PainWeek®

3 Doors, Lost Keys:
Managing Sleep, Depression, and Chronic Pain

Gary W. Jay, MD, FAAPM

Title and Affiliation

Gary W. Jay, MD, FAAPM
Clinical Professor, Department of Neurology
Division: Headache/Pain
University of North Carolina
Chapel Hill, NC

Disclosure

- Advisory Board: Kalyra Pharma, Creative Biopeptides

Learning Objectives - 3 Doors, Lost Keys

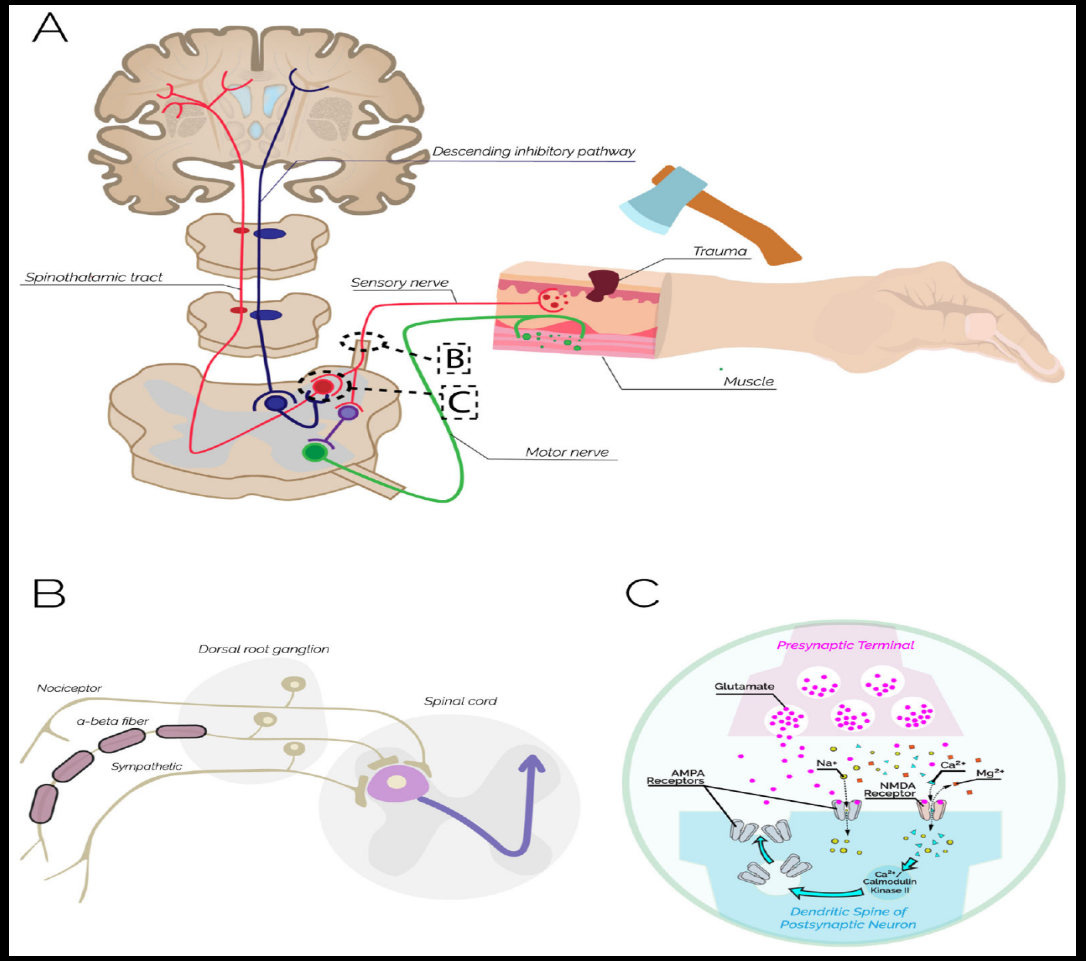
- Describe the inter-relationship of chronic pain, depression and sleep
- Summarize these issues as seen in central sensitivity syndromes
- Review the relationship of chronic pain, depression and sleep to help treatment of these patients
- List the similarities of the neurobiology of chronic pain, depression and sleep

Pain

Let's Look At:

- Let's look at two common forms of pain
  - Chronic Low Back Pain- Musculoskeletal (has many diagnoses, we will look at a MSK Dx)
  - Neuropathic pain- It is the result of nerve damage in the peripheral or central nervous system
- Both are chronic and therefore are biological-psychological-sociological (tripartite) diatheses

You Know this about Pain



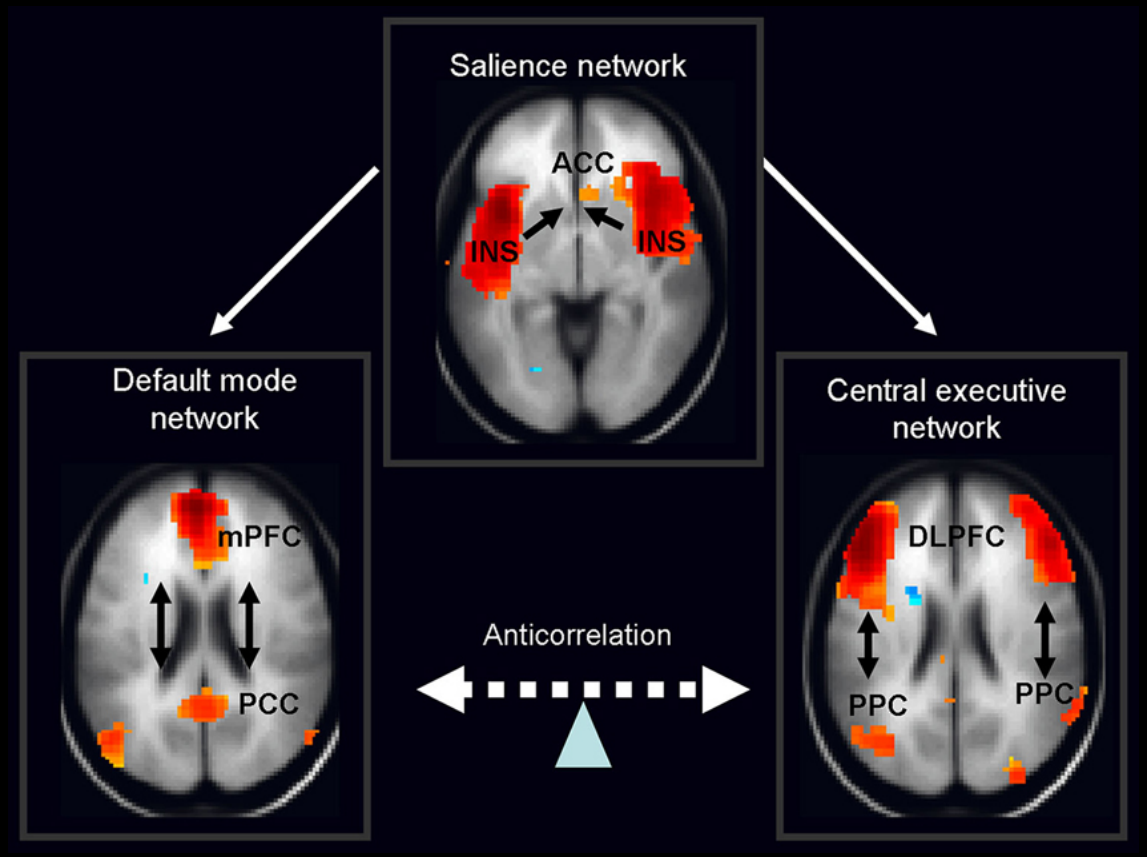
- The human body is designed to experience pain that is a response to a direct threat, like a blow from a hammer. (A) We first experience a fast, unconscious reflex, then we become aware of pain as the sensory fiber synapses on a second neuron in the dorsal horn, the second neuron crosses the midline, ascends in the spinothalamic tract, synapses in the thalamus, from which the signal is relayed to the cortex, and lastly, we can dampen the pain through a descending pathway that leads to the release of enkephalins at the level of the dorsal horn. Pain experienced over a long period of time can cause rewiring and remodeling of the nervous system, leading to the chronic pain syndrome. (B) When a pain fiber is damaged, growth factors released by macrophages at the site of the injury cause nonspecific sprouting of other axon types that can become aberrantly connected to the same cell body in the dorsal horn, allowing nonpainful stimuli to be interpreted as pain. (C) At the level of the synapse, prolonged stimulation of the C fiber leads to increased release of presynaptic glutamate, activation of the postsynaptic AMPA receptors, depolarization of the postsynaptic neuron, expulsion of Mg2+ that was previously blocking the NMDA receptor channel, calcium flux into the cell triggering the activation of second messengers and gene transcription, and ultimately the docking of more AMPA receptors on the postsynaptic cell membrane. This increase in AMPA receptors strengthens the connection between the peripheral and central nervous system and enhances future signal transmission. AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; NMDA, N-methyl-D-aspartate.

Baller EB, Ross DA. Your system has been hijacked: the neurobiology of chronic pain. Biol Psychiatry 2017; 82(8): e.61-.-63. doi:10.1016/j.biopsych.2017.08.009.

Chronic Pain-1

- Molecularly, chronic pain syndromes begin as hypersensitization within the spinal cord dorsal horn- this is called central sensitization.
  - This is associated with upregulation of ionotropic and metabotropic glutamate receptors (mGluRs), similar to long-term potentiation (LTP)
    - LTP occurs in regions of the brain including the amygdala and hippocampus, which are also part of the memory- and fear- related cerebral circuitry
    - Patients with chronic pain may develop pain-related anxiety and pain-related fear
    - On a molecular level, central sensitization may be reversed via degradative glutamate receptor pathways, but this is rare-
      - Cortical brain regions serve in a regulatory capacity for the maintenance or alleviation of pain.
  - CP alters functional connectivity in the default-mode network (DMN) and salience network
    - The medial prefrontal cortex (mPFC), critical to fear-related brain circuits, the DMN and salience network may be driving forces in this process

Salience Network

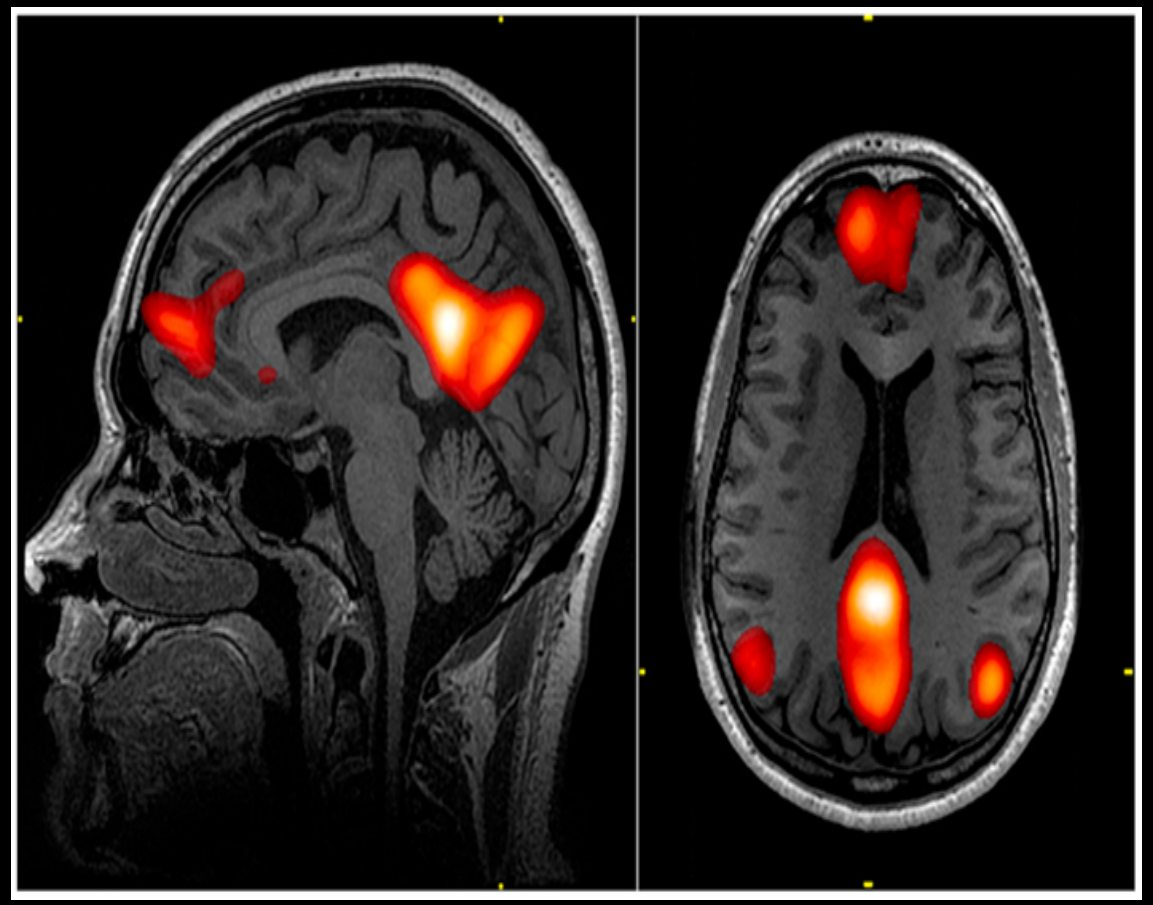


- The salience network (SN) is a large-scale brain network of the human brain that is primarily composed of the anterior insula (AI) and dorsal anterior cingulate cortex (dACC). It is involved in detecting and filtering salient stimuli, as well as in recruiting relevant functional networks. Together with its interconnected brain networks, the SN contributes to a variety of complex functions, including communication, social behavior, and self-awareness through the integration of sensory, emotional, and cognitive information.
- The network is detectable through independent component analysis of resting state fMRI images, as well as seed-based functional connectivity analysis. In addition to the AI and dACC, the salience network also consists of the substantia nigra, ventral tegmental area, ventral striatum, amygdala, dorsomedial thalamus, and hypothalamus. The functional connectivity has been linked with structural connectivity through diffusion tensor imaging, which reveals white matter tracts between the AI and dACC.

