The Effects of Acupuncture on Neurochemical and Immunological Biomarkers of Generalized Anxiety Disorder – A Literature Review

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Chapter 1: Introduction

Generalized Anxiety Disorder (GAD) affects 6.8 million adults, or 3.1% of the U.S. population (HIMH, 2015). In fact, 18% of the U.S. population or 40 million adults ages 18 and older have an anxiety disorder diagnosis, making anxiety disorders the most common mental illness in the United States (HIMH, 2015; Hyman, 2009) (Please see Images 1 and 2).

As of 2015, no study has yet been published summarizing the recent literature (post 2005) of the support of acupuncture and its effects on anxiety specifically. Neither has there been a study summarizing the current research on how acupuncture affects the neurochemistry and immunological mechanisms

related to anxious thoughts, emotions, and behavioral patterns. Most studies are either too broad (looking at anxiety and depression) or too specific (many of which are highlighted in this capstone). Furthermore, in the studies that are published on acupuncture and its affect on neurochemistry and/ or immunological markers, there is little to no studies explaining the mechanism involved in how acupuncture can modulate the relationships among acupuncture, neurochemistry and immunology.

One example of a more generalized or broad study is the clinical systematic review on randomized control trial published a study on the effects of acupuncture on anxiety and depression in efforts to summarize existing evidence on acupuncture as a therapy for anxiety and depression in women (Sniezek & Siddiqui (2013). They found that there was a high level of evidence to support that acupuncture can alleviate depression among pregnant women, yet their results were not as promising for supporting the use of acupuncture to treat anxiety (Sniezek & Siddiqui ,2013). Overall, they concluded that there was a lack of high quality research on the effect of acupuncture on anxiety and depression among women. Another more broad publication on the effects of acupuncture on anxiety, found that, overall, acupuncture was beneficial for the treatment of anxiety among individuals who are resistant to conventional treatments for anxiety (Errington-Evans, 2012). The search parameters were extremely broad and consisted of several poorly designed studies, thus highlighting the need for future studies on the effect of acupuncture on anxiety need to be stricter in their design.

In 2007, Pinkerton et al. published a systematic review of the then current studies on acupuncture for the treatment of anxiety. Using mostly randomized control trials, Pinkerton et al. (2007) concluded that there was currently promising, yet statistically insignificant research to support the effectiveness of acupuncture for the treatment of anxiety. Given the limitations of recently published literature reviews and systematics reviews, the overviews of research studies on the topic of acupuncture for anxiety are limited or inconclusive.

There is a great need for a current literature review of more well designed research studies to help the field of acupuncture move ahead to provide more significant data on the validity of acupuncture as a proven treatment for anxiety disorders.

Significance

As more and more people are looking to integrative medicine to help with chronic stress and generalized anxiety disorder, this capstone project with help people have a greater understanding of the possible mechanisms as to how acupuncture changes the biomarkers involved in GAD and the potential of combining both Eastern and Western approaches to treating the causes and reducing the symptoms of generalized anxiety disorder. Once published, this paper will serve as a readable guide for the general public to gain tools in how to better manage GAD and will hopefully be published in complementary and western medical journals and publications to reach across disciplines to educate practitioners and academics on the benefits of an complementary approach to

managing and treating GAD.

Purpose

The purpose of this paper is to provide a review of the current well designed studies on the effectiveness of acupuncture on anxiety and Generalized Anxiety Disorder (GAD). There is a great need of a literature synthesis on the current research on the effectiveness of acupuncture on both generalized anxiety disorder as well as anxiety in general. This capstone aims to be a solid foundation for future research studies in providing an overview of well-designed current studies on acupuncture and its effectiveness on subjective experiences of anxiety and objective biomarkers of anxiety. The goal of this paper is to provide a comprehensive yet concise overview of research studies on how acupuncture can affect the biomarkers of GAD, specifically brain chemistry (serotonin, GABA) and immunologic markers (cytokines and c-reactive protein). The studies discussed in the paper, conducted on humans and animals, exhibit how symptoms and causes of GAD can be addressed and improved through acupuncture by balancing brain chemistry and boosting immune function.

