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Integrative Pain Management for Optimal Patient Care

The Pain Practitioner

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THE ACADEMY 2013 ANNUAL MEETING WE EXPLORED THE SCIENCE + PRACTICED THE ART...

A Review of the Academy Meeting

Microglia: Pointing us to a New Paradigm

Pain Providers as Lifesavers in Combat Trauma

Academy News, and more...

PAIN PRACTITIONER
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Clay Jackson, MD (center) closing the meeting with *Real Pain in the Real World*; (Left, top to bottom) Daniel Duhigg, DO, Richard Payne, MD, Heidi Kraft, PhD, and Robert Bonakdar, MD, presenting thought-provoking plenary sessions.
PHOTOGRAPHY: MARK LOYACK, DAVID BUTTERFIELD

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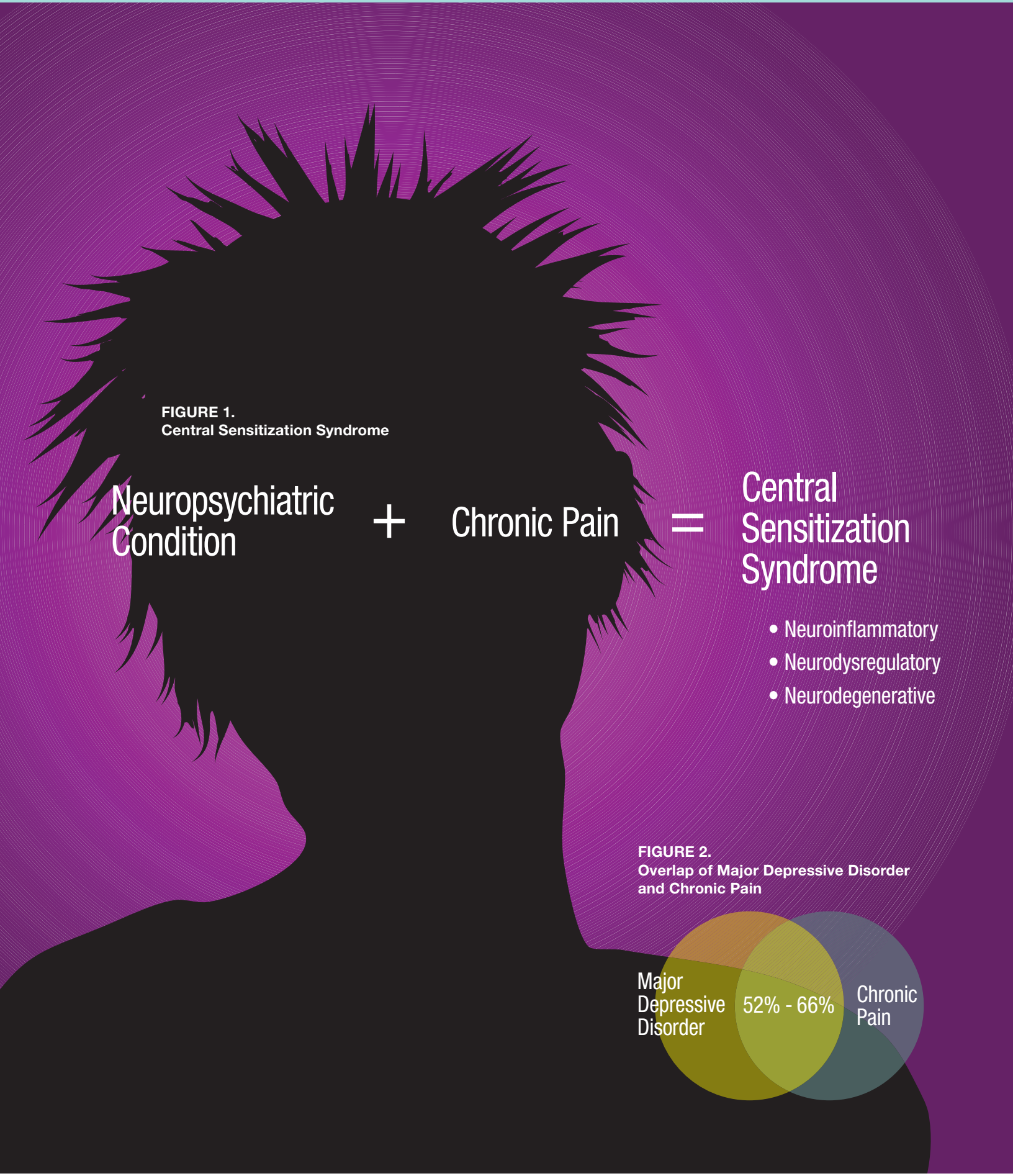


FIGURE 1.
Central Sensitization Syndrome

FIGURE 2.
Overlap of Major Depressive Disorder and Chronic Pain

Microglia: Pointing Us Toward a New Paradigm for Understanding and Treating Chronic Pain and Depression?

