Quality of life (P-FiQ) study\(^{13,56,57}\) evaluated a variety of pain assessment tools in persons with hemophilia exploring validity of a variety of patient reported pain assessment tools. Results indicated all assessment tools demonstrated known-group validity and may have practical applicability in evaluating adults with hemophilia in clinical and research settings in the United States
- Find the pain tool that works best for you and your patient, and use consistently for proficiency

**PHARMACOLOGICAL APPROACH TO PAIN MANAGEMENT**
The WHO analgesic ladder was proposed by the World Health Organization (WHO), in 1986, to provide adequate pain relief for cancer patients as part of a WHO Cancer Pain and Palliative Care Program aimed at improving strategies for cancer pain management through educational campaigns, the creation of shared strategies, and the development of a global network of support. This analgesic path, developed following the recommendations of an international group of experts, and has undergone several modifications over the years. Since its inception, this ladder is now used to manage acute and chronic non-cancer painful conditions and to a broader spectrum of diseases. (see Appendix; Diagram 3.)

- The Center for Disease Control and Prevention (CDC) in 2016, developed opioid guidelines to assist providers in the management of non-cancer pain. This guideline provides recommendations for primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care and end-of-life care.

- In 2015, the National Hemophilia Foundations (NHF) Medical And Scientific Advisory Council (MASAC) multi-disciplinary pain task force was challenged by MASAC to develop guidelines to assist HTC providers in management of pain in their bleeding disorder patients. This guideline has since been adopted as MASAC Document #260; Management of Chronic Pain in Persons with Bleeding Disorders: Guidance for Practical Application of The Centers for Disease Control’s Opioid Prescribing Guidelines. This document is available on the NHF website: [https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-260-management-of-chronic-pain-in-persons-with-bleeding-disorders-guidance-for-practical-application-of-the-centers-for-disease-controls-opioid-prescribing-guidelines](https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-260-management-of-chronic-pain-in-persons-with-bleeding-disorders-guidance-for-practical-application-of-the-centers-for-disease-controls-opioid-prescribing-guidelines) This document will be discussed in more detail in the opioid section. The document does not address opioid usage in children and pregnant women. It is recommended that you review package inserts if considering prescribing opioids in these populations.

- Assessment of depression and anxiety should also be done when assessing pain, as these issues can coexist in the presence of pain. Utilize your HTC team experts to help with these assessments.

- There are several tools that can be utilized for assessment of depression and/or anxiety. (see Appendix: Table 3.)

- Additional useful tools for pain assessment are available (see Appendix: Table 4.)

In the following section; we will address pain management utilizing the WHO pain ladder.

**Acetaminophen**

- The first level of the WHO ladder identifies acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) for mild pain

- Acetaminophen is the most frequently used pain medication in PWBD from 46-53%

- A review of the literature indicates that acetaminophen is recommended for mild pain in PWBD.

- Most common prescribed analgesic used for acute/chronic pain during the prior 6 months was acetaminophen (acute pain: 62% vs. persistent pain: 55%)57.

- Acetaminophen belongs to a class of drugs called analgesics (pain relievers) and antipyretics (fever reducers).
• The exact mechanism of action (MOA) of acetaminophen is not known. It may reduce the production of prostaglandins in the brain. Prostaglandins are chemicals that cause inflammation and swelling64.

• Acetaminophen relieves pain by elevating the pain threshold, that is, by requiring a greater amount of pain to develop before a person feels it.

• Acetaminophen has a ceiling effect (more drug does not equate to increased pain relief) thus their doses are limited65,66.

• Side effects of acetaminophen use include; rash, nausea, headache, hypersensitivity reactions, skin reactions, kidney damage, anemia, and potential for thrombocytopenia66.

• When using acetaminophen, caution needs to be taken in those with co-morbid liver disease (such as hepatitis), with the co-administration of alcohol, and or in combination with medications that contain acetaminophen (combination pain relievers or cold remedies) that may increase the risk of acetaminophen overdose.

• Watkins et al. (2006) in 200667 studied healthy subjects using acetaminophen for 14 days. Significant hepatic transaminase elevations were noted in more than 30% of the participants. Based on this study, the American Liver Foundation recommends limiting daily dosages of acetaminophen to 4 gm/day. This link identifies pediatric dosages as well and is available at:
  
  (https://www.drugs.com/dosage/acetaminophen.html#Usual_Adult_Dose_for_Pain; https://liverfoundation.org/acetaminophen-risks/)

• Liver and renal function should be monitored on a regular basis.

• If acetaminophen is utilized, the medication should be given on a regular schedule for both pediatric and adult patients experiencing an acute pain crisis or persistent pain68.

• Be aware of other combined analgesics and cold remedies that may contain acetaminophen which may increase the overall 24 hour dose intake to dangerous levels.

• The MASAC Opioid guidance document (#260) recommends49: Non-pharmacologic and non-opioid pharmacologic therapy is preferred 1st choice in the management of persistent pain49.

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**Non-Steroidal Anti-inflammatory Drugs (NSAIDs)**

• PWBD reported non-steroidal anti-inflammatory drugs were used for pain management from 34% to 49%^69.

• NSAID use in the bleeding disorder population remains controversial considering evidence that reviews the risks and benefits of standard NSAIDs alone versus Cox-II inhibitors.

• The mechanism of action of NSAIDs: These drugs work by inhibition of the enzyme cyclo-oxygenase (COX), which we now know to have at least two distinct isoforms: a) the constitutive isoform, COX-1, and the b) inducible isoform, COX-2. COX-1 has clear physiologic functions. Its activation leads to the production of prostacyclin, which when released by the endothelium is anti-thrombogenic and when released by the gastric mucosa is cytoprotective70.
• The COX-2 NSAIDs induced by inflammatory stimuli and cytokines in migratory and other cells. The anti-inflammatory actions of NSAIDs are due to inhibition of COX-2, whereas the unwanted side-effects, such as irritation of the stomach lining, are due to inhibition of COX-1. Drugs that have the highest COX-2 activity and a more favorable COX-2: COX-1 activity ratio will have a potent anti-inflammatory activity with fewer side-effects than drugs with a less favorable COX-2: COX-1 activity ratio.70

• MASAC guideline #162 states: A class of non-steroidal anti-inflammatory drugs (NSAIDs) known as cyclooxygenase-2 (COX-2) inhibitors, with similar efficacy to NSAIDs, is approved for use in arthritis and menorrhagia. Individuals with bleeding disorders and pain have used these agents with good pain relief.

