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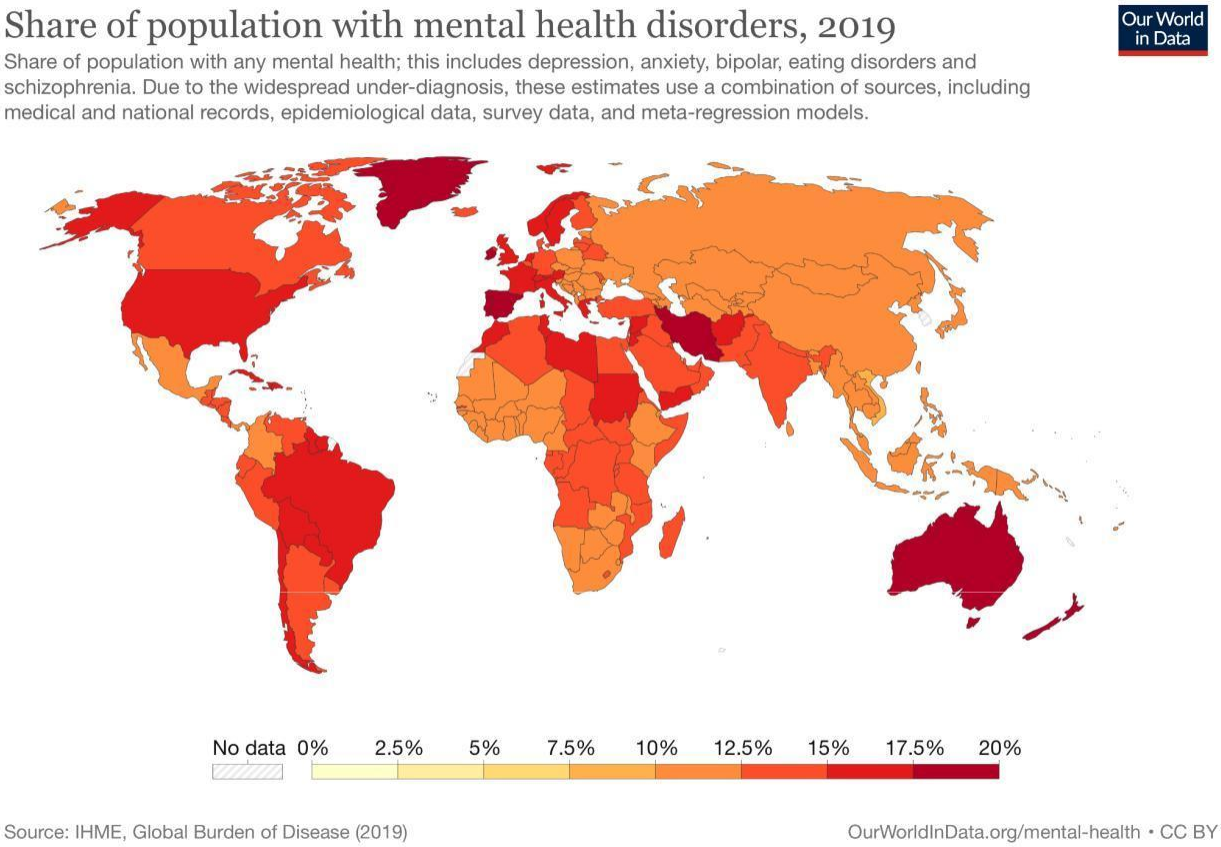
The Role of Microglial Cell Activation in Mental Illness

Major depression, anxiety, alcohol/substance use disorders, schizophrenia, bipolar disorder, and dysthymia (persistent mild depression) are among the leading causes of disability in the United States. Mental disparities such as these affect approximately 970 million people worldwide, generally females (11.9%) more than males (9.3%). Mortality

rates of those individuals are significantly higher than the general population, resulting in a median life expectancy loss of 10.1 years and accounting for around 8 million

deaths yearly. Medical expenses are significant and rising. Expected costs to treat anxiety and depression worldwide is estimated to be $147 billion by the year 2030.



Empirical evidence has demonstrated mental illness as a pro-inflammatory condition with common underlying themes of microglial cell activation and dysfunction, neuroinflammation and excitotoxicity, and oxidative stress causing neurotransmitter imbalances and damage to neurons. Depression, neurodegenerative disease, anxiety, bi-polar, and schizophrenia are biomarkers of neuroinflammation and neurodegeneration.

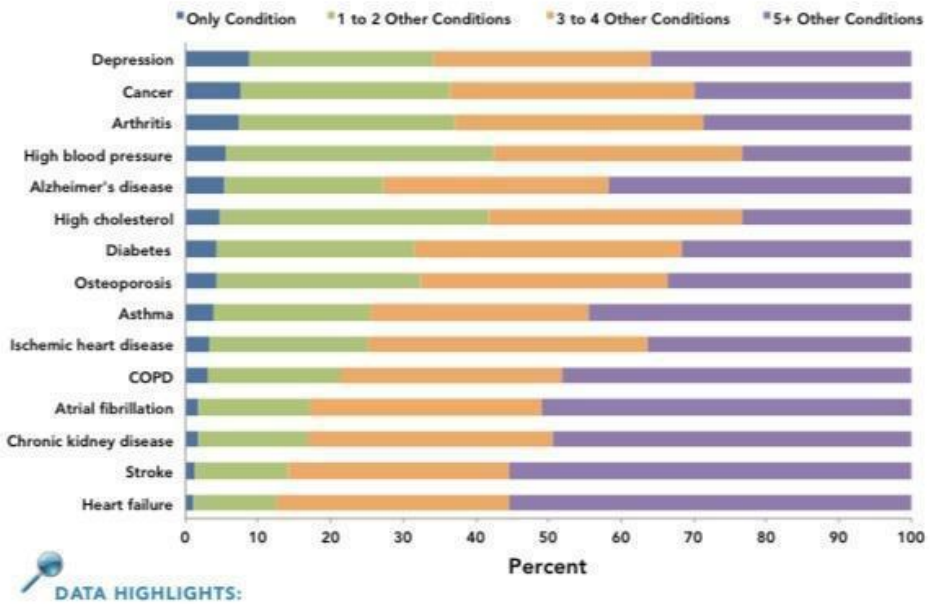
All neurological presenting complaints are inflammatory.

Pharmaceutical research guides scientists towards the development of synthetic drugs with very specific modulating, inhibiting or up regulating mechanisms of action not always known or fully understood. A holistic functional treatment perspective questio

the root causes of the dysregulated mechanisms to determine effective naturopathic methodologies for increasing the functionality of the mechanism.

Roughly 30% of individuals with depression have more than 5 other conditions; 88% of are metabolically ill. 43% have diabetes, 70% are overweight or obese, and 24% have fatty liver disease. IBS, diabetes, cardiovascular disease, thyroid conditions, autoimmune diseases, and others are largely linked to mental health conditions. The naturopathic perspective questions how a mental health crisis can be resolved during an infectious disease crisis with drugs that are immunosuppressive.

