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Chronic postsurgical pain: a review

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CHRONIC POSTSURGICAL PAIN: A REVIEW

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DEDICATION

I would like to dedicate this work to my dog Charlie.

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I would like to thank Dr. Symes for her patience and endless support.

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ABSTRACT

The problem of chronic post surgical pain is not a new one. For years now, it has gone underreported and remains a problem despite advances in surgical and anaesthetic techniques. Recent studies have shown that rates can vary from 18-65% of surgical patients. These patients experience decreased quality of life and strain the healthcare both from an economic and resource aspect. Individually, many of the patients do not attain their presurgical quality of life and experience financial hardship. The majority of postsurgical pain issues arise through the process of central sensitization where, due to neuroplasticity, the body becomes hypersensitized to normal stimuli and the inhibitory pathways no longer function normally. This process starts with increased peripheral sensitization due to the tissue damage associated with surgical incisions. When this occurs, the neurons of the spinothalamic pathway in the spinal cord are overwhelmed and undergo modification.

The current methods and organization of treatment are lacking and do not meet the demand of surgical patients. Typically, patients selected for surgery are admitted, undergo the surgical procedure, and then receive outside help if pain management schemes become necessary. More often than not, in the past, this pain management scheme has heavily relied on opioid analgesics. However, due to the opioid epidemic and the adverse drug events heavily associated with opioid use, alternatives are required. New and more proactive strategies are required to reduce the incidence of chronic postsurgical

pain. Several screenable risk factors have been identified that increase the risk of developing chronic postsurgical pain. Implementation of a pre-screening process that identifies at risk patients indicating them for more specific and complex pain management has shown good results. Additionally, better selected anesthetic techniques by the anesthesiologists in the pre and perioperative have been shown to help reduce the development of both peripheral and central sensitization. Techniques such as multimodal therapy can reduce opioid consumption and minimize adverse drug effects and increase the patient's quality of life. Through utilizing different combinations of drugs, the entire pain pathway can become a target and more comprehensive analgesia can be achieved. Instead of the main analgesic target being the μ opioid receptors in the central pathway, drugs such as pregabalin, paracetamol, and ketamine can hit a variety of targets and better prevent central sensitization. By reviewing the literature on chronic postsurgical pain, I describe a complete understanding of the pain pathways. Furthermore, I look to understand the risk factors associated with the development and identify ways to specifically address the current issues in treatment. Finally, I look at current working models that have sought to address the many issues and highlight how they might be implemented at other hospitals and centers that perform surgeries.

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LIST OF ABBREVIATIONS

ADEs	Adverse Drug Events
APS	American Pain Society
cAMP	Cyclic Adenosine Monophosphate
CNS	Central Nervous System
COMT	Catechol-O-methyltransferase
COX	Cyclo-oxygenase
CPSP	Chronic Postsurgical Pain
DRG	Dorsal Root Ganglion
ERAS	Enhanced Recovery After Surgery
GABA	Gamma-Aminobutyric Acid
GDP	Guanosine Diphosphate
GTP	Guanosine Triphosphate
IASP	International Association for the Study of Pain
IHR	Inguinal Hernia Repair
NGF	Nerve Growth Factor
NMDARs	N-methyl D-aspartate Receptors
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OIH	Opioid Induced Hyperalgesia

OTF	Opioid Task Force
PAINAD	Pain in Advanced Dementia
PKC	Protein Kinase C
PMPS	Postmastectomy Pain Syndrome
SNPs	Single Nucleotide Polymorphism
TPS	Translational Pain Service

INTRODUCTION

By various estimates, chronic postsurgical pain (CPSP) occurs in 18-65% of surgical patients depending on the procedure being performed.[1,2] One study looking at chronic pain in mastectomy patients noted that up to 52.2% of patients had pain 9 years after the surgery.[3] Over the long term, CPSP tends to lead to overwhelming reduction in quality of life insofar that it affects daily activities, prevent participation in sport, and even lead to joblessness. On a macroscopic scale, the cost of CPSP is exorbitant and with the number of surgeries increasing, the issue will continue to worsen. The response to both treating and attempting to understand chronic pain has not been good enough. Many patients with known risk factors are not identified early enough and many do not receive the necessary individualized care required to address their needs.

In the first part of this thesis, the pain pathways will be examined and the mechanisms by which we experience pain will be identified. Following this, I will seek to illuminate the incidence of chronic pain in various types of common procedures. Using this information and data from the literature, the current methods in preventing and treating CPSP will be pinpointed and their respective issues highlighted and examined. In the final part, this thesis will look to identify models through which outcomes can be improved and how they specifically address current issues highlighted in the literature.

ANATOMY AND PHYSIOLOGY OF PAIN

The transmission and perception of pain can be broken down into four main components: transduction, transmission, modulation, and perception.[4] Transduction is a process that involves activation of the peripheral nerve endings called nociceptors. When these nociceptors are activated, the signal is then transmitted to the central nervous system by a variety of pathways, but the most important is the spinothalamic tract. The transmission process is carried out by myelinated afferent fibers or, in other words, neurons that carry information away from the periphery and towards the central nervous system. The degree of myelination of the fiber directly relates to conduction speed of the signal. Highly myelinated fibers carry messages at a significantly faster rate than unmyelinated ones. When the signal reaches the thalamus, the pain signal is then modulated. From the thalamus, the pain signal reaches the cortex where we then register the pain signal as the sensation of pain. The pain perception process is complicated and takes into account a variety of things such as memory, emotions, and other sensory messages. In our everyday lives, this is how we experience acute pain from bumping our knees or getting a paper cut. Chronic pain occurs when the homeostatic mechanisms that control this process go wrong. Understanding these acute pain processes is essential to our understanding of how chronic pain originates.

Nociceptors

Nociception begins at the peripheral ends of the first-order neurons and are unmyelinated. These sensory receptors are divided into categories based on the noxious

stimulus to which they respond. These stimuli are broken down into three categories: mechanical, thermal, and chemical.[5] Mechanical receptors function as stress detectors and when they undergo conformational change due these stresses, they alter ion permeability and trigger and action potential.[5] Chemical receptors respond to when inflammatory mediators and other chemicals such as bradykinin, serotonin, cytokines, acids, potassium, acetylcholine, and even proteolytic enzymes.[5,6] When these bind the nociceptors, they influence ion permeability which may cause the action potential to trigger. Additionally, chemicals like prostaglandins and substance P may bind indirectly and influence ion permeability.[5] Many classes of thermal nociceptors exist and each have certain properties that allows them to respond to specific levels of heat. These receptors are specific to the types of primary afferent fibers and do not exist equally across them.[7] The typical threshold for noxious heat to be detected is approximately 40□-45□, but some of the unique types of thermal nociceptors may not be activated until >53□.[7] Transduction of nociceptive cold stimuli is less well defined than with heat stimuli and varies wildly based on homeostatic mechanisms, but generally speaking are activated at approximately 15□. [7]

Primary Afferent Fibers

Nociceptors sit at the end of the pseudounipolar sensory fibers which have their cell bodies located in the dorsal root, trigeminal, and nodose ganglia.[5] There are two classes of primary afferent fibers that sit within the pain network: A and C type fibers. The A class fibers are further divided into Aβ and Aδ fibers. The Aβ fibers are highly

myelinated and the largest of the fibers at 5-12 μm in diameter and have encapsulated nerve endings.[5] Due to their high levels of myelination, they have relatively fast conduction velocities of approximately 30-70m/s. The Aβ fibers are, however, not responsible for transducing noxious stimuli and instead respond to light touch via their low receptor activation threshold.[6,8,9] The Aδ fibers are lightly myelinated and considerably smaller ranging from 1-5 μm in diameter. These fibers are responsible for transducing mechanical and thermal stimuli and activation typically results in a rapid feeling of sharp pain.[6,8,9] Importantly, these fibers are activated in the initial reflex response to pain. Lastly, the smallest of the fibers are called C fibers. These are completely unmyelinated and have a very low conduction velocity of lower than 2m/s.[6] Furthermore, they have a high receptor activation threshold and respond to mechanical, thermal, and chemical stimuli. These fibers differ from the Aδ in that when activated, they result in the dull and diffuse pain felt after the initial incident or the pain felt in the viscera during a stomach ache. [6,8,9] Anatomically these fibers extend from the periphery to the spinal cord where they enter at the tract of Lissauer and synapse with second-order neurons in the rexed lamina. The majority of these neurons have their cell bodies located in the dorsal root ganglia and after entering branch to innervate spinal segments both rostrally and caudally; each one of these ganglia contain several thousand cell bodies that encode and transmit pain information.[5,7] Fibers in the Lissauer tract contain both C fibers and Aδ fibers. The former typically ascend one segment before terminating in the substantia gelatinosa of Rexed lamina II and the latter ascend three to four segments before terminating in the Rexed lamina I, II, or V.[5,10]

