5-2019

Chronic Pain: A Review

Jacob Stein
Philadelphia College of Osteopathic Medicine

Jacob Stein

May 24th 2019

CHRONIC PAIN: A REVIEW

Abstract: Chronic pain can be a debilitating condition which weighs heavy upon its sufferers and the healthcare system at large. Although such a common condition, chronic pain can be an ambiguous term that incorporates many emotional, psychological, and physical states. Due to epidemiologically relevant psychological and physical conditions between chronic pain patients and substance-use disorder populations, a model relating to the latter population has been suggested. The CReAM (Combined reward anti-reward model) has been used to develop a better understanding of the feed-forward nature of deteriorating pain conditions. Researchers have identified certain anatomical regions that may play a role in the pathological condition, both cortical and subcortical regions of the brain and the spinal cord. Appropriate molecular mechanisms have been implicated in the development of chronic pain, including long-term potentiation and depression at the synaptic level. The mapping of cortical circuits and systems relating to chronic pain conditions has been a continually growing topic in this research field as additional areas, and connections continue to be discovered and understood. This mounting input of data has led to complex interweaving cortical networks involving mesolimbic, mesocortical, basal ganglia, endogenous analgesic system, reward, anti-reward, and many more systems working together in this pathological state. Due to the numerous potential causes, areas affected, the span of psychological and physical symptoms, and lack of options treatment of chronic pain has been a challenging prospect. This challenge has led to a number of unintended consequences that burden the healthcare system, such as the opioid crisis currently faced in the United States. Overall chronic pain is a challenge that is enormous, but necessary to face as the condition takes its toll on the millions of sufferers.

Introduction

Pain is an evolutionarily significant response; necessary for survival and under the modern lens of medicine a critical diagnostic tool. Pain is also debilitating, psychologically grueling, and can be life-changing. Although only a singular word, pain encompasses many things; from the acute sensation of stubbing a toe to the emotional feelings of loss and heartbreak. Further, beyond the variety of sensation, the time periods of pain differ as well on a scale from acute to chronic. However, what precisely chronic pain is, differs from sources and the mechanisms and principles behind the idea are still vague; traditional acute pain mechanisms linked to direct injury or sensations are more evident than chronic pain.

The mechanism and pathway of acute pain are well documented. In general pain first stimulates nociceptive sensory neurons in the periphery, from there the signal hitches a ride on nerve fibers through the dorsal root ganglion synapsing onto the dorsal horn of the spinal cord. From the dorsal horn, the information travels to the brain via the spinothalamic tract where it travels to multiple locations via thalamic tracts primarily the somatosensory cortices (S1 & S2). Cortico-limbic structures interpret the stimuli and modulate these signals based on multiple variables. The pain may be modulated via the endogenous analgesia system from inputs of the cortico-limbic structures. (Elman & Borsook 2016). While these pathways are reasonably well-understood, the transition to chronic pain remains elusive. Chronic pain outlasts regular time of healing if associated initially with disease or injury (Grichnik & Ferrante 1991). In a sense, this was a clue that chronic pain involves the modulation of central nervous system circuits and structures,

which is most likely the result of allostasis. Allostasis referring to the physiological and behavioral fluctuating homeostatic changes undergone by the body in response to stressors. When the allostatic load, allostasis over time (McEwen & Stellar 1993), increases the failure of homeostasis to meet the demands which have shown to cause dysregulation of reward and anti-reward circuitry in the brain (Borsook et al. 2016).

The primary reward circuit involves dopaminergic neurons in three primary structures the ventral tegmental area (VTA), nucleus accumbens (NAc), and medial prefrontal cortex (mPFC). Other structures play a role in this circuit as well including limbic structures such as the amygdala and hippocampus. This circuit, when activated, portrays pleasurable or hedonic information that relates to wanting or motivation to pursue or continue an action. Essential distinctions have been made in this pathway indicating orbitofrontal cortex and opioids, endogenous or exogenous, induce the pleasurable aspects of reward and pain modulation, while ventral striatal dopamine is implicated in the motivational avoidance of painful stimuli (Becker et al. 2012). These processes are opponents of the anti-reward or pain circuits in the brain which serve as aversive signals of an action. An interesting structure found in this aversive pathway is the habenula (Hb). Particularly the lateral habenula (LHb) has been shown to reduce dopaminergic activity in the tegmental area, and inhibition of this area reveals inhibition of aversive activity in mice (Stopper & Floresco 2014). In reference to both pain and reward, there has been a multitude of overlapping structures identified in both processes including: dorsal and ventral striatum, anterior cingulate cortex, orbitofrontal cortex, insula, and habenula. These structures are of interest because these have similar modifications in both chronic pain and pain treatment. For example, the habenula has

shown similar characteristic changes in both addiction models (Lecca et al. 2014) and chronic pain models (Shelton et al. 2012).