• Although COX-2 inhibitors are not associated with platelet dysfunction in vitro, there are anecdotal reports that use of these drugs has caused clinically significant bleeding in some individuals with bleeding disorders. Hence, caution is advised with the use of COX-2 agents (e.g. celecoxib) in individuals with bleeding disorders.71

• Providers should maintain close vigilance for symptoms and signs of heart attack, stroke, or gastrointestinal bleeding and should discuss these potential risks in the context of their potential benefits with their patients.71

• Adverse cardiovascular profile of NSAIDs includes risk of atherothrombotic events like myocardial infarction (MI) and stroke. The increased cardiovascular risk has been observed both in people with a prior high risk of cardiovascular disease and in previously healthy individuals.71

• Apart from rofecoxib, diclofenac is the agent most associated with an increased risk of cardiovascular events: a 40%–60% higher relative risk of serious cardiovascular events, compared to non-use of NSAIDs, has been reported.73

• In the general population, the risk of bleeding and of cardiovascular events is considerably higher in older people, of whom many take medicines known to interact with NSAIDs.74

• Use at the lowest effective dose for the least necessary duration.71

• Individuals sensitive to sulfa should be aware that the COX-2 inhibitor, celecoxib (Celebrex®), contains sulfa groups which may precipitate allergic reactions.71

**Adjuvant Therapies**

• Although pain is thought to be nociceptive in nature, due to the constant irritation of the nervous system from frequent joint bleeds, many PWH may experience neuropathic pain.

• In the National Pain study, patients reported a burning (24%) or shooting pain (37%), suggestive of a neuropathic component.15 The WHO pain ladder suggests the use of adjuvant therapies as a 1st and 2nd approach to pain management.58 Non-opioid adjuvants, is defined as drugs with other indications but have analgesic effect in certain pain conditions, and are recommended to be added at all steps of the ladder based on the type of pain and clinical context.75

• Depression and anxiety can interplay with pain issues. Treatment of these conditions can help to manage the pain experience.
• While many drugs are not FDA approved for pain syndromes, adjuvant medications have been shown to be effective in various types of neuropathic pain syndromes.
• Adjuvant analgesics such as antidepressants, anticonvulsants, and corticosteroid medications have been established for neuropathic pain.
• The therapeutic goals for combining opioids with adjuvant analgesics include improved pain control relative to opioids alone, reduced opioid doses, potentially reduced opioid-related side effects, and improved function.
• Commonly used adjuvant analgesics are a diverse group of medications which include corticosteroids, antidepressants, and anticonvulsants.
• Potential adjuvants include: Gabapentin, Dexamethasone, Pregabalin, Lidocaine patches, Prednisone, Carbamazepine, Citalopram, Amitriptyline, Venlafaxine, to name a few.
• **Antidepressants (ADs).** Current research suggests the *mechanism of action* of antidepressant effects on pain are mediated by the blockade of norepinephrine and serotonin reuptake thereby resulting in increased levels of these neurotransmitters and enhancing the activation of the descending inhibitory neurons. Serotonin, acetylcholine, and histamine have been identified as pain mediators. In addition to activating primary afferent nerve pathways via 5-HT3 receptors, serotonin produces mechanical hyperalgesia by acting at a different receptor in the periphery—most likely the 5-HT1a receptor subtype. Beta-adrenoceptors have been demonstrated to mediate the analgesic effects of desipramine and nortriptyline.
• Serotonin and norepinephrine reuptake inhibitor antidepressants (SNRIs) can provide enhanced pain relief over the Selective Serotonin reuptake inhibitors (SSRIs)
• **Anti-convulsant** drugs *mechanism of action* act by blocking sodium channels in order to provide pain relief. This classification of drugs can also be used as mood stabilizers which, in turn, may have beneficial effects on pain management. Mood stabilization is accomplished via anti-kindling effects, enhancement of GABAergic transmission, diminished excitatory amino acids, and inhibition of voltage-sensitive Na+ channels.
  o Gabapentinoids are known to reduce bone and visceral pain
  o Amitriptyline has been shown to improve neuropathic pain and reduces opioid dose requirements in animal models.

**OPIOIDS**

Several definitions need to be understood before the use of opioids in any population.

**TOLERANCE**

This can occur with the use of medication where decreasing effects are noted of a drug at a constant dose. There is a need for higher dose of a drug to main effect. This is considered a physiological response that is expected. **THIS IS NOT ADDICTION**.

**PHYSICAL DEPENDENCE**

This is an expected physiologic phenomenon manifested by development of withdrawal syndrome after abrupt discontinuation of therapy. A withdrawal syndrome can be produced by abrupt
cessation, rapid dose reduction, and decreasing blood level of the drug\textsuperscript{31}. THIS IS NOT ADDICTION.

ADDITION

Addiction is a primary, chronic neurobiologic disease, with genetic psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one of more of the following\textsuperscript{31}:

a) Impaired control over drug use
b) Compulsive use, craving, continued use despite harm
c) Seeking out drug despite potential harm to self or others

PSEUDOADDICTION

Abuse-like behaviors may develop in response to the ‘under-treatment’ of pain. When pain is appropriately managed, with the correct dosage of medication, this behavior disappears. This is commonly mistaken for addiction\textsuperscript{31}.

BREAKTHROUGH PAIN

This condition occurs when a patient currently on a pain management program experiences a transient flare of severe pain\textsuperscript{31}.

1. **Incident pain** – Pain related to an increase in activity. It can be treated with a short acting rescue pain medication administered as closely to the event as possible.
2. **Volitional Incident Pain** – Pain caused by an activity that can be anticipated and controlled. An example may include: to increase activity after an acute bleed, a patient may need to take an immediate release opioid prior to physical therapy knowing it will be painful.
3. **End of Dose Pain** – Pain experienced frequently at the end of a scheduled dose of an opioid. An example can include: A patient on sustained release morphine every 12 hours experiences a pain increase at the 10\textsuperscript{th} hour consistently. This can be treated with a dose adjustment.
4. **Idiopathic Pain** – when all other areas are explored and an answer is not forthcoming, occasionally patient scan experience higher than usual pain experiences. Disease progression is a consideration that should be investigated.

SUBSTANCE USE DISORDER (SUD) previously known as Substance Abuse

- Not all patients receiving opioids will suffer from substance use disorder. An important subset of patients with chronic pain syndromes may suffer from a SUD or a prior history of addiction\textsuperscript{80}.
- Some behaviors suggestive of SUD may include\textsuperscript{80}:
• Using other people’s analgesics
• Accelerating dosing
• Running out of medications early
• Seeking opioids from more than 1 provider
• Selling prescription drugs
• Forging prescriptions
• Using alternative routes of ingestion
• Multiple incidences of lost medications or prescriptions
• Theft of paraphernalia from hospitals for injection use.

• Assessment requires the provider to use a standardized systematic approach to all patients who will be receiving (or are at risk of misusing) opioids. Practitioners are encouraged to embrace a “universal precautions” and rational approach to the treatment of pain.

