TOTAL RECOVERY
SOLVING THE MYSTERY OF CHRONIC PAIN & DEPRESSION

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Disclosures

- Nothing to disclose
What if the beginning isn’t the beginning?
Figure 1. Approximate number of people suffering with chronic pain in the United States
Annual Economic Burden of Pain

- $560 - $625 Billion

Disability in the United States

- 47.5 million people report a disability

- Top two reported disabilities:
  1. Arthritis and Rheumatism ➔ 8.6 million
  2. Back and Spine Problems ➔ 7.6 million

  TOTAL = 16.2 MILLION PEOPLE
What is the leading cause for disability in the U.S. for ages 15 to 44?

Major Depressive Disorder (MDD)

Number of individuals suffering from a mental disorder...

- 14.8 million ➔ Major Depressive Disorder
- 3.3 million ➔ Dysthymia or Chronic Depression
- 6.8 million ➔ Generalized Anxiety Disorder
- 7.7 million ➔ PTSD
- 6 million ➔ Panic Disorder

TOTAL = 38.6 MILLION PEOPLE
Economic Cost of Mental Illness

- Total costs = $148 Billion

- Out of the $148 Billion:
  - Depression → $83 - $100 Billion
  - Anxiety Disorder → $42 Billion

The comorbidity of neuropsychiatric disease (depression, GAD, PTSD) and chronic pain are common.
Chronic Pain

- 50% to 65%
- 6.6% per year = 21 M people
- 16.7% over a lifetime = 51 M people
- ♀ > ♂ 2:1 ratio

Major Depressive Disorder

- 15% = 47 M people

When depression and chronic pain occur together, treatment success is dramatically lower and cost is dramatically higher than when these conditions occur separately.

Figure 2. Overlap of Major Depressive Disorder and Chronic Pain

2, 3, 5, 12, 15, 24, 27, 38
Cost of treatment of individuals suffering from both these conditions is 25-50% higher than the cost of treatment for either condition alone.

Disability is greater when both conditions are present than in either condition alone.

Likelihood of recovery from either is less 47% vs. 9%.

Increased morbidity and mortality.
- Common genetic vulnerabilities
- Common neurobiology
  - Neuroanatomy
  - Neuroendocrinology
  - Neuroimmunology
  - Neurotransmitters

- **Neurotransmitters**
  - Inflammatory cytokines alter the metabolism of serotonin and dopamine
  - Dysregulation of serotonin and norepinephrine
  - Dysregulation of glutamate

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**Deregulation of the Hypothalamic-Pituitary-Adrenal Axis**

Damage to hippocampal neurons and reduces neurogenesis

- Disruption of the normal circadian cycle
- Reduced basal cortisol levels

*Figure 4. Deregulation of the hypothalamic-pituitary-adrenal axis*
- Elevated inflammatory cytokines
  - IL-1
  - IL-6
  - (TNF)-alpha
  - Loss of gray matter

Depression and chronic pain share common neurophysiology and neurobiology. They are mutually reinforcing neuropathologic processes.
What if we are thinking about this all wrong??

Depression and chronic pain are neuroinflammatory, neurodysregulatory, and neurodegenerative conditions.
The mediators of inflammation in the brain and spinal cord are glia cells and microglia are the major neuroregulatory glia cells.
Neuroglia

- Connective Tissues of the CNS
- Insulate neurons/form myelin
- Supply nutrients and oxygen to the neurons
- Modulate neurotransmission
- Destroy pathogens
- Create CSF
- Form BBB and Blood CSF Barrier

Figure 5. Pie chart of the distribution of neuroglia cerebral cortex
Figure 6. Microglia and the Central Nervous System. Adapted from *Human Anatomy* by M.P. McKinley, and V.D. O’Loughlin, 2006.

Microglia

- “Microglia are resident cells of the brain involved in regulatory processes critical for development, maintenance of the neuronal environment, injury and repair”
- “Electricians” of the CNS
- Innate immune cells of the CNS

A = Neuron
B = Astrocyte
C = Oligodendrocyte
D = Capillary
E = Microglia

18, 19, 25, 41
Microglia “Electricians”

- Exist apart from and are not connected to the neuronal circuits
- “Resting” (Ramified) microglia are sessile not inactive
- Maintain the integrity of the CNS circuitry
- “microglia can potentially influence information processing in the CNS, either indirectly via their interactions with astrocytes, or directly by interacting with synapses”

Microglia Innate Immune Function

- Functional plasticity/Chameleon-like phenotype
- Low threshold of activation
- Rapid responders to CNS pathology
- Graded response to changes in their environment

18, 19, 49, 25, 43
MICROGLIOSIS
1. Increase cell number
2. Morphologic changes
3. Phenotypic changes
4. Protein expression
5. Release of immunoregulatory products

17, 50

NEUROIMMUNE INTERFACE
REACTIVE MICROGLIOSIS
DAMPS

Neuronal Death Damage

IMMUNE ACTIVATORS
ATP
MMP9
Cytokines
Chemokines
NRG1

Infection
PAMPS

17, 50, 51
Microglia cells are responsive to and activated by a wide variety of environmental stimuli.
Microglia cells possess “memory” and repetitive stimulation can lead to a chronic inflammatory state in the CNS.
In the spinal cord, this chronic inflammatory state results in neuropathic pain and myofascial pain—this is called **central sensitization**.

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**Central Sensitization Syndrome**

9. **CSS = Chronic Pain + Neuropsychiatric Condition**

- Neuroinflammatory
- Neurodysregulatory
- Neurodegenerative
What we thought was...

Depression
&
Chronic Pain caused...
  Inflammation
  Dysregulation, and
  Degeneration of the brain

What we now know is...

  Inflammation
  Dysregulation, and
  Degeneration of the brain
  Actually cause Depression and
  Chronic Pain
DISEASE
vs.
SYMPTOMS

Chronic pain and depression are symptoms of inflammation in the brain.
Inflammation is a result of cumulative assaults on the brain

Treatment of CSS

A comprehensive treatment requires individualization and includes:

1. Addressing etiologic & cofounding issues
2. Meditation
3. Exercise
4. Nutrition
5. Sleep
6. Medications
7. Acupuncture
8. Psychotherapy
9. Physical Therapy
TOTAL RECOVERY IS POSSIBLE

- Treat the root cause **NOT** the symptoms
- Treatment must be individualized and comprehensive

I kindly thank you for your attention.

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