BY GARY E. KAPLAN, DO, AND JULIANA HEIMUR, BA

The comorbidity of chronic pain and some psychiatric conditions—specifically, major depressive disorder (MDD), post-traumatic stress disorder (PTSD), and generalized anxiety disorder (GAD)—is common. Individuals suffering with chronic pain and one of these psychiatric conditions are particularly resistant to treatment, incur substantially higher medical costs, and can expect poorer treatment outcomes. Chronic pain and psychiatric illnesses tend to occur together, as they share a common neurobiology. An abundance of epidemiologic and neurophysiologic data supports the following hypothesis: Chronic pain coupled with MDD, PTSD, and/or GAD reveal mutually reinforcing neuropathologic processes that may, in fact, represent a distinct condition: central sensitization syndrome (CSS) (Figure 1). Recognition of this paradigm necessitates changes in the manner in which health care providers diagnose and treat patients with these co-occurring illnesses.

Chronic pain, MDD, PTSD, and GAD have similar events at the neurocellular level. In particular, each has the ability to activate microglia and consequently promote central sensitization (CS). Central sensitization is defined as a pathological precursor of dysregulated nociception that sustains pain symptoms long after the initial insult to the body's nervous system, which may transition from a localized pain problem to a generalized pain disorder (1). At the level of the brain, CS results in dysregulation of numerous neuro-processes, which may account not only for the comorbidities of chronic pain and mental illness, but also a multitude of other comorbidities commonly seen with these illnesses. Understanding the neurobiology of microglia provides an understanding in how a number of seemingly unrelated diseases/events can result in the co-occurrence of chronic pain and mental illness, which may provide insight into developing new treatments for addressing chronic pain and comorbid psychiatric conditions.

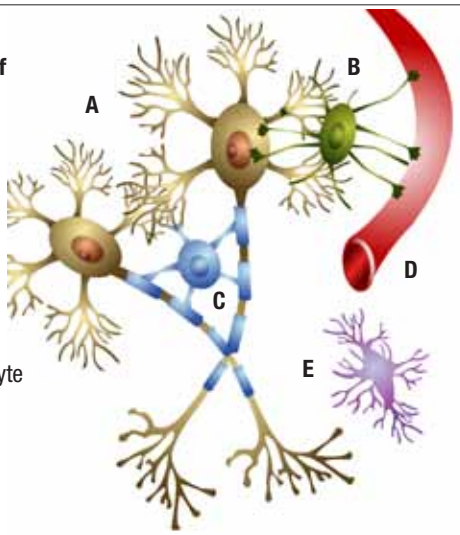
Epidemiology: The Overlap Between Chronic Pain and MDD

In a large study of primary care medical practices that included 12,000 subjects, 45% suffered with chronic pain, and about 7% had MDD. Nationally, about 6.6% of the population (21 million) suffers from chronic pain every year, and 16.27% of Americans (51 million) experience chronic pain during their lifetimes. Furthermore, approximately twice as many women as men suffer with chronic pain (2-4).

In a study of individuals suffering from MDD, 66% also had chronic pain (41% with chronic, disabling pain; 25% with non-disabling, chronic pain)(2). A different study further supported and expanded upon this epidemiology, in which 52% of individuals with MDD also suffered from chronic pain, and 65% with chronic pain also suffered from MDD (5). These statistics elucidate the finding that the comorbidity of chronic pain and MDD is very common (Figure 2).