Menon, V; Uddin, LQ (June 2010). "Saliency, switching, attention and control: a network model of insula function". Brain Structure & Function. 214 (5–6): 655–67. doi:10.1007/s00429-010-0262-0.
Menon V. (2015) Salience Network. In: Arthur W. Toga, editor. Brain Mapping: An Encyclopedic Reference, vol. 2, pp. 597-611. Academic Press: Elsevier.
https://med.stanford.edu/content/dam/sm/scsnl/documents/Menon_Salience_Network_15.pdf Peters, SK; Dunlop, K; Downar, J (2016). "Cortico-Striatal-Thalamic Loop Circuits of the Salience Network: A Central Pathway in Psychiatric Disease and Treatment". Frontiers in Systems Neuroscience. 10: 104. doi:10.3389/fnsys.2016.00104

Nekovarova, Fajnerova, Horacek, Spaniel - Bridging disparate symptoms of schizophrenia: a triple network dysfunction theory, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=62546913

Default-Mode Network- Anatomy



- Posterior cingulate cortex (PCC) & precuneus: Combines bottom-up (not controlled) attention with information from memory and perception. The ventral (lower) part of PCC activates in all tasks which involve the DMN including those related to the self, related to others, remembering the past, thinking about future, and processing concepts plus spatial navigation. The dorsal (upper) part of PCC involves involuntary awareness and arousal. The precuneus is involved in visual, sensorimotor, and attentional information.
- Medial prefrontal cortex (mPFC): Decisions about self processing such as personal information, autobiographical memories, future goals and events, and decision making regarding those personally very close such as family. The ventral (lower) part is involved in positive emotional information and internally valued reward.
- Angular gyrus: Connects perception, attention, spatial cognition, and action and helps with parts of recall of episodic memories
- Dorsal medial subsystem: Thinking about others

- Functional hubs: PCC, mPFC, and angular gyrus
- Dorsal medial prefrontal cortex (dmPFC): Involved in social directed thought such as determining or inferring the purpose of others' actions
- Temporoparietal junction (TPJ): Reflects on beliefs about others, also known as theory of mind
- Lateral temporal cortex: Retrieval of social semantic and conceptual knowledge
- Anterior temporal pole: Abstract conceptual information particularly social in nature
- Medial temporal subsystem: Autobiographical memory and future simulations

- Functional hubs: PCC, mPFC, and angular gyrus
- Hippocampus (HF+): Formation of new memories as well as remembering the past and imagining the future
- Parahippocampus (PHC): Spatial and scene recognition and simulation
- Retrosplenial cortex (RSC): Spatial navigation
- Posterior inferior parietal lobe (pIPL): Junction of auditory, visual, and somatosensory information and attention

Andrews-Hanna, Jessica R.; Smallwood, Jonathan; Spreng, R. Nathan . "The default network and self-generated thought: component processes, dynamic control, and clinical relevance". Annals of the New York Academy of Sciences. 2014; 1316 (1): 29–52. Bibcode:2014NYASA1316...29A. doi:10.1111/nyas.12360

John Graner, Neuroimaging Department, National Intrepid Center of Excellence, Walter Reed National Military Medical Center, 8901 Wisconsin Avenue, Bethesda, MD 20889, USA. - http://www.frontiersin.org/Neurotrauma/10.3389/fneur.2013.00016/full, Public Domain, https://commons.wikimedia.org/w/index.php?curid=25872800

Default-Mode Network- Function

- In neuroscience, the default mode network (DMN), is a large-scale brain network best known to be active when a person is not focused on the outside world and the brain is at wakeful rest, such as during daydreaming and mind-wandering. It can also be active during detailed thoughts related to external task performance. Other times that the DMN is active include when the individual is thinking about others, thinking about themselves, remembering the past, and planning for the future.
- Though the DMN was originally noticed to be deactivated in certain goal-oriented tasks and is sometimes referred to as the task-negative network it can be active in other goal-oriented tasks such as social working memory or autobiographical tasks The DMN has been shown to be negatively correlated with other networks in the brain such as attention networks

Buckner, R. L.; Andrews-Hanna, J. R.; Schacter, D. L. "The Brain's Default Network: Anatomy, Function, and Relevance to Disease". Annals of the New York Academy of Sciences. 2008; 1124 (1): 1–38. Fox, Michael D.; Snyder, Abraham Z.; Vincent, Justin L.; Corbetta, Maurizio; Van Essen, David C.; Raichle, Marcus E. "The human brain is intrinsically organized into dynamic, anticorrelated functional networks". Proceedings of the National Academy of Sciences of the United States of America. 2005;102 (27): 9673–9678. Broyd, Samantha J.; Demanuele, Charmaine; Debener, Stefan; Helps, Suzannah K.; James, Christopher J.; Sonuga-Barke, Edmund J. S. "Default-mode brain dysfunction in mental disorders: A systematic review". Neuroscience & Biobehavioral Reviews. 2009; 33 (3): 279–96. Sormaz, Mladen; Murphy, Charlotte; Wang, Hao-Ting; Hymers, Mark; Karapanagiotidis, Theodoros; Poerio, Giulia; Margulies, Daniel S.; Jefferies, Elizabeth; Smallwood, Jonathan. "Default mode network can support the level of detail in experience during active task states". Proceedings of the National Academy of Sciences. 2018; 115 (37): 9318–9323.

Chronic Pain-2

- The mPFC may form new neural circuits through the long-term potentiation (LTP) that may cause extinction of pre-existing pain pathways found in the fear-related brain circuits, and DMN and the salience network

Central Sensitization-4

- Chronic pain is also modulated by glial cells, specifically astrocytes and microglia
  - Increased astroglial activity enhances the release of excitatory neurochemicals such as proinflammatory cytokines and glutamate precursors and affects chronic pain by its influence on nociceptive input and the recycling of glutamate
  - Astroglial cells convert extracellular glutamate into glutamine, and provide presynaptic neurons with the ingredients needed to continue to produce glutamate
  - Astroglial activity produces pro-inflammatory cytokines which increase nociceptor activity
  - Activation of microglial cells mediates neuronal excitability by the reversal of inhibitory effect of GABA
  - After neuronal injury, activated microglia release brain derived neurotrophic factor (BDNF) which downregulates KCC2 in the SC Dorsal horn, facilitating central sensitization via GABA excitation

Guo, W., Wang, H., Watanabe, M., Shimizu, K., Zou, S., LaGraize, S. C., et al. Glial-cytokine-neuronal interactions underlying the mechanisms of persistent pain. J. Neurosci. 2007; 27:6006–6018; Milligan, E. D., and Watkins, L. R. Pathological and protective roles of glia in chronic pain. Nat. Rev. Neurosci. 2009; 10: 23–36; Broer, A., Deitmer, J. W., and Broer, S. Astroglial glutamine transport by system N is upregulated by glutamate. Glia 2004’ 48: 298–310; Chiang, C. Y., Dostrovsky, J. O., Iwata, K., and Sessle, B. J. Role of glia in orofacial pain. Neuroscientist 2011; 17: 303–320; Zhang, J. M., and An, J. Cytokines, inflammation, and pain. Int. Anesthesiol. Clin. 2007; 45: 27–37; Uçeyler, N., Schäfers, M., and Sommer, C. Mode of action of cytokines on nociceptive neurons. Exp. Brain Res. 2009; 196:67–78

Central Sensitization-5

- Regardless of glial cell activation and recycling of glutamate via the glutamate-glutamine changes, ionotropic and mGluRs undergo degradative pathways
- Research has shown that degradative pathways also exist for NMDArs, Kianate receptors and mGluRs
- Therefore- critical receptors involved in central sensitization undergo degradation
  - HOWEVER- if receptor degradation were the primary mechanism that could reverse central sensitization over time, chronic pain would abate with time- BUT IT TYPICALLY DOES NOT

Scott, D. B., Michailidis, I., Mu, Y., Logothetis, D., and Ehlers, M. D. Endocytosis and degradative sorting of NMDA receptors by conserved membrane-proximal signals. J. Neurosci. 2004; 24:7096–7109; Ehlers, M. D. Reinsertion or degradation of AMPA receptors determined by activity-dependent endocytic sorting. Neuron 2000; 28: 511–525; Lerma, J., and Marques, J. M. Kainate receptors in health and disease. Neuron 2013: 80: 292–311; Latremoliere, A., and Woolf, C. J. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J. Pain 2009; 10: 895–926; Klein, M. E., Castillo, P. E., and Jordan, B. A. Coordination between translation and degradation regulates inducibility of mGluR-LTD. Cell Rep. 2015; 9: 1459–1466

Central Sensitization-6

- Central sensitization occurs by heterosynaptic facilitation.
- Central sensitization is not the same as windup, which is secondary to homosynaptic facilitation
  - Windup is secondary to increased magnitude of incoming C-fiber activation and is associated with hyperalgesia and allodynia
    - With central sensitization, neurons at the SC Dorsal horn respond to a lower threshold to peripheral inputs, with increased receptive fields and increased rates of spontaneous firing
      - These structural and functional changes help explain why chronic pain patients experience allodynia and secondary hyperalgesia
    - This appears similar to both the molecular and cellular changes that occur during long-term potentiation (LTP) in cortical and subcortical brain regions
      - Similar processes may be occurring in spinal structures and in cortical/subcortical regions that drive the change from acute to chronic pain

Rygh, L. J., Svendsen, F., Fiskå, A., Haugan, F., Hole, K., and Tjølsen, A. Long-term potentiation in spinal nociceptive systems—how acute pain may become chronic. Psychoneuroendocrinology 2005; 30:959–964; Latremoliere, A., and Woolf, C. J. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J. Pain 2009; 10: 895–926; Woolf, C. J. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011; 152; S2–S15; Campbell, J. N., and Meyer, R. A. Mechanisms of neuropathic pain. Neuron 2006; 52: 77–92; Sandkühler, J. Understanding LTP in pain pathways. Mol. Pain 2007; 3:9; Ji, R. R., Kohno, T., Moore, K. A., and Woolf, C. J. Central sensitization and LTP: do pain and memory share similar mechanisms? Trends Neurosci. 2003; 26:696–705.

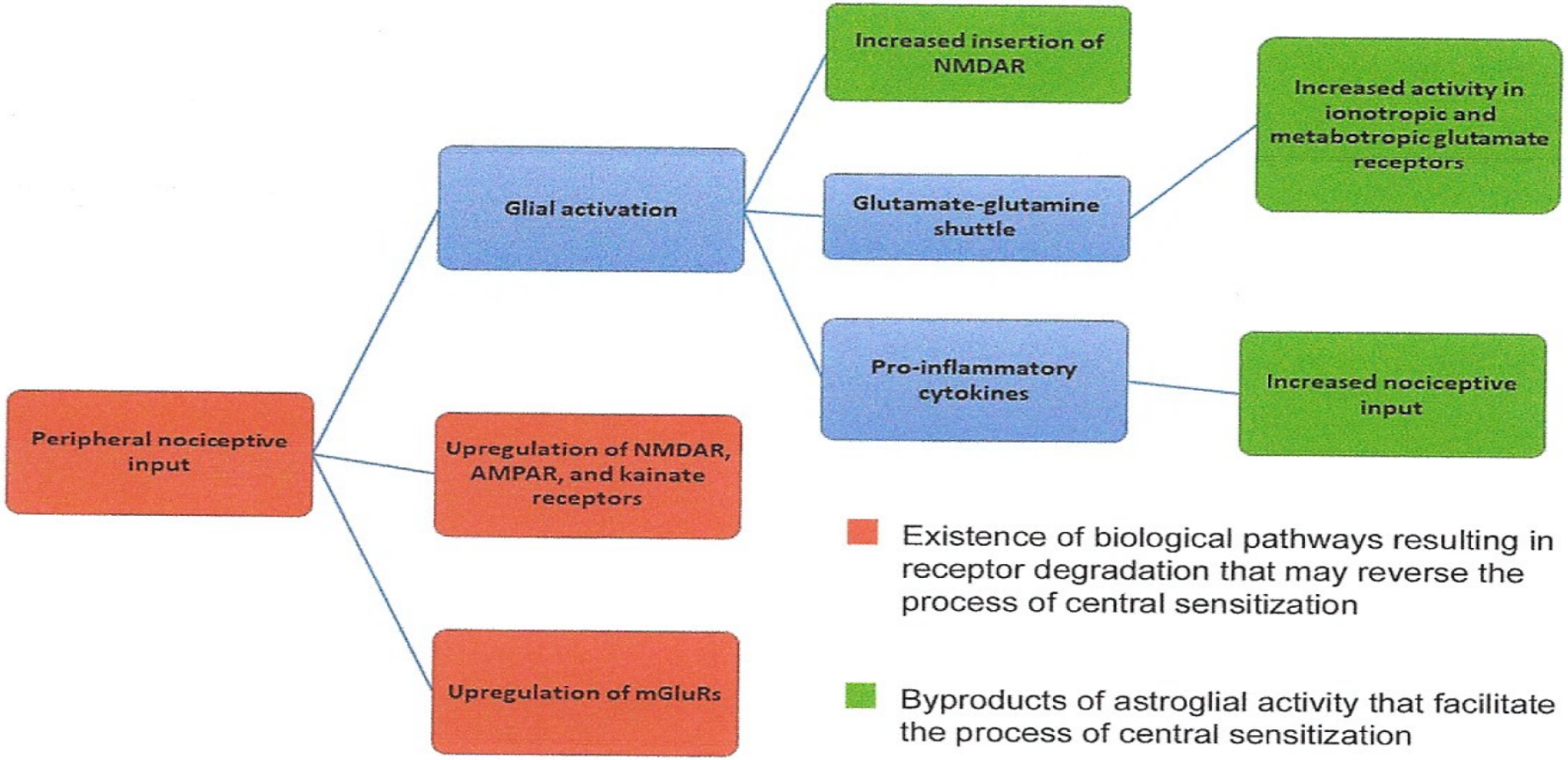


FIGURE 1 | Mechanism for central sensitization. Central sensitization (central nervous system hypersensitivity) is initiated from the upregulation of ionotropic glutamate receptors (NMDAR, AMPAR, kainite receptors) and metabotropic glutamate receptors (mGluRs) in the presence of peripheral nociceptive input. As a result, neurons in the dorsal horn of the spinal cord and central nervous system respond to nociceptive input at lower thresholds, with new enlarged receptor fields, and undergo increased rates of spontaneous firing. Glial activation can further maintain the mechanisms underlying central sensitization by increasing NMDAR and AMPAR insertion in postsynaptic membranes. Glial cells release pro-inflammatory cytokines, serving as further nociceptive input. Astroglial cells also help to maintain glutamate levels via the glutamate-glutamine shuttle, which can influence both ionotropic and mGluR activity. As shown in red, ionotropic, metabotropic receptors and nociceptors are capable of being degraded. Given that degradative pathways exist, the process of central sensitization can be reversed. Activity by astroglial cells, however, may mitigate the effects of receptor degradation by upregulating and facilitating the process of central sensitization. Given that central sensitization does not reverse itself with time, it seems that astroglial activity overpowers the existence of degradative receptor pathways.