Figure 4.1 *Co-morbidity among Chronic Conditions for Medicare FFS Beneficiaries: 2010*



DATA HIGHLIGHTS:

Six percent of beneficiaries with high blood pressure had no other condition present, while 23% had 5 or more additional conditions.

Stroke and heart failure were highly co-morbid conditions with about 55% of beneficiaries with these conditions having 5 or more additional chronic health conditions.

This pattern of co-morbidity held for men and women, with beneficiaries 65 years and older and dual-eligibles having greater co-morbidity.

CHRONIC CONDITIONS AMONG MEDICARE BENEFICIARIES, CHARTBOOK: 2012 EDITION 26

70% of Americans are overweight or obese, and the diabetes belt of America uses the most psychiatric drugs. Hyperglycemia, high body fat, and fatty liver disease all directly influence mental health disorders and neurodegeneration. Monoclonal antibodies block interleukin-6. Increased body fat mass increases inflammation by secreting excess interleukin-6 which stimulates the liver to produce C-reactive protein and interleukin-6 stimulates microglial activation. The nature of immunosuppressant drugs come with severe effects.

Monoclonal antibodies are designer antibodies that target specific proteins in the body by blocking pro-inflammatory cytokines. The mechanism of action of the drug Humira used for the treatment of irritable bowel disease blocks and neutralizes the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-alpha). This drug has potential side effects like immunosuppression, increased risk of infection, and death. Consumers are not always fully aware of the implications of inhibiting the immune system’s ability to convey a pro-inflammatory message to the body. While pharmaceutical drugs can prevent some signaling causing symptoms and damage, they also inhibit the body's ability to combat infection and to remodel tissues.

SSRIs are selective serotonin reuptake inhibitors that are prescribed for depression. Effective treatment with these medications are marginal and have severe side effects like suicidal ideation. Newer pharmaceuticals that block interleukin 6, a pro-inflammatory cytokine/anti-inflammatory myokine, are prescribed in treatment-resistant depression. Blocking interleukin 6 can prevent some neuroinflammation and disrupted brain chemicals but the medications have a long list of deleterious potential side effects such as increased risk of infection.

Depression, anxiety, bipolar disorder, and schizophrenia are epigenetic inflammatory diseases driven by oxidative stress and inflammation, each potentiating the other. The cytokine storm creates oxidative, inflammatory, and nitrosative molecules, affecting neurogenesis and neural homeostasis.

Microglial activation is the underlying etiological factor in all inflammatory diseases driven by oxidative stres

Oxidative Stress

- Depletes levels of glutathione (GSH) needed for efficient NMDA receptor site function
- Can destroy digestive enzymes needed to break down casein and gluten
    1. Produces inflammation and leaky gut allowing toxins into the bloodstream and crossing the blood-brain barrier (BBB)
- Leads to poor immune function
- Disrupts methylation cycle

Microglial cells are the white blood cells of the central nervous system. These are innate immune cells and the first line of defense in protecting the brain. Microglial cells are the primary frontline defense and act as phagocytic and antigen presenting cells and regulate neuroinflammation with a supportive role of astrocytes. They guard against foreign invaders like pathogens and toxins, and initiate an adaptive immune response. These defenders coregulate neuroplasticity and neurogenesis by participating in synaptic trimming and pruning.The rewiring of neural connections through neuroplasticity and synaptic trimming and pruning are a focal point of neural development and neurodevelopmental disorders.

The activity of microglial cells is extremely important when trying to improve neurodevelopment or prevent neurodegeneration by regulating the development of neural networks. They can be supportive to CNS and brain healing or they can promote pathogenesis and pathophysiology, each depending on how the SNPs (single-nucleotide polymorphism; the most common type of genetic variation among people) are phenotypically expressing themselves.

The underlying physiology and biochemistry of all neurodegenerative disease involves oxidation and microglial activity.

Microglial cells are innately quiescent until they receive input signals from pro-inflammatory cytokines like interleukin 6 and TNF-alpha alerting the need for response.

The M1 microglial proinflammatory phenotype factor is neuro destructive. LPS, TNFa, IFNy, IL-6, IL-1β, superoxide, neopterin, quinolinic acid and MMP9, and influences cytotoxicity, excitotoxicity, neuroinflammation, antigen presentation, acute immune response, breakdown of the blood brain barrier (BBB) and damage molecular pattern signaling.

The M2 microglial anti-inflammatory phenotype factors are neuroprotective and neuroregenerative. IL-4, IL-13, IL-10, BDNF, GDNF, IGF-1, TGF-β1, and NGF influence phagocytosis, anti-inflammatory signaling, homeostasis restoration, extracellular matrix protection, and neuroprotectiveness.

Microglial homeostasis can prevent excessive neural inflammation and oxidative stress leading to leaky brain and neurodegeneration. This happens under normal circumstances, however, excessive microglial activating triggers initiate the imbalance.

Major factors that trigger microglial activation

- Food allergies/intolerance
- Nutrient Insufficiencies (Vitamin C, D, A, K, B9, B6, B12, E, Zinc, Omega 3 etc.)
- Extracellular zinc
- Homocysteine
- Fatty live

- Inflammation/cytokines
- Stress/cortisol
- Microbes (bacteria, fungi, parasites, viruses)
- Heavy Metals (Mercury, Lead, Arsenic etc.)
- Toxicants (BPA, Phthalates, Parabens, Glyphosate etc.)
- Inflammatory Cytokines (IL-6, IL-1β, TNFα, IFNγ)
- Oxidative Stress (ROS, RNS, Free Radicals etc.)
- Histamine (MCAS, Allergies, Food intolerances etc.)
- Gut Dysfunction (Dysbiosis, Leaky Gut etc.)
- HPA Axis Dysfunction (cortisol, norepinephrine etc.)
- Heat or Cold Stress
- Head Injury (TBI, concussion etc.)
- Trauma and Social Isolation
- Insulin Resistance and Hyperglycemia

Microglial cells respond in the way they are programmed to respond based on the input signals they receive through the environment. Whether the environment is pro inflammatory, pro oxidative, toxic, stressful or health promoting, the microglial cells will respond accordingly.

Microglial activation, neural inflammation, and excitotoxicity pathways directly alter neurotransmitter activity. Activated microglial cells can release a variety of mediators. Some are neuroprotective like brain derived neurotrophic factor (BDNF) which facilitates neuroplasticity and neurogenesis while others are inflammatory and cytotoxic like Quinolinic acid.

Key Mediators in Microglial Release

- BDNF
- Glycine
- Quinolinic acid
- Adenosine
- IL-1B
- IL-6
- IFNY/TNFa
- Nitric oxide
- Superoxide
- Prostaglandins
- Neopterin
- APP
- HMGB1
- GLP-1
- IGF1
- MPO
- CRP
- MMP

The use of exogenous BDNF is being studied for the clinical treatment of type 1 diabetes using a mouse model which injects the rodents with lipopolysaccharide endotoxins to stimulate inflammation and neurodegeneration. Researchers then inject the mice with exogenous BDNF, resulting in regeneration of beta cells in the pancreas and decreased hepatic glucose excursions with improved blood sugar regulation.