Chapter 2: Literature Review

Chinese Medical Perspective on Anxiety

In chinese medicine, anxiety is mostly related to fear; and is often related to “unresolved fear” (Maciocia et al, 2013).). In chinese medicine, the causes of anxiety are due to a persons’ constitution, irregular diet (excessive consumption

of damp-producing foods that produce phlegm), loss of blood, and overwork (Maciocia, 2008). There are 3 main disease entities that closely resemble anxiety in chinese medicine. “Fear and Palpitation” (Jing Ji), “Panic Throbbing” (Zhen Chong), and “Agitation” (Zang Zao). Both “Fear and Palpitation” and “Panic Throbbing” involve fear, anxiety and worry, yet the physiological sensation of fear is located in the chest with palpitations, or throbbing in the chest and below the umbilicus, respectively (Maciocia et al., 2013 Maciocia, 2008). “Fear and palpitations” are usually caused by external events (fright/ shock/ trauma) and comes and goes (Maciocia et al., 2013). “Panic throbbing” is not caused by external events and is continuous and chronic and is considered more serious than “Fear and palpitation” and is likened to panic attacks. “Agitation” or “visceral restlessness” which the person is in a constant state of tension fear; this latter type of anxiety is most closely related to Generalized Anxiety Disorder (Maciocia, 2008).

What is generalized anxiety disorder (GAD)?

According to Dr. Datis Kharrazian, inflammation, poor blood sugar regulation and hormone imbalances can “sabotage neurotransmitter function; ” as such, it is essential to address the entire body system to treat GAD (Kharrazian, 2013). Anxiety may start out as a general sense of unease, followed by more notable symptoms such as tight muscle tightness or pain, poor immune function, sleeping difficulties, gastrointestinal impairments an overall sense of feeling overwhelmed. Generalized Anxiety Disorder (GAD) is “an

excessive uncontrollable worry about everyday things. This constant worry…can cause physical symptoms…and often occurs with other anxiety disorders and depressive disorders" (Maciocia et al., 2013). Common physical symptoms include muscle tension, sweating, nausea, cold, clammy hands, difficulty swallowing, jumpiness, GI problems (including IBS), irritability, fatigue, chronic pain, migraines and headaches, insomnia, palpitations, chest pain, difficulty breathing, dizziness, fear, chills and hot flashes (Maciocia et al, 2013).

The Fifth Edition of the Diagnostic and Statistical Manual (DSM-V) was updated in 2013 and the definition of GAD has been refined to include "The presence of excessive anxiety and worry about a variety of topics, events, or activities. Worry occurs more often than not for at least 6 months, and is clearly excessive."[i] (American Psychiatric Association, 2013).[1]

A healthy brain function starts in healthy synapse function and proper synaptic transmission (synapse) in both the presynaptic neuron (the neuron that sends the neurotransmitter) and the postsynaptic neuron (the neuron that receives the neurotransmitter) (Kharrazian, p.255). The brain, due to imbalances in the whole body system may have trouble making enough of certain neurotransmitters, or there may be impairments in either the presynaptic or postsynaptic cleft. Another factor to look at in GAD is the excitation or inhibition of certain from neurotransmitters. When there are imbalances in these neurotransmitters, both physical and psychological symptoms may occur.

Neurons are either excitatory or inhibitory when they communicate,

[1] Please see endnotes for the DSM-V Criteria for GAD)

depending on they type and amount of certain neurotransmitters involved in the synapse (Kharrazian, p.256). Serotonin is an excitatory neurotransmitter, and is involved in feelings of pleasure and happiness. Symptoms of low serotonin include loss of pleasure in hobbies and interests, feelings of inner rage and anger, feelings of depression, difficulty finding joy in life's pleasures, depression when it is cloudy or lack of sunlight, loss of enthusiasm for favorite activities and foods, not enjoying relationships, unable to fall into deep restful sleep (Kharrazian, p. 283).

Gamma-aminobutyric acid (GABA) is the "anti-anxiety" neurotransmitter and is associated with calm feelings. Symptoms low GABA include feelings of anxiousness or panic for no reason, feelings of dread, feelings of being overwhelmed for no reason, restless mind, hard to turn off your mind once you want to relax, disorganized attention, worry about things you never had a thought about before (Kharrazian, p. 311).

Systemic inflammation and Anxiety

Several studies have linked both pro-inflammatory cytokines and c-reactive protein to symptoms of anxiety. Cytokines are regulatory proteins that are produced by cells of both the innate and adaptive immune system and mediate many actions of these cells (for example, monokines are produced by monocytes and lymphokines are produced by lymphocytes (Porth & Matfin, 2009). Interleukins (ILs) are cytokines that act on other leukocytes and each type of interleukin have different functions (Porth & Matfin, 2009). For more

information on the different types and functions of interleukins, please see Table 1).