Greenwald JD and Shafritz KM (2018) An Integrative Neuroscience Framework for the Treatment of Chronic Pain: From Cellular Alterations to Behavior. Front. Integr. Neurosci. 12:18. doi: 10.3389/fnint.2018.00018

Treatment- General

- ACM
- ADM
- Pain Medication (inc. opioid)

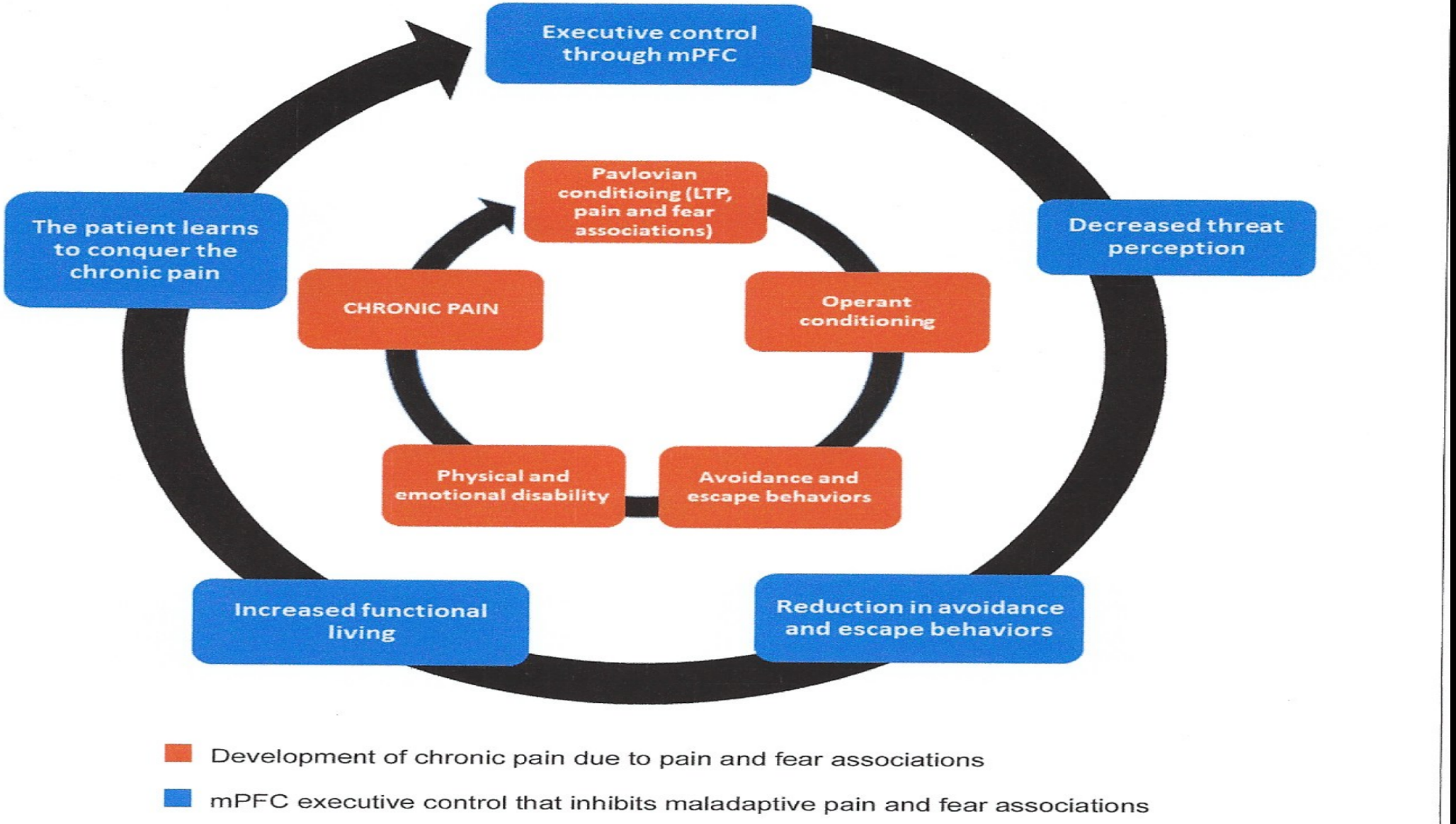


FIGURE 2 | Mind-body approach to healing that promotes executive control originating from mPFC. The inner circle indicates the behavioral mechanisms underlying chronic pain. This approach to healing, grounded in cognitive reappraisal, mindfulness meditation, and functional rehabilitation, will promote new synaptic connections necessary for fear extinction (outer circle). Notice that the inner circle does not go away. Instead, by strengthening the components of the outer circle, the mPFC can exercise executive control by inhibiting maladaptive pathways (inner circle). As a result, chronic pain patients learn how to better cope with pain, in essence giving them the power to conquer the debilitating nature of their pain.

Greenwald JD and Shafritz KM (2018) An Integrative Neuroscience Framework for the Treatment of Chronic Pain: From Cellular Alterations to Behavior. Front. Integr. Neurosci. 12:18. doi: 10.3389/fnint.2018.00018

Depression

Comorbidity-1

- Co-occurrence rate of Major Depressive Disorder (MDD) and chronic pain has been reported to be 30%- 60%
  - Some forms of chronic pain like Fibromyalgia (FMG) have such a common incidence that the two conditions are considered:
    - Separate illnesses with high comorbidity
    - Different symptomatic manifestations of a single underlying condition
  - Cumulative evidence suggests that depression and chronic pain do not just co-occur, but one facilitates the development of the other, such that chronic pain is a strong predictor of subsequent onset of MDD and visa versa

Cho HJ, Skowera A, Cleare A, et al. Chronic fatigue syndrome: an update focusing on phenomenology and pathophysiology. Curr Opin Psychiatry. 2006;19(1):67-73; Bair MJ, Wu J, Damush TM, et al. Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. Psychosom Med. 2008;70(8):890-8

Comorbidity-2

- When CP and MDD coexist, they tend to make treatment of each more difficult
  - Pain presents a major obstacle to achieving remission when treating depression
  - A significant risk of relapse exists
- A 3-year longitudinal study showed that painful symptoms significantly reduced the chances of recovery in a group of older depressed patients
  - More patients with MDD alone attained recovery (47%) compared to 9% of patients with CP and MDD
  - A higher level of pain can delay remission when treating MDD, reducing the likelihood of an adequate or excellent outcome

Bair MJ, Robinson RL, Eckert GJ, et al. Impact of pain on depression treatment response in primary care. Psychosom Med. 2004;66(1):17-22; Fava M. Depression with physical symptoms: treating to remission. J Clin Psychiatry. 2003;64(suppl 7):24-28; Geerlings SW, Twisk JW, Beekman AT, et al. Longitudinal relationship between pain and depression in older adults: sex, age and physical disability. Soc Psychiatry Psychiatr Epidemiol. 2002;37(1):23-30; . Karp JF, Scott J, Houck P, et al. Pain predicts longer time to remission during treatment of recurrent depression. J Clin Psychiatry. 2005;66(5):591-597; . Ohayon MM. Specific characteristics of the pain/depression association in the general population. J Clin Psychiatry. 2004;65(suppl 12):5-9.

Comorbidity-3

- Comorbidity among chronic pain, mood disorders, anxiety disorders, sleep disorders, cognitive impairment, fatigue and chronic stress creates an enormous challenge to treat multiple types of chronic pain
  - They not only complicate the diagnosis of the conditions
  - They complicate and compromise treatment outcomes
  - They induce severe limitations on daily function and QOL of these patients (> 100M CP patients; 37% prevalence of CP in the population of 10 developed countries (WHO))

Bair MJ, Wu J, Damush TM, et al. Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. Psychosom Med. 2008;70(8):890-897; 7. Goldenberg DL. Pain/depression dyad: a key to a better understanding and treatment of functional somatic syndromes. Am J Med. 2010;123(8):675-682; Argoff CE. The coexistence of neuropathic pain, sleep, and psychiatric disorders: a novel treatment approach. Clin J Pain. 2007;23(1):15-22; Finan PH, Smith MT. The comorbidity of insomnia, chronic pain, and depression: dopamine as a putative mechanism. Sleep Med Rev. 2013;17(3):173-183: Senba E. A key to dissect the triad of insomnia, chronic pain, and depression. Neurosci Lett. 2015;589:197-199; Howe CQ, Robinson JP, Sullivan MD. Psychiatric and psychological perspectives on chronic pain. Phys Med Rehabil Clin N Am. 2015;26(2):283-300; Gerrits MM, van Marwijk HW, van Oppen P, et al. Longitudinal association between pain, and depression and anxiety over four years. J Psychosom Res. 2015;78(1): 64-70; Johannes CB, Le TK, Zhou X, et al. The prevalence of chronic pain in United States adults: results of an Internet-based survey. J Pain. 2010;11(11):1230-1239; Dzau VJ, Pizzo PA. Relieving pain in America: insights from an Institute of Medicine committee. JAMA. 2014;312(15):1507-1508.

Comorbidity-4

- Chronic pain increases the risk of MDD by 2- to 5-fold
  - The risk is mediated by the number of pain conditions, not the pain severity
  - Dose-response relationship between among pain, depression and anxiety
    - Patients with CP in 1 body regions, the prevalence of generalized anxiety disorder (GAD) and MDD was 30% and 20% respectively
    - In Patients who experienced pain in 2 or more regions the prevalence of GAD and MDD was increased to 54% and 32%
    - Patients with FMG were 4.3 times more likely than healthy controls to develop MDD and 4.7 times more likely to develop an anxiety disorder
      - Depression and anxiety are the most common comorbidities of FMG, with prevalence ranging from 20% to 80 % and 13% to 63.8% respectively

Howe CQ, Robinson JP, Sullivan MD. Psychiatric and psychological perspectives on chronic pain. Phys Med Rehabil Clin N Am. 2015;26(2):283-300; Manchikanti L, Pampati V, Beyer C, et al. Do number of pain conditions influence emotional status? Pain Physician. 2002;5(2):200-205; 7. Weir PT, Harlan GA, Nkoy FL, et al. The incidence of fibromyalgia and its associated comorbidities: a population based retrospective cohort study based on International Classification of Diseases, 9th Revision codes. J Clin Rheumatol. 2006;12(3):124-128; Fietta P, Fietta P, Manganelli P. Fibromyalgia and psychiatric disorders. Acta Biomed. 2007;78(2):88-95.

Comorbidity-5

- The relationship between depression and pain seen as bidirectional
  - Studies show that 30% to 60% of depressed patients also suffer from a painful condition
  - Pain more likely to be associated with greater fatigue, sleep disturbance which depletes a patient's ability to enjoy life and enhances negative affect.
- MDD and CP each have a significantly associated association with suicide attempts and completion
  - Consistent evidence suggests that people with CP have a 2 to 3-fold increase in the risk of suicide compared to healthy controls
  - A 20% lifetime prevalence of suicide attempts among chronic pain patients has been found
    - This does not involve the marked increase in suicide since the CDC Guidelines have been out

Bair MJ, Wu J, Damush TM, et al. Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. Psychosom Med. 2008;70(8):890-897; . Zautra AJ, Fasman R, Parish BP, et al. Daily fatigue in women with osteoarthritis, rheumatoid arthritis, and fibromyalgia. Pain. 2007;128(1-2):128-135; Boakye PA, Olechowski C, Rashiq S, et al. A critical review of neurobiological factors involved in the interactions between chronic pain, depression, and sleep disruption [published online May 28, 2015]. Clin J Pain. doi: 10.1097/ AJP.0000000000000260; . Finan PH, Smith MT. The comorbidity of insomnia, chronic pain, and depression: dopamine as a putative mechanism. Sleep Med Rev. 2013;17(3):173-183; Fishbain DA, Lewis JE, Gao J. The pain suicidality association: a narrative review. Pain Med. 2014;15(11): 1835-184; Jay GW, Barkin R. Perspectives on the Opioid Crisis from Pain Medicine Clinicians . Dis A Month, Oct. 2018, 64: 451-466.