Second-Order Connecting Neurons & Spinal Tracts

After the primary afferent neurons travel vertically, they synapse with second-order neurons which decussate immediately in the ventral white commissure. There are three types of second-order neurons which receive input from the primary afferent neurons: nociceptive specific, wide dynamic range, and low threshold.[11] Nociceptive specific neurons respond to noxious stimuli and express neuropeptides such as substance P, calcitonin gene-related peptide, enkephalin, and serotonin.[5,11] Wide dynamic range neurons respond to both noxious and non-noxious stimuli. Their large receptive field keeps these two responses distinct.[5] Low threshold neurons respond specifically to innocuous stimuli only.[11]

The primary tract by which second-order neurons ascend the spinal cord is the spinothalamic tract. This can be broken down into three portions: the neospinothalamic tract, the paleospinothalamic tract, and the archispinothalamic tract.[10] The neospinothalamic tract begins with nociceptive neurons in Rexed lamina I. The second order-neurons follow the path in the ventral white commissure and ascend in the lateral portion of the tract where they synapse with third-order neurons located in the ventral posterolateral nucleus and the ventral posterior nucleus.[10] Organization of this tract is primarily contralateral, but some ipsilateral projections exist.[5] Somatotopic organization is such that lower limbs are connected dorsolaterally and upper limbs are connected ventromedially.[5] Nociceptive stimuli from the face and intraoral structures are transmitted via first-order neurons that enter in the trigeminal ganglia.[10] Information from this area is then transmitted first through the pons before synapsing in the ventral

posteromedial nucleus, parafascicular nucleus, and the centromedian nucleus.[10] After synapsing in the thalamus, the information is carried to the somatosensory cortex via the third-order neurons.

The paleospinothalamic and archispinothalamic tracts mediate both emotional and visceral responses to pain. For the former, the first order neurons are found in Rexed lamina II and travel anteriorly before they project bilaterally onto the mesencephalic reticular formation, periaqueductal gray, tectum, parafascicular nucleus, and centromedian nucleus.[10] These projects continue towards the somatosensory cortex, brainstem nuclei, and limbic areas.[10] The archispinothalmic tract also originates in the Rexed Lamina II and project to Rexed lamina IV and VIII.[10] After projecting to the midbrain reticular formations and the periaqueductal gray, projects continue to the hypothalamus and limbic system nuclei.[10]

Other tracts such as the spinoreticular tracts function in accessory to the spinothalamic tracts. The spinoreticular tract ascends in the ventrolateral spinal cord and terminates in the ventral medial portion of the medulla reticular formation, medulla oblongata centralis, pars ventralis, and nucleus gigantocellularis. Primarily this tract is thought to be involved with the emotional aspect of nociception, but may also provide input to the antinociceptive and homeostatic responses.[5] The spinomesencephalic tract has also been identified and projects to the midbrain periaqueductal gray matter and superior colliculi.[12] This tract originates in laminae I and V and its function has been primarily associated with pain modulation.[13]

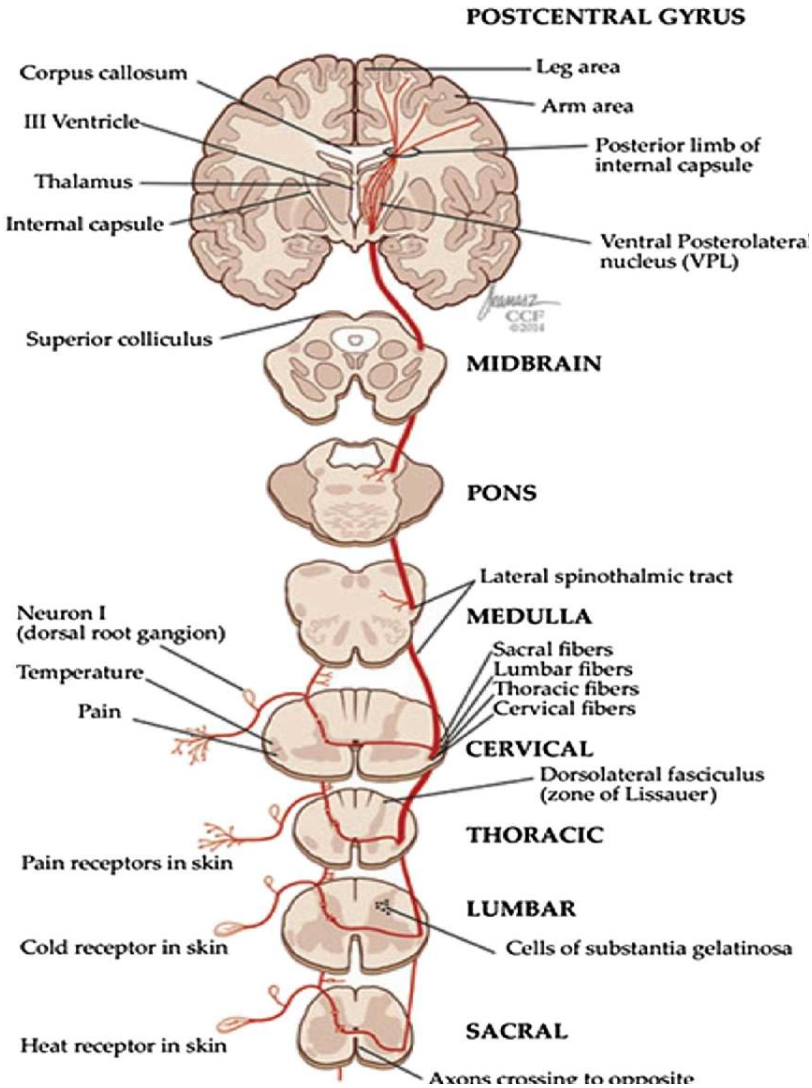

Figure 1: Spinothalamic Tract

Figure 1 illustrates the pathway of pain nociception. After primary afferent neurons reach the spinal cord and decussate, they ascend on the contralateral side synapsing in the thalamus. From here they travel to the cortical areas of the brain allowing for the conscious sensation of pain.[5]

Thalamus & Cortical Areas

The thalamus' primary function in pain transmission is to integrate signals and project them to cortical areas. The thalamus itself is divided into medial, lateral, and anterior groups by the intralaminar nuclei.[13] On the lateral aspect of the thalamus sits the reticular nucleus. In regards to the pain transmission pathways, the ventroposterior nuclei and the central nuclei are the most significant.[5,13,14] The ventroposterior nuclei are somatotopically organized where in information from the face travels to the ventroposterior medial nucleus and information from the limbs travels to the ventroposterior lateral nucleus.[5] The receptive fields for these nuclei vary, but many of the ventroposterior nuclei receive input both from specific and wide dynamic range neurons indicating that there is some measuring of stimulus intensity done here.[5] Information sent to the ventroposterior nuclei then goes onto to synapse with the primary somatosensory cortex.[13] The central nuclei, which includes central medial nuclei, parafasicularis, the medial dorsal nucleus, and the centralis laterals, receive inputs from the spinothalamic tract and push outputs towards the cerebral cortex and striatum.[5,13] Specific thalamocortical pairings have been established and understanding them might uncover future targets for pain therapies. In addition to the ventroposterior-primary somatosensory cortex, it has been shown that there are links between the lateral portion of the medial dorsal nucleus and the anterior cingulate cortex, the posterior triangular nucleus and the posterior insular cortex, and the submedius nucleus and the ventrolateral orbital cortex.[14]

Descending Pathways & Pain Inhibition

Pain stimuli received in the brain by afferent pathways are mediated by the descending efferent pathways at multiple levels. The primary pathway involved in pain modulation involves long-range modulatory inputs that act at the level of the dorsal horn in the spinal cord.[13] Inputs from the hypothalamus, amygdala, and cortex signal the periaqueductal gray which projects neurons that synapse in the rostral ventral medulla.[13] From here, the rostral ventral medulla sends serotonergic neuronal projections in the raphe nuclei that inhibit in the dorsal horn.[13] It also sends inputs to the locus coeruleus and the subcoeruleus that release substance P which when activated triggers neurons that also act on the dorsal horn. [5,13] The primary way that this pathway modulates pain is via a blockade of the lamina V interneurons.[5] In addition to the projections to the rostral ventral medulla, the periaqueductal gray has been shown to have direct connections to the spinal cord and indirect projections to the parabrachial nuclei.[5]