C-reactive protein (CRP) is thought to be protective as it binds to the surface of invading pathogens and targets them for destruction by phaggocytosis (Porth & Matfin, 2009). Most people maintain a low level of CRP, yet this level rises when there is an acute inflammatory response or among persons with increase risk for myocardial infarctions of coronary heart disease (Porth & Matfin, 2009). Cytokines are related to the immune system and are the main communication system that controls systemic inflammation (Hyman, 2009). Cytokines either promote or reduce inflammation and can be triggered by toxins, allergens, stress, poor diet, and poor behavioral patterns such as a sedentary lifestyle (Hyman, 2009). C-Reactive Protein (CRP) is found in the blood is a maker marker for inflammation in both the brain and the body (Hyman, 2009).

Research supports that depression and anxiety may be a systemic inflammatory disease (Hyman, 2009; Das, 2007; Anisman & Merali, 2003). Pro-inflammatory cytokines (IL-1, IL-6, TNF alpha – molecules that set off the inflammatory responses) produce symptoms of anxiety and depression (Hyman, 2009). Cytokines are also known to over activate the HPA (hypothalamic-pituitary-adrenal) axis, which can lead to more symptoms of anxiety (Hyman, 2009). Additionally, cytokines increases Indoleamine 2,3-dioxygenase (IDO), an enzyme that breaks down tryptophan (a chemical that helps to produce serotonin), leading too a lack of sufficient serotonin in the brain (Muller & Schwartz, 2007). Furthermore, research has found that persons with severe

depression (neurochemically similar to persons with anxiety disorders) have an overactive immune system and brain inflammation (Hyman, 2009). Research has also found that immunosuppressive therapies, such as interferon therapy, triggers depression and anxiety (Hyman, 2009).

Chapter 3: Methodology

Phase 1: Before commencing my search on Pubmed, I consulted theoretical overview and consulted eastern and western sources to gain a better foundation of the root of the connections among brain chemistry, immunological function and symptoms of anxiety. I read Dr. Datis Kharrazian's book *Why Isn't my Brain Working* and Mark Hyman's book, *The UltraMind Solution: Fix Your Broken Brain by Healing your Body First*, to have a better sense of psychoneuroimmunology and the causes and symptoms of anxiety disorders in general as well as those specific to GAD. I consulted Giovanni Maciocia's, *The Psyche in Chinese Medicine: Treatment of Emotional and Mental Disharmonies with Acupuncture and Chinese Herbs* to gain a better perspective on the Chinese medical perspective on understanding GAD. The sources written by Datis Kharrazian, Mark Hyman and Giovanni Maciocia were used to explain the background of the neurochemistry and immunological biomarkers of anxiety and GAD.

Phase 2: At first, I searched the National Center for Biotechnology Information (NBCI) / Pubmed Next for studies assessing acupuncture and generalized anxiety disorder. Keywords included*:* Acupuncture, Anxiety, Generalized Anxiety, Stress, Chinese medicine, serotonin, dopamine, GABA.

Inclusion Criteria included articles after 2005 only, Randomized Control Trial, Systematic Review, preference for peer reviewed journals and articles written in English. Inclusion criteria included randomized control trials, clinical trials, animal and human studies, systematic review, preference for peer reviewed journals and articles written in English. Exclusion criteria were case studies, articles written before 1998, articles in non-peer reviewed journals, and articles not written in English.

Phase 3: After conducting the initial literature search, I found that most studies were too general and had too wide of an inclusion criteria, lacked randomized control trials for human studies and offered little to no studies on clinical trials with animals. I decided to become more specific with my search criteria and look at specific neurochemical (serotonin and GABA) and immunological biomarkers (pro-inflammatory cytokines and c-reactive protein) of anxiety and GAD. Using the National Center for Biotechnology Information (NBCI) / Pubmed, search criteria was revised to include only anxiety, generalized anxiety, depression[2], GABA, serotonin, brain chemistry, randomized control trial, clinical trial, animal studies, systematic review, preference for peer reviewed journals and articles written in English. Exclusion criteria were case studies, articles written before 1998, articles in non-peer reviewed journals, and articles not written in English.

Phase 4: A fourth literature search on National Center for Biotechnology Information (NBCI) / Pubmed was conducted to assess how systematic

[2] The neurochemistry of depression and anxiety are similar.

inflammation contributes to anxiety and GAD. Keywords included*:* Anxiety, Generalized Anxiety, inflammation, immunological markers, IL6, c-reactive protein and cytokines. Inclusion criteria included articles written after 1998 only, Randomized Control Trial, animal studies, systematic review, and clinical trials with a preference for peer reviewed journals and articles written in English. The exclusion criteria included articles written prior to 1998, case studies, surveys literature reviews and articles not in written in English.