Quinolinic acid is a cytotoxic substance released by microglial cells, neurons, and other glial cells that can increase NMDA receptor activity, neurotoxicity, or excitotoxicity that drive symptoms like anxiety and depression, and breakdown of blood-brain barrier (BBB).

An inflammatory event in the CNS will cause damage to the brain cells and neurons. As damage occurs, cells release damage associated molecular patterns which include HMGB 1. If a pathogen crosses the BBB, it triggers microglial activation and neuroinflammation resulting in cell damage. All the neurons spill out different damage associated molecular patterns such as HMGB 1 that bind to specific pattern recognition receptors, like the mach 1, stimulating more M1 microglial activity. Excessive M1 phenotypical expression drives more inflammation and more neuronal damage. It is a self-perpetual cycle.

Gut dysbiosis, translocation of endotoxins, exotoxins, mycotoxins, gram negative dysbiotic bacterial overgrowth, broken mucosal barrier, and food antigens send signals through the vagus nerve to the brain for microglial cell activation. Microglial activity can cause a breakdown of endothelial blood brain barrier leading to leaky brain. Endotoxin translocation drives inflammation systemically, creating the breakdown of the blood-brain barrier resulting in pro-inflammatory toxins and mediators in cytokines that travel into the central nervous system resulting in contamination of the CNS.

The psychiatric system is based on the theory of mental illness known as the monoamines theory which focuses on mental illness through the lens of brain chemicals. The frontline medications are designed to work by modulating the activity of neurotransmitters like serotonin, dopamine, glutamate, GABA, and others.

The cytokine theory of mental illness examines the role of cytokines in influencing mental health through the mechanisms of microglial occupation and the trophic theory which focuses on neurotrophic factors like brain derived neurotrophic factor and nerve growth factor.

Proinflammatory conditions among Americans result from a variety of metabolic dysregulations such as obesity, diabetes, fatty liver, leaky gut/dysbiosis, leptin resistance, hormone imbalances, HPA axis dysfunction, thyroid problems, nutrient deficiencies, methylation dysfunction, hypertension, leaky brain, and inflammation. With the strong correlation between metabolic physiology and mental illness, metabolic components need to be addressed through behavior modification for a positive mental health outcome to occur.

Fatty liver, including non-alcoholic fatty liver, will increase free fatty acids, ceramides and unconjugated bilirubin, that can break down the blood-brain barrier and trigger microglial activation.

Impaired bioenergetics of the brain can result from poor mitochondrial functionality or low mitochondrial density. Dysfunction can increase reactive oxygen species production, like hydroxyl radicals, that trigger the neuroinflammatory process. Naturally improving mitochondrial function can be achieved through lifestyle modification of diet and exercise.

Neuroinflammation inhibits CNS detoxification and promotes excitotoxicity. The activation of microglial cells impacts the breakdown of the blood brain barrier. Neuroinflammation and excitotoxicity cause neurotransmitter imbalances and damage neurons.

Reduction of Microglial Activation

Choose organic foods that promote proper digestion and absorption. Whole food diets, including fresh fruits, vegetables, nuts, seeds, and whole grains are health-promoting options. Mediterranean-type of diets, minus dairy, appears to be the most beneficial.

Dairy is among the top allergens among humans, followed by wheat, then eggs. Vegan diets do not permit any products that come from animals and can significantly lower systemic inflammation. Microbiome dysbiosis diets include FODMAP, anti-fungal, gluten-free, and histamine diets which can be beneficial for different individuals.

Elemental diets are used for people who have malabsorption, IBD, SIBO, and other intestinal disorders. It is used to treat dysbiosis and consists of a bitter drink that is used for 2 to 3 weeks to reduce inflammation in the digestive tract. There is no food on this diet therefore can induce rapid weight loss. A nutrition professional should be involved to ensure proper calorie intake.

Most individuals will experience tremendous benefit by eating an organic whole food diet that is plentiful in colorful plant foods, nuts, seeds, oils, low-sweet fruit, and some complex carbs. Nutritious food choices help to develop a healthy relationship with food and self.

Exercising is medicine. It can potentially increase neuroplasticity. Clean drinking water with adequate electrolyte and mineral concentration can hydrate the cells and is crucial for all health. Coffee, tea, and other water-based beverages are fine in moderation.

Processed drinks and alcohol should be limited. Intermittent Fasting has been shown to have an antidepressant like effect and increases neuroplasticity, which may be of therapeutic value in mental illness and neurodegenerative conditions.

When managed effectively, stress can make us more resilient and help us cultivate our character. Many struggle to effectively manage stress and should consider various modalities like mindfulness, meditation, breath work, spiritual practice, exercise, and others. Excess stress signaling through the HPA axis is devastating to the gastrointestinal tract and mental health.

Quality sleep is essential to health. Most adults need 7 to 9 hours of deep and restful sleep each night. Following the circadian rhythm of the sun, limiting and blocking artificial light, and creating a soothing bedtime routine can all be helpful to optimize sleep. Non-ionizing radiation (wifi) is a probable carcinogen. EMF has been shown to increase oxidative stress and inflammation in the body. Electronics, including tv, should be kept out of sleeping quarters and away from the body during sleep.

The vagus nerve serves as the highway of communication between the Central Nervous System (CNS) and Enteric Nervous System (ENS). Vagus Nerve Stimulation was approved as a treatment option for ‘treatment resistant depression’ by the FDA in 2010. Vagus Nerve Stimulators are implanted into people and controlled by an external battery pack. Because of this, it might not be the most practical option. Experiments have been done with TENS units (transcutaneous electrical nerve stimulation) that show some efficacy, but somewhat impractical and low results. Cold/heat exposure and breath work also seem to improve vagal tone.

Low stomach acid, inadequate bile, and pancreatic insufficiency are commonly compromised. Adequate digestive juices/ enzymes spore-based probiotics are the next-generation in probiotics. Spore probiotics survive the acidic digestive juices and are able to more effectively reach the intestines where they will morph into their active bacterial form and exert their healing effects. Research demonstrates that spore probiotics help improve microbial diversity, abundance of key-stone strains, increase short chain fatty acid production, decrease GI inflammation, improve immune function, and heal the mucosal barrier and epithelial lining.

Omega 3 fatty acids contain EPA which is particularly helpful for decreasing neuroinflammation and improving cognitive health. Doses of 6 grams daily can improve mental dysfunction within 3 days.

Zinc is crucial for immunity, detoxification, neuroplasticity, neurotransmitter function and more. The ‘nervous system calming’ mineral is needed for countless biochemical pathways.

Various phenolic compounds have been shown to decrease inflammation and oxidative stress. These include green tea, curcumin, resveratrol, and others. Some research suggests they may help boost BDNF and neuroplasticity as well.