There also exists dopaminergic control of pain signals through the dorsal horn. In the periventricular region of the hypothalamus, there are dopaminergic descending neurons that dictate, with β-endorphins, an antinociceptive effect or pronociceptive effect in lamina I via the periaqueductal gray.[5,13,15] Dynorphin and enkephalin containing neurons are found in laminae I and V, the periaqueductal gray, and the midbrain reticular formation.[5,13,15] Additionally, the periventricular region projects to the spinal trigeminal nucleus caudalis which may play a role in modulating orofacial pain.[15]

Gate Control Theory of Pain

In 1965, Melzack and Wall proposed the gate control theory of pain that sought to explain how pain is modulated and refute the then two dominant theories that focused on specificity and patterns. The system they proposed had three parts. One, the substantia gelatinosa functions as the main gate keeping structure whereby it modulates afferent nerve impulses before they influence pain transmission cells (T cells).[16] Two, the afferent firings themselves act as triggers that activate the modulating mechanism.[16] Three, the T cells activate neural mechanisms responsible for how we perceive pain.[16] Long fibers of Lissauer's tract and short fibers connect the cells of the spinal cord to those of the substantia gelatinosa.[16] Activity in the long fibers increase inhibitory effects of the substantia gelatinosa and activity in the short fibers decrease it: this is described as the central control system.[16] Depending on the activity of the substantia gelatinosa's inhibitory effects, the initial pain transmission from the long and short fibers will then act on the T cells where they signal the action system and the stimulus will be interpreted.[16] The importance of this theory, is that it provides a physiological basis for understanding the subjective experience of pain. It also explains why we instinctively rub our knee after we bang it on the coffee table; the increased firing of the long fibers inhibits transmission. The implications of this theory in regards to our understanding of chronic pain are important to highlight. Breakdowns in this system whereby our body becomes unable to reduce or modulate pain signals may explain hyperalgesia or instances where pain is experienced by patients after surgical damage has healed.

Electrophysiology and Electrical Variances during Nerve Conduction

The primary nociceptor neurons function like most other nerves in the body. Noxious stimuli bind the nociceptors and this signal is then transduced into an electrical impulse. This depolarization occurs in a standard fashion. A negative membrane potential of about -70mV is maintained via the electrical gradient that exists from the active transport of potassium and sodium ions in and out of the cell respectively.[6] When a stimulus of ample threshold is detected, the sodium ion channels open and the subsequent influx causes the membrane potential to swing positively to approximately 40mV.[6] This action potential then propagates down the nerve and the signal can be relayed. More specifically however, a primary way that nociceptors are activated is through inflammatory mediators which are released when tissue damage occurs. Mediators such as prostaglandins, cytokines, and bradykinin activate nociceptors directly and can lead to primary sensitization, the result of which is a reduced threshold needed for a pain stimulus to trigger an action potential.[6] In other words, the affected area becomes more sensitive to pain.

The method by which every neuron function is through a mechanism called an action potential. On a cellular level, this mechanism functions through depolarization of the cell's electrical potential. A sudden influx of sodium brings the cell from a negatively polarized state towards a neutral state. After this sudden depolarization, the cell enters the recovery period.

In studying pain mechanisms, this recovery period is helpful in understanding hypersensitivity following a painful stimulus and other physiological experiences. If we

are to take the largest group of fibers previously discussed, it displays a recovery phase of approximately 100ms.[9] During this return to equilibrium the nerve will exhibit several potential fluctuations which Livingston termed “after potentials”.[9] While these after potentials are not entirely consistent and are dependent on physical and chemical environmental factors, they generally follow the trend of a negative then positive.[9] The period in which the nerve experiences a positive after potential indicates that the nerve is hypersensitive to subsequent stimuli following the initial action potential. In other words, the threshold needed to activate the primary afferent nociceptors decreases such that seemingly minor stimuli might be incredibly painful.

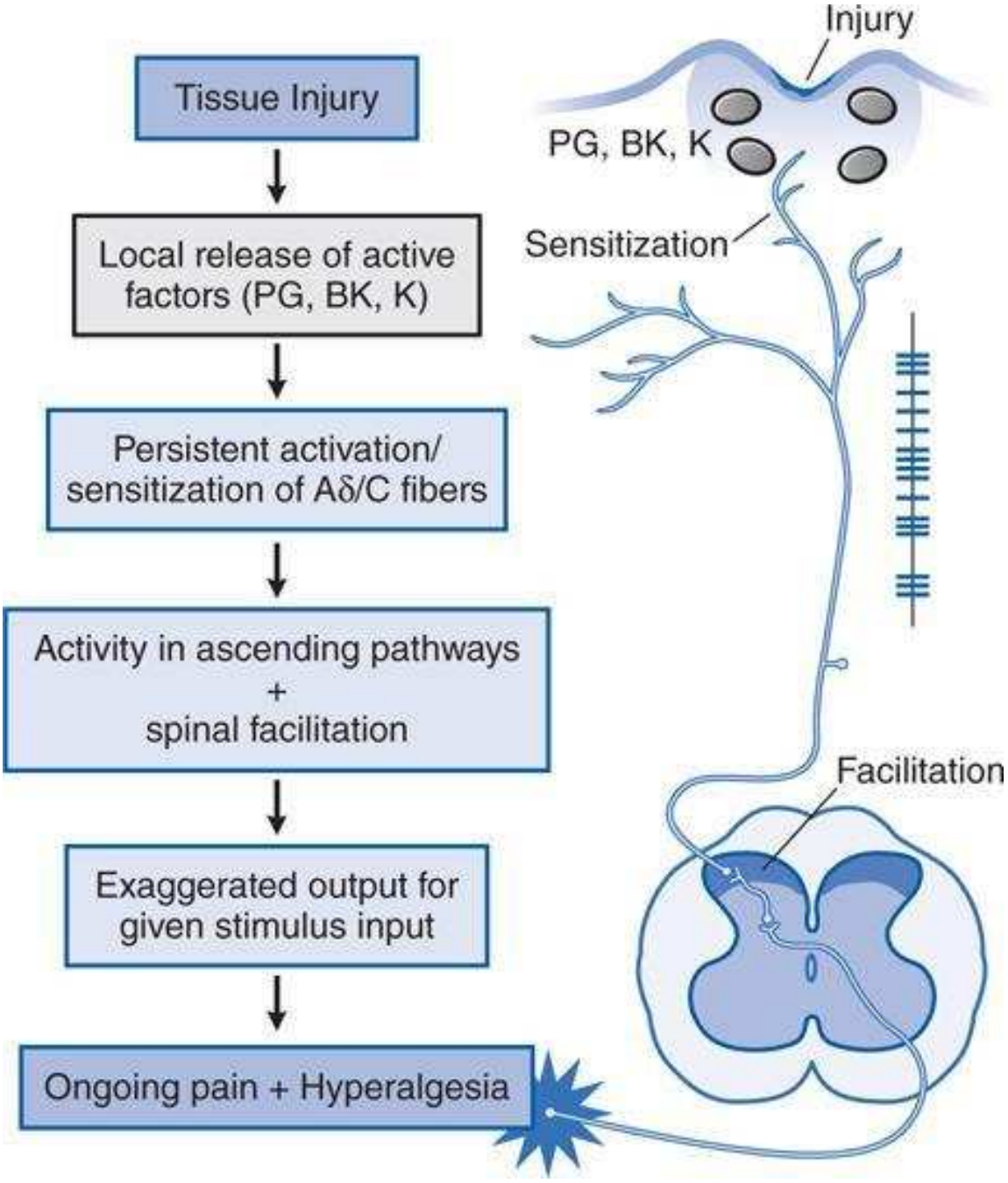

Figure 2: Tissue Injury Evoked Nociception Cascade

Figure 2 demonstrates the cascade involved in hyperalgesia. When local factors are activated and released in the periphery, this leads to persistent activation of the Aδ fibers causing neuroplastic changes centrally.[17]