• Even though no single tool has been shown to have both high inter-observer reliability and high sensitivity, the standardized approach has still been shown to be superior to subjective care giver assessment.

• There are many potential predictors of misuse and abuse of opioids.
  1. History of mental health diagnosis
  2. Family history of abuse
  3. Previously history of substance abuse
     a. ETOH, tobacco, cocaine, cannabis
     b. Most consistent predictor of opioid abuse & misuse
     c. Age: younger age carries greater risk but does not mean any age is free of risk
     d. Gender is not always a predictor
     e. Chaotic family/social environment or poor support

• Common opioid misuse assessments are available: Links to these tools are available in Table 5. in the appendix.
  o Current Opioid Misuse Measure (COMM)
  o Opioid Risk Tool (ORT)
  o Opioid compliance check list
  o Brief risk interview
  o Addiction behaviors checklist
  o Opioid use disorder tool (OUD)
  o Screening tool for addiction risk (STAR)
  o Screener & opioid assessment for persons in pain (SOAPP-R)

Opioids

• PWH reported a 21-24% report usage of opioids in PWBD
• A chart review indicated opioid usage of 56% of adult & 21% of pediatric patient
• Long-acting opioids were infrequently used specifically for chronic but not acute pain (morphine, 7%; methadone, 6%; fentanyl patch, 2%)
• The CDC opioid guidelines were established in 2016 to guide providers in pain managements who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care.

• The WHO pain ladder identifies an opioid trial when pain becomes moderate to severe in nature, is adversely impacting a person’s function or quality of life, previous trials of non-opioid strategies have failed and the benefits of opioid treatment have been determined to outweigh the burdens of treatment58.

• This is a mutually agreed upon decision between the provider and the patient.

• Opioids are scheduled drugs as classified by the FDA

• The mechanisms of action of opioids are such that opioids connect to the specific opioid receptors as a lock and key mechanism. There are considered to be three opioid receptors. These receptors are all G-protein-coupled receptors, and were originally named mu, delta, and kappa. The classical opioid receptors are distributed widely within the central nervous system and, to a lesser extent, throughout the periphery. Within the central nervous system, activation of mu receptors in the midbrain is thought to be a major mechanism of opioid-induced analgesia. Here, mu agonists act by indirectly stimulating descending inhibitory pathways which act upon the periaqueductual grey (PAG) and nucleus reticularis paragigantocellularis (NRPG) with the net effect of an activation of descending inhibitory neurons91

• Opioids are classified as short acting and long acting. Opioids can be given orally, intravenously, intramuscularly, subcutaneous, topically, or rectally based upon the formulation.

Mechanism of short and long acting opioids92

<table>
<thead>
<tr>
<th></th>
<th>Short acting opioids</th>
<th>Long acting opioids (ER)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma half-life</td>
<td>2-4 hours</td>
<td>6-12 hours</td>
</tr>
<tr>
<td>Analgesic effect</td>
<td>3-4 hours</td>
<td>8-72 hours</td>
</tr>
<tr>
<td>Onset of action</td>
<td>15-30 minutes</td>
<td>15-30 minutes</td>
</tr>
</tbody>
</table>

*ER=extended release formations

• MASAC Document49: #260: Management of chronic pain in persons with bleeding disorders: Guidance for practical application of the CDC opioid prescribing guidelines provides guidance for healthcare providers who manage PBD. While most acute and chronic pain in PBD is due to joint bleeding and damage, we expect the practices described in this document to be applicable to any patient with pain due to bleeding in locations other than joints. It is divided into several categories with recommendations in each to assist provider with opioid pain management.

A. SCREENING AND RISK ASSESSMENT

  • Rationale: Acute and chronic pain are common in PBD, particularly those with a history of joint bleeding. Mental health conditions such as
depression and anxiety are also seen in PBD, and treatment of these disorders is often an essential aspect of pain management.

B. DETERMINING WHEN TO INITIATE OR CONTINUE OPIOIDS
   ▪ Rationale: Given the risks associated with opioid use, clinicians should include patients in a shared decision-making process when considering using opioids to treat pain.

C. OPIOID SELECTION, DOSAGE, DURATION AND OTHER CONSIDERATIONS
   ▪ Rationale: Clinical practices for using opioids to treat pain are constantly evolving, based on emerging evidence of the risks and benefits of pain management using these medications.

D. OPIOID MONITORING AND TAPERING OR DISCONTINUATION
   ▪ Rationale: The risks of using opioids to treat chronic pain must be reviewed and updated periodically in all patients. Clinics need to identify methods to safely taper and/or discontinue opioids when risks outweigh benefits.
   - The MASAC guidelines recommend that non opioids and non-pharmacologic treatment options should be trialed first. Previous unsuccessful trial of non-opioid medications and non-pharmacologic strategies should be thoroughly documented.
   - A medication or treatment agreement should be signed outlining the goals of therapy, risk and benefits of treatment (including complications and side effects), and responsibilities and expectations of both the patient, parents (if a pediatric patient), and provider. A sample treatment agreement is available in the appendix (Table 6).
   - The main goals of therapy should be improvement in function (physical, psychological, social, and occupational) as well as improvement in quality of life.
   - All patients, pediatrics as well as adults, exhibit a wide variability to opioid dosage and metabolism.
   - There is no set rules for establishing a beginning dose, how quickly to escalate the dose, or what the upper dose limits are for each patient. Opioids typically do not have a ceiling dose.
   - It is best to “dose to effect” by starting with the lowest dose of a short acting opioid and slowly increasing the dose until adequate analgesia is obtained or unacceptable side effects require re-evaluation of therapy.
   - When considering a long acting opioid, take the total 24 hours dosage of the short acting opioid and covert to the same dose in a sustained release preparation.
   - If necessary, a short acting opioid may be used for break-through pain or an acute pain crisis.
   - Equianalgesia charts for converting from one opioid to another are available. (See appendix; Table 7.)
   - Studies have shown that many patients must switch opioid medications at least once, sometimes as many as 3-4 times, before achieving effective analgesic. This is known as opioid rotation.

OPIOID SIDE EFFECTS
• The most common side effects with opioid use include; sleepiness, dizziness, nausea, itching, vomiting. These symptoms may resolve with time and are minimized with slow dose escalation.
• Constipation is the most common side effect of chronic opioid use and will not resolve over time. **Always** consider a bowel regimen if an opioid is initiated.
• Respiratory depression can be a side effect and slow, low dosing is recommended and well as close monitoring of the patient when an opioid is initiated.