Phase 5: Using Pubmed, a literature search was conducted to assess how acupuncture can increase serotonin and GABA production in the brain. Keywords included acupuncture, GABA, anxiety, depression, serotonin. Inclusion criteria included articles written after 1998 only, Randomized Control Trial, systematic review, animal studies, and clinical trials with a preference for peer reviewed journals and articles written in English. The exclusion criteria included articles written prior to 1998, case studies, surveys literature reviews and articles not in written in English.

Phase 6: Using Pubmed, a literature search was conducted to assess how acupuncture can decrease systematic inflammation in the body as well as symptoms of anxiety. Keywords included acupuncture, inflammation, Immune function, c-reactive protein, and cytokines. Inclusion criteria included articles written after 1998 only, Randomized Control Trial systematic review, and clinical trials with a preference for peer reviewed journals and articles written in English. The exclusion criteria included articles written prior to 1998, case studies, surveys literature reviews and articles not in written in English.

Chapter 4: Analysis

Acupuncture and neurotransmitter regulation

Research as found that acupuncture can stimulate the production of serotonin and 5-HTP (a precursor to serotonin). In a recent study, stimulation of certain acupuncture points on the body have been found to boost 5-HTP, a precursor to serotonin rat pups. Park et al. (2012) found that stimulation of acupuncture point, HT7, boosted serotonin levels among maternally separated rat pups. Another study addressing the gut-brain connection in serotonin regulation and pain perception, found that acupuncture at acupoint ST36 was associated with a significant reduction of serotonergic activities (more serotonin in the synaptic cleft) among rats with irritable bowel syndrome (Wu et al., 2010). Yoshimoto et al. (2006) assessed how bilateral stimulation of acupoint Shenshu (UB 23) for 60 minutes in free moving rats affected Dopamine (DA) and serotonin (5-HTP). They found that acupuncture bilateral stimulation of UB23 had more significant effects on serotonergic neurons in the brain than unilateral stimulation of UB 23 or sham acupuncture (Yoshimoto et al., 2006).

In assessing the relationship between acupuncture and serotonin activity in human subjects, Qu et al. (2013) conducted a randomized control trial over a 6 week period (with a 4 week follow up), assessing the affect of acupuncture on serotonin levels (measured by amount of SSRI dose needed), dose of paroxetine ("Paxil") needed, and perceived depressed mood (Hamilton Depression Rating Scale and the Self-rating Depression Scale) among 160 patients who were

diagnosed with Major Depressive Disorder (MDD). Subjects were randomly selected to the paroxetine (PRX) alone group, PRX plus manual acupuncture group (MA), and PRX plus electrical acupuncture group (EA). Both the MA and the EA group has a significantly greater reduction in score on the Hamilton Depression Rating Scale and the Self-rating Depression Scale from baseline to week 6 than the PRX alone group (P = .0004). The proportion of patients that required an increase dose of PRX was significantly lower in the MA and EA group, when compared to the PRX group alone (P =.019). This study illustrates that acupuncture can accelerate the clinical response to SSRI (selective serotonin reuptake inhibitors) and prevent the aggravation of depression (Qu et al, 2013). Another study found that electoracupuncture 5 times a week for 6 weeks on DU20, ST36, LV3, SP6, PC6 and HT7 had similar effect on depression levels (as measured by the Hamilton Depression Rating Scale) as the control group who took 20mg/day of fluoxine for 6 weeks (Sun et al, 2013).

Acupuncture and GABA

Stimulation of HT 7 has also been found to block GABA receptors antagonists in rats (Lee et al. (2014) and stimulation of Bai Hui (Du 20) was found to increase dopamine levels of the cerebral cortex of rates with chronic cerebral ischemia (Chuang & Hsieh, 2007). Another study found that acupuncture at acupoint SI5 (but not at control point LI5) can mediate the GABA receptor system, reducing the need more morphine seeking behavior among rets (Lee et al, 2012). In a follow up study, Lee et al. (2013) found that again, SI5 (but

not control acupoint LI5) suppressed the reinstatement of morphine seeking behavior by mediating the GABA receptor system, suggesting implications for treating humans with dysregulation of the GABA receptor system (Lee et al. 2013).