Transition from Acute to Chronic Pain & Sensitization

The transition from acute to chronic pain is a relatively misunderstood process, but it is generally accepted that chronic pain occurs through mechanisms of central sensitization.[18] In specific regards to surgery, this typically happens due to excessive neural stimuli being applied in the periphery which produce neuroplastic changes in the central nervous system. Receptive fields in the dorsal horn are not fixed and have the potential to undergo neuro-remodelling after temporal and spatial summation in the peripheral receptive fields.[19,20] The nociceptive inputs from the peripheral nervous system via C-fibers trigger the release of glutamate in the spinal circuits which act on the N-methyl-D-aspartate receptors (NMDARs). NMDARs, which are highly permeable to calcium, cause specific cascades that can cause excitotoxicity and neuronal death due to increased feedforward activation postsynaptically.[21,22] When this process occurs centrally in the descending pathways that modulate and inhibit pain stimuli occurs, it leads to an inability to suppress afferent pain signals.[23]

Peripheral sensitization plays a key role in the development of central sensitization. Because the primary afferent neurons respond to inflammation at the level of the nociceptor in a way that lowers the threshold required for activation, when there is tissue damage, as in the case with many surgeries, we see peripheral sensitization. The immune cells initially responding to the tissue damage acts as mediators in this process.[24] Cytokines, nerve growth factor (NGF), proteases, histamine, and bradykinin are all released by immune cells during the inflammation process that act on nociceptors. NGF in particular plays a key role through the phosphorylation of TRPV1, a thermal receptor,

which allows for insertion into the membrane.[24] TNF-α, IL-1β and IL-6 get released during local infiltration by macrophages and monocytes in a way similar to glial cells in the central nervous system.[25] These act on the neurons and upregulate TRPA1, TRPV1, and Nav1.7-1.9, which all work to increase hypersensitivity to heat and mechanical stimuli.[24] Under normal circumstances, peripheral sensitization is a natural process that is required for humans to experience pain, however, when tissue damage is severe or overstimulation occurs, peripheral sensitization will contribute to central sensitization.

Sensitization is the main understood pathophysiology of the transition from acute to chronic pain and therefore acts as the prime target for intervention in order to prevent it. However, the pain pathways are still largely misunderstood. Additional studies exploring new mechanisms might help better understand the associated risk factors and unearth new areas to target.

CURRENT METHODS OF PAIN TREATMENT

More than 80% of surgical patients experience postsurgical acute pain.[26] Inadequate treatment of postoperative, which as the evidence suggests occurs in more than half the patients, can lead to pain chronicity. There are several reasons that inadequate postsurgical analgesia is provided, such as poor assessment or lack of planning.[27] The aim of this section is to outline and examine the current methods and highlight specifically how they can be used to greater effect.

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

In the wake of the opioid epidemic, it is deemed desirable to reduce opioid analgesics when possible. Commonly used NSAIDs are cyclo-oxygenase (COX) inhibitors which act by either inhibiting the COX-I enzyme, the constitutively active form, or the COX-II enzyme, the inducible form. The former is found in many tissues and has a variety of functions such as platelet function. The latter is found specifically at inflammatory sites. [6] By blocking these enzymes, prostaglandin production is inhibited and therefore reduced inflammation occurs. Bleeding is a common side effect of these drugs due to platelet inhibition. Centrally acting forms such as paracetamol or acetaminophen may be used to avoid this complication as both of these drugs do not inhibit peripheral COX, but instead restrict their activity to the nervous system and as a result do not act as peripheral anti-inflammatories. Hepatotoxicity is a common complication with these drugs and thus use must be monitored. In some orthopedic surgeries, there is concern about NSAIDs affecting tendon recovery and angiogenesis.[28,29] The mechanism of action for this issue is unclear, but certain rat models suggest that this might be due to the activity of COX-2.[30] However, in a systematic review, there was no evidence found that NSAIDs significantly impaired tendon-to-bone healing, thus it would appear that NSAIDs continue to remain a good analgesic option even for surgeries with significant musculoskeletal damage.[29]

The evidence behind the use of NSAIDs for managing postoperative pain is robust and continually demonstrates effective pain score reduction and opioid use reduction across a wide variety of surgeries.[31–34] A benefit of the use of NSAIDs is that the research supports the use of them at all stages of the surgical timeline. In a double-

blind study, NSAIDs given preoperatively to children undergoing oral surgery, it was found that they significantly reduced postoperative pain and anxiety.[35] Additionally, in the postoperative setting, it seems to work synergistically with drugs like bupivacaine as a non-opioid therapy.[36]

Opioids

Opioids are the gold standard pain relief and extremely effective at relieving pain. There are three main receptors involved through which opioids can be categorized: μ, κ, and δ. However, the mu-receptor is the one primarily responsible for analgesia in the central nervous system.[37] The periaqueductal grey, locus coeruleus, and rostral ventral medulla all show high concentrations of opioid receptors.[37] In the periaqueductal grey, a mu-agonist will stimulate the descending inhibitory pathways which reduces the amount of nociceptive signaling to the thalamus.[37] Intracellularly, the opioid receptors have been identified as G-protein-coupled-receptors. When an agonist binds, the G-protein swaps the previously bound guanosine diphosphate (GDP) for a guanosine triphosphate (GTP). After this occurs, the α-GTP and βγcomplexes will interact with downstream proteins that cause changes within the neuron. Primarily, we see a reduction of intracellular cyclic adenosine monophosphate (cAMP), decreased opening of calcium channels, increased potassium currents, and increased activation of protein kinase C (PKC).[37,38] Naturally occurring opioid receptor agonists exist, such as enkephalins, endorphins, and endomorphins.[38]

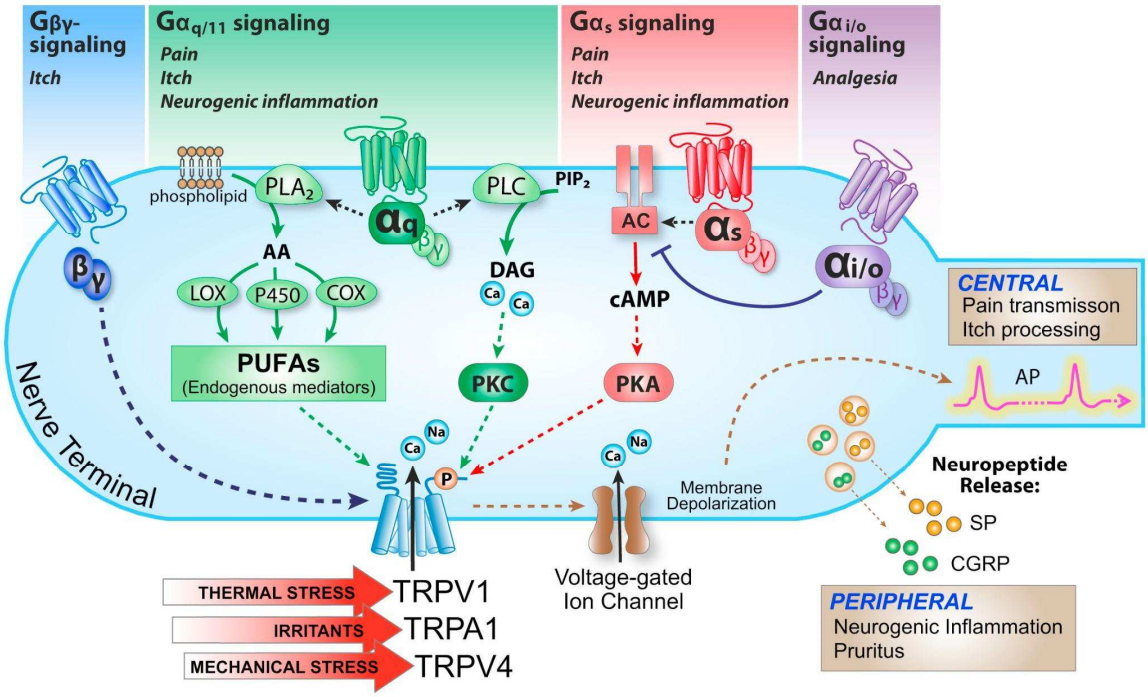

Figure 3: GPCR signaling Pathway for Pain

When the α subunit-GTP complex becomes activated after agonist binding, the activation of cAMP acts on the TRP receptors which interact with the calcium channels. When cAMP is inhibited by the αι & αo the channels do not open, inhibiting membrane depolarization and propagation of the action potential [39]