Pathophsiology-1

- Genetic aspects (rsk genes for chronic pain, depression and anxiety:
  - 5-HTTLPR, involved in regulating synthesis of serotonin transporter
    - Implicated in MDD, Anxiety disorders, substance abuse and FMG
  - Other genes associated with risk of MDD and pain code for:
    - Serotonin 5-HT2A and 5-HT1A receptors
    - Dopamine D4 receptor
    - Catechol-O-methyltransferase, an enzyme involved in catecholamine metabolism
    - Proinflammatory cytokines interleukin-1 and IL-6
  - Both Monoamines and inflammatory cytokines work to modulate GABA and glutamate neurons, as well as glial cells constituting peripheral pain pathways and central circuits that are involved in the pain response and regulation of mood

Maletic V, Raison CL. Neurobiology of depression, fibromyalgia and neuropathic pain. Front Biosci (Landmark Ed). 2009;14:5291-533; Goldenberg DL. Pain/depression dyad: a key to a better understanding and treatment of functional somatic syndromes. Am J Med. 2010;123(8):675-682; Han C, Pae CU. Pain and depression: a neurobiological perspective of their relationship. Psychiatry Investig.2015;12(1):1-8

Pathophysiology-2

- Cerebral anatomic circuits that deal with pain (the pain matrix) are also involved in the stress response and emotional modulation
  - Imaging studies show that the dorsal anterior cingulate (central to experiencing negative affect in response to physical pain), also mediates distress in response to the "pain" of social exclusion
  - Continuous reorganization of the prefrontal cortices is seen as a consequence of enduring chronic pain
    - A reduction of gray matter in the dorsolateral prefrontal cortex (DLPFC)
    - Functional activation of the medial prefrontal cortex (mPFC)
      - Both correlate with the duration and experience of chronic back pain
    - The DLPFC is a "hub" of the "cognitive-executive functional network"

Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. Prog Neurobiol. 2009;87(2):81-97; Maletic V, Raison CL. Neurobiology of depression, fibromyalgia and neuropathic pain. Front Biosci (Landmark Ed). 2009;14:5291-5338; Eisenberger NI, Lieberman MD, Williams KD. Does rejection hurt? An FMRI study of social exclusion. Science. 2003;302(5643):290-292.

Pathophysiology-3

- The mPFC is a key component of the default mode network (DMN), which also comprises the posterior cingulate cortex and the hippocampus
  - The DMN deals with diverse activities including self-reflection, daydreaming, reminiscing, planning, processing of social information, and creative thinking.
  - Negative neuroplastic changes in the DMN are common in both MDD and CP, and may be associated with rumination and catastrophizing (key clinical manifestations of MDD and CP
    - And linked to pervasive negative affect and sleep disturbance

Maletic V, Raison CL. Neurobiology of depression, fibromyalgia and neuropathic pain. Front Biosci (Landmark Ed). 2009;14:5291-5338; Nekovarova T, Yamamotova A, Vales K, et al. Common mechanisms of pain and depression: are antidepressants also analgesics? Front Behav Neurosci. 2014;8:99.

Pathophysiology-4

- Structural and functional changes in the amygdala and hippocampus have been found in MDD, FMG and neuropathic pain
  - Dysfunction of these limbic system entities may contribute to the disruption of the neuroendocrine, autonomic and immune function, which contribute to aggravated mood and pain symptoms
  - Excessive hypothalamic-pituitary-adrenal axis and sympathetic activation, associated with elevation in proinflammatory cytokine production and release probably plays a role in the pathophysiology of MDD and CP disorders

Maletic V, Raison CL. Neurobiology of depression, fibromyalgia and neuropathic pain. Front Biosci (Landmark Ed). 2009;14:5291-5338; Goldenberg DL. Pain/depression dyad: a key to a better understanding and treatment of functional somatic syndromes. Am J Med. 2010;123(8):675-682; Gracely RH, Ceko M, Bushnell MC. Fibromyalgia and depression [published online November 19, 2011]. Pain Res Treat. 2012;2012:486590. doi: 10.1155/2012/486590. (Assessed 7/19/2020)

Pathophysiology-5

- Changes at cellular, subcellular and molecular levels show CP and MDD to be associated with:
  - Problematic neuron-glial relationships
  - Abnormalities in glutamatergic, GABA, glycine, substance-P, opioid, 5-HT, norepinephrine and dopamine signaling
  - Dysfunction of both intracellular signaling cascades and neurotrophic signaling
  - Compromised homeostatic function in prefrontal cortical-limbic circuitry is compromised in MDD and CP
    - AND disrupting autonomic, neuroendocrine and neuroimmune regulation

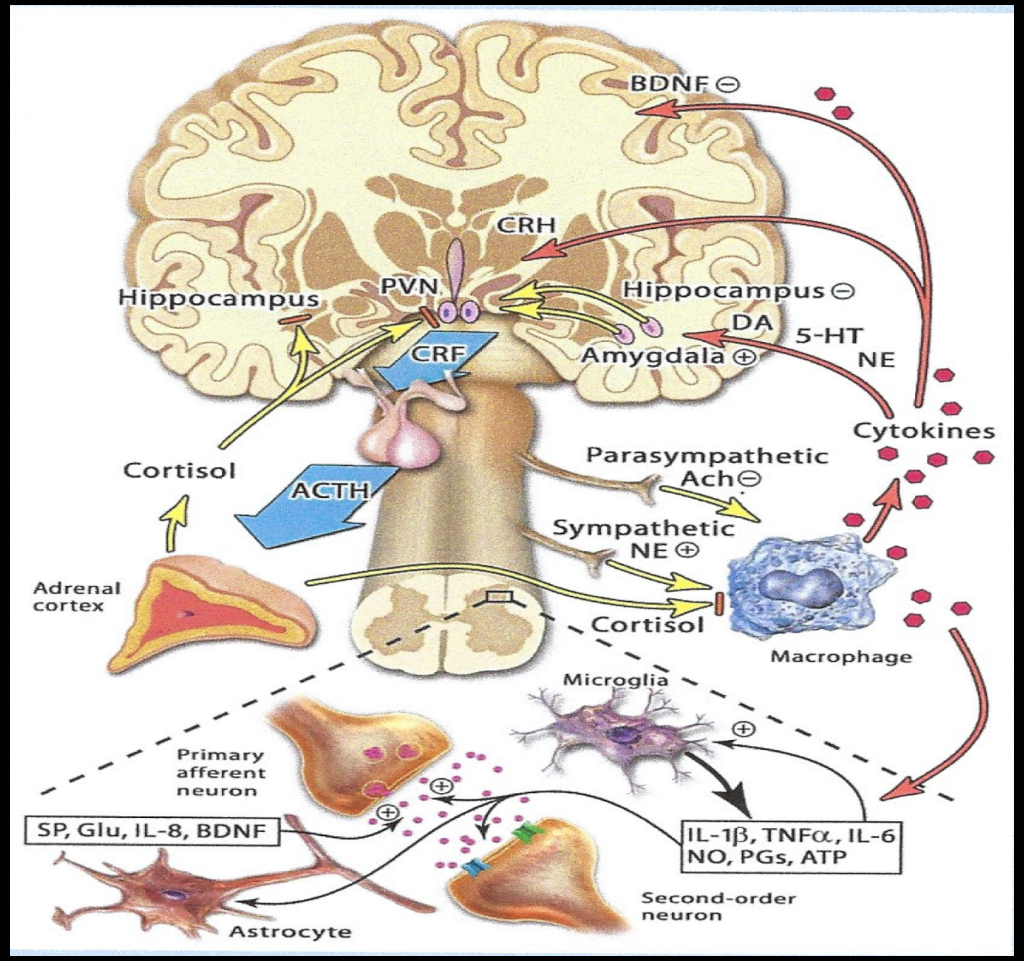
Maletic V, Raison CL. Neurobiology of depression, fibromyalgia and neuropathic pain. Front Biosci (Landmark Ed). 2009;14:5291-533; Boakye PA, Olechowski C, Rashiq S, et al. A critical review of neurobiological factors involved in the interactions between chronic pain, depression, and sleep disruption [published online May 28, 2015]. Clin J Pain. doi: 10.1097/ AJP.000000000000026; Finan PH, Smith MT. The comorbidity of insomnia, chronic pain, and depression: dopamine as a putative mechanism. Sleep Med Rev. 2013;17(3):173-183; Jann MW, Slade JH. Antidepressant agents for the treatment of chronic pain and depression. Pharmacotherapy. 2007;27(11):1571-1587; Han C, Pae CU. Pain and depression: a neurobiological perspective of their relationship. Psychiatry Investig. 2015;12(1):1-8.

Pathophysiology-6

- Abnormalities in monoamine signaling in CP and MDD may give rise to profound anhedonia, cognitive impairment, anxiety, insomnia, sensitivity to stress as well as poor functioning of descending pain-regulatory pathways, which are primarily monoaminergic in nature, using 5-HT and norepinephrine
- Convergent evidence shows that CP and MDD amplify each other and contribute to treatment resistance in both disorders
  - The Comorbidity between CP and MDD is frequent, common and the 2 conditions exhibit substantial epidemiological, clinical and neurobiological overlap
  - They facilitate development of each other
  - CP is a strong predictor of subsequent onset of MDD (and vice verse)
    - Understanding this shared pathophysiological pathophysiology can help one develop an individualized, personalized, integrated treatment plan

Maletic V, Raison CL. Neurobiology of depression, fibromyalgia and neuropathic pain. Front Biosci (Landmark Ed). 2009;14:5291-533; Boakye PA, Olechowski C, Rashiq S, et al. A critical review of neurobiological factors involved in the interactions between chronic pain, depression, and sleep disruption [published online May 28, 2015]. Clin J Pain. doi: 10.1097/ AJP.000000000000026; Finan PH, Smith MT. The comorbidity of insomnia, chronic pain, and depression: dopamine as a putative mechanism. Sleep Med Rev. 2013;17(3):173-183; Jann MW, Slade JH. Antidepressant agents for the treatment of chronic pain and depression. Pharmacotherapy. 2007;27(11):1571-1587; Han C, Pae CU. Pain and depression: a neurobiological perspective of their relationship. Psychiatry Investig. 2015;12(1):1-8; Ohayon MM. Specific characteristics of the pain/depression association in the general population. J Clin Psychiatry. 2004;65(suppl 12):5-9.

Major Depression and Chronic Pain Disorders: Common Pathophysiology



Compromised homeostatic function of prefrontal cortical-limbic circuitry in major depressive disorder (MDD) and chronic pain disrupts autonomic, neuroendocrine, and neuroimmune regulation, shown here.

1. Stress, pain, and depression lead to excessive, untimely release of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoids

2. Sympathetic overactivity, combined with diminished parasympathetic tone, contributes to immune activation and release of proinflammatory cytokines (eg, tumor necrosis factor-α [TNF-α, interleukin-1 [IL-1], and interleukin-6 [IL-6]) from macrophages and other immune cells

3. Inflammatory cytokines further interfere with monoaminergic and neurotrophic signaling. Proinflammatory cytokines also can reduce central glucocorticoid receptor sensitivity, leading to further disruption of (1) the hypothalamic-pituitary-adrenal (HPA) axis and (2) immune system regulation

4. Disturbances of serotonin (5-HT), norepinephrine (NE), and dopamine (DA) signaling in MDD and chronic pain impair the function of descending pain modulatory pathways. Elevated mediators of the inflammatory response, combined with excessive sympathetic tone, can further affect dorsal column processing of pain signals by contributing to activation of microglia and astroglia

5. Activated microglia exchange chemical signals with astrocytes and nociceptive neurons, thus amplifying pain-related transmission of glutamate (Glu), substance P (SP), adenosine triphosphate (ATP), brain-derived neurotrophic factor (BDNF), pro-inflammatory cytokines (IL-1, IL-6, interleukin-8, TNF-α, nitrogen oxide (NO), and prostaglandins (PGs)

Ach: acetylcholine; ATP: adenosine triphosphate; CRF: corticotropin releasing factor; PVN: paraventricular nucleus of hypothalamus

Maletic V, Raison CL. Neurobiology of depression, fibromyalgia and neuropathic pain. Front Biosci (Landmark Ed) 2009; 14:5291-5338