Acupuncture and perceived anxiety (and depression) levels

There is a high comorbidity rate of GAD and other psychiatric disorders, including depression (McPherson & McGraw, 2013). The Hamilton Depression Rating Scale (1997) assesses both subjective depression and anxiety symptoms and is often used to assess the efficacy of acupuncture on symptoms of low serotonin (anxiety and depression). In a single blind, randomized controlled study, Zhang et al. (2013) found that patients treated with dense cranial electrical acupuncture (DCEAS) had a significant reduction in the Hamilton Rating Scale for Depression when compared to those with sham acupuncture (19.4 % versus 8.8%) (Zhang et al. 2013). The use of dense cranial electroacupuncture (DCEAS) was also found to reduce depression[3] among post-stroke patients (Man et al. 2014). In a single blind, randomized control trial, 43 patients with post-stroke depression were randomly assigned to different experimental groups: 12 sessions of DCEAS plus SSRI (selective serotonin reuptake inhibitor) plus body EA (electroacupuncture) or sham acupuncture (non invasive acupuncture) plus SSRI plus body electroacupuncture (EA). Those in the DCEAS group showed

[3] Depression and anxiety are both related to low serotonin. The Hamilton Depression Rating Scale also assesses anxiety levels. As such, this study was included in to exhibit that acupuncture can help reduce neuropsychiatric symptoms among human subjects.

greater reduction in the Hamilton Depression Rating scale, exhibiting that a combination of DCEAS and body acupuncture can considered a treatment for depression [and anxiety] among humans (Man et al., 2014).

Research has found that systemic inflammation is related to anxiety. Among rats with inflammatory bowel disease, inflammation induced by injection of dextran sodium sulfate (DSS) exacerbated anxiety in rats (Chen et al. 2014). The DDS rats developed anxiety and depression like behaviors 10-20 days after the start of inflammation, but not in the control rats (Chen et al, 2014). Another study, assessing the relationship between anxiety and inflammatory markers in humans, found that elevated inflammation (as measured by c-reactive protein) was present in persons with current anxiety disorders (Vogelzangs et al., 2013). Another study found that somatic symptoms of anxiety (as measured by the Netherlands Study of Depression and Anxiety (NESDA)) was associated with higher levels of c-reactive Protein, IL-6, and TNF-alpha, and cognitive anxiety symptoms were associated with higher levels of c-reactive protein (Duivis et al., 2013). Another study found that serum pro-inflammatory cytokine levels were found to have a positive association with severe anxiety and depression (as measured by the Hospital Anxiety and Depression Scale- HADS) among persons with colon cancer (Miranda et al. (2014).

Acupuncture and systematic inflammation

One recent study found that acupuncture reduces the inflammatory response (C-reactive protein) among rats with spastic cerebral palsy ($P<.05$) (Qi

et al., 2014). Compared to the control group, the rats that received acupuncture had significantly lower inflammatory cells, immune injury and muscle spasms and tension (Qi et. al., 2014). Another study assessing the relationship between acupuncture and cytokine levels found that acupuncture significantly inhibited the inflammatory response (IL-6, beta-NGF, and TIMP-1) to carrageenan injection in rats, when compared to the group of rats who did not get acupuncture treatment (Yi et al., 2007). Similarity, Chae et al. (2007) found that, among male Sprague–Dawley rats who were injected with an inflammatory substance (carrageenan), the group that received acupuncture had significantly reduced three cytokines, and other markers of inflammation, such as interleukin-6 (IL-6), *β*-nerve growth factor (*β*-NGF) and tissue inhibitors of metalloproteinase-1 (TIMP-1) when compared to the control group (Chae et al., 2007).

Another study, assessing the effect of acupuncture on inflammatory cytokines (IL-2, IL6, IL-10) among humans with chronic allergic rhinitis, found that acupuncture reduced plasma levels of IL-10 (Petti et al. 2002). Compared to the sham acupuncture group and the no acupuncture group, those who received acupuncture treatments had a significant reduction in IL-10 (not IL 6) over a 24 hour period ($P<.05$) (Petti et al 2002).