**Methadone**

• Although methadone is an older drug, its use has increased in recent years
• Unlike other mu agonist drugs, methadone has both mu and delta receptor against activity
• It is a receptor antagonist NMDA (N-methyl-aspartic acid). NMDA is known to be a ‘wind-up’ protein which can promote pain. If methadone blocks this receptor, than it is has the potential to block pain at multiple sites – at the mu opioid receptor site as well as at the NMDA antagonist site.
• It is thought to be helpful with treating neuropathic pain.
• Methadone is very inexpensive which makes it attractive to patients and providers.
• It does not have any active metabolites so can be used by those with renal and liver disease, and can be given via multiple modalities (SQ, oral, rectal, IV)
• It does have the disadvantage of a highly variable half-life (up to 150 hours), slow elimination, multiple drug-drug interactions that can affect metabolism, and the potential for cardiac arrhythmias (QT prolongation and torsade de pointes) For this reason, a baseline EKG should be performed and periodically
• Converting from one opioid to methadone requires expertise. Most conversion tables are potentially too liberal in their conversions. It is best to seek the advice of a provider who has experience with this medication and switching patients to and from this medication.

**Codeine**

• Codeine is metabolized to morphine in the body via the P450 liver cytochrome system. Some people metabolize codeine to morphine more quickly than others. These individuals are called "ultra-rapid metabolizers of codeine". This can cause an unpredictable analgesic effect and may result in toxic levels.
• Do not use this medicine if you are using or have used an MAO inhibitor (MAOI), alcohol, or other medications that may depress the CNS system which may worsen the side effects of this codeine, including dizziness, poor concentration, drowsiness, unusual dreams, and trouble with sleeping.
• Codeine is contraindicated in use with children.

**Cytochrome P450 System**

• The liver is the organ for primary drug metabolism where the cytochrome system comes into play.
Cytochrome P450 enzymes are essential for the metabolism of many medications with more than 50 enzymes evident. Cytochrome P450 enzymes can be inhibited or induced by drugs, resulting in clinically significant drug-drug interactions that can cause unanticipated adverse reactions or therapeutic failures.

- When the cytochrome system acts as an inhibitor to the metabolism of the drug, low dose effects may be observed with a potential for nonresponse.
- In the induced metabolism, there can be a rapid metabolism of the drug causing overdose, adverse reactions, and/or drug-drug interactions.

CYP450 enzyme polymorphism is responsible for observed variations in drug response among patients of differing ethnic origins.

**Opioid Monitoring Tools**

- When prescribing an opioid for pain management in any population, close monitoring is essential. Many potential red flags may exist. Repeated behaviors may suggest the need for closer observation and monitoring of the patient. Be alert for inconsistencies in patients’ descriptions and/or behaviors.
- Potential red flags may be identified \(^{31,101}\) (See appendix. Table 8)
- Any time a person is started on opioid therapy, close monitoring is essential. A commitment on the part of the Hemophilia Treatment Center (HTC) is necessary to be available for patients as they are assessed and reassessed during therapy \(^{102}\).
- As always, start low and go slow with close observation

1. **Pain agreements**: This format provides clear guidelines for providers and caregivers with respect to responsibilities of each party. This tool also demonstrates a commitment on the part of the HTC in recognizing the patient’s pain and willingness to address and manage the pain. A sample is available in the appendix \(^{93}\).
   
   Key components of a pain agreement include:
   
   i) Clear treatment goals
   ii) Use of one provider to order pain medication
   iii) Use of one pharmacy to dispense pain medication
   iv) Close monitoring will occur
   v) Taking medication only as prescribed
   vi) Review of potential side effects of opioid use
   vii) Clear consequences if non-adherence is identified

2. **Pain Log**: This tool can be particularly helpful for the provider as well as patients to document their pain level, effects of pain medication prescribed, and the duration of its effects. A written review can help patients visualize the improvement of their pain and factors that may exacerbate the pain. It can also help providers with dose adjustments regarding frequency or dose of the medications for optimal effects \(^{47}\). (see Appendix; Diagram 4.)

3. **State Monitoring Programs**: These programs provide an electronic monitoring system for quick review of a patient’s scheduled medication use within the state and include: name of medication, date prescribed, amount prescribed, prescriber information, and
which pharmacy filled the prescription. This can be helpful in determining potential doctor shopping, pharmacy shopping, or frequent ER visits. Most states have some type of electronic monitoring program. Regular use of this program as prescriptions are written and documenting the findings on the state monitoring program (i.e. negative additional prescriptions found) can help providers with clear monitoring of their patients. Review your state website for the monitoring system within your respective state. It is unclear at this time, if these programs cross to other states for ongoing monitoring of patients.

4. **Urine drug screens:** The use of drug screening can be two-fold; a) ensure that the medication prescribed is being utilized appropriately; b) screen for other medications or illicit drugs. Drug screening does carry risks in that false positives can occur. Additionally, providers need to be aware of the metabolism of some opioids which convert to other formulations when reported in a drug screen. Some drug screens are not all inclusive of all opioid formulations. It is important to utilize an expert in this area for appropriate interpretation of results. Decisions should not be made on one positive drug screen due to the possible risk of false positives and should be used to detect ongoing confirmation of diversion or opioids prescribed and/or illicit drug ingestion.

5. **Pill counts:** Regular counting of prescribed medications can ensure that patients are taking medications as prescribed. If a patient calls earlier for a prescription, additional questions are needed, such as was there an acute pain flare that necessitated additional ingestion of pain medications. This may provide an opportunity for readjustment of the pain program in place. Repeated monthly dose shortages raises a red flag for potential abuse of the opioid prescribed.

6. **Limited prescriptions with office visits:** In some cases providing a prescription for an opioid on a weekly basis with regular follow up can assist with monitoring a patient until there is demonstrated adherence to the regimen. Stretching out the amount of the prescription can be completed when adherence and/or dose adjusting is achieved. At this time refills for Schedule II drugs are not available. This provides an opportunity for providers to touch base with the patient on a monthly basis to assess ongoing pain experience and successful management of pain.

7. **REMS (Risk Evaluation Mitigation System)**: This system provides a communication plan to inform key audiences about the risks of a drug. Websites are set up to assist providers in a number of areas:
   a. Proper education of the drug prescribed
   b. Proper patient selection
   c. Proper surveillance and monitoring of the medication use
   d. Provision of relevant safety messages
   e. An intervention when a signal (deviation from protocol) is detected.

**NALOXONE**

- As part of prescribing an opioid, naloxone should be part of the pain program for your patient, it is now standard to also dispense naloxone kits for potential overdose reversal.
- Patients and families should be educated on its use.
- Naloxone can be given via nasal spray or IM injector. More than 1 dose may be needed depending on the amount of opioid ingested.
• An ambulance should be immediately called regardless of the naloxone application as
patients require ongoing monitoring for full reversal of potential opioid overdose.
• The MASAC Document: #26049: Management of chronic pain in persons with bleeding
disorders: Guidance for practical application of the CDC opioid prescribing guidelines,
also recommends the dispensing of naloxone if an opioid is prescribed as part of the pain
program.