Neuroanatomical Changes with MDD

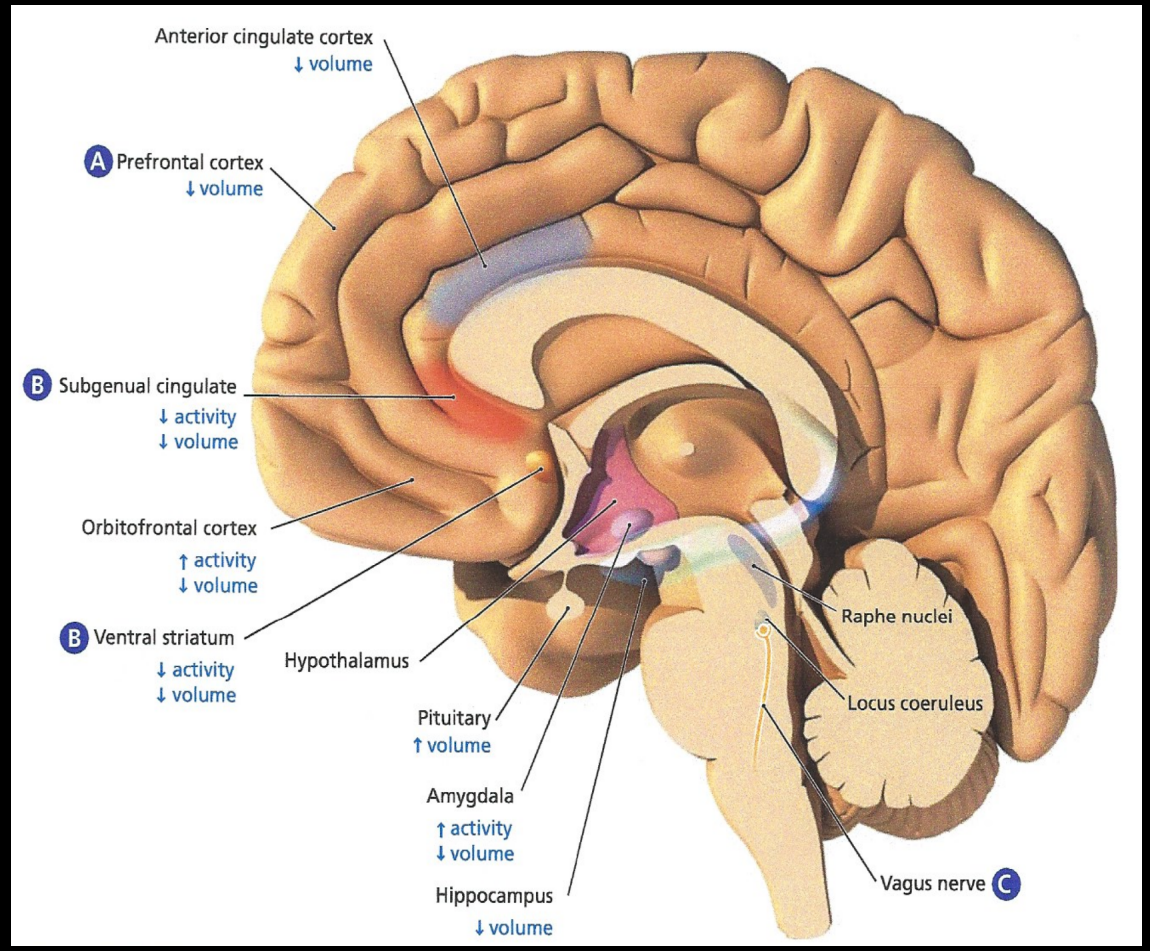
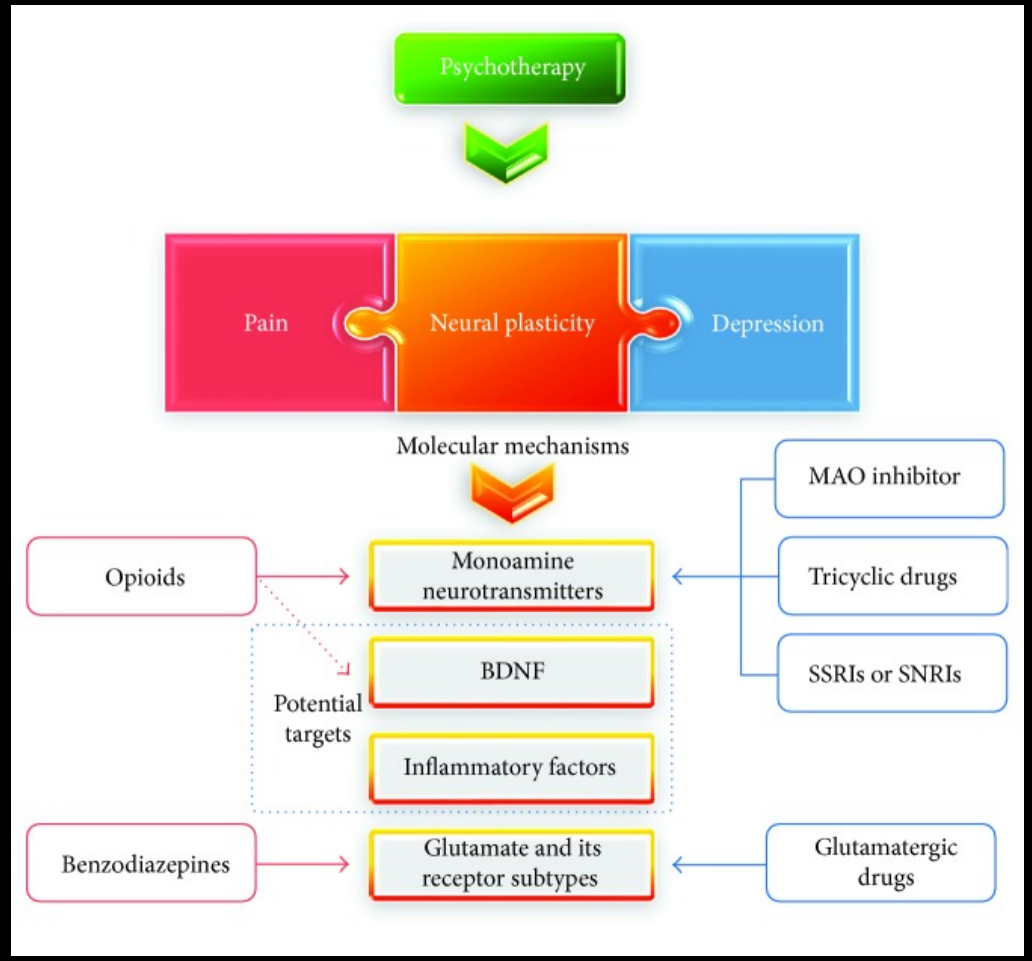


Figure 4: Structural and functional brain abnormalities in patients with major depressive disorder, and the site of action of novel neurostimulation techniques with antidepressant potential. Structural abnormalities in the brains of patients with major depressive disorder have been observed in the cortical and subcortical regions. The anterior cingulate cortex, especially the subgenual cingulate, may show volume reduction. This has also been observed in other subregions of the prefrontal cortex as well as in the orbitofrontal cortex. Subcortical regions in which volume reduction has been observed include the amygdala, hippocampus and ventral striatum. (A) Transcranial magnetic stimulation of the dorsolateral prefrontal cortex and (B) deep-brain stimulation of the subgenual cingulate have been shown to have antidepressant effects in some patients. The rationale for deep-brain stimulation of the subgenual cingulate or the ventral striatum is largely based on neuroimaging findings of functional dysregulation in this region. (C) Vagus nerve stimulation might have antidepressant properties via its effects on the locus coeruleus, an area in the brain stem from which norepinephrine neurons originate.

Rot MAH, Mathew SJ, Charney DS. Neurobiological mechanisms in major depressive disorder. CMAJ 2009; 180(3):305-312.

Depression and Pain



- Pain and depression are closely correlated from the perspectives of both brain regions and the neurological function system, whereby chronic pain may lead to depression. One of the important causes for chronic pain leading to depression appears to be the crucial effect of common neuroplasticity changes on the occurrence and development of the two disorders in question. Nevertheless, current efforts in this field fail to sufficiently and explicitly explain their connection. Further investigations into the common neuroplasticity changes shared by pain and depression are warranted to promote the identification of new drug targets and to free patients from chronic pain-induced depression.

Sheng J, Lui S, Wang Y, et al. The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain. Neural Plast. 2017; 2017:9724371

Other Aspects of Depression-1

- Approximately 52% of patients with pain are susceptible to developing depression and 85% of patients with chronic pain are affected by severe depression, being three times more likely to be suffering from distress.
- Multiple studies show that the interactions between chronic pain and depression occur because they have pathophysiological and neurobiological similarities

Sheng J, Liu S, Wang Y, Cui R, Zhang X. The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain. Neural Plast 2017; 2017: 9724371.; 5. Xiao X, Zhang YQ. A new perspective on the anterior cingulate cortex and affective pain. Neurosci Biobehav Rev 2018; 90: 200-211; 4. Robinson MJ, Edwards SE, Iyengar S, Bymaster F, Clark M, et al. Depression and pain. Front Biosci (Landmark Ed) 2009; 14: 5031-5051.

Other Aspects of Depression-2

- CP patients have activation of limbic areas and cerebral changes similar to those found in depression
  - Activation of the medial prefrontal cortex (mPFC), the hippocampus, the anterior cingulate cortex (ACC) and insular cortex (IC)
  - The ACC interconnects neurons of the frontal cortex, the thalamus and the amygdala, thus integrating cognitive, emotional and autonomic functions
  - ACC is recruited in pain processing and injuries to the ACC will decrease pain sensitivity
  - The IC is recruited in both acute and chronic pain
    - The posterior portion of the IC deals with somatosensory characteristics of the pain while the anterior portion is related to affective aspects

Boakye PA, Olechowski C, Rashiq S, Verrier MJ, Kerr B, et al. A Critical Review of Neurobiological Factors Involved in the Interactions Between Chronic Pain, Depression, and Sleep Disruption. Clin J Pain 2016; 32(4): 327-336; 5. Xiao X, Zhang YQ. A new perspective on the anterior cingulate cortex and affective pain. Neurosci Biobehav Rev 2018; 90: 200-211; . Barthas F, Sellmeijer J, Hugel S, Waltisperger E, Barrot M, et al. The anterior cingulate cortex is a critical hub for pain-induced depression. Biol Psychiatry 2015; 77(3): 236-245.

Other Aspects of Depression-3

- Clinical evidence has shown that CP can lead to anatomical and functional changes in the IC that are correlated with cognitive and affective disorders
  - The ACC and IC develop functional and morphological alteration in depressive states
    - Decreased connectivity
    - Altered glucose metabolism
    - Decreased ACC volume
  - When compared to healthy people, depression has a higher recruitment of the rostral and dorsal ACCs in an attempt to inhibit negative stimuli
  - People with depression need greater cognitive effort to inhibit negative information

Burkhouse KL, Kujawa A, Keenan K, Klumpp H, Fitzgerald KD, et al. The relation between parent depressive symptoms and neural correlates of attentional control in offspring: A preliminary study. Psychiatry Res Neuroimaging 2017; 263: 26-31; . Lu C, Yang T, Zhao H, Zhang M, Meng F, et al. Insular Cortex is Critical for the Perception, Modulation, and Chronification of Pain. Neurosci Bull 2016; 32(2): 191-201; . Barthas F, Sellmeijer J, Hugel S, Waltisperger E, Barrot M, et al. The anterior cingulate cortex is a critical hub for pain-induced depression. Biol Psychiatry 2015; 77(3): 236-245.

Other Aspects of Depression-4

- Mood and pain are controlled by common neurotransmitters: Serotonin, glutamate and GABA
  - The biochemical theory of depression suggests that a monoamine imbalance occurs
  - The neural mechanisms common to pain and depression are also linked to humoral areas of the brain, such as the IC and the amygdala, which help modulate pain
  - In CP patients, serotonin is reduced, which won't allow suppression of painful stimuli
- GABA and glutamate are the major inhibitory and excitatory neurotransmitters
  - An imbalance between them can cause psychiatric and neurological disorders
  - There is a hypofunction of the GABAnergic system and hyperfunction of the glutamatergic system in depression
  - Loss of GABA inhibitory neurotransmission in the SC dorsal horn leads to the development of neuropathic pain

Boakye PA, Olechowski C, Rashiq S, Verrier MJ, Kerr B, et al. A Critical Review of Neurobiological Factors Involved in the Interactions Between Chronic Pain, Depression, and Sleep Disruption. Clin J Pain 2016; 32(4): 327-336.; 0. Goesling J, Lin LA, Clauw DJ. Psychiatry and Pain Management: at the Intersection of Chronic Pain and Mental Health. Curr Psychiatry Rep 2018; 20(2): 12; 1. Thompson T, Correll CU, Gallop K, Vancampfort D, Stubbs B. Is Pain Perception Altered in People With Depression? A Systematic Review and Meta-Analysis of Experimental Pain Research. J Pain 2016; 17(12): 1257-1272; 2. Benson C, Mifflin K, Kerr B, Jesudasan SJ, Dursun S, et al. Biogenic Amines and the Amino Acids GABA and Glutamate: Relationships with Pain and Depression. Mod Trends Pharmacopsychiatry 2015; 30: 67-79.

Other Aspects of Depression-5

- Depression and CP cause hyperactivity of the hypothalamic-pituitary-adrenal axis
  - Pts with CP and Depression have increased activity of the hypothalamus inducing the release of corticotropin releasing hormone (CRH) leading to secretion of the adrenocorticotropic hormone (ACTH by the anterior pituitary)
  - ACTH binds to adrenal cortex receptors stimulating glucocorticoid secretion
  - Glucocorticoids act by regulating the HPA axis, but in pts with CP AND depression, this regulation does not occur leading to increased glucocorticoids in the blood
  - HPA axis hyperactivity is related to both chronic pain and depression
    - In pts with depression, the HPA axis can be stimulated if the same individual has chronic pain by stressors such as perception of nociceptive stimuli

Boakye PA, Olechowski C, Rashiq S, Verrier MJ, Kerr B, et al. A Critical Review of Neurobiological Factors Involved in the Interactions Between Chronic Pain, Depression, and Sleep Disruption. Clin J Pain 2016; 32(4): 327-33; . Oleary K, Oneill S, Dockray S. A systematic review of the effects of mindfulness interventions on cortisol. J Health Psychol 2016; 21(9): 2108- 2121.

Other Aspects of Depression-6

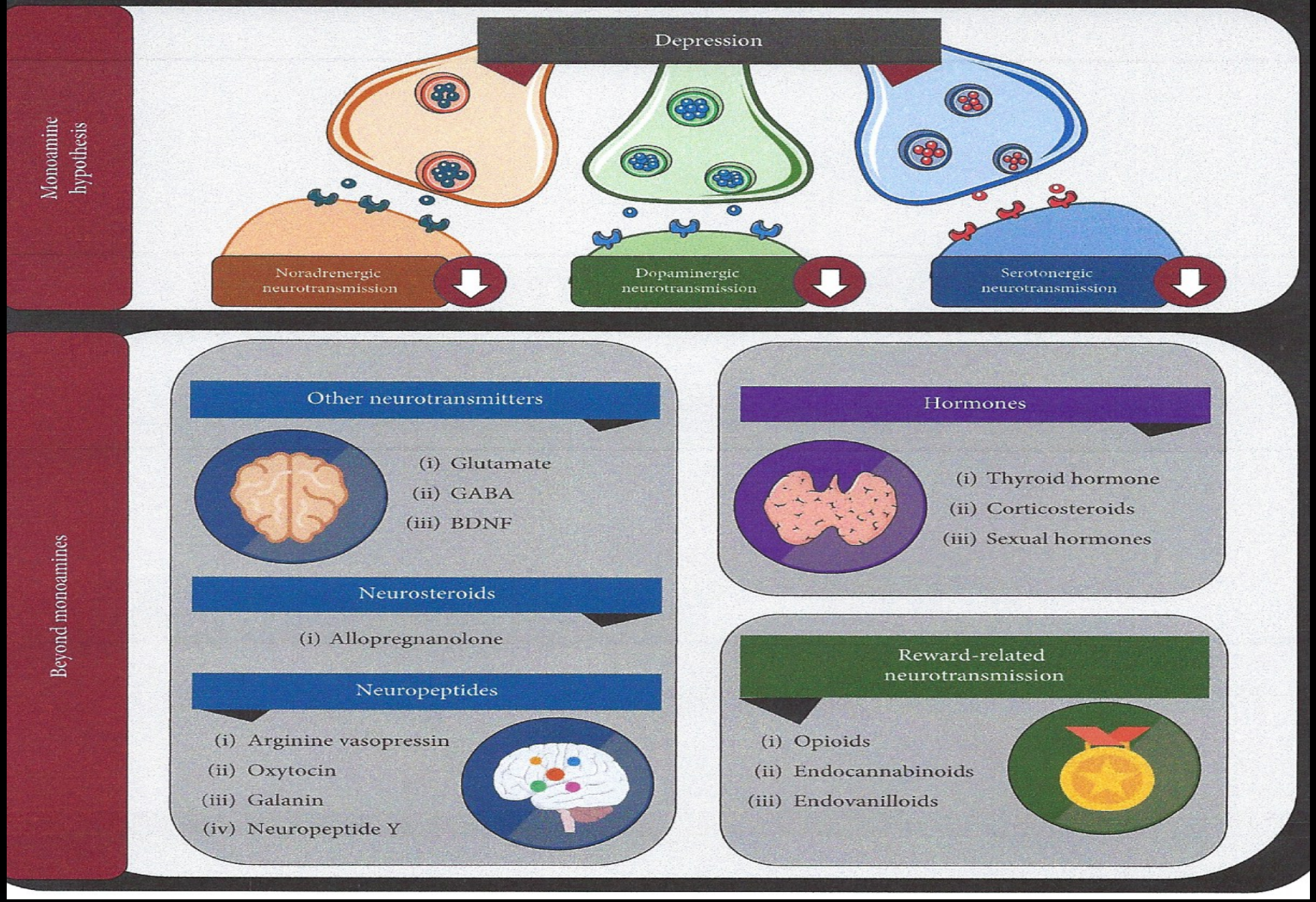
- Depression and CP are both subject to inflammation
  - Studies have shown that inflammatory markers C-reactive-protein and proinflammatory cytokines (IL-6) are increased in pts with depression
  - Depression and CP have a high prevalence in patients with chronic levels of inflammation
  - Studies have show that high levels of inflammation increase the risks for depression
  - Other studies suggest that an increase in inflammatory signaling deregulates the neurotransmitter metabolism and changes neural activity in regions of the brain that are mood related
  - Released cytokines reach the brain and increase inflammation in the CNS by changing the production, metabolism and transport of neurotransmitters including 5-HT, dopamine and glutamate, thus affecting mood