Pharmacologically, there are various classes of opioids based on their chemical structure. These are opium alkaloids, semisynthetic derivatives, synthetic opioids, diphenylpropylamine derivatives, and then opioid antagonists.[38] One of the most commonly used opioid analgesics is morphine, an opium alkaloid commonly administered intravenously, but has the severe drawback of low bioavailability which results in slow onset. In the acute setting, alfentanil, fentanyl, and remifentanil, all synthetic opioids, are much more common due to their high lipid solubility allowing for fast onset.[37] Care is usually taken with prolonged administration in order to prevent

storage in fat. For chronic pain uses, codeine (opium alkaloid), oxycodone, and buprenorphine, both semisynthetic derivatives, are frequently prescribed for oral consumption. Codeine must first be metabolized and 5%-10% of the population may lack the enzyme for this process to occur and thus may not be appropriate.[37] For patients that suffer severely from the side effects, such as respiratory function or reduced consciousness, it may be appropriate to administer an antagonist. These include Naloxone and Naltrexone, which both act as antagonists to all three receptor subtypes.[37]

The Opioid Crisis & Why Opioid Reduction Matters for CPSP

It would be impossible to discuss pain management without addressing the opioid crisis and the harm that it has caused worldwide. Between 2001 and 2013 the use of prescription opioids doubled; in 2009 90% of this use was found to be in the United States, Western Europe, and Australasia.[40] Currently, approximately 99% of surgical patients receive opioids as part of their surgical care and pain management routines.[41] In the perioperative period, 84-100% of patients receive opioids as part of their general anaesthesia program to address both anaesthetic and hemodynamic issues.[41,42] As part of their postoperative pain management regimen, 77-91% of patients receive prescription opioids for both major and minor surgeries.[41,43,44] In these high-income countries that prescribe the majority of the world's opioid supply, opioid use disorders often are produced iatrogenically and results in illicit use.[45] Over prescription and over reliance on opioid analgesics to treat non-cancer chronic pain has resulted in a sharp spike in opioid use disorders exacerbating the number of overdose deaths and heroin use.[46] Additionally,

the excessive prescription of opioids often results in opioid diversion which is the transfer of opioid analgesics prescribed to a patient to another party such as friends and family.[47] This is partially do to the inaccurate prescribing of opioid analgesics where in by too large of a prescription leads to excess after the surgical patient is pain-free. Surgical patients that had opioids prescribed, but had leftover opioid tablets ranged from 67%-92%.[47] A study examining variation in opioid prescribing looked at 642 patients from 5 different outpatient surgeries: partial mastectomy, partial mastectomy with sentinel lymph node biopsy, laparoscopic cholecystectomy, laparoscopic inguinal hernia repair, and open inguinal hernia repair. They concluded that only 28% of prescribed pills were taken averaged across the 5 surgeries across which there was a variety of rates.[43] By reducing the number of pills prescribed, it can reduce opioid consumption overall and opioid diversion.[41]

Beyond the opioid crisis, there are several good reasons to address the over prescription of opioids in both the perioperative and postoperative stages and explore alternative drug choices. In the short term, opioids are heavily linked with adverse drug events (ADEs) and carry significant risk which include: nausea, vomiting, constipation, urinary retention, postoperative ileus, pruritus, dizziness, decreased cognitive function, and diminished psychomotor coordination.[48] Furthermore, the respiratory depression produced by inhibition of the respiratory centers in the brain stem carries significant risk of unexpected death or requiring mechanical ventilation.[48,49] These risks increase in the perioperative and postoperative periods due to the intensity of surgical procedures.[48] One study examining 6,285 patients found that of 6,274 that received postsurgical opioids,

11.5% of them experienced an opioid-related ADE.[49,50] In a review study that examined a larger cohort of 36,529 patients, 4955 (13.6%) experienced an opioid-related ADE.[48] There are several risk factors associated with opioid-related ADEs and therefore, patients receiving opioids as part over the course of the surgical setting should be identified for risk factors. Factors associated with increased risk were: age, male sex, obesity, and prior opioid use.[48]

Beyond severe adverse effects, opioids carry the risk of inducing hyperalgesia (OIH), which sits in opposition to the goal of perioperative pain regimens looking to prevent central sensitization and allodynia. Clinically, there is debate around the possibility of OIH, but the phenomenon has been documented numerous times over the past 150 years.[51,52] Several proposed mechanisms exist based on animal models, but many suggest that neuroplasticity plays a key function in the adaptive response. It is believed that the presence of opioids which act on the μ-receptor, in both the periphery and the central nervous system, causes functional changes in the peripheral neurons that lead to "local physical dependence."[51] These signals of physical dependence lead to symptoms of tolerance and of hyperalgesia. Another possible target is through the B2-adrenergic receptors. Studies have shown that repeated morphine injections enhance nociceptive sensitization.[51] Centrally, several targets have been identified. Cytokines such as IL-1β and fractalkine, genes for PKC-γ, and the NMDA-receptor all seem to be involved with spinal sensitization, but the mechanism behind these remain unclear and require further clinical testing to be confirmed.[51] Due to the nature of the proposed spinal sensitization mechanisms, it could be that ketamine could help prevent OIH even when

given in subanesthetic doses as part of a multimodal regimen.[53] For this same reason, methadone, due to its NMDA receptor antagonist properties, might be beneficial in an opioid switching program to discourage opioid tolerance development.[51] This could be particularly effective in patients who have a history of opioid-use or have developed a tolerance.

Opioids remain an integral part of many pain management regimens and for many patients improve pain scores significantly. However, it is vital that physicians treating surgical pain understand the consequences of opioid use and the risk factors associated with the various negative outcomes. Each patient should be examined individually to determine appropriate prescription of opioids.

Local Anaesthetics

When surgical incisions are made, the resulting inflammation stimulates nociceptive neurons and causes them to depolarize. This process occurs and during this, voltage gated sodium ion channels open to allow a flood of Na+ ions into the cell. On a cellular level the sodium channels consist of 4 subunits (I, II, III, and IV). During the depolarization phase, subunit IV rotates, therefore opening the channel and allowing a rapid influx of Na+ ions. Physiologically, this change occurs when the membrane potential reaches approximately -55mV and it is this influx that allows for the rapid generation of the action potential.

Local anaesthetics by nature are lipophilic and function by crossing the phospholipid membrane of the neuron.[54] Once they cross the membrane, the molecules

dissociate and the ionized moieties bind the voltage gated channels in a reversible and concentration dependent manner.[54] This binding scales in a phasic manner, or, in other words, the binding increases with the rate of depolarization of the nerve. This binding increases the refractory period and when an optimal concentration is reached, the local anaesthetic will inhibit all nerve conduction. Pharmacokinetically, their absorption and distribution are typically concentration dependent. Peak plasma concentrations are reached more quickly in areas such as the intrapleural and intercostal spaces than subcutaneous, sciatic, and femoral areas.[54]

Local anaesthetics are effective short term options for analgesia and the most commonly used are lidocaine and bupivacaine. Local anaesthetics bind sodium channels in all types of neurons, including motor neurons meaning that high levels can lead to motor weakness and in severe cases where plasma levels rise too high cardiovascular and CNS toxicity may occur.[6] The short duration of effect limits local anaesthetics use in long term pain management plans. However, use in a multimodal approach to help prevent primary sensitization and overall sensitization of the nervous system can facilitate and help prevent chronic pain issues.[18]

Ketamine

Ketamine functions differently compared to other analgesics in the sense that it induces a cataleptic state. It functions as a non-competitive NMDA antagonist when given in low doses which acts centrally within the brain and spinal cord.[55,56] Ketamine has also been shown to reduce opioid tolerance and therefore might have opioid sparing

effects.[56] Additionally, ketamine has synergistic effects with a number of other drugs making it a candidate for multimodal therapy. Ketamine has been shown to potentiate GABA inhibition via interactions with the GABA-A complex, but it is unclear if this is clinically relevant or not due to evidence of this only occurring at extremely high doses.[57] Sodium channel inhibition has also been demonstrated and is hypothesized to function similarly to a local anaesthetic by inhibiting depolarization.[57] When used as part of a preemptive analgesic routine, ketamine has been shown to assist with opioid reduction and improve pain scores.[55] In one study, it was found that ketamine could reduce morphine consumption by 35% and improve rehabilitation without increasing the incidence of adverse effects in total knee arthroplasty. [58] A review looking examining ketamine use in preventing chronic pain after thoracotomies found that when given perioperatively ketamine was ineffectual.[59] However, due to the heterogeneity in methods of ketamine administration and dosage in the studies, it may require further evaluation.[59] When given in low doses, ketamine typically does not show severe adverse effects, but it is linked to severe dysphoria, sympathetic overdrive, and hypersalivation.[60] Use in patients with heart or neurological diseases might not be appropriate and limits its use as a widespread anaesthetic.