DOCUMENTATION

For optimal management of pain, clear ongoing documentation should always occur in the
following areas. This also minimizes the potential for censure. Review of documentation
requirements with each prescription refill will provide necessary information the appropriate
effects are achieved as well as monitoring for any potential aberrant behaviors. Persons who are
at higher risk for abuse/diversion should have a more structured environment, providing
additional monitoring strategies outlined and more frequent office visits for closer observation.

1. Documentation of current pain level utilizing the 7 steps of assessment
2. Documentation of current pain regimen
3. Effectiveness of current pain regimen
4. Any adverse effects/side effects
5. Current pain level – average, highest, lowest
6. Durations of analgesia relief
7. Effect of treatment on QoL, sleep, activities
8. Any visits to the ER for pain issues
9. Review of procedures for monitoring to detect drug diversion

Appropriate documentation includes the “6 A’s” of pain management102.

• What analgesia is in use and its affect
• What is the patients’ current activities of daily living
• Are there any adverse effects when using the pain medication
• Are there any aberrant activity with the pain medication
• Regular scheduled assessment of the pain
• Document an action plan.

NON-PHARMACOLOGICAL PAIN MANAGEMENT STRATEGIES

• The exact nature a patient’s pain experience can be multi-faceted. Pain is a personal
experience necessitating an individual approach to pain management. In order to address
these issues, pain management should encompass a “Multi-modal” approach105.
• A multi-modal approach may include non-pharmacologic interventions, lifestyle changes,
complementary and alternative medicine (CAM), and physical medicine and
rehabilitation102.
• Definitions:  
  o Complimentary: Therapy used with conventional medicine  
  o Alternative: Therapy used in place of conventional medicine  
  o Integrative: Combination of conventional and integrative medicine  

• There are 4 domains to CAM therapy:  
  o Mind-Body Practices  
  o Manipulative and body based  
  o Natural Products  
  o Energy Therapies

1. Mind-Body Practices  
• These techniques utilize the mind’s interaction with bodily function. There are several techniques that have been used in PWBD. There are multiple mind-body strategies available, where a few will be reviewed here.

Yoga: This involves a spiritual and ascetic discipline, a part of which, including breath control, simple meditation, and the adoption of specific bodily postures, is widely practiced for health and relaxation\textsuperscript{106}.
  • The WFH exercise booklet supports the use of yoga in PWBD\textsuperscript{107}  
  • A study done with 27 boys (8=16 years noted differences in quality of life, bleeding episodes and school absences\textsuperscript{108}.  
  • Improvement in quality of life in youth with chronic medical conditions was noted\textsuperscript{109}.  
  • Yoga played a significant role in lessening the rate of bleedings, referrals to the haemophilia clinic, & the school non-attendance\textsuperscript{110}.

Cognitive Reframing: The purpose of cognitive behavioral therapy is to examine and clarify the appraisal of pain. With the guidance of a certified therapist, the goal is to change negative beliefs (catastrophizing) to active coping by reviewing past achievements in pain management and encourage ability over disability. It includes the use of sight, sound, or a combination of senses to imagine a state different than what currently exists. Also incorporated in this technique are relaxation exercises, controlled breathing, and use of distraction.
  • Cognitive reframing was helpful to reduce pain intensity and predicted better physical QoL regardless of age. It also reduced negative thoughts with predicted better mental QoL\textsuperscript{111}  
  • In a controlled study of 19 PWH, a significant improvement in the control of symptoms & pain management scores on the Self-Efficacy Scale, QoL, self-esteem, emotional status, pain scores were noted\textsuperscript{112}.

Biofeedback: Is initially taught to the patient by a certified specialist. The goals of therapy include: performance of self-relaxation without feedback equipment to use as needed to minimize distress and discomfort\textsuperscript{113}. A machine is attached to the patient using audible tones and an immediate digital readout provides instant feedback and control for
the patient. It requires frequent sessions that allows the attainment of a general state of relaxation. It is non-invasive, and considered safe in persons with bleeding disorders.

- Two case studies in 1981 in PWH where thermal biofeedback measurements were used demonstrated clinically significant reductions in arthritic pain perceptions\textsuperscript{113}.
- Bradley et al. (84) identified biofeedback was associated with reductions in pain behavior & self-reports of pain & disability\textsuperscript{114}.
- Has been recommended in the use in pain management in PWH\textsuperscript{115}.

**Distraction:** This technique comes in many forms from reading, watching television, playing games, pet therapy, and music therapy to name a few.

- Additional distraction techniques include the:
  - Buzzy Bee\textsuperscript{©}: This is a combination vibratory and cold device that has been used with children as a method of distraction during IV access and/or treatment infusions\textsuperscript{116}.
  - The Magic Glove\textsuperscript{©} is a hypnotic/distraction & meditation technique typically used for needle sticks in children. Boggia et al (2019) studied 14 patients (age 4-14 yrs.) where a reduction in pain perception between 57% - 100% was noted in all patients\textsuperscript{117}.
- Elander (2011) in a RCT in PWH identified a motivational-volitional model with DVD format improved motivational impact and influenced pain intensity in joint pain\textsuperscript{118}.
- In a RCT of children with hemophilia, median age 12 yrs., using virtual reality was as positive distraction to reduce pain & time with IV insertions\textsuperscript{119}.

**Relaxation/meditation:** Meditation is a contemplative practice, engaged across various religious and spiritual traditions as a means of quieting, focusing and transforming the mind. Meditation cultivates self-awareness, and provides the optimum conditions for practicing the skill of mindfulness. The goal of meditation is to intensify personal and spiritual growth, in addition to calming the mind and body\textsuperscript{120}.

- Recommended use for pain management in hemophilia\textsuperscript{23,121}
- Varni (1981) identified a case report of progressive muscle relaxation in 3 PWH with improvements in pain, sleep, mobility, & decreased analgesia use\textsuperscript{122}.
- In a RCT of 80 Hem A & B patients, relaxation/meditation was able to reduce patients’ pain intensity, improve their pain belief & perception, & enhance their pain acceptance\textsuperscript{12}.

**Neuroplasticity:** This is the brain's ability to reorganize itself by forming new neural connections throughout life. It allows the neurons (nerve cells) in the brain to compensate for injury & disease & to adjust their activities in response to new situations or to changes in their environment\textsuperscript{123}. It is noted that pain & depression independently induce long-term plasticity in the central nervous system\textsuperscript{124}.