Walker AK, Kavelaars A, Heijnen CJ, Dantzer R. Neuroinflammation and comorbidity of pain and depression. Pharmacol Rev 2015; 66(1): 80-101; . Veltman EM, Lamers F, Comijs HC, Stek ML, van der Mast RC, et al. Inflammatory markers and cortisol parameters across depressive subtypes in an older cohort. J Affect Disord 2018; 234: 54-58; 6. Derry HM, Padin AC, Kuo JL, Hughes S, Kiecolt-Glaser JK. Sex Differences in Depression: Does Inflammation Play a Role? Curr Psychiatry Rep 2015; 17(10): 78; 7. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol 2016; 16(1): 22-34.

Other Aspects of Depression-7

- Inflammatory cytokines promote dysregulation of the HPA axis by increasing the release of glucocorticoids
  - In depressed pts, the feedback mechanism is inactive, increasing the glucose levels in blood
  - Inflammation can cause resistance to glucocorticoids causing an uncontrolled inflammation which increases the symptom
  - Studies suggest CP is associated with increased levels of inflammation and that this generates hyperalgesia
  - It is notable that CP is also frequently found in pts with depression, since it generates an amplified sensitivity that causes depressive symptoms
  - The association between pain and depression appears reciprocal- greater pain is associated with higher prevalence of depression and lower pain decreases depression

Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull 2014; 140(3): 774-815; . Kiecolt-Glaser JK, Derry HM, Fagundes CP. Inflammation: depression fans the flames and feasts on the heat. Am J Psychiatry 2015; 172(11): 1075-1091.



Expanding views on the neurobiology of depression, GABA, BDNF. The imperfect results found with currently available ADM medications have propelled the discover of other potential pharmacologi-cal targets aside from the monoamines.

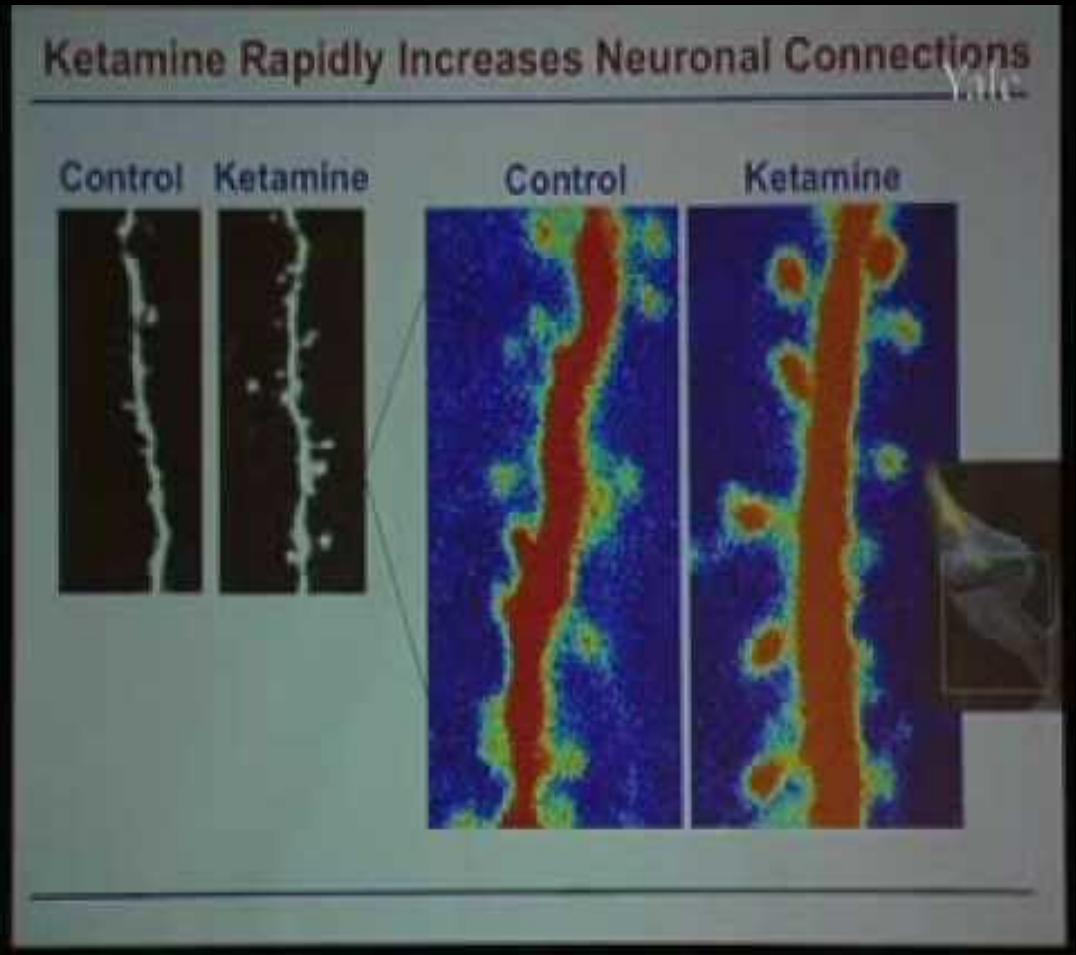
Chavez-Castillo M, Nunez V, Nava M, et al. Depression as a Neuroendocrine Disorder: Emerging Neuropsychopharmacological Approaches beyond Monoamines Hindawi Approaches Beyond Monoamines. Adv In Pharmacological Sciences 2019; Article ID 7943481: 1-20. Https://doi.org/10.1155/2019/7943481

Still More- NMDArs-4

- KETAMINE, a noncompetitive NMDA receptor antagonist has been shown to induce rapid antidepressant effects within 24 hours of use at subanesthetic doses, lasting for at least several days after a single infusion (leading to the term “Rapid acting Antidepressant”)
- Es-ketamine as been approved for use intranasally (56 mg- 84 mg)
- Ketamine is a mu-opioid receptor agonist with excellent affinity for NMDA receptors
  - It antagonizes NMDA receptors on GABAnergic interneurons and on postsynaptic neurons resulting in disinhibition of cortical glutamatergic neurons and increased synthesis of intracellular growth factors

Valentine GW, Mason GF, Gomez R, et al.. 2e antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by [1H]-MRS, Psychiatry Research: Neuroimaging, 2011; vol. 191, no. 2, pp. 122–127; Berman RM, Cappiello A, Anand A, et al.. Antidepressant effects of ketamine in depressed patients,”Biological Psychiatry, 2000; vol. 47, no. 4, pp. 351–354; Iadarola, ND, Niciu JM, Richards EM, et al. Ketamine and other N-methyl-D-aspartate receptor antagonists in the treatment of depression: a perspective review, Aerapeutic advances in chronic disease, 2015; vol. 6, no. 3, pp. 97–114; Homayoun H, Moghaddam B. NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons, Journal of Neuroscience, 2007; vol. 27, no. 43, pp. 11496–11500; Autry AE, Adachi M, Nosyreva E, et al., NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses, Nature, 2011; vol. 475, no. 7354, pp. 91–95.

New Mechanisms Elicited with Ketamine in Treatment-Resistant Depression



Another ketamine effect in the treatment of depression.

Duman RS. New Mechanisms Elicited with Ketamine in Treatment-Resistant Depression. (Lecture)Yale Psychiatry, Oct 3, 2012
https://www.youtube.com/watch?v=hNsliq-5354

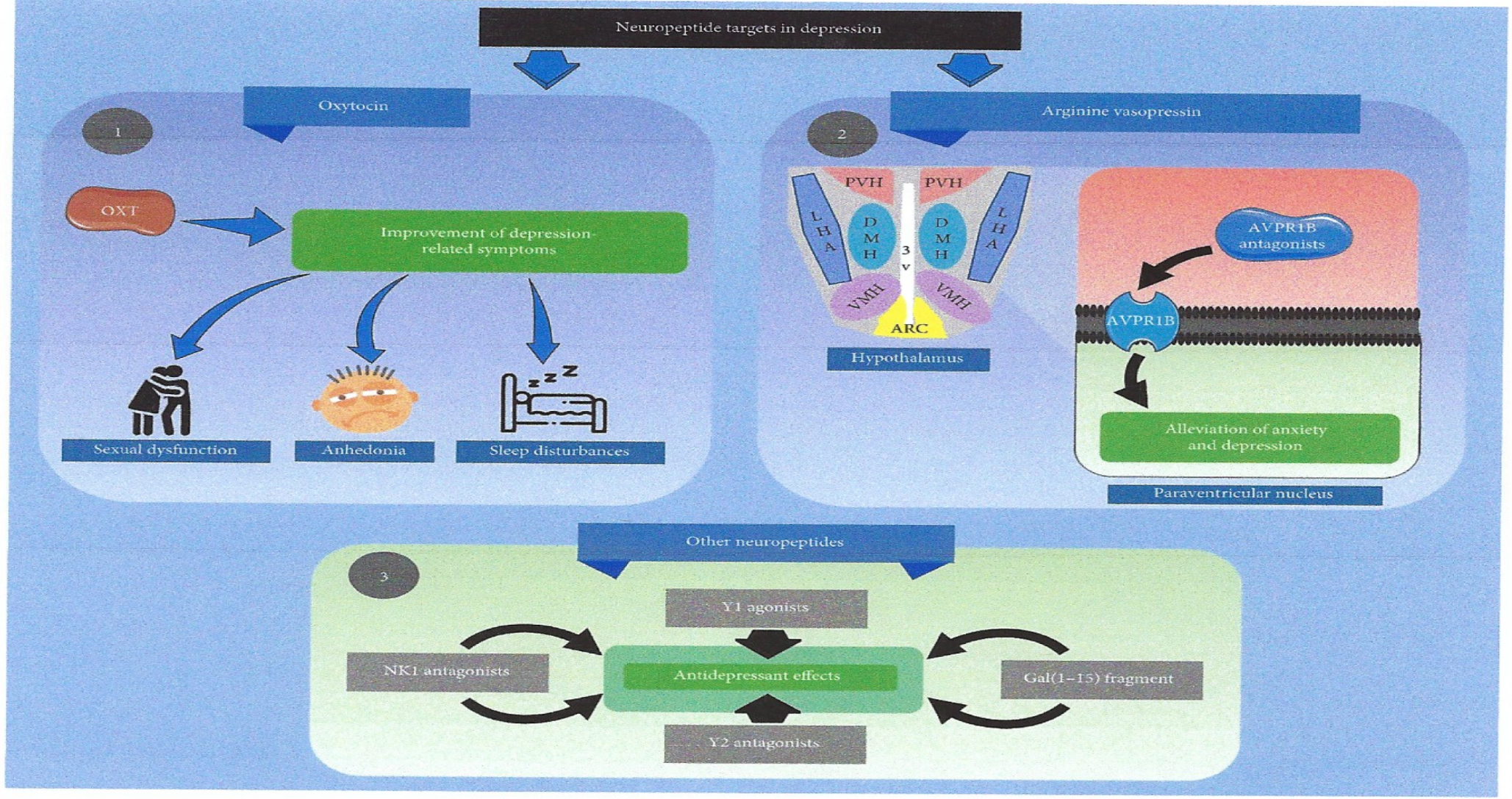


FIGURE 3: Neuropeptide pharmacotherapeutic targets in depression. OXT: oxytocin; LHA: lateral nucleus; PVH: paraventricular nucleus; DMH: dorsomedial nucleus; VMH: ventromedial nucleus; ARC: arcuate nucleus; AVPR1B: arginine vasopressin receptor 1B; NK1: neurokinin 1. Key findings regarding the current knowledge on neuropeptides in the neuropsychopharmacology of depression include the following: (1) Abundant preclinical and clinical evidence suggests oxytocin may significantly contribute to the improvement of depression-related symptoms such as sexual dysfunction, anhedonia, and sleep disturbances. (2) AVPR1B antagonists appear to reduce symptoms of anxiety and depression in both animal and human models. (3) Several modulators of neuropeptide signaling have shown antidepressant activity; however, further research is required to characterize their significance and utility.