GABA Analogues

Gabapentin and Pregabalin are two anticonvulsant medications that were introduced in 1993 and 2004 respectively. The latter was designed to treat both epilepsy and neuropathic pain and is likely the better choice for preemptive or perioperative administration due to its increased lipid solubility and therefore bioavailability. The

primary mechanism of action for these drugs are on the alpha-2-delta subunit in the voltage gated calcium channels of presynaptic neurons in the dorsal horn which experience upregulation in pain transmission.[60] These drugs have little effect on modulation of standard nociception, but operate as analgesics through their ability to prevent allodynia and central sensitization.[61] A review that looked at the effect of perioperative administration of Gabapentin and Pregabalin across a variety of surgeries and found that administration of either significant reduction of acute and chronic pain with little incidence of adverse effects.[61] Additionally, they were shown to have opioid sparing effects.[61] A study looking at minimally invasive gynecological surgeries suggested that GABA analogues may not work as well in minor surgeries due to not inducing enough nociception for their anti-central sensitization effects to make a difference, thus administration might not be appropriate for all surgeries.[60]

Additional Therapies

In addition to the most common options, other options like antidepressants can be effective pain management tools as well. Antidepressants help facilitate the descending inhibitory serotonergic and noradrenergic pathways by increasing the concentration of serotonin and noradrenaline in the CNS.[6]

Alternative nonpharmacologic methods are being explored. One such approach is the scrambler method designed for addressing chronic neuropathic and cancer pain. The device designed for the method uses artificial neurons that produce electrical stimulation to reprogram the signals transmitted by C-fibers.[62] In other words, the neuroplasticity of the pain circuit that can cause neuropathic pain is utilized in reverse. It seeks to cause the

body to encode pain as "non-pain." From the point of view of CPSP, this could be applied in the case that pain from surgery is not entirely nociceptive and the body is in a hyperalgesic or allodynic state. Randomized clinical trials are still necessary and thorough testing is required, but this technique represents another way of looking to treat chronic pain.

Preemptive Analgesia

Prior to the painful stimulus occurring, preemptive administration of pharmacological agents may help block nociceptor activation. The main goal of this technique is to prevent central sensitization from occurring and thus keeping the pain threshold at homeostatic levels. Studies suggest that pre-emptive analgesia can lower analgesic consumption postoperatively and if done epidurally can lower pain scores. [27]

Multiple combinations and individual drug doses have proved effective in reducing pain after surgery.[22] The three main classes used in preemptive analgesia are local anaesthetics, opioids, and NSAIDs. Individually local anaesthetics, opioids, and NSAIDs have all been shown to reduce postoperative pain when administered individually.[22] Additionally, when used combinatorially, these drugs have shown positive effects in reducing postoperative pain, but there remains a lack of research to determine whether or not this offers significant advantages over individual administration.[22] Because not all medications are appropriate or even tolerable for every patient, it is necessary that robust clinical trials be performed in order to test the efficacy of multimodal preemptive analgesia. Alternatively, GABA-analogues and steroids used in

combination with other drugs have also shown efficacy in reducing postsurgical pain and should be studied further as preemptive treatments.[22,63]

Multimodal Approach to Pain Management

The idea of multimodal analgesia is to utilize the different mechanisms analgesics target to get a result greater than the sum of its parts. In many cases, this seems to be the most effective way to manage both acute and chronic pain.[34,64,65] The multimodal approach seeks to minimize stimulation of neurons along the nociceptive pathways on a systematic level.

Multimodal therapy has become more standard and has become a part of the Enhanced Recovery After Surgery Protocol (ERAS) that seeks to improve patients outcomes in a broad way post surgery.[66] However, multimodal methods vary wildly across surgeries and hospitals alike. Even when controlling for factors like age, comorbidities, patient demographics, there is little consistency to the way physicians and surgeons design pain management strategies.[67] This indicates that strategies are not necessarily dictated by patient needs, but rather through individual judgement leaving both room for error and improvement. In fact, even in multimodal programs, a study found that non-opioid analgesics were underutilized further indicating that there is an opportunity to further reduce opioid usage and to mitigate negative side effects. When choosing a multimodal therapy plan, it is essential to tailor the plan to the individual. For example, patients with certain comorbidities might not be appropriate candidates for COX-2 inhibitors or gabapentinoids.[67] Randomized clinical trials have confirmed that local anaesthetics administered using techniques such as transverse abdominis plane

block or wound infiltration are safe and minimize risk of potential negative side effects indicating that this might be a sufficient and appropriate alternative for patients that fall under this category.[68]

INCIDENCE OF CHRONIC PAIN

The rate at which patients develop chronic pain varies dramatically between types of surgery. Some surgeries show very rare developments of CPSP, while others, such as orthopaedic surgeries and thoracotomies, show high incidence rates. A major factor in varying rates of chronic pain lies in the definition. The International Association for the Study of Pain (IASP) recommends that chronic pain be defined as three months, although six months is preferred for academic use.[69] However, this is not universally accepted and many studies adjust this duration of time. Additionally, researchers that have focused on chronic pain have looked into chronic pain very specifically. In other words, studies often have small sample sizes or are focused on individual surgeries, which prevents capturing the whole picture of CPSP. In this section, data from past studies will be presented and analyzed in order to identify risk factors and highlight the rates at which chronic pain occurs across various surgical procedures.

Inguinal Hernia Repair

Inguinal Hernia Repair (IHR) has rates of CPSP ranging from 14.4%-51.6%.[2,70–73] Axman et al. examined 18,370 IHRs based on a national registry questionnaire and found that the incidence of CPSP ranged from 14.8-15.7% based on the type of mesh used. The rate of CPSP found by Axman directly contrasts that found by Dwyer in a 2004 study.

Dwyer found that rates of CPSP after IHR could reach 51.6%.[74] It is unclear exactly why this difference exists. Both groups had examined patients 12 months out from surgery. Liu et al. examined a group of 236 patients after exclusion criteria and found the rate of CPSP amongst patients to be 14.4%.[72] Despite this being a single institution survey, this result is inline with Axman's national study. In a self-administered questionnaire study, it was found that out of 1166 patients, 335 or 28.7% of them experienced chronic pain 12 months after surgery.[73]

Mastectomy

Post surgical pain after mastectomies is normally referred to as postmastectomy pain syndrome (PMPS), but the IASP does not supply a different definition of chronic pain for PMPS, thus it is common to use the 3 month period suggested for chronic pain.[69] The incidence of CPSP for mastectomy ranges from 30% to 52.9%.[75–78] Cui et al. found that of 420 patients, 152 had pain for longer than minimum 3 months after surgery. The study was conducted using a questionnaire sent to patients at a major city hospital after a phone interview. In a meta analysis examining 19813 patients across thirty studies, it was found that the risk of pain was 30% in the absence of risk factors.[77] On average, the rate of CPSP for mastectomy seems high for the obvious reason that the procedure has a high risk for tissue damage. Fabro et al. found in a study looking at a cohort of 203 patients that had undergone surgical treatment for breast cancer at the National Cancer Institute in Brazil that the rate of CPSP could reach 52.9%.[76] The disparity between the numbers might be explained by the relatively small sample size used by Fabro, but nevertheless, it reinforces that chronic pain is experienced by many mastectomy patients.

Caesarean Section

CPSP from caesarean section has been to occur at rates in between 5.9% and 38.6%.[79–83] Defined as pain at 1 year post surgery, Kainu et al. found in a questionnaire study that 42 women of the 229 that responded were experiencing chronic pain.[79] Kehlet found that chronic pain occurs in 12.3% of patients at the 3 month mark. [83] Nardi et. al had results similar to these two finding that CPSP occurs in 15% of patients.[81] As a whole compared to other major surgeries, the rate of CPSP is far less than was seen in mastectomy and in IHR. From a surgical viewpoint, this may be due to the effectiveness of the Pfannenstiel type incision in avoiding nerve damage or that the caesarean section is less prone to causing central sensitization. However, based on a review of the literature, there seems to be a lack of thoroughly in-depth studies with large sample sizes looking at the rates of chronic pain after gynaecological surgery compared to other common surgeries. It is my recommendation that we would greatly benefit from such a study in order to gain a more comprehensive understanding.