- van Vulpen (2018) identified that education is needed in PWBD about neurophysiology of chronic pain that aims at re-conceptualizing pain. Neuroplasticity helps to implement effective physiotherapy & exercise. to prevent chronicity & maladaptive behavior\textsuperscript{125}.
Hypnosis: This is the induction of a state of consciousness in which a person apparently loses the power of voluntary action and is highly responsive to suggestion or direction\textsuperscript{126}.

- Hypnosis was first reported in PWBD in 1975 where a reduction of transfused factor products & reported reduced pain was identified\textsuperscript{127}.
- Children with hemophilia as young as 3 years of age demonstrated the ability to selectively turn off or reduce their perception of pain in designated extremities\textsuperscript{128}.
- In a case report, a 43 year old female with a bleeding disorder demonstrated reduction of bleeding during tooth extraction with the use of hypnosis\textsuperscript{129}.
- LeBaw in 1992 reported 2 Case reports of 2 young boys with hemophilia utilizing hypnosis; a) 5 year old resulted in self-reported reduction of factor infusions by 50%; b) 19 year old was able to reduce hospitalizations from bleeding episodes\textsuperscript{130}.
- A RCT with 20 PWH was completed examining the use of hypnosis. Results identified significantly improved in pain interference with normal work & perception of health status. There was no report of harm. Hypnosis may be a promising intervention to manage hemophilia-related pain & promote HRQoL benefits lasting up to three months\textsuperscript{131}.
- Palareti et al. (2021) evaluated 7 clinical trials involving 362 participants in RCT. Data from 264 participants available for analysis. All treatments were safe; no major side effects were reported. Hypnosis promotes a sense of self-efficacy & better self-management skills\textsuperscript{132}.

2. MANIPULATIVE AND BODY PRACTICES

- These practices focus primarily on the structures & systems of the body including: bones, joints, soft tissues, & the circulatory & lymphatic systems.
- There are multiple strategies available including physical therapy, some of which will be reviewed here.

REST, ICE COMPRESION, ELEVATION (RICE)

- RICE has been the mainstay of pain management in PWBD for many years and is well supported by many organizations\textsuperscript{133,134}.
- Typically ice is recommended for treatment for an acute bleeding episode initially.
- Application of heat is now being explored as additional methods of pain management as some patients tolerate heat better than ice. Forsyth et a. (2010) states: Although ice can help manage acute, hemarthrosis-related pain, there are other available interventions that will not impair coagulation & hemostasis\textsuperscript{135}.

Hydrotherapy, Physical Therapy, Braces

- These therapies have been well documented in the literature as a method for pain management where: pool therapy\textsuperscript{136,137}, physical therapy (NHF, WF), and braces,\textsuperscript{132,133,138} all have all demonstrated positive effects in pain management.
- In a literature review of RCTs evaluating manual therapies the findings identified were: a) No clear demonstration of benefit for manual therapy &
exercise over education & home exercises for elbow pain; b) Hydrotherapy had a more positive effect on knee pain than land-based exercise; c) there was no clear benefit on pain intensity when comparing mobilization & exercise with manual therapy & exercise.

Manipulation therapy
- The aim of manipulation therapy is to retrain and restore the bodily functions lost as a result of operations, trauma, strokes, disease, etc., by applying mild pressure, heat, water and/or manipulation or strengthening techniques to the moving parts of the body. The physical therapist is integral in this area with manual manipulation as well as use of other devices to assist patients.
- In one case study, safety & efficacy of manual therapy in a patient with hemophilia & an inhibitor was explored. Results found that manual therapy may be safe in patients with hemophilia & inhibitor. This type of therapy may improve joint condition, pain, & joint range of motion in patients with hemophilia & inhibitor.
- In a RCT of 65 hemophilia A/B pts, manual therapy was evaluated using fascial therapy on joint bleeding, joint pain & joint function in patients with hemophilic ankle arthropathy. Results suggest a positive effect on the frequency of joint bleeding, joint health, & the perception of ankle joint pain.
- Tat et al. (2021) evaluated 17 participants with HA were randomized to Manual Therapy & Exercises Group for treatment of the elbow where bleeding frequency & activity pain were decreased.

Massage Therapy
- The use of massage therapy was previously questioned due to the potential for increased bleeding and/or bruising if not performed by a trained massage therapist with a good understanding of bleeding disorders. Research is beginning in this area as an additional method of pain management.
- Jadhav et al (2013) reported 84% Indian PWH used massage therapy as a form of pain management.
- Passeri et al (2019) found that massage therapy post-surgery was helpful to reduce scar tissue.
- Stromer et al. (2021) indicated that massage techniques can be indicated for analgesic purposes in patients with hemophilia. Sufficient factor replacement prior to therapy as recommended.

Acupuncture
- Is a system of integrative medicine that involves pricking the skin or tissues with needles, used to alleviate pain and to treat various physical, mental, and emotional conditions. Originating in ancient China, acupuncture is now widely practiced in the West.
- Acupuncture has been utilized in PWBD for pain management.
• It was first reported by Koh (1981) with 2 case reports\textsuperscript{145}. The 1\textsuperscript{st} patient was free of pain > 5 months post treatments. The 2\textsuperscript{nd} patient reported a reduction in use of oral pain medications. It is RECOMMEND FACTOR TX PRIOR to treatments.
• Rosted & Jorgensen (2002) also reported on a case study where a 38 yr. PWH utilized acupuncture as a method of pain management\textsuperscript{146}. The pt reported reduction in pain & opioid usage.
• Wallny et al. (2006) demonstrated that 12 patients who used acupuncture reported a reduction in pain 10/12 pts without procedural bleeding noted\textsuperscript{147}.
• It should be noted that there was a documented report of bleeding resulting in an Iliopsoas muscle hematoma despite self-factor replacement\textsuperscript{148}.
• Lambing et al (2012) followed 9 PWH who were treated with acupuncture as a method of pain management\textsuperscript{149}. 6 patients were from the US and thus received factor therapy pre procedure, whereas 3 patients from India did not receive any pre-procedural factor infusions. Seven of the 9 patients reported an improvement in pain and QoL scores. None of the patients suffered any bleeding/bruising whether they received pre-procedural factor or not.
• Martini et al. (2014) reported on an a single case report of a female with type III vWD & chronic migraines. Improvement in migraine pain without bleeding/bruising was noted\textsuperscript{150}.
• In a RCT, Pires et al. (2020) examined acupuncture vs. TENS to determine the effectiveness of acupuncture in reducing intensity in chronic pain, changes in QoL, joint function & impact on treatment satisfaction of haemophilia patients\textsuperscript{151}. Results indicated that acupuncture was effective in reducing pain intensity in hemophilia patients with chronic joint disease when compared to TENS.