Studies on the comorbidity of chronic pain with PTSD and GAD demonstrate similar rates of occurrence (6-8). Not surprisingly, the cost of treating an individual harboring both conditions is much higher than the cost of treating a patient with only one condition. More specifically, the financial burden of treating a patient with both chronic pain and MDD is 25% to 50% higher than addressing merely one condition alone (9,10). As one might expect, an individual's level of disability is greater when both conditions are present, and his/her likelihood of recovery from the condition is lowered. In fact, in a study of elderly patients, those suffering from both MDD and chronic pain were shown to have only a 9% chance of recovering from one or both of the conditions. In contrast, those who were afflicted with only one of these conditions had a 47% chance of recovery. It has been well-documented that individuals with comorbid chronic pain and depression have a shorter lifespan (11-14).

FIGURE 3.
Schematic of Microglia Environment



A Neuron
B Astrocyte
C Oligodendrocyte
D Capillary
E Microglia

FIGURE 4.
Various States of Microglia

Resting (ramified) Activated Macrophage

Chronic Pain and Depression: Overlapping Pathophysiologic Processes in the Brain and Body

Arnow et al. (2009) analyzed the relationship among depression, chronic pain, and medical cost, concluding that "pain is a major predictor of depression and anxiety, and depression seems to be an important predictor of work disability of patients with chronic pain (9)." That the two conditions so often present together is not surprising; chronic pain and depression share overlapping pathophysiologic processes in the brain, including common neuroanatomy, neuroendocrinology, and neuroimmunology. Perhaps of even greater significance, there is evidence that both conditions are neurodegenerative.

Neuroanatomy: Chronic Pain and Depression

Neuroanatomic regions implicated in both chronic pain and MDD include the somatosensory cortex II, insula, anterior cingulate cortex, hippocampus, and amygdala (15-21). In addition, loss of gray matter volume in specific regions of the brain has been documented in both chronic pain and MDD (22-24). While not yet conclusive, there is increasing research data, specifically neuroimaging studies in humans, indicating that the loss of gray matter volume occurs as a result of both of these conditions, and therefore, chronic pain and MDD are neurodegenerative diseases. There is also evidence that successful treatment of these conditions can reverse the gray matter loss (25,26).

Multidimensional Roles of Microglia

Microglia are involved in processes critical for the development and maintenance of the nervous system, while also constituting the innate immune system of the central nervous system (CNS) (27,28).

These cells exist apart from, and thus are not connected to, the neuronal circuits. In their resting (ramified) state, microglia are unattached from their surroundings and monitor their environment. They constantly prune and maintain the integrity of the CNS's circuitry. Microglia have the ability to influence the central nervous system, whether directly by interacting with synapses or indirectly by interactions with signaling molecules produced by astrocytes (Figure 3) (28-30).

Microglia possess a tremendous amount of functional plasticity, to the extent that microglia have been described as having a "chameleon-like phenotype (28)." In the developing brain, microglia are in an amoeboid state, actively guiding the development of a child's CNS by ensuring that healthy synapses are forming. In an adult, microglia usually remain in a resting state unless there is an assault on the nervous system. Amazingly, these cells can progress through various stages: from a resting (ramified) state into an active state, then to a hyperactive state, and finally into a macrophage that engulfs invading bacteria or viruses (Figure 4). Thus, microglia's response to their environment is both rapid and graded (29-31).

What Activates Microglia?

Researchers have discovered that microglia can express receptors for more than 35 different molecules (Table 1) (27,30). Further, numerous well-documented studies have shown that a variety of pathologies can activate microglia (Table 2) (28,30,31). Once the receptors on the cell-

TABLE 1.
Types of Molecular receptors on Microglia

- Cytokine/chemokine
- Toll-like
- Opioids
- Cannabinoid
- Benzodiazepine

TABLE 2.
Microglial Activation

- Trauma
  - Psychological
  - Physical
- Hypoxia
- Ischemia
- Neurodegenerative diseases
  - Alzheimer's
  - Parkinson's
  - Multiple Sclerosis
  - AIDS-related dementia
- Infections
- Bacteria
- Viruses
- Toxins
  - Lead
  - Diesel exhaust particles
- Medications: opioids

membrane surface determine the events of the surrounding area, the microglia can respond by releasing a wide range of molecular substrates. Microglia have the ability to produce more than 30 different substances including cytokines, chemokines, brain-derived nerve-growth factor, fibroblast-growth factor, quinolinic acid, glutamate, amyloid-precursor protein, and interleukins. This potpourri includes both inflammatory and noninflammatory factors (28,30).