Chavez-Castillo M, Nunez V, Nava M, et al. Depression as a Neuroendocrine Disorder: Emerging Neuropsychopharmacological Approaches beyond Monoamines
Hindawi Approaches Beyond Monoamines. Adv In Pharmacological Sciences 2019; Article ID 7943481: 1-20.
Https://doi.org/10.1155/2019/7943481

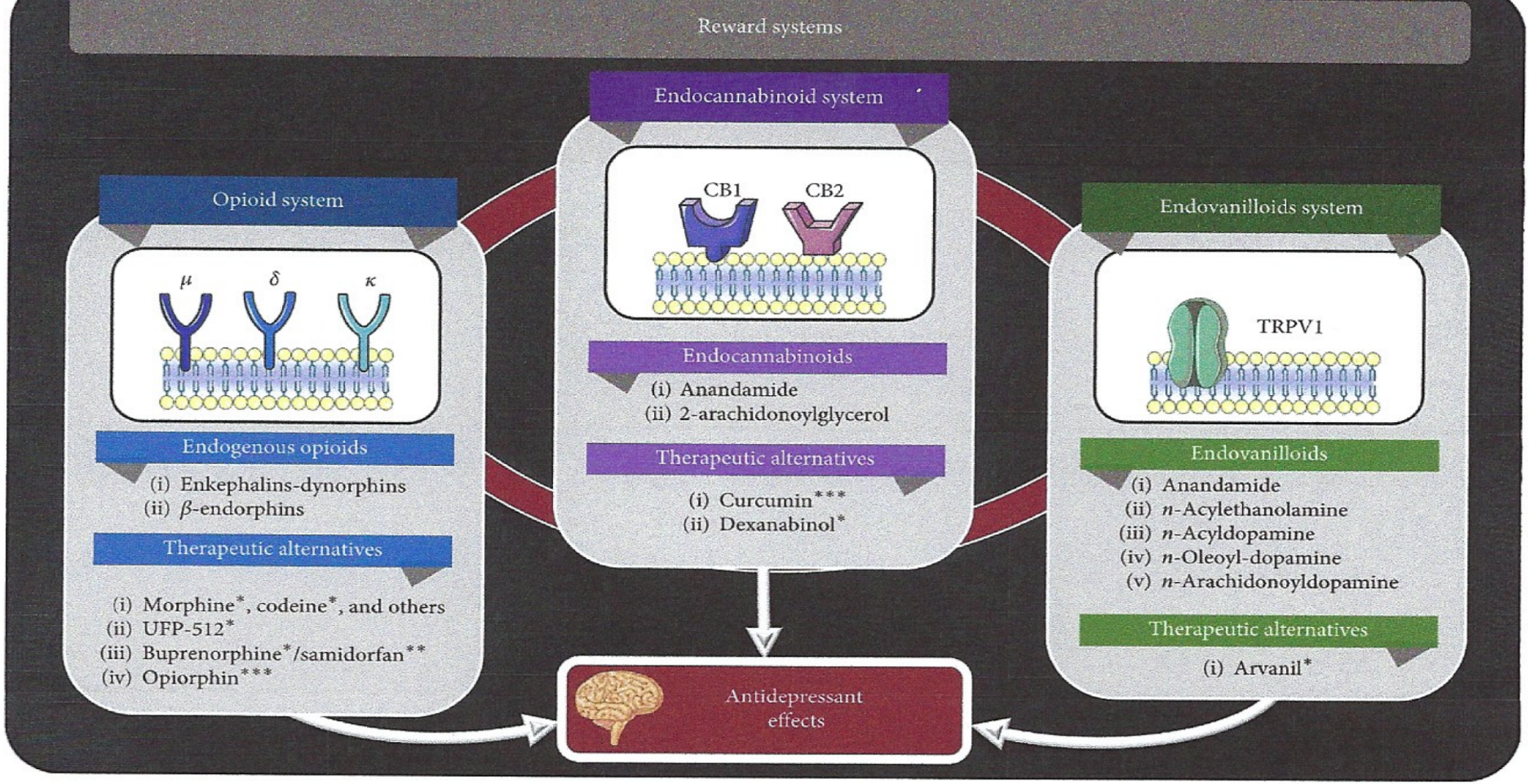


FIGURE 4: Pharmacotherapeutic targets for depression in reward neurocircuits. *Agonist. **Antagonist. ***Modulator. μ: μ-opioid receptor. δ: δ-opioid receptor. κ: κ-opioid receptor. CB1: cannabinoid receptor 1. CB2: cannabinoid receptor 2. TRPV1: transient receptor potential cation channel V1. Research on pharmacotherapeutic targets for depression in the reward system remains principally preclinical. Currently available results presume some potential clinical utility for these substances for the treatment of depression, with varying degrees of efficacy and differing pharmacological profiles.

Chavez-Castillo M, Nunez V, Nava M, et al. Depression as a Neuroendocrine Disorder: Emerging Neuropsychopharmacological Approaches beyond Monoamines
Hindawi Approaches Beyond Monoamines. Adv In Pharmacological Sciences 2019; Article ID 7943481: 1-20.
Https://doi.org/10.1155/2019/7943481

Treatment-1

Pharmacotherapy of psychiatric disorders in a setting of comorbid pain

Comorbid state	Recommended agents
Depression and pain	SNRIs TCAs
Depression, pain, and anxiety	Duloxetine Venlafaxine
Depression, pain, and cognitive complaints	SNRIs (?)Vortioxetine
Depression, pain, and sleep disturbance	TCAs Adjunctive gabapentin Adjunctive pregabalin
Depression, pain, and fatigue	Milnacipran Adjunctive bupropion Adjunctive modafinil

SNRI: serotonin-norepinephrine reuptake inhibitor; TCA: tricyclic antidepressant

- Vortioxetine has shown promise in improving cognitive function in adults with MDD
  - Its cognitive benefits independent of its ADM effects

- For sleep (in patients with CP, MDD and sleep disturbance:
  - TCA (sedating)
  - Gabapentin or pregabalin can be added to an SNRI
  - Anticonvulsants
- Cognitive behavioral interventions
  - Eval and deal with sleep hygiene

- AVOIDANCE OF DRUG-DRUG INTERACTIONS IS IMPERATIVE!

Maletic V, DeMuri B. Chronic pain and depression: treatment of 2 culprits in common.Part 2. Current Psychiatry. 2017; 15(3): 41. 47-52; McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. Int J Neuropsychopharmacol. 2014;17(10):1557-1567

Recommendations for use of ADMs

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*
Selective serotonin reuptake inhibitors are more likely than placebo to produce depression remission in the primary care population.	B
Serotonin-norepinephrine reuptake inhibitors are slightly more likely than selective serotonin reuptake inhibitors to improve depression symptoms, but they are associated with higher rates of adverse effects such as nausea and vomiting.	B
For treatment-naive patients, all second-generation antidepressants are equally effective. Medication choice should be based on patient preferences, with adverse effect profiles, cost, and dosing frequency taken into consideration.	C
Antidepressants are most effective in patients with severe depression.	A
Preferred agents for older patients with depression include citalopram (Celexa), escitalopram (Lexapro), sertraline (Zoloft), mirtazapine (Remeron), venlafaxine, and bupropion (Wellbutrin). Because of higher rates of adverse effects in older adults, paroxetine (Paxil) and fluoxetine (Prozac) should generally be avoided.	C
Treatment for a first episode of major depression should last at least four months. Patients with recurrent depression may benefit from prolonged treatment.	C

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.

Arroll B, Elley CR, Fishman T, et al. Antidepressants versus placebo for depression in primary care. Cochrane Database Syst Rev. 2009;(3):CD007954; . Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Ann Intern Med. 2011;155(11):772-785; . Machado M, Einarson TR. Comparison of SSRIs and SNRIs in major depressive disorder: a meta-analysis of head-to-head randomized clinical trials. J Clin Pharm Ther. 2010;35(2):177-188; 2. Qaseem A, Snow V, Denberg TD, Forciea MA, Owens DK. Using secondgeneration antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians [published correction appears in Ann Intern Med. 2009;150(2):148]. Ann Intern Med. 2008;149(10):725-733; Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med. 2008;5(2):e45.

Treatment-6

Non-drug options for treating chronic pain and major depressive disorder (MDD)
Cognitive-behavioral therapy
• Has established efficacy as stand-alone or adjunct treatment of chronic pain, MDD, anxiety disorders, and insomnia
• Diminishes catastrophizing and ruminations
• Supports maintenance of improvement
Mindfulness-based therapy
• Established efficacy as monotherapy or adjunctive treatment of chronic pain, MDD, and anxiety disorders
Other behavioral and psychological approaches[a]
• Acupuncture
• Biofeedback
• Deep diaphragmatic breathing and relaxation training
• Guided imagery
• Hypnosis
• Supportive group therapy
Exercise and restorative therapies
• Evidence supports adjunct use in treatment of MDD and chronic pain. Exercise improves pain control, mood, cognition, strength, functionality, and cardiometabolic and bone health
[a]These are mostly helpful as components of a mind–body integrated treatment of chronic pain and depression

- Special forms of CBT- rumination-focused is good for the CP patient with MDD
  - Deals with catastrophization

Maletic V, DeMuri B. Chronic pain and depression: treatment of 2 culprits in common.Part 2. Current Psychiatry. 2017; 15(3): 41. 47-52/

Sleep

Salvator Dali: Sleep 1937

Sleep and Chronic Pain-1

- Sleep disturbance can make coping with chronic pain more difficulty and increase pain
- Chronic pain patients with sleep disturbances tend to be more frustrated; they get irritated more easily
- Sleep disturbances can make chronic pain worse
  - On-going lack of refreshing sleep stresses the CNS
    - The CNS becomes more reactive, with the increased reactivity amplifying the pain signals, making the pain worse
    - Pain triggers poor sleep: pt with CLBP may experience several intense microarousals (a change in the sleep state to a lighter stage of sleep) per each hour of sleep, leading to awakenings
    - Microarousals are innocuous for a person not experiencing chronic pain

https://www.instituteforchronicpain.org/understanding-chronic-pain/complications/sleep-disturbance Assessed 7/24/2020; https://www.sleepfoundation.org/articles/pain-and-sleep Assessed 7.24.2020

Sleep and Chronic Pain-2

- Sleep disturbance is common in patients with chronic pain (CP).
- Sleep and pain are bidirectional; pain can interfere with sleep and sleep disturbance can exacerbate pain.
- Cognitive behavior therapy (CBT) has the potential to improve both pain and sleep quality.
- CBT is given as part of Neuro-Rehabilitation program

Cheatle MD, Foster S, Pinkett A, et.al. Assessing and managing sleep disturbance in patients with chronic pain. Anesthesiology Clin 2016; 34(2016): 379-393

Sleep Problems are Associated with Chronic Pain Over and Above Mutual Associations with Depression and Catastrophizing

- Questionnaire study of 101 Chronic Pain patients: measuring pain, sleep and mood; also physical assessments performed by physiotherapist
- 75.2% had insomnia, and 84.3% reported at least 1 sleep problem
- Significant positive correlations with pain were detected for depression, catastrophizing, insomnia, short sleep duration and poor sleep quality
  - Sleep duration had significant independent association with pain after accounting for depression and catastrophizing
  - Sleep duration also had independent association with physical function after accounting for pain and catastrophizing
- Conclusion: Sleep has an important and unique contribution to pain and physical function; it is important that sleep disturbances are addressed both in assessment and treatment of chronic pain

Roberts MB. Drummond PD. Sleep Problems are Associated with Chronic Pain over and above Mutual Associations with Depression and Catastrophizing. Clin J Pain 2016; 32(9): 792-799.

Comorbid insomnia, psychological symptoms and widespread pain among patients suffering from musculoskeletal pain in general practice: a cross-sectional study

- Conclusion: one in two patients in general practice report MSK pain. Comorbid MSK pain and insomnia are common and associated with a higher prevalence of anxiety and depression
- 390 general practice patients (12 YOA and older) included: 183 patients with MSK pain (weekly for at least the prior month) and 207 patients without MSK pain
- Pts with MSK pain had a significantly higher prevalence of insomnia (difference 25.5%, p,0,0001); anxiety (difference 24.3%, p,0,0001); and depressive symptoms (difference 11%, p<0,0001) compared to patients without MSK pain
- Pts with MSK pain and comorbid insomnia had significantly higher levels of anxiety and symptoms of depression compared with MSK patients without insomnia (p<0.0001)
  - Relationships still robust when controlling for age, sex and BMI in linear regression

Sørensen L, Jensen MSA, Rathleff MS, et al. Comorbid insomnia, psychological symptoms and widespread pain among patients suffering from musculoskeletal pain in general practice: a cross-sectional study. BMJ Open 2019; 9:e031971. doi:10.1136/ bmjopen-2019-031971

Common Sleep Disturbances in Chronic Pain Pts

- Insomnia
- Hypersomnia
- Sleep Apnea
- Restless Leg Syndrome

https://www.instituteforchronicpain.org/understanding-chronic-pain/complications/sleep-disturbance Assessed 7/24/2020

Sleep Hygiene

Table 1. Tips for Sleep Hygiene

- Avoid napping during the day because this can make it difficult to fall asleep at night
- Avoid stimulants such as caffeine, nicotine, and alcohol 1-3 hours before bedtime
- Avoid having a big meal 1-3 hours before bedtime
- Engage in a relaxing bed-time routine
- Get enough natural light to establish a healthy wake-sleep cycle

Asih S, Hartzell M, Gatchel, RJ. Differentiating Insomnia and Depression in Chronic Pain Therapy. Practical Pain Management. 15(9).1-15 https://www.practicalpainmanagement.com/pain/other/co-morbidities/differentiatinginsomnia-depression-chronic-pain-therapy Accessed July 18, 2020

CBT for Pain and Insomnia

Table 2. Combined Cognitive Behavior Therapy for Pain and Insomnia (CBT-PI)

Pain Management Component	Insomnia Management Component
Pain education	Sleep restriction
Physical activation	Stimulus control
Goal setting	Sleep hygiene
Relaxation	Relaxation
Cognitive restructuring identifies unhelpful thinking patterns and negative thoughts, and then replaces them with more constructive ways of thinking. Thus, the pain intensity may not necessarily lessen, but pain interferes less with daily life activities.	Cognitive restructuring identifies sleep-interfering thoughts and worries, calming an active mind that will not shut off when the patient is trying to sleep and relax. The key is shifting from "trying hard to sleep" to "allowing sleep to happen."
Guided imagery	
Activity pacing	

Adapted from Castel et al, 2012; Pigeon et al, 2012; Tang et al, 2012; Vitiello et al, 2013

Asih S, Hartzell M, Gatchel, RJ. Differentiating Insomnia and Depression in Chronic Pain Therapy. Practical Pain Management. 15(9).1-15 https://www.practicalpainmanagement.com/pain/other/co-morbidities/differentiatinginsomnia-depression-chronic-pain-therapy Accessed July 18, 2020

Fibromyalgia

Pathophysiology-1

- While FMS is recognized as a biological–psychological–sociological problem associated with
  - prolonged distress
  - myofascial pain
  - "pain behavior"
  - anxiety, and depression
- It is also associated with
  - Central sensitization
  - Neuroendocrine disturbance
  - Autonomic nervous system dysfunction
  - Sleep Disorder
- It appears that the main problem is central in origin. It is the trigger or pathoetiology to the disorder that appears to be unknown.