Chapter 5: Discussion and Conclusion

Research is promising that acupuncture can significantly help with both subjective assessments of anxious feelings in humans and objective anxious behaviors and biomarkers in both humans and animals. Acupuncture has been

found to show anti-depressant effects as well as concurrent reduction in inflammatory markers. Kwon et al. (2012) found that acupuncture stimulation significantly lowered depression-like behavior and concurrently reduced inflammation among mice, indicating that acupuncture has anti-depression-like as well as anti-inflammatory effects (Kwon et al., 2012). As depression and anxiety are linked by similar biomarkers (low serotonin and GABA), it can be extrapolated that, based on the findings of this study, that acupuncture may also have anti-anxiety effects; however, further research is needed to confirm this conclusion. The studies discussed in this capstone support that acupuncture significantly decreases systemic inflammation, decreases C-reactive protein levels, lowers pro-inflammatory cytokines, and boosts serotonin and GABA levels. Interestingly, though the findings of the mentioned studies are significantly, there is little explanation of the mechanisms by which acupuncture can modulate the signs and symptoms of anxiety. *How can these mechanisms be explained?* The answer may be in the bi-directional communication between the brain and the gastrointestinal tract, the enteric nervous system, or the "Gut – Brain Axis" (Kharrazian, 2013).

Acupuncture and the Vagus Nerve: A possible underlying mechanism of how acupuncture affects biomarkers of GAD via the Enteric Nervous System

There is significant literature in both western medicine and functional medicine supporting how impaired brain function can affect the digestive system

and, conversely, how impaired gut function can affect brain chemistry (Kharrazian, 2008; Perlmutter, 2015). According to Kharrazian (2013), “one of the earliest signs of a poorly functioning brain is poor digestion” (Kharrazian, 2013, p. 164). Furthermore, the digestive system has its own nervous system called the “enteric nervous system,” which communicates with the brain via the vagus nerve (Kharrazian, 2013). The connection begins when the brain activates the brainstem, the brainstem activates the vagus nerve, and the vagus nerve stimulates the enteric nervous system, which then stimulates the intestinal motility, absorption and elimination (Kharrazian, 2013). Lack of sufficient stimulation of the vagus nerve can lead to low hydrochloric acid (HCL), poor enzyme release and the impairment of the intestines to absorb food properly, leading to a lack of sufficient absorption of nutrients (Kharrazian, 2013). Consequently, intestinal impairments (including lack of sufficient and diverse gut flora) are associated with a lower production of serotonin and GABA in the gut (Fettisov & Decholette, 2011; Desbonnet et al, 2008).

According to David Perlmutter MD, high levels of systematic inflammatory markers such as c-reactive protein, are associated with mood disorders : the typical western diet “high in refined carbs and factory fats…are associated with higher levels of c-reactive protein” (Perlmutter, 2015). As the immune system begins in the gut, the inability for the commensal (normal gut flora) organisms to flourish is hindered, leading to an overgrowth of yeast and non-commensal bacteria as well as increased systemic inflammation. Furthermore, numerous studies have shown that those with anxiety disorders show higher levels of

inflammation in the gut, higher levels of systemic inflammation, higher levels of cortisol, and over – active stress response than those who do not have an anxiety disorder (Glaus et al., 2014; Autry & Monteggia, 2012). Additionally, when repairing the systemic and gut inflammation with prebiotics, symptoms of anxiety improved among those who had been diagnosed with anxiety disorder (Schmidt et al., 2014). Similarly, among anxious mice, those that were fed probiotics exhibited significantly much less anxious behavior than those who were not fed probiotics (Bravo et al., 2011).

As impaired function of the enteric nervous system adversely affects the neurochemical and immune systems, we can deduce that repairing the function of the enteric system can improve brain function and subjective and objective markers of anxiety. More information and future studies are needed to assess how acupuncture can regulate and repair the enteric nervous system. Perhaps futures studies can address how stimulation of the vagus nerve via acupuncture can repair and support better communication between the brain and the gut. No study yet has tested this theory in a RCT design. Future research is needed to explain *how* acupuncture may possibly repair communication between the brain and the gut by sending blood flow to the digestive organs, helping them to function more optimally, and helping to create a more diverse flora so that the brain and body function optimally.