Water soluble B vitamins are crucial for proper neurochemistry and detoxification. B vitamin insufficiencies are extremely common.

B6, B9, B12, B3, and B5 are crucial for neurotransmitter synthesis and metabolism.

Multiple mitochondrial nutrients and antioxidants have been studied for their efficacy in mental health dysfunction. Mitochondria require adequate nutrients to provide the body and brain with cellular energy.

Endocannabinoids have strong evidence to boost GABAergic activity and decrease neuroinflammation. It is a powerful antioxidant nutrient that can boost immunity, decrease oxidative stress and inflammation, and decrease microglial activation.

Vitamin D regulates the permeability of the gut and blood brain barrier (BBB) and can decrease microglial activation while boosting neuroplasticity.

Medicinal mushrooms like reishi, chaga and turkey tail have powerful immunomodulatory properties and can improve the health of the mycobiome (fungal microbiome), gut, immune system, and brain.

Leafy greens, sunflower seeds, watercress, soybeans, pumpkin seeds, mushrooms, broccoli, and peas contain tryptophan, the precursor to serotonin.

Many botanical adaptogens have been shown to modulate HPA axis activity, balance cortisol and stress hormones, improve neuroplasticity, and balance neurotransmitters.

Adaptogens

- Panax ginseng
- Acanthopanax senticosus, previously known as Eleutherococcus senticosus
- Rhodiola crenulata
- Schisandra chinensis

Quercetin has many anti-inflammatory, immunomodulatory, and neuroprotective properties.

Magnesium is highly insufficient in the standard American diet. A diet that is high in magnesium and tyrosine-rich foods are the building blocks of dopamine production. Tyrosine is an amino acid. Tyrosine is in sesame seeds, soybeans, and nuts and contains the precursor amino acids to dopamine, norepinephrine and epinephrine. It's absorbed into the body and then goes to the brain, where it's converted into dopamine. Foods known to increase dopamine include almonds, apples, avocados, bananas, beets, chocolate, green leafy vegetables, green tea, lima beans, oatmeal, oranges, peas, sesame and pumpkin seeds, tomatoes, turmeric, watermelon and wheat germ.

IMMUNE SYSTEM and GUT HEALTH

A network of neurons overlay the bowel.

The human body is considered to be a hologiont organism, also known as a superorganism, that is composed primarily of microbes. There are more microbial components to the human body than any other thing, including human cells. What this means, is that we are more microbes than we are human. What we know thus far is that most diseases have a disturbance in the microbiome. This is called dysbiosis and leads to dysfunction of the tissues that microbes inhabit.

The Immune system was designed to protect the body from microbes. So how does a system designed to protect us from something, live in the very same thing?

The reason for this has been explained. Research suggests that the microbes and the immune system have continuous conversations back and forth. The microbes that naturally inhabit the area will alter the immune system when an outsider invades the mucosa. Because this process is so important in immune response, it is to say that the immune system would cease to exist without microbes.

Symbiogenesis is the result of the permanent coexistence of various bionts to form the hologiont (namely, the host and its microbiome). Ricardo Guerrero et al, Aug 2013

Reductions in hippocampal volume have been reported in patients suffering from a variety of psychiatric disorders including depression, addiction, and schizophrenia. Loss of smell is the 1st marker of hyposmia (inflammation of hippocampus).

All disease begins in a leaky gut which stimulates zonulin release, creating intestinal permeability. Zonulin release, gluten, and small exposures to large amounts of bacteria are the most powerful triggers.

Gliadin activates the innate immune system via TLR4 the protective mechanisms against bacteria. In the digestive tract it is located in the proximal part of the small intestine. TLR4 activates nuclear factor kappa B (NF-κB) which produces IL-1 beta (IL-1β) , IL 6, tumor necrosis factor, interferon gamma, and the entire innate immune cytokine cascade.

Gluten is misinterpreted by the zonulin pathway as a potential harmful component of a microorganism. The protein structure of gluten and wheat is similar to harmful components of microorganisms. Gliadin is what can cause immediate increase in gut permeability. This process immediately takes place in all individuals who ingest gluten, within minutes. Gluten is not essential and has no significant biological value to the body. IgA anti-gliadin antibodies react with blood vessel structures in the brain. It can take 2-4 months to heal inflammation from one small exposure to gluten. Lesions in the brain can be reversed with a gluten-free diet. A family history of autoimmune disease warrants an assessment of gluten sensitivity (celiac, Chrohns. Etc).

The majority of chronic inflammation results from gluten. More than 65% of patients get better after removing it. When the cause of neurological disease is unknown, the percentage of patients with elevated antibodies to gluten is 57% (ratio is 8:1) as seen in depression. IgA (anti-gliadin antibodies) cross-reacts with the blood antibodies to wheat and attack the blood vessels of the brain creating leaky brain whereby pathogenic material and debris enter and cause an inflammatory storm.

All disease begins in the gut.

Immune System Response

Innate immunity involves basophils, eosinophils, neutrophils, mast cells, and natural killer cells. They are nonspecific, act quick, and require inflammation. Tissue damage occurs in this phase and can create extensive damage to healthy cells where repair will be needed. This phase should only last a couple of hours to a couple of days before moving into the adaptive immunity phase.

The adaptive immunity phase can last a few days to a few weeks. Here, the T cells and B cells undergo pattern recognition to identify and destroy invaders. B cells provide antibodies while T cells will reduce a pathogen specific immune response.

Macrophages and dendritic cells identify pathogenic invaders and present them to the B and T cells. A pathogen-specific immune response then occurs.

Innate immunity Adaptive Immunity (B and T cells) requires inflammation.

When a virus enters the body, the release of interferon occurs. It is a protein that is released in response to pathogenic activity. It is what ultimately is responsible for creating a fever. Both the infected cell and microbiome can release interferon. The release of interferon triggers cell death, and other immune cells come to the site of infected cells.

Vitamin A provides the substrate for microbes to make interferons

Flagellin activates Pattern Recognition Receptors (PRR) which is designed to recognize patterns of pathogenic invaders. This triggers TLR5 which stimulates the release of Interleukin-18 and then Interleukin-22.

1. IL-18 is required for apoptosis (cell death)
2. IL-22 repairs and replaces damaged cells

Both IL-18 and IL-22 come from signaling from the bacteria in the microbiome. Signaling from the microbiome is required for proper immune system response. A proper immune system response requires a healthy microbiome.

Commensal natural bacteria produce short-chain fatty acids, like butyrate, which are required to increase and maintain mucus production. Mucus creates a barrier where pathogens enter the body. It increases the production of antiviral compounds to prevent viral replication.

Examples of healthy bacteria

- Bacillus: produces surfactin which prevents invasion from specific types of coronavirus.
- B. subtilis produces Levan; antimicrobial compound which inhibits different forms of viruses
- S. Subtillis, also known as P18, neutralizes influenza in vitro.
- Bacillus subtilis: produces antimicrobial lipopeptides containing fengycin and surfactin; antiviral effects.