Jay, GW, Barkin RL, Fibromyalgia, Dis A Month, 2015, 61: 66-111;

Pathophysiology-2

- Patients with FMS have psychophysiological evidence of hyperalgesia to mechanical, thermal, and electrical stimulation.
- This leads to the assumption of both peripheral and central nociceptive abnormalities.
- Peripheral nociceptive systems in the skin and musculature change significantly, with sensitization of vanilloid receptors, acid-sensing ion channel receptors, and purino-receptors.
- Tissue modulators of inflammation and nerve growth factors can excite these receptors, leading to significant changes in pain sensitivity
- In FMS patients, however, there is no consistent evidence of inflammatory soft tissue abnormalities, leading the search for the pathoetiology to the CNS.

Jay, GW, Barkin RL, Fibromyalgia, Dis A Month, 2015, 61: 66-111; Smitherman SR. Peripheral and central sensitization in fibromyalgia: pathogenetic role. Curr Pain Headache Rep. 2002;6(4):259–266; Staud R. Evidence of involvement of central neural mechanisms in generating fibromyalgia pain. Curr Rheumatol Rep. 2002;4(4):299–305; Jay GW. Fibromyalgia. In: Jay GW, ed. Practical Guide To Chronic Pain Syndromes. New York: Informa Healthcare, 2010:144–180.

Pathophysiology-3

- Both abnormal temporal summation of second pain (wind-up) and central sensitization have been described in FMS. Both of these entities rely on CNS mechanisms.
- They occur after prolonged C-fiber nociceptive input and depend on the activation of specific nociceptive neurons and wide dynamic range neurons in the dorsal horn of the spinal cord.
- Other abnormal pain mechanisms associated include dysfunction of the diffuse noxious inhibitory controls.
- These pain inhibitory mechanisms rely on both spinal cord and supraspinal mechanisms, which both facilitate and inhibit pain

Jay GW. Fibromyalgia. In: Jay GW, ed. Practical Guide To Chronic Pain Syndromes. New York: Informa Healthcare, 2010:144–180; Staud R. Evidence of involvement of central neural mechanisms in generating fibromyalgia pain. Curr Rheumatol Rep. 2002;4(4):299–305.

Pathophysiology-4

- FMS patients show a low noxious threshold to auditory tones, implicating a more global problem in sensory processing, in at least some patients.
- The idea that FMS and related central sensitivity syndromes may represent biological amplification of all sensory stimuli has strong support from functional imaging studies (fMRI) that suggest that the insula is the most consistently hyperactive region

Geisser ME, Gracely RH, Giesecke T, Petzke FW, Williams DA, Clauw DJ. The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome. Eur J Pain. 2007;11(2): 202–207;

Pathophysiology-5

- There are 3 hypotheses may play a part in the pathoetiology of FMS.
- FMS may be secondary to the following:
  - 1. Central sensitization secondary to constant peripheral nociception (pain amplification).
  - 2. A failure of the descending pain pathway (antinociceptive).
    - Brain imaging studies provide evidence of abnormal central pain mechanisms in FM.
    - Corroboration of augmented pain experienced by FM patients is seen, as well as thalamic activity that is decreased in FM patients
  - 3. A dysfunction of mu-opioid receptors, possibly contributing to the failure of the descending pain pathway.

Jay, GW, Barkin RL, Fibromyalgia, Dis A Month, 2015, 61: 66-111; Jay GW. Fibromyalgia. In: Jay GW, ed. Practical Guide To Chronic Pain Syndromes. New York: Informa Healthcare, 2010:144–180; Staud R. Evidence of involvement of central neural mechanisms in generating fibromyalgia pain. Curr Rheumatol Rep. 2002;4(4):299–305.

Table 2
Psychophysiological abnormalities in fibromyalgia (summary)

1. Hyperalgesia to mechanical, thermal, and electrical stimulation
2. Central sensitization
3. Decreased (4W) sympathetic nervous system response to pain
4. Generalized diffuse pain to minimal mechanical pressure
5. Decreased perception (4W) of heat and cold pain but not perception thresholds

Table 3
Autonomic nervous system abnormalities in fibromyalgia (summary)

1. Abnormal sympathetic function after stress in heart rate fluctuations
2. Decreased (4W) heart rate variability and loss of circadian variation of sympathetic/vagal balance
3. Increased (↑) noradrenergically evoked pain
4. Increased (↑) nocturnal sympathetic activity

Table 4
Neurochemical abnormalities in fibromyalgia (summary)

1. Abnormal metabolism of serotonin
   a. Decreased (↓) serum levels
   b. Decreased (↓) cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid (5-HIAA)
   c. Decreased (↓) platelet serotonin
2. Decreased (↓) serum beta-endorphin concentration
3. Increased (↑) CSF dynorphin
4. Increased (↑) CSF substance P (SP)
5. Increased (↑) CSF nerve growth factor in patients with primary fibromyalgia
6. Increased (↑) CSF calcitonin gene-related peptide (CGRP)
7. Decreased (↓) neuropeptide Y (NY)
8. Increased (↑) interleukin-6 and 8 (IL-6 and IL-8)
9. Increased (↑) serum brain-derived neurotrophic factor (BDNF)
10. Gi protein hypofunction
11. Decreased (↓) dopamine and metabolites
12. Decreased (↓) endocannabinoid tonus

Jay, GW, Barkin RL, Fibromyalgia, Dis A Month, 2015, 61: 66-111

Table 5
Neuroendocrine abnormalities in fibromyalgia (summary)

1. Hypothalamic–pituitary–adrenal axis changes
   a. Decreased (↓) 24-h urinary free cortisol
   b. Decreased (↓) diurnal cortisol fluctuation and decreased (↓) evening cortisol levels
   c. Increased (↑) adrenocorticotropic hormone (ACTH) response to corticotrophin-releasing hormone (CRH)
   d. Decreased (↓) cortisol relative to increased (↑) ACTH
   e. Decreased (↓) release of ACTH after stimulation of interleukin-6
   f. Decreased (↓) growth hormone (GH)
   g. Decreased (↓) thyroid-stimulating hormone to thyrotropin-releasing hormone
   h. Decreased (↓) free triiodothyronine (T3)

Table 6
Functional cerebral abnormalities, CNS structural changes, and MR imaging of voxel-based morphometry (MR-VBM) in fibromyalgia (summary)

1. Decreased (↓) levels of regional cerebral blood flow (rCBF) in thalamus and caudate nucleus via single photon-emission tomography
2. Bilateral cerebral activation to unilateral painful stimulation, with increased (↑) rCBF
3. Decreased (↓) thalamic response to pain, via decreased (↓) rCBF
4. Decreased (↓) gray matter in the cingulate cortex, insular cortex, and medial frontal cortices
5. Decreased (↓) microstructural and volume changes in the central neuronal networks involved in both sensory

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Sleep Disorder

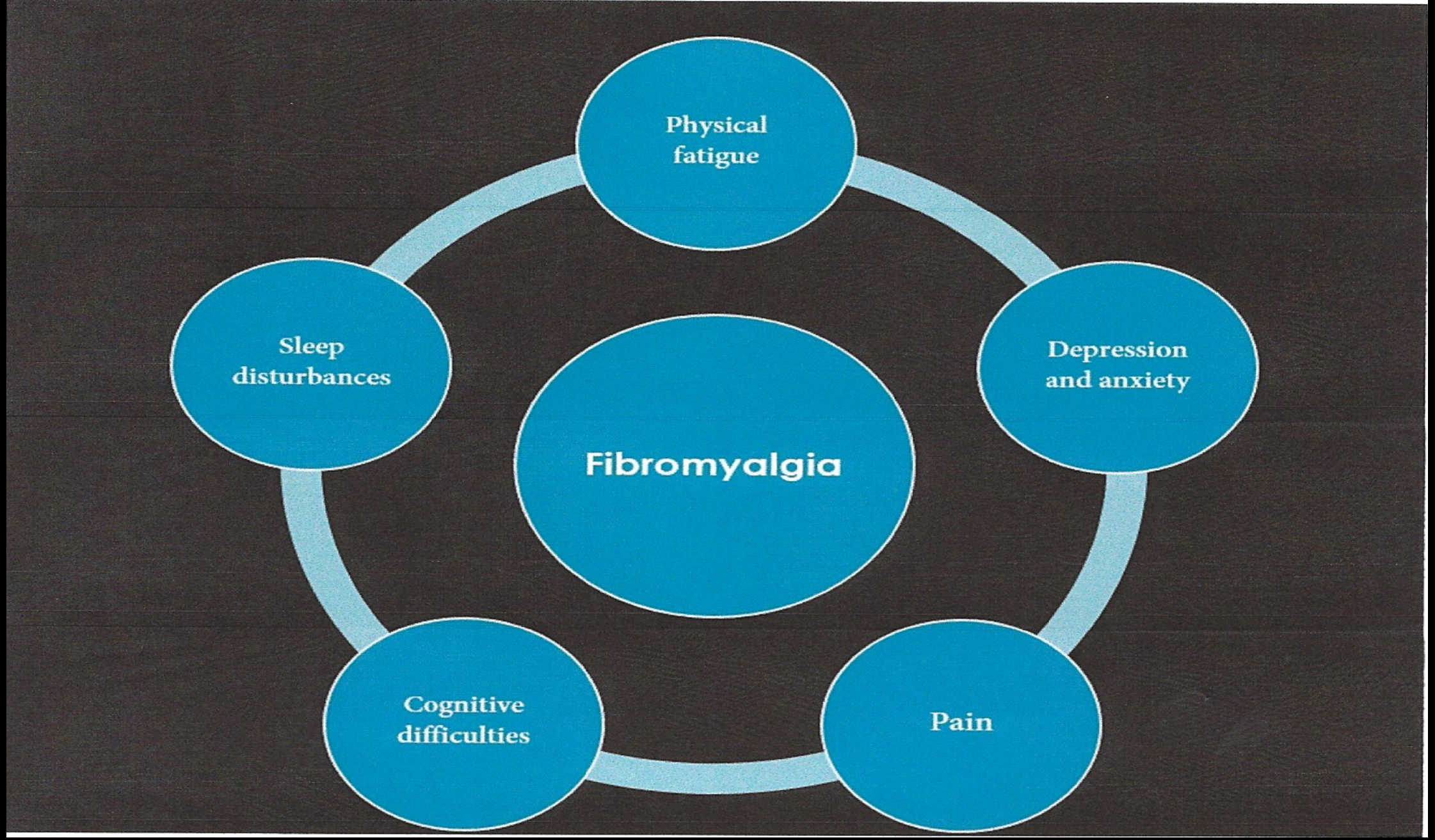
- Sleep disorders are also well known to have a part in the disorder in which nonrestorative sleep is one of the most common complaints, and an electroencephalographic abnormality (alpha intrusion in delta sleep abnormality) is seen in many, but not all, FMS patients
- Moldofsky did the first research documenting the alpha intrusion into delta sleep- and the ability to reverse it
  - Alpha-delta sleep is the abnormal intrusion of alpha activity (8-13 Hz oscillations) into the delta activity (1-4 oscillations) that defines slow wave sleep- especially prevalent in FMG patients (and associated with non-refreshing sleep, fatigue and increased muscle and tissue pain) that characterizes FMG
  - Alterations in $GABA_B$ currents and two thalamic currents (hyperpolarization-activated current and a potassium leak current, transform a circuit that normally produces delta oscillations into one that produces alpha-delta activity

Moldofsky H, Scarisbrick P, England R, et al. Musculoskeletal symptoms and non-REM sleep disturbance in patients with “fibrositis” syndrome and healthy subjects. Psychosom Med. 1975;37:341–351; Vijayan S, Klerman EB, Adler GK, Kopell NJ. Thalamic mechanisms underlying alpha-delta sleep with implications for fibromyalgia. J Neurophysiology 2015: 114(3): 1923-1930; Perlis ML, Giles DE, Bootzin RR, et al. Alpha sleep and information processing, perception of sleep, pain and arousability in fibromyalgia. Int J Neurosci. 1997;89:265–280. Moldofsky H, Lue FA, Smythe HA. Alpha EEG sleep and morning symptoms in rheumatoid arthritis. J Rheumatol. 1983;10:373–379. Branco JC, Atalaia A, Paiva T. Sleep cycles and alpha–delta sleep in fibromyalgia syndrome. J Rheumatol. 1994;21: 1113–1117. Drewes AM, Gade J, Nielsen KD, et al. Clustering of sleep electroencephalopathic patterns in patients with the fibromyalgia syndrome. Br J Rheumatol. 1995;34:1151–1156.

Medication Treatment and More

- Amitriptyline
- Pregabalin
- Duloxetine
- Milnacipran

- Aerobic Exercise
- CBT
- Mindfulness
- Biofeedback



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