Table 1: Summary of Individual Clinical Trial Findings

Study	Patient Number	CPSP Incidence	CPSP Percentage	Surgery Type
Borges et al.	462	118	25.00%	Caesarean
Kainu et al.	229	42	18.00%	Caesarean
Kehlet et al.	220	85	38.64%	Caesarean
Nardi et al.	167	43	26.00%	Caesarean
Nikolajsen et al.	220	27	12.30%	Caesarean
Yimer et al.	N.A.	0	4-41%	Caesarean Review
Massaron et al.	1440	256	18.70%	IHR
Nikkolo et al.	0	0	51.60%	IHR
Axman et al.	0	0	14.8 to 15.7%	IHR
Liu et al.	236	34	14.40%	IHR
Nielsen et al.	1166	335	28.70%	IHR

Simanski et al.	0	0	42.90%	Mastectomy
Cui et al.	420	152	36.20%	Mastectomy
Fabro et al.	174	0	52.90%	Mastectomy
Wang et al.	Meta-analysis 19813 pts	0	30% w/o risk factors	Mastectomy
Edgley et al.	229	149	65.00%	Ortho

RISK & PROTECTIVE FACTORS OF CHRONIC PAIN

Numerous risk factors for development of CPSP have been identified and confirmed in many studies. Some of these factors are targetable and changeable, weight or emotional state, whilst others, such as age and genetics, are immutable. Identification and knowledge of these risk factors is vital for cohesive planning to avoid the transition of acute to chronic pain.

Age

Younger patients are associated with a higher risk of developing CPSP across various surgeries. In the meta-analysis produced by Wang et al., they examined a total of 11,030 patients across 22 studies and found that every 10 year increment down from 70 increased risk of developing CPSP in breast cancer surgery.[77] This evidence is supported

by other studies that found that younger aged patients also had higher risks of developing chronic pain post surgery.[71,76]

It is unclear why this seems to be a risk factor confirmed by many studies. In fact, in an epidemiological study by mills et al. that found while chronic pain in general seems to be more common amongst older age groups due to increased opportunity to being exposed to noxious stimuli, CPSP specifically is common amongst younger aged patients.[84] The problem with deciphering this trend may be two-fold. Firstly, there is a lack of comprehensive studies looking specifically at patients in younger aged groups. While the rule is not absolute, for example, it is much more difficult to look at younger populations undergoing mastectomy for the simple reason that breast cancer and therefore mastectomy is less common in these groups. [85] Secondly, collecting data for older patients comes with the problem that comorbidities exist at higher rates, attitudes about pain differ, and cognitive issues are likely to be more common.[86] Comorbidities make it more difficult to assess the exact cause of chronic post surgical pain. With self-reporting being the most reliable way to assess pain despite its subjectivity, attitudes towards pain disclosure may affect study results. Many of the studies assessed utilized a mail-based questionnaire to assess pain after surgery, but cognitive issues may affect ability to complete this task. Specialized tools such as the Pain in Advanced Dementia (PAINAD) or the Doloplus-2 are recommended. [86]

Preoperative Pain & History of Chronic Pain

Based on our physiological understanding of pain, it comes as no surprise that preoperative pain is a risk factor for developing chronic pain after surgery. The pain is thought to originate from presensitization of the surgical area. This presensitization causes structural changes within the central nervous system that lower the threshold necessary for nociceptors to activate and transmit the presence of noxious stimuli. In other words, when the surgery acts as a noxious stimulus, the effect is amplified.

Many studies have shown this to be the case.[71,82,83] Wang et al., in a study looking at 2504 mastectomy patients across 8 different studies, found that the presence of preoperative pain can increase your chances of developing CPSP by 6-11% depending on whether or not the preoperative pain is persistent or not. [77] The presence of pain in the perioperative setting is a factor that can be actively mitigated. Pre Screening individuals with the Numerical Rating Scale may prove to be beneficial in minimizing perioperative pain as a contributing factor in CPSP development.

Severe Acute Postoperative Pain

Severe acute postoperative pain is common, especially in surgeries associated with significant nerve damage such as thoracotomies or amputation. Postoperative acute pain as a risk factor has been firmly established and can play a key role in the transition from postoperative pain to chronic pain.[18,84] The trauma and pain experienced during surgery can lead to prolonged inflammation and therefore sensitization in the postoperative period. Postoperative pain, however, is a prime target to reduce CPSP

incidence. Active intervention in the postoperative period and optimization of surgical techniques to minimize tissue damage can help reduce postoperative pain. [18,87]

Sex

Several clinical studies and reviews have identified that the female sex demonstrates a higher prevalence for chronic pain and pain sensitivity compared to men.[88–92] The exact reason for this clinical finding is unclear, but most research indicates that estrogens may underpin the increased sensitivity. Estrogen Receptor, ER-α, has been found on DRG cells and in areas of the brain that are involved in pain signaling such as the amygdala and the periaqueductal gray.[91] Another suggestion is that hormones interfere with the efficacy of analgesics, but this needs further examination.[93] The exact importance of sex in CPSP cannot be easily quantified, but clinical evidence alone should suggest that it should be a factor considered in assessing the overall risk for an individual patient.

Psychosocial Factors

Pain is ultimately a psychological experience. In the final part of the pain circuit, the somatosensory information is processed by the insula, anterior cingulate cortex, and the prefrontal cortex. Therefore, it is no surprise to find that CPSP has a long list of associated psycho-social risk and protective factors. The literature has firmly established that anxiety, depression, and pain catastrophizing as being linked to increased chronic pain.

Pain catastrophizing can be described as a mental state involving unrealistic beliefs that the current situation will lead to the worst possible pain outcome.[94] It involves an extremely negative mental state around a pain experience. Evidence shows that pain catastrophizing and its relation to the pain experience functions due to grey matter changes and a reduced function of the descending pain modulatory system.[95] Birch et al. evaluated a group of 615 patients that either underwent total knee arthroplasty or unicompartmental knee arthroplasty. In the study, subjects completed The Pain Catastrophizing Scale prior to surgery; the Oxford Knee Score, Short Form-36 and the EuroQol-5D were completed both before and after surgery, 4 months, and 12 months.[96,97] Patients with <11 scores on The Pain Catastrophizing Scale had significantly better scores on the Oxford Knee Score, Short Form-36, and the EuroQol-5D than patients who scored >21 on The Catastrophizing Score.[96] Overall, patients that were prone to catastrophizing pain scored far worse at all points of testing in both pain scores and physical ability. It is unlikely that the link between physical recovery and catastrophizing scores is causal, but it does indicate these patients have worse overall outcomes and can be identified.

Catastrophizing as a risk factor may be surgery dependent. Although in many instances it is found to be a risk factor for CPSP, a study examining psychosocial risk factors in IHR found that catastrophizing was not associated with CPSP. [98] It was reported that surgeries with shorter acute postsurgical pain phases may be less prone to development of the fear-avoidance dynamic with which catastrophizing appears to be associated.

Additionally, anxiety and depression are both factors that are linked to CPSP.[52,99–103] In a study looking to identify risk factors in total knee arthroplasty, Singh et al. found that when controlling for demographic and clinical risk factors, anxiety and depression were highly correlated with CPSP at both the 2 and 5 year post surgical time mark. In a similar 2003 study, analysis showed that patients with depression were more likely to utilize postsurgical resources and complain of pain after surgery. [99] Brander et al. also found that the addition of Beck Depression Inventory and State-Trait Anxiety Index or similarly validated psychosocial examinations might be useful as a prescreening tool in order to identify patients that are at higher risk for needing additional postsurgical resources. As preoperative risk factors, both anxiety and depression are firmly established, however it is suggested that anxiety and depression are a part of the postsurgical pain experience and can exacerbate the situation after the fact. Further studies examining similar testing measures in the postsurgical period might be helpful in unveiling the true effect of these comorbidities beyond the extent as a presurgical risk factor.

The amount of evidence linking various psychosocial factors highlights their promise as a point of intervention for reducing chronic pain. The effects of pain catastrophizing have been shown to decrease following cognitive therapy and offers perhaps the most accessible point of intervention as far as psychosocial risk factors are concerned.[95] While depression and anxiety can be addressed, the longer intervention required may make them harder to address in a presurgical situation. However, randomized controlled trials have shown antidepressants such as amitriptyline to be

efficacious in reducing neuropathic pain as well as having an opioid sparing effect suggesting they may be both useful and appropriate in a multimodal pain management approach for patients experiencing depression.[104]

Genetics

Identifying genetic mutations and gene therapy represents one of the most promising aspects for addressing not only CPSP, but pain in general. According to various twin studies and genomic wide association studies, heritability of pain ranges from 30-70%.[105] There are many genetic targets to examine including neurotransmitter catabolizing enzymes, ion channel proteins, receptors, transporters, and transcription factors.[105,106] It would be impossible to reasonably cover every genetic variation that can contribute to chronic pain, however, this thesis will examine them in groups and some of the most promising ones individually.