If a pathogen enters a healthy mucosa containing flagellin, the presence of pathogenic invaders is quickly recognized due to the many pattern recognitions (PRR) available. On the flip side, an unhealthy microbiome will delay the immune system's response. A disruption in the microbiome (dysbiosis) occurs with the use of antibiotics and can inhibit the body's ability to fight off disease. Thus, the principle remains that administering antibiotics for a virus weakens the body's ability to fight off the illness and does not

create memory recognition of the pathogenic organism. Long term immunity is then not attained.

Macrophages identify a virus and then eat the infected cells to control the rate of its replication. Dendrites locate and eat the free virus particles, and send them to the lymph nodes in the late illness phase. Once the virus is in the lymph nodes, CD4 and CD8 T-cells are activated. CD4 activates B cells that produce antibodies against the specific pathogens, while CD8 cells turn into cytotoxic cells and directly kill infected cells.

Stages of Immune Response

1. Early innate response
2. Late innate response (inflammation)
3. Early adaptive response (anti-inflammatory state)
4. Long term adaptive immunity

When damage to cells occurs, the body also releases cells like proteins in effort to assist with repair. During this process, the immune system can accidentally identify those cells as part of the pathogenic invaders and then create B cells against it. This causes an autoimmune response.

Reducing inflammation can reduce the potential for an autoimmune response.

ALL STAGES OF TRUE IMMUNITY DEPEND ON THE MICROBIOME

- If the microbiome is dysfunctional, stages of immunity are halted and inflammation remains.

- If the microbiome is inadequate to provide an anti-inflammatory response, inflammation remains and cytokines continue to be released. Cytokines play a key role in the regulation of immune system response.

THE MICROBIOME AND LYMPHOID ORGANS

There are two classifications of lymphoid organs.

1. Primary lymphoid organs
2. Secondary lymphoid organs

The primary lymphoid organs consist of the thymus and bone marrow. This is where the majority of the immune system is made. These cells are immature and do not yet have the ability to recognize pathogenic invaders. They require moving into secondary lymphoid organs and tissues where they mature and learn pathogenic pattern recognition.

Secondary lymphoid organs and tissues include Walderyer's rings lymph nodes, tonsils, adenoids, bronchus-associated lymphoid tissues, other lymph nodes, bone marrow, spleen, lamina propia, Peyer's patches, and mesenteric lymph nodes.

The microbiome promotes the maturation of the secondary lymphoid organs.

The entire inside of the body is covered in mucosa and trillions of microbes live in there. The mucosa is the largest surface area in the body, measuring around 4,000sq feet. It outnumbers the amount of human cells. Everything that enters the body will enter through the mucosa. The naturally occurring commensal microbes in the mucosa are the first to detect a pathogenic disruption. All immune system activity occurs in the mucosa. This is where an attack on a cell is decided.

All immune response happen in the mucosa. The immune system would cease to function without the support of the microbiome.

A chronic inflammatory state of the microbiome results in constant immune system activation. This delays time for the pathogens to replicate, causing tissue damage, high fever, and immune response. Additionally, it delays the Treg cells, giving opportunity for autoimmune response to develop.

Chronic low grade inflammation continually triggers inflammatory signals.

Healthy, endogenous, commensal microbes in the lumen continually communicate with the immune cells by way of cross-talk. For example, butyrate, from the microbiome, binds to surface proteins like GPR109A (G-Protein Coupled Receptor) which release dendrites and macrophages to reduce inflammatory cytokines. This is part of the late innate immune response.

The early stages of adaptive immunity will yield macrophages and dendrites that create an anti-inflammatory response. When butyrate, a short-chain fatty acid, is added onto macrophage and dendrite surfaces, inflammation stops and anti-inflammation begins. In the same fashion, when butyrate binds with HDAC. Treg cells are activated. T Regulatory cells will suppress the immune responses to the body's own cells that are released during inflammation. This will decrease an autoimmune response.

The microbiome help controls the immune response

Improving Immunity

1. Professional-grade probiotics
2. Heal leaky gut
3. Eliminate inflammation
4. Improve plant-based diet
5. Lower stress
6. Get into nature

An anti-inflammatory response is required for immunity.

CONCLUSION

Mental illness is a multifaceted chronic inflammatory condition with many solutions.

At the core of all mental illness is chronic microglial inflammation that creates a breach of the blood brain barrier. This breach allows toxins and pathogens to enter the brain where the microglial cells become hyperactive. The brain becomes inflamed from neuroinflammation and excitotoxicity, causing neurotransmitter imbalances and damage to neurons. The activity of microglial cells is extremely important when trying to improve neurodevelopment or prevent neurodegeneration. One of the major factors that trigger microglial activation is leaky gut.

Leaky gut (increased intestinal permeability) can allow large amounts of exorphins to enter the bloodstream from the digestive track and access the brain. The enzyme dipeptidyl peptidase-IV (DPP–IV) breaks down gliadorphin and casomorphin into harmless amino acids. The DPP-IV function can be inhibited by gliadin components of gluten. Inhibition results in less gliadorphin and casomorphin break down, leaving more to access the brain. A diet excluding grains and dairy products can reduce mental dysfunction and improve recovery.

DPP-IV Insufficiency Causes

- Wheat and dairy products
- Genetic susceptibility
- Antibiotics
- Gelatin from vaccines
- Candida
- Mercury and other heavy metals
- Pesticides
- Nutritional deficiencies
- Food allergies
- Cerebral allergies

Cellular physiology is highly dynamic. Testing for various biomarkers can help identify areas of imbalance for individualized care plans. Fecal inflammatory markers can assess the degree of inflammation in the gut whereas serological blood biomarkers assess inflammation in the periphery. Testing infers the likelihood of microglial activation and neuroinflammation of the CNS. A meta-analysis examining C-reactive protein found a direct correlation between serum levels of C-reactive protein versus central nervous system levels of neuroinflammation.

Identify All Triggers of Inflammation

- Elevated antibody panels
- Neuroinflammation
- Neurotoxicity
- Neurotransmitter balance
- Methylation and epigenetic
- Oxidative and nitrosative stress
- Neurotrophic activity and neuroplasticity
- Nutrient insufficiency
- IgE and IgG
- Food intolerance
- Core markers: Homocysteine, KPU, MMP-(myeloperoxidase, neopterin)

Most Americans have a dysbiotic leaky gut, poor microbiome diversity, lack of ketone strains, excess toxic load, low short-chain fatty acids, impaired digestive capacity, and excess antigen load. Optimizing metabolic health through lifestyle, nutrition and fitness improves diversity and functionality of the microbiome. Supporting the body through nutraceuticals in nutritional medicine is essential for positive mental health success. Supplements must be closed specifically to halt microglial activation through targeting each molecular target.

Organic food is not optional, it is critical due to the toxic chemical pesticides incorporated into the vacuoles of the plant's cells. These toxic compounds disrupt the neurotransmitter systems and can create a multitude of unwanted psychiatric disorders.