In recent years there has been a noticeable overlap of the reward and anti-reward circuits in the brain which has similar characteristics in both opioid overuse and chronic pain. Effectively in both instances, "[p]atients with chronic pain exhibit certain psychopathological and clinical features in common with addiction. Both pain (Wood, 2008, Wood et al., 2007) and opioids (Tanda et al., 1997) activate dopamine transmission in the brain reward circuitry, including the [nucleus accumbens] whereas prolonged periods of pain or opioid drug consumption produce the opposite effect (Wiech and Tracey, 2013)"(Borsook et al. 2016). Further, lack of understanding of acute to chronic neuropathic pain transition has led some researchers to propose a look at addiction circuits due to similarities in disruptions of hedonic homeostasis (Ghitza 2016); specifically, modifications in the mesolimbic system in structures such as the ventral tegmental area and nucleus accumbens.

At a macroscopic level, similar behavioral and sensory perceptional changes can be observed in both groups. Behavioral characteristics of both substance-use disorder groups and chronic pain groups are vast. A very notable psychological change is anhedonia, the lack or inability to gain pleasure is experienced by the two groups likely due to the reward-deficient state brought on by their respective allostatic loads (Borsook et al. 2016). This anhedonia is likely linked to both groups having hypodopaminergic states in their striatal and PFC due to chronic stressors and drug exposure, which may also have common ties to high suicidality rates in both groups (Elman et al. 2013). Linked to the suicidality of both groups is the common thread of mood disorders having a

higher prevalence in both groups than the average population. In chronic pain groups, 21.7 % of the population (McWilliams et al. 2003) and 19.67% of substance-use disorder groups (Grant et al. 2004) have mood disorders in comparison with 10% in the general population (McWilliams et al. 2003). A common sensory condition experienced by the two groups of interest is hyperalgesia or heightened sensitivity to stimuli (Borsook et al. 2016); although human studies are limited due to both groups exclusively receiving opioids, this hypersensitivity is documented independently of opioid use in animal models of chronic pain (Scott et al. 2018).

Due to these similar characteristics in chronic pain and substance-use disorder patients,' there is a similarity in the psychological treatment to both of these groups. Probably the most widely used behavioral therapy used for both groups is cognitive-behavioral therapy. CBT is based on several principles regarding thoughts relating to behaviors. These include the idea that psychological issues are derived in part by unhelpful ways of thinking, that there are problematic learned behaviors, and by learning ways to cope with these psychological problems patients can learn to lead healthier lives (APA 2018). This approach is widely used because it has been proven efficacious in practice regarding these subsets of patients. In one meta-analysis study involving CBT and chronic pain patients it "revealed that cognitive-behavioral treatments produced significantly greater changes for the domains of pain experience, cognitive coping and appraisal" (Morely et al. 1999). Similarly, for substance-use disorder mindfulness-based interventions, which are a subset and part of CBT, revealed effectiveness in reducing cravings and relapse (Chisea & Serretti 2014).

More controversial are the pharmaceutical approaches to both of these prevailing conditions, specifically regarding opioid-use. Opioids have proven effective for chronic pain relief (Goldstein 2019), including the common hyperalgesia associated with the pain state aforementioned (Severino et al. 2018). However, the understanding of opioid effects both endogenous and exogenous from a biochemical to circuit level is still not well established. There is a considerable heterogeneity of opioid receptors and their subtypes. To compound the complexity of opioid response, they seem to have different mechanisms of action depending on the agent and site of pain (Bodnar 2017). Although pharmacologically most analgesic based opioid drugs target the mu-opioid receptor, even this specificity has left many more questions; such as why clinicians often have to switch patients from one drug to another to find the most effective drug for their patient (Pasternak & Gavril 2005). Further, there is evidence of sex-based differences in effectiveness in opioid drug analgesic properties (Averitt et al. 2019). Although opioids are effective in treating pain, there are mixed reports on the effectiveness of long-term opioid use and chronic pain (Genie & Kevin 2018).