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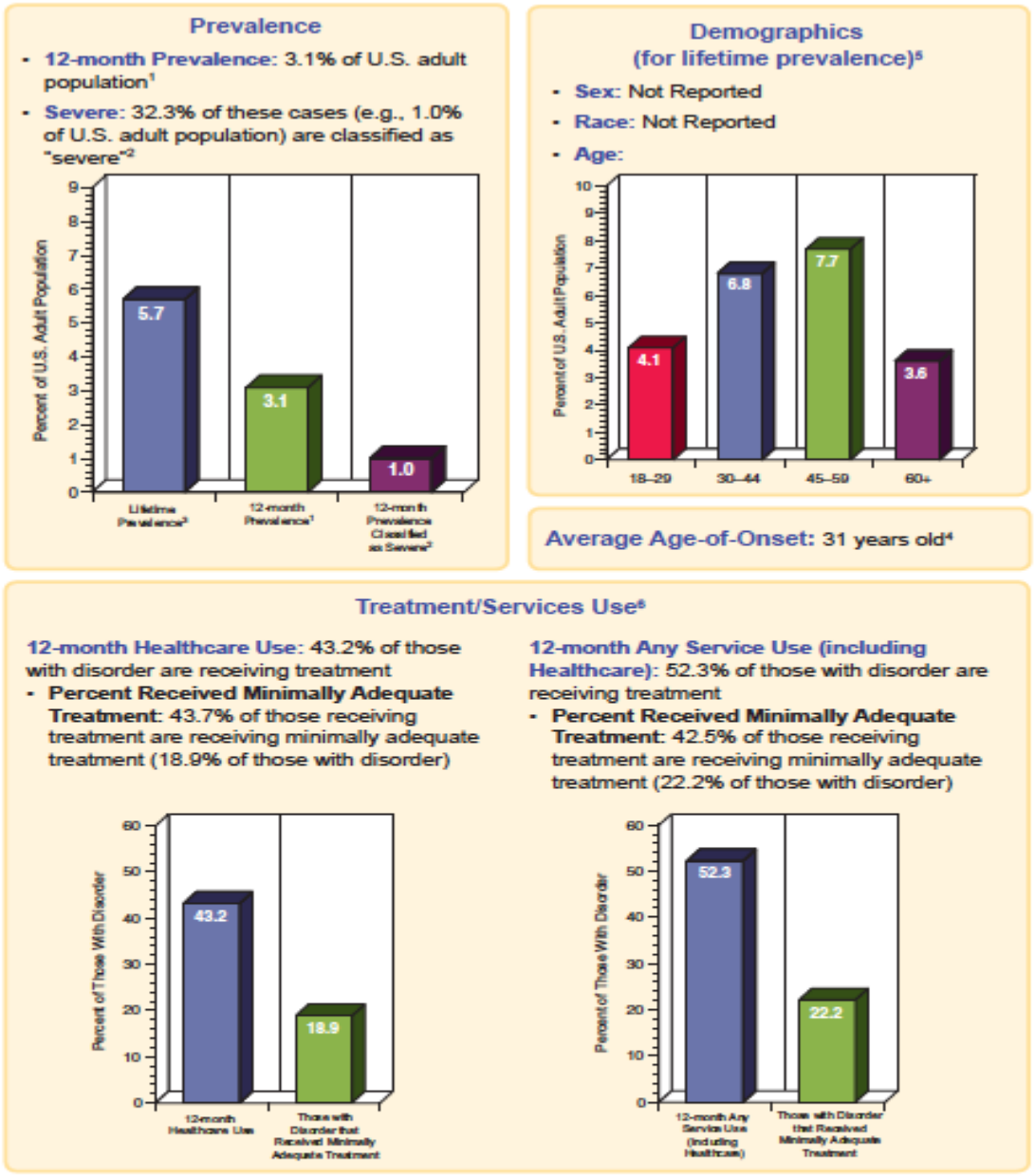
Chapter 7: Tables and Charts

Image 1: General Anxiety Disorder Statistics



[1]Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Archives of General Psychiatry*, 2005 Jun;62(6):617-27.

[2]Ibid

[3]Kessler RC, Berglund PA, Demler O, Jin R, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Archives of General Psychiatry*. 2005 Jun;62(6):593-602.

[4]Ibid

[5]Ibid

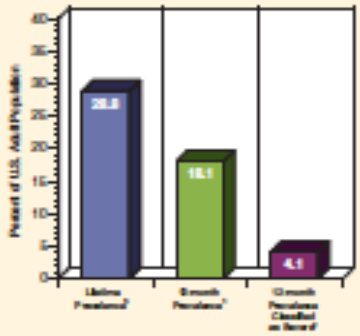
[6]Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve month use of mental health services in the United States. *Archives of General Psychiatry*. 2005 Jun;62(6):629-640.