Food intolerances lead to mental problems by causing disruption to neurotransmitter function due to their proinflammatory nature. Gluten and casein are top contributors of mental dysfunction. Exorphins gliadorphin and casomorphin are short strains of amino acids absorbed from partially digested food and bind to opiate receptors in the brian. Normal levels of exorphins have roles in food-seeking and appetite regulation. High levels drive addictions and alter sensory perceptions that can cause speech and hearing problems, brain fog, constant fatigue, irritability, aggression, moodiness, anxiety, depression, and sleep problems.

There are millions of microglial cells in every single one of the central nervous system's cells, each of which can be doing different things. One part of the brain might be fighting pathogenic invaders while another is breaking down neural networks associated with a non-serving belief system. Modulating the expression of genes can be induced by environmental input signals, psychological input signals, diet, lifestyle, and more. Methylation and acetylation are important factors in the process.

Biomarkers: Test and Retest

- Antibodies to brain tissue
- Breach of BBB
- Optical and ANS disorders
- Brain autoimmunity
- Dopamine
- GABA

Copper to zinc ratio the most sensitive biomarker for inflammation

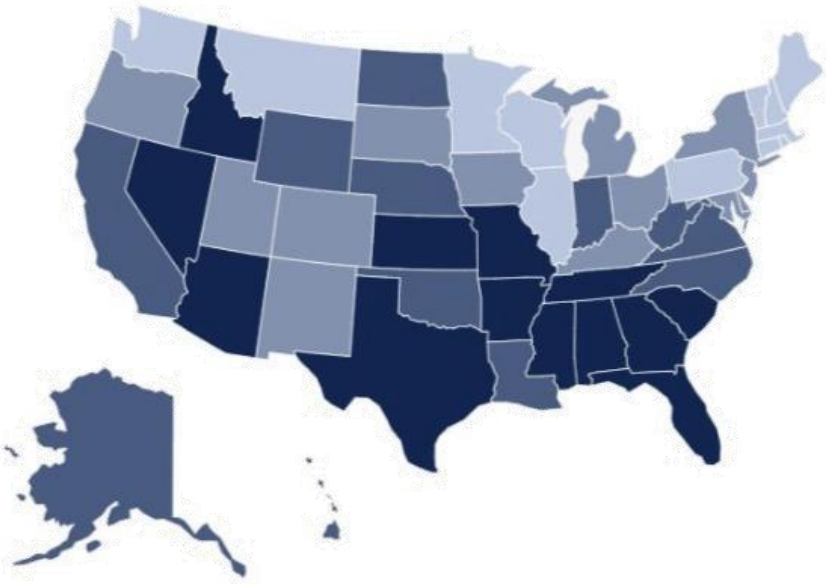
Mental health is a crisis in the United States and prescription medications are soaring. Medications come with significant health risks, contributing to the rise in suicidal deaths. At the core of these problems is brain inflammation due to a variety of factors. Addressing these issues can result in a decrease of microglial activity, promoting a calm brain and sense of peace and overall well-being.

Access to Care Rankings

The Access Ranking indicates how much access to mental health care exists within a state. The access measures include access to insurance, access to treatment, quality and cost of insurance, access to special education, and mental health workforce availability. A high Access Ranking (1-13) indicates that a state provides relatively more access to insurance and mental health treatment.

The nine measures that make up the Access Ranking include:

1. Adults With AMI Who Did Not Receive Treatment
2. Adults With AMI Reporting Unmet Need
3. Adults With AMI Who Are Uninsured
4. Adults With Cognitive Disability Who Could Not See a Doctor Due to Costs
5. Youth With MDE Who Did Not Receive Mental Health Services
6. Youth With Severe MDE who Received Some Consistent Treatment
7. Children with Private Insurance that Did Not Cover Mental or Emotional Problems
8. Students Identified with Emotional Disturbance for an Individualized Education Program
9. Mental Health Workforce Availability



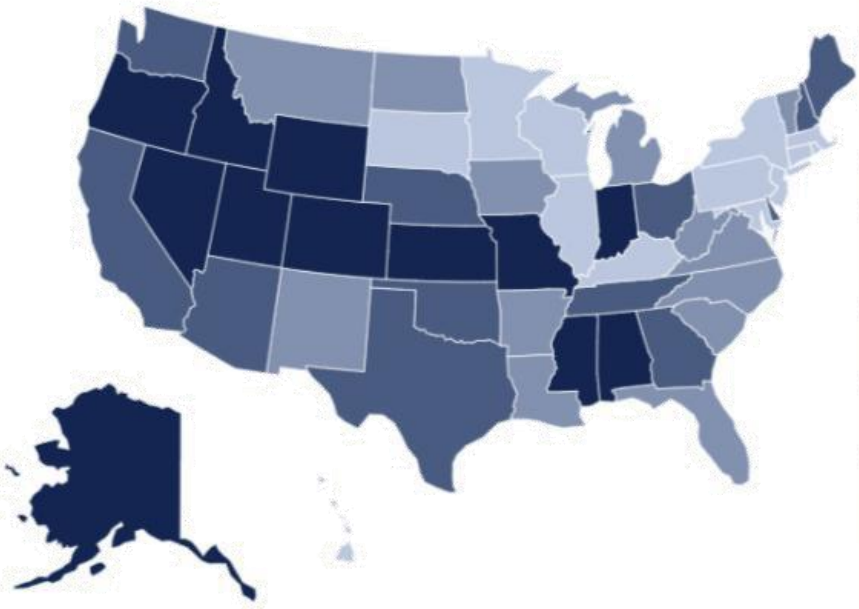
Rank	State
1	Vermont
2	Massachusetts
3	Maine
4	Wisconsin
5	Minnesota
6	New Hampshire
7	Rhode Island
8	Pennsylvania
9	Connecticut
10	District of Columbia
11	Washington
12	Montana
13	Illinois
14	Maryland
15	New York
16	Kentucky
17	Delaware
18	Iowa
19	Oregon
20	New Mexico
21	Colorado
22	Ohio
23	South Dakota
24	New Jersey
25	Michigan
26	Utah
27	North Dakota
28	Oklahoma
29	West Virginia
30	California
31	Hawaii
32	Indiana
33	Nebraska
34	Alaska
35	Louisiana
36	Wyoming
37	Virginia
38	North Carolina
39	Nevada
40	Arkansas
41	Missouri
42	Idaho
43	South Carolina
44	Kansas
45	Tennessee
46	Arizona
47	Mississippi
48	Georgia
49	Florida
50	Alabama
51	Texas

Adult Rankings

States that are ranked 1-13 have a lower prevalence of mental illness and higher rates of access to care for adults. States that are ranked 39-51 indicate that adults have a higher prevalence of mental illness and lower rates of access to care.