Further, the adverse drug events of opioids are plentiful, including both GI and central nervous system effects, like constipation and drowsiness/fatigue. In the most extreme cases such as overdoses, respiratory depression can occur, which is often fatal. In addition to the ADRs, as mentioned previously, opioid-use disorder (OUD) is a huge issue facing the United States. A large percentage of the problem seems to reside in clinical settings. Whether it is proper dosing, screening for OUD, or even prescribing opioids to individuals who have previously overdosed; approximately 91% of those who have overdosed were prescribed opioids within 299 days of the incident (Genie & Kevin

2018). Physicians, aware of the limitations of screening for substance-use disorder prior to prescribing, have implemented some measures; such as the SOAPP, screener, and opioid assessment for patients with pain, questionnaire. However, once an individual develops OUD, the chances of remaining opioid-free are relatively small and that is not just due to the addictive seeking of opioids, but because of the treatment for OUD. The most common medical assisted treatments used for OUD, according to SAMHSA, are methadone and buprenorphine, which are full and partial opioid agonists. The full long-term effects of both of these medications are not fully known.

Since the dawn of medicine, remedies for pain have been sought out to rid humans of this condition. In this pursuit, there have been many achievements and also unforeseen consequences. Among those consequences is perhaps the largest and one of the most pertinent health crises facing the United States. The opioid crisis has some alarming statistics from the NIH which include: a 54 percent increase in opioid overdoses in 16 large U.S. cities, a 30 percent increase in overdoses in 45 states from July 2016 to September 2017, and roughly 2 million people suffer from an opioid-related substance-use disorder. However, one statistic that should be of great interest to the pain management community is that 21-29 percent of opioids prescribed for chronic pain are misused (Vowles et al. 2015). This overlap may represent hundreds of thousands of patients as chronic pain is a similarly prevalent issue facing American healthcare systems; according to the Institute of Medicine of the National Academies 100 million Americans suffer from chronic pain.

Mapping Ambiguity

The complexities associated with cortical circuitry in as ambiguous of sensations that may exist, as pain is, are quite possibly near infinite. Circuitry associated with the sensations and chronification of pain includes reward, learning, memory, emotional (Navratilova et al. 2016), endogenous analgesic (Ossipov et al. 2010), and noxious pain processing (Borsook et al. 2016).

The mesocorticolimbic system, commonly attributed as the reward circuit, has been shown to have modifications during the process of chronic pain (Taylor et al. 2015). A particularly well-studied aspect of this circuit is the primary neurotransmitter involved in this circuit: dopamine. As discussed earlier, hypodopaminergic states are likely to contribute to the reward deficiency aspect of the CReAM theory. Once again in this model repeated activation of the dopaminergic system may lead to a depletion of dopamine; thus, this may contribute to the psychological experience of anhedonia or the deficiency of pleasure (Borsook et al. 2016). Further, this hypodopaminergic model may contribute to the understanding of the overlap in comorbidities of depression and addiction in substance-use disorder and chronic pain (Elman et al. 2002).

There used to be a linear approach to pain modulatory systems from the central nervous system. Traditionally the pain modulation was considered to originate in the periaqueductal gray (PAG) and descend through the rostroventral medulla (RVM). More recently, through neuroimaging and electrical stimulation, researchers have discovered a much more complex network of structures involved in the system. This network includes cortical and limbic structure, like the amygdala and prefrontal cortex, which has inputs into the endogenous analgesia system (Ossipov et al. 2010).

The antireward system has gained traction in the understanding of chronic pain, and the primary structure of interest in this system is the habenula. This small structure posterior to the thalamus has many various afferents and efferent connections (Shelton et al. 2012). Further, this fundamental structure has two subdivisions the lateral habenula (LHb) and medial habenula (MHb). Especially interesting in the process of pain is the LHb which has both afferent and efferent connections to the limbic forebrain, hindbrain, and midbrain which suggest roles in aversive learning and emotional aspects related to pain (Bianco & Wilson 2009, Borsook et al. 2016). As the nucleus accumbens is thought of the primary site of the interface in the reward system, so does the habenula seem a primary relay station in an antireward network (Stopper & Floresco 2014).

Long-Term Potentiation in Chronic Pain

Long-term potentiation has been shown to have a role in chronic pain states in various nervous system regions that have been implicated in chronic pain (Bliss et al. 2016). Primarily long-term potentiation is the induction of increased excitability pre or postsynaptically due to increased high-frequency stimulation of the synapse (Nicholls et al. 2012). Primary culprits in this molecularly facilitated activity are two glutamate receptors α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and n-methyl-D-aspartate (NMDA), which are facilitators in the memory process in the hippocampus (Bliss et al. 1993). The idea is that increased rates or magnitudes of synaptic stimulation increase glutamate release presynaptically, which facilitates more extensive excitatory postsynaptic potentials (EPSPs). The large magnitude EPSPs surpass the threshold for NMDA opening, which in turns further increases the EPSP. Ultimately,

this leads to the production of more AMPA receptors via a signaling cascade involving protein kinase C, adenylyl cyclase, protein kinase A, and CREB. These upregulated post-synaptic receptors create long-term increased EPSP magnitude. (Nicholls et al. 2012). LTP is not restricted post-synaptically however, nor is it solely facilitated through ionotropic glutamate receptors, and there are other mechanisms which can facilitate LTP pres-synaptically for example through kainite glutamate receptors (Bliss et al. 2016). There have been multiple structures observed in correlation to LTP and chronic pain as aforementioned. Primary anatomical regions so far implicated in chronic pain facilitation via LTP are the dorsal horn of the spinal cord, anterior cingulate cortex, and the insular cortex.