**TENS:** (Transcutaneous electrical nerve stimulation): This therapy involves the use of low-voltage electric currents to treat pain. A small device delivers the current at or near nerves. TENS therapy blocks or changes your perception of pain\textsuperscript{152}.
• TENS was first documented in 1985, where 36 hemophiliac patients received either active or placebo TENS treatment. Subjects reported at least 50% pain relief Roche et al (1985)\textsuperscript{153} and since has been documented as a potential method of pain relief\textsuperscript{54}.

3. **NATURAL PRODUCTS**
• Natural products are plants typically found in nature that are felt to have anti-inflammatory & relaxation qualities. They can be taken orally, or applied topically as an essential oil, or inhaled. Currently, these products are NOT closely FDA monitored. Typical products in this category include vitamins, herbal products, essential oils, and aromatherapy.
• The literature has identified that there are some vitamins thought to have anti-inflammatory properties\textsuperscript{156-158}.
• These include: Vitamin C\textsuperscript{158,159}, D\textsuperscript{160}, E\textsuperscript{161}, B12\textsuperscript{162} and tumeric\textsuperscript{163}. It is thought that these anti-inflammatory effects are mediated by reduced cytokine & prostaglandin release & effects on T-cell responses.
• It is important to note that some vitamins may have the potential for increased bleeding as well, and with fat soluble vitamins (D, E, B12), high doses can accumulate causing size effects. There have been no research studies done in PWBD, although in other pain conditions, there were conflicting results.
• There are multiple herbal products that are suggested to have anti-inflammatory properties. A non-exhaustive list is identified here.

<table>
<thead>
<tr>
<th>Lavender</th>
<th>Boswellia</th>
<th>Omega 3 fatty acids</th>
<th>Feverfew</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosemary</td>
<td>Cat’s claw</td>
<td>Resveratrol (in red wine, grapes, berries)</td>
<td>Alovera</td>
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<tr>
<td>Peppermint</td>
<td>Green tea</td>
<td>Wintergreen</td>
<td>Fish oil</td>
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<td>St John’s wart</td>
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<td>Corydalis</td>
<td>Devil’s claw</td>
<td>American skull cap</td>
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<td>Ginger</td>
<td>Frankincense</td>
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<td>White willow bark</td>
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<td>California poppy</td>
<td>Stinging nettle</td>
<td><em>Europhorbia resinera</em></td>
</tr>
<tr>
<td>Calendula flower</td>
<td>Ginko Baloba</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• It is important to note that there may be potential for interactions with other medications.
• Many of these herbal products have the potential for increased bleeding in some patients.
• It is important to ask the question to patients regarding ingestion of herbal, and/or over the counter therapies. Many people feel they may be safe. A frank discussion is needed to review the risk/benefits of the products in question to ensure safety of the patient.
• No research studies have been done in PWBD to date in the use of herbal therapies for pain management.
  o Stromer (2021) made the following recommendations in the use of herbals for PWBD\textsuperscript{115}.
    1. Mixed evidence regarding their efficacy for pain therapy
    2. Cochrane review of arthritis of the hip & knee and the use of plant-based medicines is neither recommended nor advised against
    3. Body of sufficient evidence with analgesic effects for them to be rated as well established use or at least traditional use of: Rampion or devil’s
claw (Harpagophytum procumbens), Willow bark extract, Frankincense (Boswellia serrata) Comfrey root

4. Possibility of side effects & interactions should not be underestimated
5. Potential interactions that affect blood coagulation have to be considered: garlic & ginkgo biloba can reduce platelet aggregation when taken at the same time as anticoagulant ginseng can reduce the effect of anticoagulants

Cannabis

- Cannabis has been medicinally since before Christ; likely started in Asia in 500 BC\textsuperscript{165,166}
- In 2008, archeologists in Central Asia discovered over two-pounds of cannabis in the 2,700-year-old grave of an ancient shaman. After scientists conducted extensive testing on the material's potency, they affirmed, "The most probable conclusion ... is that [ancient] culture[s] cultivated cannabis for pharmaceutical, psychoactive, and divinatory purposes\textsuperscript{166}.
- In recent years, the interest in cannabis usage has grown.
- United States Laws are constantly changing at the state and federal level with respect to the use of cannabis for pain management\textsuperscript{167}
  - 1850-1942: Included in US Pharmacopeia as treatment for physical and psychological conditions
  - 1937: Federal Tax Law criminalized and restricted all but industrial uses.
    - Opposed by the AMA in support of research
  - 1970: Controlled Substances Act signed into law by R. Nixon
    - Repealed the Marijuana Tax act. Listed MJ as a Scheduled I drug
  - 1972: The National Commission in Marijuana and Drug Abuse recommends partial prohibition and lower penalties for possession
    - Ignored by Nixon Administration
  - Part of the Controlled Substance Act of 1990; classified as a schedule 1 substance
  - 1996: Compassionate Use Act
    - California becomes the first state to legalize medicinal marijuana
  - 2014: President Obama signed the Farm Bill which redefined industrial hemp as distinct from marijuana, and legitimized hemp research
  - Colorado becomes the first state allowing dispensaries to sell marijuana for recreational use
  - 2016: FDA approves the first Marijuana based Drug (Epidiolex)
  - 2018: industrial Hemp becomes legal in the U.S.
  - 2019: U.S. Government allocates $3M to research on CBD and pain
  - 1970: The National Organization for the Reform of Marijuana Laws (NORML) was founded to provide education
  - 2020: U.S. House passed the Marijuana Decriminalization Bill
• **2019:** The Marijuana Opportunity, Reinvestment, and Expungement (MORE) Act: reintroduced in 2021 with changes

• **2022: April:** The MORE ACT was passed by the House of Representative
  - Removes marijuana from Controlled Substance Act
  - Decriminalize cannabis federally
  - Eliminates the existing conflict between state and federal marijuana laws
  - Provides the states with authority to establish their own cannabis laws free from federal interference.
  - Marijuana products to be taxed 5% to establish a Trust fund

- Legalization of cannabis continues to vary from state to state. Review your state website for cannabis laws.
- Review your country’s law with respect to cannabis use and legal issues for prescribing and dispensing

**Medicinal marijuana**\(^{168,169}\)

- Cannabis in 2022 has over 600 strains
  - Much more potent:
    - 1980-1990s the amount of THC was about 10mg
    - Today it can be as high 60mg-150mg
- There are 2 types of Cannabis plants;

1. **Marijuana – Cannabis Indica**
   - CBD (cannabidiol) – main medical derivative with anti-inflammatory and analgesic properties
   - THC (delta-9-tetrahydrocannabidiol) - primary psychoactive ingredient which gives the feeling of euphoria and may have hallucinogenic effects
     - THC* content 5-30+%
     - Federally classified as an illegal drug - scheduled I
     - Use: Recreational/medicinal purposes