Much of the work done on understanding chronic pain susceptibility and experiences originates from the idea that the individual experience of all types of pain varies greatly amongst patient populations. Research into genetic mutations has shown that they are accountable for some of this individual variation.[106] Some of the best studied mutations in this realm are the single-nucleotide polymorphisms (SNPs) that affect the catechol-O-methyltransferase (COMT) enzyme. COMT is responsible for modulating catecholamines such as dopamine. A model proposed by Zubieta et al. suggests that when COMT loses efficacy, consequently there is an uptick of dopaminergic receptors in the neuron which causes a compensatory upregulation of the μ-opioid receptors in the brain.

[107] The increased μ-opioid receptors, which activate in response to pain, subsequently lower the threshold for experiencing pain due to their increased abundance.[107]

Another genetic target is the P2RX7 which is an ATP receptor that exists on certain immune cells and is involved in the recruitment of cytokines and other inflammatory mediators.[105] Animal models suggest that P2RX7 contributes top pain modulation via interaction with both peripheral tissues and alterations in nervous system processing. [108]Theoretically, by mitigating the amount of proinflammatory mediators that interact with damaged nerves, a reduction of overall inflammation will reduce neuropathic pain. Patient studies confirm this and suggest that the P2RX7 gene is a reasonable target for therapy, but more clinical studies are needed.[109]

Genetic variations that relate to neurotransmitter functionality are promising and particularly useful given that many pharmacological agents have similar targets. More specifically, it has been shown that a single SNP mutation within the HTR2A gene, which codes for serotonin receptor 2A, increases the risk for post-surgical pain burden.[106] Aoki et al. showed that women specifically with the T/T genotype that had the 102T/C had polymorphism had significantly higher pain sensitivity and had higher opioid consumption post surgery. [110]

Ion channel mutations have been implicated in both an increase and decrease in chronic pain. Mutations in ion channel proteins affect pain thresholds essentially by adjusting the required impulse to depolarize and therefore transmit messages along the pain pathway. Mutations in genes such as KCNS1 and CACNG2 that affect voltage gated

potassium and calcium channels respectively have been implicated in increasing CPSP risk in surgeries such as amputation and mastectomy.[111,112] On the other hand, some ion channel mutations might offer a protective factor. In a study looking at *Drosophila* and mice inheritance, it was found that the CACNA2D3, a gene for a calcium channel subunit, played a role in thermal nociception, which was associated with lower chronic pain.[113] While further research is required, the studies so far suggest they make likely targets for genetic pre-screening before surgery.

Surgical Factors and Anaesthetic Technique

For obvious reasons, aspects of the actual surgery have an effect on the outcome. One study showed that the Misgav Ladach method of caesarean section was faster, patients had less acute pain, and used less postoperative analgesics.[87] Minimally invasive surgical techniques that prioritize limiting nerve and tissue damage might be effective in reducing CPSP.[114] However, techniques such as video assisted thoracic surgery have not been shown to reduce chronic pain.[115] A possible explanation for this is that the technique does not do enough to minimize nerve damage despite smaller incisions.

CURRENT WORKING MODELS & PROPOSED FIXES

Acute pain knowledge has transformed tremendously over the past two decades. The opioid crisis alone has forced physicians to think differently about pain. However, despite this advancement, CPSP remains a fundamental issue that needs further attention. As evidenced by the many CPSP incidence studies, rates of CPSP have changed very

little over the years. In this section, various proposed fixes will be identified and discussed in an effort to pinpoint where strides can be made.

Pre-Surgical Assessment

In 2016, the American Pain Society (APS) published a series of recommendations of clinical guidelines for postsurgical pain management.[26] In the preoperative stage they made the recommendation of:

1. Patient education and clarification of goals
2. Counselling on analgesic administration and pain assessment
3. Preoperative evaluation of risk factors
4. Flexible pain management schemes
5. Use of validated pain assessment tools

Specifically, it seems that recommendations 1, 3, and 5 are most relevant to the discussion so far, whilst 2 and 4 are mostly self-evident in importance.

Recommendation 1 suggests that educating patients about pain management and documenting pain goals might assist in managing presurgical anxiety levels. Given the heightened risk of CPSP for patients that catastrophize and have high anxiety levels, this seems consistent with the information examined thus far.[100,116] The APS states specifically that the evidence for this is inconclusive and that the content of an early education program has not been evaluated indicating the need for further studies on this topic.[26]

Recommendation 3, as evidenced by the extensive discussion on risk factors heretofore, is critical in devising an active pain management plan to prevent development of chronic pain. Risk factors that can be changed, such as psychosocial factors or preoperative pain, and history of analgesic use are useful targets to reducing adverse events post surgery. In the case of the latter, understanding the opioid use history of the patient might be critical and make him or her a prime candidate for multimodal therapies in order to reduce opioid requirements.[117] The goal of the risk factor assessment should be to develop a complete picture and prescribe a plan that suits the individual patient and recovery goals.

The fifth recommendation is vital to tracking and updating pain management schemes. Use of validated pain management tests can make it easier to confirm pain changes. The APS suggests the use of a numerical rating scale such as the four-point, a visual analogue scale, pain thermometer, or faces-rating scale.[26,118] In addition, the use of an appropriate scale depending on the patient's condition is vital. Dementia patients for example may not be able to accurately complete one of the recommended assessments and others may be necessary.[86]

Another model is the Transitional Pain Service (TPS) at Toronto General Hospital. At the TPS, they comprehensively address pain at the pre, peri, and postoperative stages.[119] By managing pain at every stage of the operation, they can focus on how the patient is coping with the surgery and make constant adjustments each step in order to ensure a high quality of life after surgery.

Pre and Perioperative Stage

Much of their success comes from identifying patients at risk for developing CPSP early on in the surgical pre-admission visit where they go through a detailed assessment of the patients. Identifying patients at risk early on the intraoperative period allows for personalization of the pain management regiment as well as providing information as to how to best use analgesics. The latter of which allows for the patient to become an active participant in the postoperative pain management process. One example of how this effective, is identifying a patient with a history of opioid use early on allowed them to work to reduce his opioid consumption in advance of the surgery and made greater use of the multimodal treatment plan.[119]

Postoperatively

After discharge, patients are followed up with a phone call after three days. After that, patients are seen after two to three weeks in clinic in order to adjust any issues they are having. During this clinic visit, patients are assessed for addiction risk, weaning opioid medication, and the overall efficacy of the treatment plan. Alternatively, patients get offered physiotherapy and acupuncture in effort to aid pain relief. This biweekly assessment occurs for 6 weeks to 6 months postoperatively typically whereby they transition to seeing their primary care physician.

By taking control of the entire pain management process and constantly monitoring it at every step of the way, the TPS is able to take advantage of the more efficacious pain management strategies. Furthermore, by having complete control over the process, they are able to make individualized adjustments every step of the way. This is in direct

contrast to the more common method of referring patients to other physicians or pain management services that may not understand the complete picture.

The model implemented at Toronto General Hospital is similar to the Opioid Task Force (OTF) implemented at the Hospital for Special Surgery.[117] While the goal of the OTF is not necessarily to design a comprehensive pain service, it sought to create a comprehensive group containing all of the staff with which the patient would interact and implement programs that would reduce opioid consumption for orthopedic patients hospital wide. Much of their work emphasizes the same principles as the TPS. The OTF emphasizes in-depth presurgical screening, patient education, prescription of alternative medications, and reduction of opioid use. There are clear differences and the study outlining this model lacks significant clinically relevant data to validate the success of the OTF, but integration of all parts of the pain management process has proved effective in other models and looks to be a promising way to improve patient outcomes in a generalizable way.[117]

CONCLUSIONS

CPSP is an issue that is both commonly mishandled and misunderstood. In order to address this, physicians must be open to adopting new methods and strategies to help combat it. Patients need to and can be identified early for risk factors indicating that they might require additional pain management planning. Once they have been identified, their pain management needs to be comprehensive and everyone involved in the surgical process should be informed of the individual patient's needs. Hospitals serious about

improving patient outcomes should look towards the models outlined and implement similar standards and strategies as a start.

However, these models are not perfect, nor are they robustly clinically validated. Further studies looking at the efficacy and cost efficiency of these methods are needed for them to be truly generalizable and recommended for implementation. Additionally, rigorous clinical trials on CPSP that seek to mitigate the heterogeneity of surgical procedures would be helpful in understanding chronic pain.

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