Aforementioned chronic pain is often accompanied by states of hyperalgesia both psychologically and physically. A recurring topic of study in hyperalgesia is the induction of LTP in nociceptive pathways within the dorsal horn of the spinal cord. Intuitively this surmises that if there is a significant initial insult to the area, this may replicate a high magnitude stimulus which turns the gears of receptor-mediated LTP at the first site of the nociceptive pain pathway (Ruscheweyh et al. 2011). There has been a multitude of studies implicating the involvement of NMDARs with the involvement of sensitization of spinothalamic tract neurons which lead to states of allodynia and hypersensitization, which is noted to be shared among chronic pain sufferers (Willis 2002). However, it seems this central sensitization is not only reliant on NMDARs but also requires the Neurokinin 1 for induction of LTP (Liu & Sandkühler 1997). NK1 receptor binds substance p, which is an appealing implication in the induction of LTP as substance P is implicated in a wide array of activities which are critical to injury and

healing. These activities include: “hematopoiesis, wound healing, microvasculature permeability, neurogenic inflammation, leukocyte trafficking, cell survival… and it has been associated with tumorigenesis and metastasis (Garcia-recio & Gascón 2015). These induction methods of hyperalgesia and allodynia seem cogent and well-studied. Further, there is more LTP facilitated molecular reasoning behind chronic pain located further up into the cerebrum.

The primary areas of the cortex associated with the unpleasantness sensation of pain are the anterior cingulate cortex (acc) and insular cortex. The ACC, in particular, has been well documented with this function as a neurosurgical procedure, an anterior cingulotomy has been developed in deployed in some cases of chronic intractable pain with some success (Sharim & Pouratian 2016). Similar to the dorsal horn of the spinal cord, the ACC has been well studied to have LTP associated with pain states. The mechanisms of ACC LTP are similar to the ones already mentioned, as AMPA and NMDA receptor-mediated LTP has been established in this area of cortex. Most pertinent is that in animal models, LTP has been linked to the development of allodynia along the same time scale (Bliss et al. 2016). In one study researchers observed the effects of hindpaw amputation on LTP in the ACC, they concluded from their findings that the amputation increased synaptic responses in the anterior cingulate cortex (Li et al. 2013). This could be one of the mechanisms which underlie chronic phantom limb pain experienced in approximately 50-80 percent of amputees (Li et al. 2013).

Similar to the anterior cingulate cortex, insular cortex has also been found to have glutamate facilitated LTP, which contributes to chronic pain (Lu et al. 2016). The insular cortex has shown involvement in aversive learning, pain experience, and part of a more

extensive salience network (Uddin et al. 2017). The primary neurotransmitter in the insular cortex is glutamate, and there are abundant AMPA and NMDA receptors in this cortical region. Further, both in vitro and in vivo studies have shown the capacity for synapses in this brain region to undergo NMDA facilitated long-term potentiation (Zhuo 2016).

Beyond these central nervous system sites, there are many other studies which have shown capacity for LTP via electrophysiological recordings in vivo or in vitro. These may implicate a likely molecular basis for a systematic understanding of chronic pain, and possibly enforce the previously mentioned combined reward and anti-reward model of chronic pain.

Predisposed to Pain?

Predisposing factors to addiction have long been cited and as early as the 1950s, and perhaps earlier, researchers understood an interplay along the bio-psycho-social model of addiction. Risk factors for addiction according to the National Institute of Drug Abuse (NIDA) include: genetic, history of mental health concerns, family systems, environmental factors, medical issues/surgery, availability and accessibility to substances, lack of parental supervision, risk-taking tendencies, impulsivity, the method of drug usage, stress, the age of first use, social pressures, and trauma. A substance-use disorder is not developed in all people who use drugs legal or otherwise; it is also known that not every condition that leads to chronic pain in some leads to chronic pain in others. Due to some neuro-circuitry commonalities of substance-use disorder and chronic pain, it

may be merited to view chronic pain as a disease state that may be a predisposed disease based upon the biopsychosocial model of illness.