2. **Hemp – Cannabis Sativa**
   - THC content less than 0.3%
     - Classified as food
     - Removed from controlled substances due to Farm Bill
     - Use: Foods, oils, textiles, rope, fabrics, and medicinal purposes

- Many formulations currently available have variations of concentrations of both CBD and/or THC
- There are 100s of varieties with different medicinal effects.
- **The mechanism of action** of cannabis: The cannabinoid system is a widespread neuromodulatory system that plays important roles in central nervous system
development, synaptic plasticity, and the response to endogenous and environmental insults comprising of cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and the enzymes responsible for the synthesis and degradation of the endocannabinoids.\textsuperscript{168}

- The most abundant cannabinoid receptors are the CB1 cannabinoid receptors & CB2 cannabinoid receptors
- Formulations include: inhalation, oral drops or other food formulations, tinctures, topical & rectal formulations

Cannabis Research

- There is limited research in cannabis use due to the number of organizations that must be involved, legal issues and as well as obtaining, research grade cannabis for study
- In a meta- analysis systematic review of randomized trials for non-cancer pain\textsuperscript{170}:
  - 15/18 RCT demonstrated an analgesic effect of cannabinoid when compared with placebo; improved sleep, and no serious adverse effects
  - Considered safe and modestly effect in neuropathic pain
- In a systematic review and meta-analysis\textsuperscript{169}:
  - 79 trials demonstrated a non-statistical improvement in symptoms
  - Improved nausea and vomiting
  - Greater reduction in pain scale assessment
- Cannabinoids, when co-administered with opioids, may enable reduced opioid doses without loss of analgesic efficacy\textsuperscript{171} (i.e., an opioid-sparing effect)
  - Takakuwa & Sulak (2020) explored the use of medical cannabis as a potential strategy to decrease opioid usage\textsuperscript{172}
    - Convenience sample survey of patients 525 patients
    - 40.4% (n=204) stopped all opioids, 45.2% (n=228) reported some decrease in their opioid usage, 13.3% (n=67) reported no change in opioid usage, and 1.1% (n=6) reported an increase in opioid usage.

\textbf{Essential Oils:} These are made from compounds extracted from plants that capture the plant’s scent & flavor, or “essence.” Unique aromatic compounds give each essential oil its characteristic essence. Essential oils obtained through distillation (via steam &/or water) or mechanical methods (cold pressing). Once the aromatic chemicals have been extracted, they are combined with a carrier oil\textsuperscript{173,174}.

- Currently, there is no research exploring the use of essential oils in PWBD.
- Aroma Therapy: is a holistic healing treatment that uses natural plant extracts to promote health & well-being. It is sometimes called essential oil therapy. Aromatherapy is thought to medicinally improve the health of the body, mind, & spirit, in having both physical and emotional health\textsuperscript{175}
- Vicol (2013) documented the use of aromatherapy to manage side effects of HIV, stating it is currently under study for potential benefit in treating Hepatitis C & Hemophilia\textsuperscript{176}.
ENERGY THERAPIES

- Energy therapies are based on the belief that a vital life energy flows through & around your body. The goal is to unblock the flow of energy & restore balance. It involves the use of gentle pressure or places hands through energy fields, use of additional tools such as light or magnets to assist with the manipulation of energy fields

- Examples of energy therapies include but are not limited to: Reiki, therapeutic touch, magnet therapy, color therapy, light therapy, and prayer.

- There is limited research in this area with respect to PWBD.

- Based upon the therapy descriptions, there appears to be minimal risk to PWBD. Any treatment should be discussed with providers.

- PWH reported use of faith and prayer, 21-29% for acute & persistent pain.

**Reiki**: This therapy is based on the idea that there is a universal (or source) energy that supports the body’s innate healing abilities. Practitioners seek to access this energy, allowing it to flow to the body and facilitate healing. It appears to be generally safe and no serious side effects have been reported.

  - In 2012, the HOG blog identified the use of reiki in a PWH to assist with management of pain after a motor vehicle accident.

**Therapeutic Touch**: While using Therapeutic Touch, therapists place their hands on or near their patient's body with the intention to help or heal. In doing so, therapists believe that they are consciously directing or modulating an individual's energies by interacting with his or her energy field. The focus is on balancing the energies of the total person and stimulating the body's own natural healing ability rather than on the treatment of specific physical diseases.

  - There are no clinical trials that evaluate this method of pain management in PWBD.

  - In 1 case report: therapeutic touch was used on a PWH, to assist with side effects of Hepatitis C treatment.

  - The risk is low for PWBD as minimal bleeding risk is evident

**Magnet Therapy**: Magnetic Therapy is a form of alternative medicine using magnetic fields to treat medical conditions. Permanent magnets are placed close to the body in order to cause bones to heal faster, relieve pain and induce other therapeutic effects. It is most commonly recommended by practitioners as a cure for joint disorders and back problems. This is similar to Polarity therapy, where magnetic forces with relative orientation to the magnetic poles (north/south) are used.

**Light Therapy**: A high dose of light has an inhibitory effect—which is primarily used therapeutically to inhibit pain. In light therapy, a light source—either a laser or light emitting diode (LED) — is held near to or in contact with the skin over the area of pain. Pain is decreased when less of the pain signal reaches the brain. Color therapy is also
included in this type of therapy also called chromotherapy, is a method of treating ailments by using colors. The therapy is done by shining an appropriate color on the particular area of the body. It is also done through eyes by looking at a particular color\textsuperscript{184}.

- Eid & Aly (2015) performed a RCT with 30 boys, aged 9-13 years, with moderate hemophilia\textsuperscript{185}. They were randomized to an a) exercise group, b) laser therapy group where light therapy was targeted to knee joints, c) electromagnetic group. Results indicated: Laser therapy induced significant improvement than electromagnetic therapy in treatment of hemarthrosis-related problems in children with hemophilia.

KEY POINTS for Pain Management

- Pain is a unique experience to each individual
- Thus, the treatment for pain is unique to each individual
- A treatment for one person may be successful, whereas, that same treatment option may not be successful for another individual
- It is important to be open minded to different treatment options for pain that may benefit patients as long as risks are low; review risk/benefit profile
- A multimodal approach is paramount to managing pain. Oral medications should not be the only pain management option employed
- A multidisciplinary approach to pain management is essential as it includes not only the physical aspect of pain management, but also brings in the social and psychological components that are known to pain management. It is essential that other key HTC staff members are included in the process of pain management. (social workers, physical therapists, psychologists, pain management experts, etc.)
- Pain is a journey; an ongoing process. There will be good days and bad days. Pain management may need adjustment as other factors may influence the pain experience at any given time.
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