The seven measures that make up the Adult Ranking include:

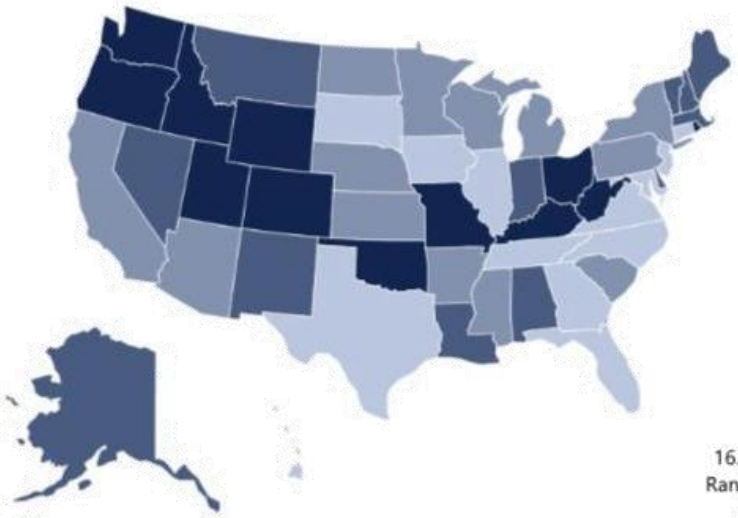
1. Adults With Any Mental Illness (AMI)
2. Adults With Substance Use Disorder in the Past Year
3. Adults With Serious Thoughts of Suicide
4. Adults With AMI Who Did Not Receive Treatment
5. Adults With AMI Reporting Unmet Need
6. Adults With AMI Who Are Uninsured
7. Adults With Cognitive Disability Who Could Not See a Doctor Due to Costs



Rank	State
1	New Jersey
2	Wisconsin
3	Massachusetts
4	Connecticut
5	New York
6	Minnesota
7	Hawaii
8	Pennsylvania
9	Maryland
10	Illinois
11	Rhode Island
12	South Dakota
13	Kentucky
14	Iowa
15	New Mexico
16	Arkansas
17	Montana
18	Michigan
19	Vermont
20	Virginia
21	North Carolina
22	South Carolina
23	West Virginia
24	North Dakota
25	Florida
26	Louisiana
27	Nebraska
28	California
29	Tennessee
30	New Hampshire
31	Georgia
32	Washington
33	Texas
34	Delaware
35	Arizona
36	Ohio
37	Maine
38	Oklahoma
39	Idaho
40	Nevada
41	Mississippi
42	Kansas
43	Indiana
44	Missouri
45	District of Columbia
46	Alaska
47	Alabama
48	Utah
49	Oregon
50	Wyoming
51	Colorado

Adult Prevalence of Mental Illness

Adults With Any Mental Illness (AMI)



19.86% of adults are experiencing a mental illness.

Equivalent to nearly 50 million Americans.

4.91% are experiencing a *severe* mental illness.

The states with the largest increases in Adults With Any Mental Illness (AMI) were Ohio (2.24%), Nebraska (2.22%), Wyoming (2.22%), and Oklahoma (2.11%).

The state prevalence of adult mental illness ranges from:

16.37% (NJ) Ranked 1-13

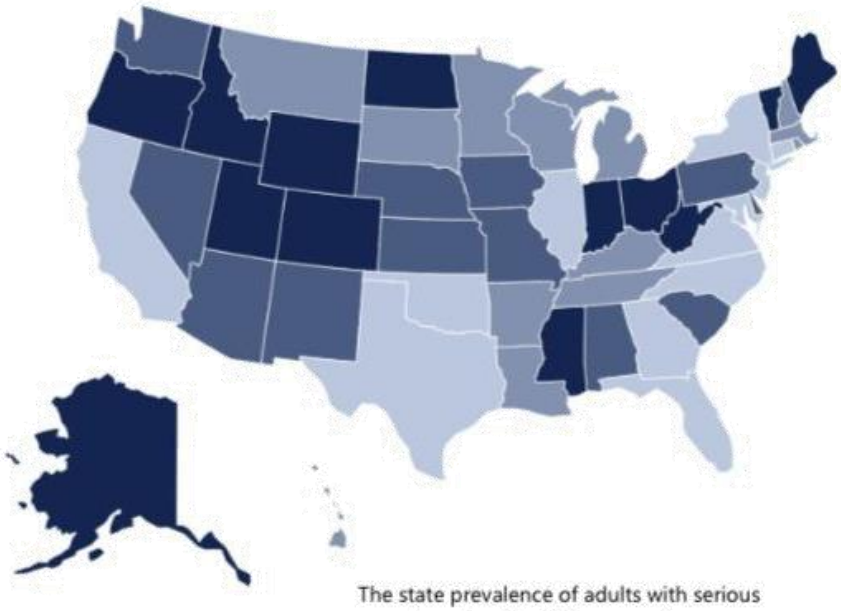
26.86 % (UT) Ranked 39-51

Rank	State	%	#
1	New Jersey	16.37	1,122,000
2	Texas	17.17	3,602,000
3	Florida	17.23	2,903,000
4	Hawaii	17.45	185,000
5	Maryland	17.57	810,000
6	Georgia	17.88	1,406,000
7	South Dakota	18.26	118,000
8	Iowa	18.50	441,000
9	Virginia	18.58	1,199,000
10	Connecticut	18.85	526,000
11	Illinois	19.18	1,858,000
12	North Carolina	19.31	1,532,000
13	Tennessee	19.40	1,006,000
14	South Carolina	19.43	760,000
15	California	19.49	5,864,000
16	New York	19.52	2,972,000
17	Pennsylvania	19.70	1,963,000
18	Arizona	20.06	1,099,000
19	Mississippi	20.16	446,000
20	Wisconsin	20.19	904,000
21	Nebraska	20.30	290,000
22	Michigan	20.32	1,571,000
23	Arkansas	20.34	460,000
24	North Dakota	20.50	116,000
25	Minnesota	20.53	876,000
26	Kansas	20.56	442,000

Rank	State	%	#
27	Montana	20.81	171,000
28	Delaware	20.92	157,000
29	Massachusetts	21.15	1,157,000
30	Louisiana	21.21	734,000
31	Alabama	21.29	794,000
32	New Mexico	21.39	338,000
33	Alaska	21.47	113,000
34	Nevada	21.97	512,000
35	Maine	22.10	238,000
36	Vermont	22.25	112,000
37	Indiana	22.29	1,125,000
38	New Hampshire	22.37	243,000
39	Rhode Island	22.38	187,000
40	Idaho	22.48	293,000
41	Oklahoma	22.54	657,000
42	Kentucky	22.54	762,000
43	Wyoming	22.56	98,000
44	Missouri	22.71	1,056,000
45	District of Columbia	22.83	129,000
46	Colorado	23.20	1,014,000
47	Washington	23.43	1,360,000
48	Ohio	23.64	2,112,000
49	Oregon	23.75	783,000
50	West Virginia	24.62	347,000
51	Utah	26.86	599,000
	National	19.86	49,564,000

According to SAMHSA, "Any Mental Illness (AMI) is defined as having a diagnosable mental, behavioral, or emotional disorder, other than a developmental or substance use disorder, assessed by the Mental Health Surveillance Study (MHSS) Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition—Research Version—Axis I Disorders (MHSS-SCID), which is based on the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)."