Dr. Beecher well studied the impact of the state of mind on pain during WWII. He observed a, "puzzlingly low incidence of pain" (Beecher 1946) while tending to soldiers with wounds that had been experienced in the heat of combat. This battlefield analgesia led researchers to study and understand the relationship between psychology and the mechanisms of endogenous pain suppression. Several psychological factors have been identified as very predictive of experiencing long-term pain: catastrophizing, pain-related anxiety and fear, and helplessness (Keefe et al. 2004). Catastrophizing is focusing on pain and evaluating one's ability to cope with that pain (Keefe et al. 2004); this has been studied and shown to impact the pain related disability associated with chronic pain (Turner et al. 2002). Both pain-related anxiety (McCraken et al. 1992) and helplessness (Nicassio et al. 1993) have shown similar outcomes in studies indicating the significant impact that predictive psychological components have on pain going from acute to chronic.

These psychological factors are finding more evidence from a neurobiological perspective. The endogenous analgesia system was tested in patients before thoracotomy surgery using a diffuse noxious inhibitory control test system. The researchers found that patients with more efficient systems were less likely to experience chronic post-operative pain (Yarnitsky et al. 2008). Similar to other centrally operating systems, there seems to be individual variability in the degree of pain suppression. Perhaps, there may be more testable factors that could impact the predictability of chronic pain in patients.

Treatment Options for Chronic Pain

Whether prescription opioids, alcohol, or other analgesia inducing substances, chronic pain sufferers as aforementioned seem especially susceptible to the biopsychosocial model of addiction. That being mentioned, the treatment options of chronic pain often include pharmacological interventions. The pharmacological interventions include: non-opioid analgesics, tramadol, antidepressants, opioid analgesics anticonvulsants, skeletal muscle relaxants, and topical analgesics (Park & Moon 2010). Each of these pharmacological treatments needs to be implemented accounting for factors such as age, severity of pain, type of pain, and other factors generally needed in prescribing drug therapies (Park & Moon 2010). Once again, due to the prevalence of the opioid crisis, pharmacotherapies recently have attempted to supplement opioids or use other therapies in conjunction with opioid use (Tompkins et al. 2017). That conjunction therapy may include psychological interventions or osteopathic manipulative medicine approaches. In a study examining operative morphine use, post-operative osteopathic manipulative techniques were found to enhance the morphine analgesia, thereby reducing post-operation analgesic use (Goldstein 2005).

As discussed, the psychological afflictions of chronic pain are varied and seem to be a component of the chronicity of the pain themselves (Borsook et al. 2016). Evidence-based treatments of the psychological aspects of chronic pain sway towards cognitive behavioral therapies (Turk et al. 2008). The chief psychological afflictions which may exacerbate, predispose, or be symptomatic of chronic pain have earlier been discussed such as feelings of helplessness, catastrophizing, and dependence. These feelings may be helped or overcome by using cognitive behavioral approaches of varying techniques, but

within the frame of cognitive behavioral therapy; which are, "techniques…geared to fostering self-control and self-management that will encourage a patient to replace their feelings of passivity, dependence, and hopelessness with activity, independence, and resourcefulness" (Turk et al. 2008).

In cases of extraordinarily, chronic and severe pain surgery may be the final option in the tiers of chronic pain treatment. As discussed earlier, the anterior cingular cortex is a critical site in pain processing, and the neurosurgical intervention of anterior cingulotomies have been conducted in cases of chronic intractable pain (Sharim & Pouratian 2016). Other surgical interventions may include implantable devices, which involves electrodes in the spine, which can change the pain processing experienced by an individual (Turk, Wilson & Cahana 2011).

Overall the most effective management systems of chronic pain seem to be multifaceted, including psychological and physical rehabilitation in combination with a pharmaceutical and surgical intervention (Turk, Wilson & Cahana).

Conclusion

This review only captures the tip of the pain iceberg as numerous studies are published monthly related to this critical healthcare topic. There most likely will be new findings by the time this review is published, but the hope is that a bigger picture has been formed in this devasting condition. From a systems level to synaptic protein complexes, there seems to be some level of peripheral and cortical change that develops as one is put repeatedly in pain states. This repetition of pain produces undesirable physical and psychological outcomes for those that suffer this condition, yet this condition is not experienced entirely similar among intragroup pain populations.

Further similar physical insults such as sciatic dysfunction or diabetic neuropathy do not always manifest chronically once primary care is taken, which calls into question predisposing risk factors to developing chronic pain. Again, in combination with the physical attributes of allodynia and hyperalgesia, these two symptoms appear psychologically in reference to emotional stressors and pain-related anxiety. The combined reward deficiency anti-reward model helps explain many of the attributes that develop in chronic pain in a systemic sense, although more experimental evidence is required to understand the opponents' process theory in biological terms fully.