Microglia Can Develop Functional Memory

There is a growing body of evidence that microglia possess the capacity to develop functional memory. Microglia detect an assault and become intensely activated. They eventually downregulate once the assault ends; however, when the central nervous system is subjected to subsequent, separate assaults over time, the microglia appear to upregulate, or reactivate, more quickly with each assault. In some individuals, it appears that microglia remain activated for long periods of time. Activated microglia can be seen in adolescents who binge drink. In response to heavy alcohol consumption, microglia upregulate, causing a pro-inflammatory condition in the central nervous system. Even after the drinking ceases, the microglia remain upregulated for years (32). This capacity of microglia to develop "functional memory" can cause an increase in disease susceptibility (33,34). Therefore, it is possible that this long-term activation of microglia may play a key role in sustaining chronic pain disorders. If so, treatments directed toward addressing microglia activity may provide a key mechanism for the development of more effective treatments for patients with CSS.

Patient Case: Fibromyalgia, Generalized Pain, and PTSD

Consider a female patient in her thirties presenting with a minor concussion associated with whiplash injury, without loss of consciousness. Her medical history reveals that at age 18, she was involved in a car accident and suffered a minor concussion. Within two years following the accident, her health devolved into, what had been diagnosed as, fibromyalgia. Further inquiry exposed that this patient had been raped at age 12. Upon description of the incident, it became clear that she suffered from PTSD.

Emerging knowledge in the field of microglia provides a new framework for understanding this patient's medical condition. Theoretically, microglia in the patient's body became intensely activated when she was sexually assaulted at 12 years old. Psychologically, she compensated for the assault, but the presence of PTSD indicated that the event was not resolved by her CNS, which remained in an activated state. It is possible that the microglia never downregulated after the traumatic event.

In this patient's case, her brain was primed at age 12 to later develop central sensitization at age 18 when a secondary, relatively minor, physical trauma occurred to her brain. If this patient's physical symptoms are to improve, the PTSD must be addressed as part of a comprehensive treatment program with the goal of downregulating microglial activity. The neurobiology of microglia provides insight into the connection that these events have on the patient's state of health.

In the majority of patients in my clinic, and virtually all of my patients with chronic pain and psychiatric conditions, the onset of the disease is rarely a singular event. More often, chronic pain evolves as a consequence of a series of assaults on the central nervous system over a period of time. Recent neurophysiology research has elucidated the importance of microglia in degenerative states. Understanding the neurophysiology suggests that comorbid conditions of chronic pain and either MDD, PTSD, or GAD may be a unified disease process mediated by microglia that is both neuroinflammatory and neurodegenerative.

Treatment Considerations: Medications

There are intensive research efforts underway to identify pharmaceutical agents that can modify microglial activity. It is important to note that several medications can affect microglia; for example, opioids cause activation of microglia. In fact, studies have demonstrated that the development of tolerance to opioids and opioid-induced hyperalgesia are, at least in part, mediated by microglia (35,36). Other studies have demonstrated that three different pharmaceutical agents (naltrexone, minocycline, and candesartan) are capable of downregulating microglia and decreasing inflammation (37-39). Currently, all three medications are under investigation for the treatment of CSS. In addition, one study showed naltrexone to be useful in treating fibromyalgia (40).

Challenges

The decision to diagnose a patient with CSS rests upon our ability to fully comprehend current research and apply that understanding to the patient's unique clinical presentation. Unfortunately, there are currently no biomarkers for CSS. Once identified, these biomarkers will allow for greater diagnostic accuracy and enable us to deliver more effective treatment for individuals with CSS.

Summary and Conclusion

The comorbidity of chronic pain and MDD, PTSD, or

GAD is common. These conditions cause neurodysregulation and neurodegeneration in the CNS. The underlying pathophysiology of these conditions is central sensitization. Central sensitization syndrome is a complex, neuroimmunologically mediated condition. At the cellular level, the fundamental mediator of CSS is microglia. Intensely and repetitively stimulating microglia can induce a type of "functional memory" that hypersensitizes these cells to future stimuli. Emerging knowledge of the pathophysiology of CSS provides an understanding in how a variety of seemingly unrelated illnesses and traumas can result in CSS. CSS has multiple, reinforcing etiologies that require considering the possibility that this condition is an evolutional process, and not simply a unique disease or the consequence of a single traumatic event. If health care professionals wish to successfully resolve CSS, they must consider adopting a clinical approach that solicits more extensive medical and social histories from patients, and that offers patients comprehensive and integrated treatment protocols.

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