Adults With Serious Thoughts of Suicide



The state prevalence of adults with serious thoughts of suicide ranges from:

3.79% (NJ) Ranked 1-13 — 6.19% (UT) Ranked 39-51

The percentage of adults reporting serious thoughts of suicide is 4.58%. The estimated number of adults with serious suicidal thoughts is over 11.4 million—**an increase of 664,000 people from last year's data set.**

The national rate of adults experiencing suicidal ideation has increased every year since 2011-2012.

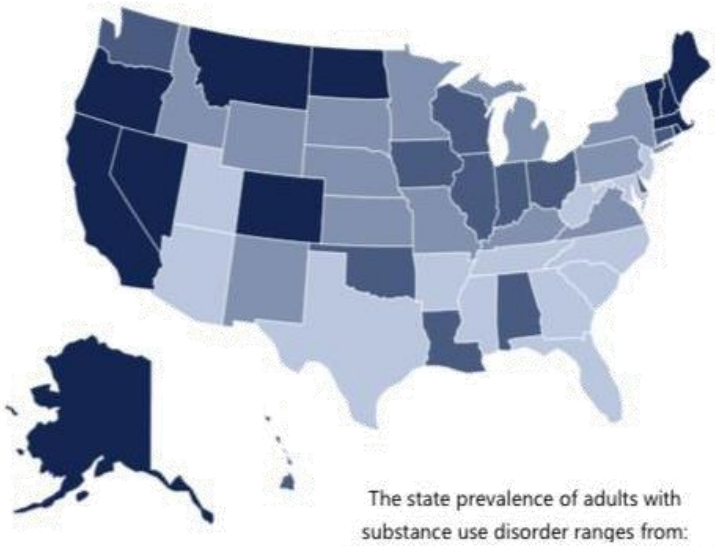
States with the highest increases in suicidal ideation were Ohio (0.92%), Wyoming (0.70%), and Pennsylvania (0.66%).

Utah has had the highest rate of suicidal ideation among adults every year since 2012-2013.

Rank	State	%	#
1	New Jersey	3.79	260,000
2	Georgia	3.85	303,000
3	Texas	3.86	812,000
4	North Carolina	3.87	307,000
5	Illinois	4.00	388,000
6	Florida	4.04	682,000
7	New York	4.21	642,000
8	Virginia	4.22	272,000
9	Maryland	4.34	200,000
10	District of Columbia	4.43	25,000
11	Connecticut	4.46	125,000
12	California	4.55	1,370,000
13	Oklahoma	4.58	134,000
14	Rhode Island	4.59	38,000
15	Michigan	4.61	357,000
16	South Dakota	4.62	30,000
17	Montana	4.63	38,000
18	Wisconsin	4.66	209,000
19	Tennessee	4.68	243,000
20	Kentucky	4.68	158,000
21	New Hampshire	4.68	51,000
22	Arkansas	4.71	107,000
23	Louisiana	4.72	163,000
24	Minnesota	4.74	202,000
25	Hawaii	4.74	50,000
26	Massachusetts	4.77	261,000

Rank	State	%	#
27	New Mexico	4.81	76,000
28	Pennsylvania	4.83	482,000
29	Alabama	4.83	180,000
30	Nebraska	4.88	70,000
31	South Carolina	4.89	191,000
32	Washington	4.92	286,000
33	Iowa	4.94	118,000
34	Nevada	4.94	115,000
35	Kansas	4.96	107,000
36	Arizona	5.01	275,000
37	Missouri	5.05	235,000
38	Delaware	5.18	39,000
39	North Dakota	5.28	30,000
40	Idaho	5.30	69,000
41	Mississippi	5.31	118,000
42	West Virginia	5.44	77,000
43	Maine	5.44	59,000
44	Colorado	5.54	242,000
45	Indiana	5.62	284,000
46	Oregon	5.65	187,000
47	Vermont	5.66	29,000
48	Wyoming	5.74	25,000
49	Ohio	6.09	545,000
50	Alaska	6.11	32,000
51	Utah	6.19	138,000
	National	4.58	11,434,000

Adults With Substance Use Disorder in the Past Year



The state prevalence of adults with substance use disorder ranges from:

5.98% (FL) Ranked 1-13

12.30% (D.C.) Ranked 39-51

7.74% of adults in America reported having a substance use disorder in the past year.

2.97% of adults in America had an illicit drug use disorder in the past year.

5.71% of adults in America had an alcohol use disorder in the past year.

The largest increases in the prevalence of adults with substance use disorder were in Hawaii (1.32%) and California (1.11%). The largest decreases were in South Dakota (1.48%) and Iowa (1.08%).

Rank	State	%	#
1	Florida	5.98	1,007,000
2	West Virginia	6.29	89,000
3	Texas	6.48	1,360,000
4	Utah	6.56	146,000
5	Georgia	6.60	519,000
6	New Jersey	6.71	459,000
7	South Carolina	6.73	263,000
8	Maryland	7.01	323,000
9	Arizona	7.11	390,000
10	Mississippi	7.15	158,000
11	Arkansas	7.16	162,000
12	Tennessee	7.22	375,000
13	North Carolina	7.26	576,000
14	Kansas	7.29	157,000
15	Pennsylvania	7.31	728,000
16	Virginia	7.33	473,000
17	New York	7.43	1,131,000
18	Michigan	7.56	585,000
19	Minnesota	7.62	325,000
20	Idaho	7.67	100,000
21	South Dakota	7.69	50,000
22	New Mexico	7.70	122,000
23	Missouri	7.71	358,000
24	Nebraska	7.71	110,000
25	Wyoming	7.84	34,000
26	Kentucky	7.87	266,000

Rank	State	%	#
27	Alabama	7.89	294,000
28	Ohio	7.94	709,000
29	Wisconsin	7.98	358,000
30	Oklahoma	8.01	234,000
31	Illinois	8.02	777,000
32	Iowa	8.05	192,000
33	Louisiana	8.06	279,000
34	Indiana	8.42	425,000
35	Connecticut	8.43	235,000
36	Hawaii	8.45	90,000
37	Washington	8.62	500,000
38	Delaware	8.79	66,000
39	Massachusetts	8.83	483,000
40	New Hampshire	8.84	96,000
41	North Dakota	8.88	50,000
42	Maine	8.89	96,000
43	Rhode Island	8.95	75,000
44	California	9.23	2,778,000
45	Nevada	9.32	217,000
46	Oregon	9.78	322,000
47	Montana	10.04	83,000
48	Vermont	10.10	51,000
49	Alaska	10.23	54,000
50	Colorado	11.75	514,000
51	District of Columbia	12.30	70,000
	National	7.74	19,314,000

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