As more knowledge in the field of neuroplasticity emerges perhaps more understanding of the detrimental plastic changes that occur in the central nervous system under chronic pain will give way to more tailored treatment options. In the meantime, it seems a combination of pharmaceutical and psychological interventions are the primary means of helping individuals with this common condition. As a society, it would be in the best interests of everyone to invest in understanding chronic pan to lessen the emotional and financial burden that this current healthcare climate is experiencing. Not just from the perspective of sufferers of pain, but those who have been causalities in the opioid crisis partially formed from efforts to relieve society from experiencing the hardships of pain.

References

Averitt, D. L., Eidson, L. N., Doyle, H. H., & Murphy, A. Z. (2019). Neuronal and glial factors contributing to sex differences in opioid modulation of pain. *Neuropsychopharmacology: Official Publication Of The American College Of Neuropsychopharmacology*, *44*(1), 155–165. https://doi.org/10.1038/s41386-018-0127-4

Becker, S., Gandhi, W., & Schweinhardt, P. (2012). Cerebral interactions of pain and reward and their relevance for chronic pain. *Neuroscience Letters*, *520*(2), 182-187. doi: 10.1016/j.neulet.2012.03.013

Beecher, HK Pain in men wounded in battle.. *Ann Surg*. (1946). *123* 96–105

Bianco, I. H., & Wilson, S. W. (2009). The habenular nuclei: a conserved asymmetric relay station in the vertebrate brain. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, *364*(1519), 1005–1020. doi:10.1098/rstb.2008.0213

Boadas-Vaello, P., Homs, J., Reina, F., Carrera, A., & Verdú, E. (2017). Neuroplasticity of Supraspinal Structures Associated with Pathological Pain. *The Anatomical Record*, *300*(8), 1481-1501. doi: 10.1002/ar.23587

Bodnar, R. J. (2017). Review: Endogenous Opiates and Behavior: 2015. *Peptides*, *88*, 126–188. https://doi.org/10.1016/j.peptides.2016.12.004

Borsook, D., Linnman, C., Faria, V., Strassman, A., Becerra, L., & Elman, I. (2016). Reward deficiency and anti-reward in pain chronification. *Neuroscience & Biobehavioral Reviews*, *68*, 282-297. doi: 10.1016/j.neubiorev.2016.05.033

Bliss, T., Collingridge, G., Kaang, B., & Zhuo, M. (2016). Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. *Nature Reviews Neuroscience*, *17*(8), 485-496. doi: 10.1038/nrn.2016.68

Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature. 1993;361:31–39. doi: 10.1038/361031a0

Chiesa, A. & Serretti, A. (2014) Are Mindfulness-Based Interventions Effective for Substance Use Disorders? A Systematic Review of the Evidence, Substance Use & Misuse,49:5, 492-512, DOI: 10.3109/10826084.2013.770027

Elman, I., Karlsgodt, K. H., Gastfriend, D. R., Chabris, C. F., & Breiter, H. C. (2002). Cocaine-primed craving and its relationship to depressive symptomatology in individuals with cocaine dependence. *Journal of Psychopharmacology*, *16*(2), 163–167.

Elman, I., & Borsook, D. (2016). Common Brain Mechanisms of Chronic Pain and Addiction. *Neuron*, *89*(1), 11-36. doi: 10.1016/j.neuron.2015.11.027

Elman, I., Borsook, D., and Volkow, N.D. (2013). Pain and suicidality: insights from reward and addiction neuroscience. Prog. Neurobiol. *109*, 1–27.

Fuchs, P. N., Peng, Y. B., Boyette-Davis, J. A., & Uhelski, M. L. (2014). The anterior cingulate cortex and pain processing. *Frontiers in integrative neuroscience*, *8*, 35. doi:10.3389/fnint.2014.00035

Garcia-Recio, S., & Gascón, P. (2015). Biological and Pharmacological Aspects of the NK1-Receptor. *BioMed research international*, *2015*, 495704. doi:10.1155/2015/495704

Genie, B., & Kevin, H. (2018). Opioid Use Disorder: Challenges and Solutions to a Rising Epidemic. *Current Psychiatry*, *17*(4), S1-S18.

Ghitza, U. (2016). Overlapping Mechanisms of Stress-Induced Relapse to Opioid Use Disorder and Chronic Pain: Clinical Implications. *Frontiers In Psychiatry*, *7*. doi: 10.3389/fpsyt.2016.00080

Goldstein, F., Geck, S., Nicholas, A., Berman, M., & Lerario, M. (2005). Preoperative Intravenous Morphine Sulfate With Postoperative Osteopathic Manipulative Treatment Reduces Patient Analgesic Use After Total Abdominal Hysterectomy. *JAOA*, *105*(6), 273-279.

Goldstein, F (2019, Jan. 9). Personal Interview. Philadelphia College of Osteopathic Medicine

Grant BF, Stinson FS, Dawson DA, et al. 2004. Prevalence and Co-occurrence of Substance Use Disorders and IndependentMood and Anxiety DisordersResults From the National Epidemiologic Survey on Alcohol and RelatedConditions. *Arch Gen Psychiatry.* ;61(8):807–816. doi:10.1001/archpsyc.61.8.807

Grichnik KP, Ferrante FM. The difference between acute and chronic pain. Mt Sinai J Med1991;583:217–20.

Institute of Medicine Report from the Committee on Advancing Pain Research, Care, and Education: *Relieving Pain in America, A Blueprint for Transforming Prevention, Care, Education and Research*. The National Academies Press, 2011.

Keefe FJ, Rumble ME, Scipio CD, Giordano LA, Caitlin L, Perri M. 2004 Psychological Aspects of persistent Pain: Current state of the science. Journal of Pain. ;4:195–211

Lecca, S., Meye, F. J., & Mameli, M. (2014). The lateral habenula in addiction and depression: an anatomical, synaptic and behavioral overview. *European Journal of Neuroscience*, *39*(7), 1170–1178. https://doi.org/10.1111/ejn.12480

Li, J., Wu, M., Zhuo, M., & Xu, Z. C. (2013). Alteration of neuronal activity after digit amputation in rat anterior cingulate cortex. *International journal of physiology, pathophysiology and pharmacology*, *5*(1), 43–51.

Li XH, Miao HH, Zhuo M. NMDA Receptor Dependent Long-term Potentiation in Chronic Pain. *Neurochem Res*. 2018;44(3):531–538. doi:10.1007/s11064-018-2614-8

Liu X.-G., Sandkühler J. (1997). **Characterization of long-term potentiation of C-fiber-evoked potentials in spinal cord dorsal horn of adult rat: essential role of NK1 and NK2 receptors.** *J. Neurophysiol*., 78 pp. 1973-1982

Lu, C., Yang, T., Zhao, H., Zhang, M., Meng, F., Fu, H., … Xu, H. (2016). Insular Cortex is Critical for the Perception, Modulation, and Chronification of Pain. *Neuroscience bulletin*, *32*(2), 191–201. doi:10.1007/s12264-016-0016-y

McCracken L.M , Zayfert C, Gross T.**The Pain Anxiety Symptoms Scale: Development and validation of a scale to measure fear of pain.** *Pain*, 50 (1992), pp. 67-73

McEwen BS, Stellar E. Stress and the IndividualMechanisms Leading to Disease. *Arch Intern Med.*1993;153(18):2093–2101. doi:10.1001/archinte.1993.00410180039004

McWilliams, L., Cox, B., & Enns, M. (2003). Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. *Pain*, *106*(1), 127-133. doi: 10.1016/s0304-3959(03)00301-4

Morley, S., Eccleston, C., & Williams, A. (1999). Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain*, *80*(1), 1-13. doi: 10.1016/s0304-3959(98)00255-3

Navratilova, E., Morimura, K., Xie, J., Atcherley, C., Ossipov, M., & Porreca, F. (2016). Positive emotions and brain reward circuits in chronic pain. *Journal Of Comparative Neurology*, *524*(8), 1646-1652. doi: 10.1002/cne.23968

Nicassio P, Radojevic V, Weisman M, Culbertson A, Lewis C, Clemmy P. **The role of helpnessness in the response to disease modifying drugs in rheumatoid arthritis** *J Rheumatol*, 20 (1993), pp. 1114-1120

Nicholls, J., Martin, A., Fuchs, P., Brown, D., Diamond, M., & Weisblat, D. (2012). *From neuron to brain* (5th ed.). Sunderland, MA: Sinauer Associates.

Opioid Overdose Crisis. (2018). Retrieved from https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis

Ossipov, M. H., Dussor, G. O., & Porreca, F. (2010). Central modulation of pain. *The Journal of clinical investigation*, *120*(11), 3779-87.

Park, H. J., & Moon, D. E. (2010). Pharmacologic management of chronic pain. *The Korean journal of pain*, *23*(2), 99–108. doi:10.3344/kjp.2010.23.2.99

Pasternak, Gavril W. 2005. Molecular Biology of Opioid Analgesia. *Journal of Pain and Symptom Management* , Volume 29 , Issue 5 , 2 – 9

Ruscheweyh, R., Wilder-Smith, O., Drdla, R., Liu, X. G., & Sandkühler, J. (2011). Long-term potentiation in spinal nociceptive pathways as a novel target for pain therapy. *Molecular pain*, *7*, 20. doi:10.1186/1744-8069-7-20

Scott J. Thompsona,b, Mark H. Pitchera,*, Laura S. Stoneb, Farid Taruma, Gang Niuc, Xiaoyuan Chenc, Dale O. Kiesewetterc, Petra Schweinhardtb, M. Catherine Bushnella (Pain, (2018)

Severino, A., Wenling Chen, Hakimian, J. K., Kieffer, B. L., Gaveriaux-Ruff, C., Walwyn, W., … Chen, W. (2018). Mu-opioid receptors in nociceptive afferents produce a sustained suppression of hyperalgesia in chronic pain. *Pain (03043959)*, *159*(8), 1607–1620. https://doi.org/10.1097/j.pain.0000000000001247

Sharim J. Pouratian N. (2016). Anterior Cingulotomy for the Treatment of Chronic Intractable Pain: A Systematic Review. *Pain Physician.* 19(8):537-550.

Shelton, L., Becerra, L., & Borsook, D. (2012). Unmasking the mysteries of the habenula in pain and analgesia. *Progress In Neurobiology*, *96*(2), 208-219. doi: 10.1016/j.pneurobio.2012.01.004

Strauber, R. (22 February 2019). *Intervention Theories and Practices.* Presented at the Recovery Centers of America Continuing Education Event-Interventions Theories and Practices. Mays Landing, NJ

Stopper, C. M., & Floresco, S. B. (2014). What's better for me? Fundamental role for lateral habenula in promoting subjective decision biases. *Nature Neuroscience*, *17*(1), 33–35. https://doi.org/10.1038/nn.3587

Taylor, A. M., Castonguay, A., Taylor, A. J., Murphy, N. P., Ghogha, A., Cook, C., … Cahill, C. M. (2015). Microglia disrupt mesolimbic reward circuitry in chronic pain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *35*(22), 8442–8450. doi:10.1523/JNEUROSCI.4036-14.2015

Tompkins, D. A., Hobelmann, J. G., & Compton, P. (2017). Providing chronic pain management in the "Fifth Vital Sign" Era: Historical and treatment perspectives on a modern-day medical dilemma. *Drug and alcohol dependence*, *173 Suppl 1*(Suppl 1), S11–S21. doi:10.1016/j.drugalcdep.2016.12.002

Turk, D. C., Swanson, K. S., & Tunks, E. R. (2008). Psychological Approaches in the Treatment of Chronic Pain Patients—When Pills, Scalpels, and Needles are Not Enough. *The Canadian Journal of Psychiatry*, *53*(4), 213–223.
Turk, D., Wilson, H., & Cahana, A. (2011). Treatment of chronic non-cancer pain. *The Lancet*, *377*(9784), 2226-2235. doi: 10.1016/s0140-6736(11)60402-9

Turner J, Jensen M, Warms C, Cardenas D. Catastrophizing is associated with pain intensity, psychological distress, and pain-related disability among individuals with chronic pain after spinal cord injury**.** *Pain*, 98 (2002), pp. 127-134

Uddin, L. Q., Nomi, J. S., Hébert-Seropian, B., Ghaziri, J., & Boucher, O. (2017). Structure and Function of the Human Insula. *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society*, *34*(4), 300–306. doi:10.1097/WNP.0000000000000377

Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain*. 2015;156(4):569-576. doi:10.1097/01.j.pain.0000460357.01998.f1.

What Is Cognitive Behavioral Therapy?. (2018). Retrieved from https://www.apa.org/ptsd-guideline/patients-and-families/cognitive-behavioral.aspx

Willis, W. (2002). Long-term potentiation in spinothalamic neurons. *Brain Research Reviews*, *40*(1-3), 202-214. doi: 10.1016/s0165-0173(02)00202-3

Yarnitsky, D., Crispel, Y., Eisenberg, E., Granovsky, Y., Ben-Nun, A., Sprecher, E., . . . Granot, M. (2008). Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. *Pain,138*(1), 22-28. doi:10.1016/j.pain.2007.10.033

Zhuo M. 2014. Long-term potentiation in the anterior cingulate cortex and chronic pain. *Philos Trans R Soc Lond B Biol Sci*.;369(1633):20130146. Published . doi:10.1098/rstb.2013.0146

Zhuo, M. (2016). Contribution of synaptic plasticity in the insular cortex to chronic pain. *Neuroscience*, *338*, 220-229. doi: 10.1016/j.neuroscience.2016.08.014