Image 2: Anxiety Disorders in the US

Anxiety Disorders

Prevalence

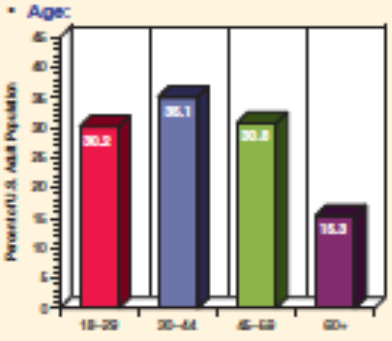
- **12-month Prevalence:** 18.1% of U.S. adult population[1]
- **Severe:** 22.8% of these cases (e.g., 4.1% of U.S. adult population) are classified as "severe"[2]



Average Age-of-Onset: 11 years old[4]

Demographics (for lifetime prevalence)[3]

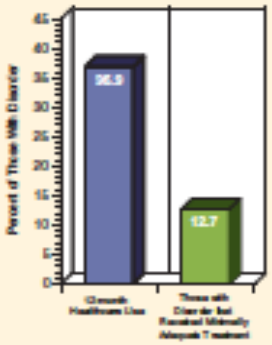
- **Sex:** Women are 60% more likely than men to experience an anxiety disorder over their lifetime
- **Race:** Non-Hispanic blacks are 20% less likely, and Hispanics are 30% less likely, than non-Hispanic whites to experience an anxiety disorder during their lifetime
- **Age:**



Treatment/Services Use[5]

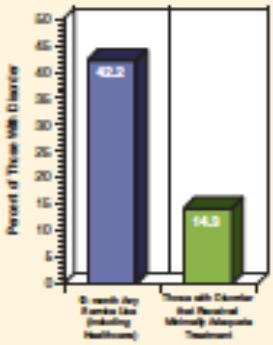
12-month Healthcare Use: 36.9% of those with disorder are receiving treatment

- **Percent Received Minimally Adequate Treatment:** 34.3% of those receiving treatment are receiving minimally adequate treatment (12.7% of those with disorder)



12-month Any Service Use (Including Healthcare): 42.2% of those with disorder are receiving treatment

- **Percent Received Minimally Adequate Treatment:** 33.8% of those receiving treatment are receiving minimally adequate treatment (14.3% of those with disorder)



[1]Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Archives of General Psychiatry*. 2005 Jun;62(6):617-27.

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[4]Ibid

[5]Ibid

[6]Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve month use of mental health services in the United States. *Archives of General Psychiatry*. 2005 Jun;62(6):629-640.

- [i] The worry is experienced as very challenging to control.

Worry in both adults and children may shift from one topic to another.

- The anxiety and worry is associated with at least 3 of the following physical or cognitive symptoms (*In children, only 1 symptom is necessary for a diagnosis of GAD.)*:

1 Edginess or restlessness.
2 Tiring easily; more fatigued than usual.
3 Impaired concentration or feeling as though the mind goes blank.
4 Irritability (which may or may not be observable to others).
5 Increased muscle aches or soreness.

Difficulty sleeping (due to trouble falling asleep or staying asleep, restlessness at night, or unsatisfying sleep).

Many individuals with GAD also experience symptoms such as sweating, nausea or diarrhea.

- The anxiety, worry, or associated symptoms make it hard to carry out day-to-day activities and responsibilities. They may cause problems in relationships, at work, or in other important areas.
- These symptoms are unrelated to any other medical conditions and cannot be explained by the effect of substances including a prescription medication, alcohol or recreational drugs.
- These symptoms are not better explained by a different mental disorder.

Table 1: Cytokines of Innate and Adaptive Immunity (Porth & Matfin, 2009)

CYTOKINES	SOURCE	BIOLOGIC ACTIVITY
Interleukin-1 (IL-1)	Macrophages, endothelial cells, some epithelial cells	Wide variety of biologic effects; activates endothelium in inflammation; induces fever and acute-phase response; stimulates neutrophil production
Interleukin-2 (IL-2)	$CD4^+$, $CD8^+$ T cells	Growth factor for activated T cells; induces synthesis of other cytokines; activates cytotoxic T lymphocytes and NK cells
Interleukin-3 (IL-3)	$CD4^+$ T cells	Growth factor for progenitor hematopoietic cells
Interleukin-4 (IL-4)	$CD4^+$ T_H2 cells, mast cells	Promotes growth and survival of T, B, and mast cells; causes T_H2 cell differentiation; activates B cells and eosinophils and induces IgE-type responses
Interleukin-5 (IL-5)	$CD4^+$ T_H2 cells,	Induces eosinophil growth and development
Interleukin-6 (IL-6)	Macrophages, endothelial cells, T lymphocytes	Stimulates the liver to produce mediators of acute-phase inflammatory response; also induces proliferation of antibody-producing cells by the adaptive immune system
Interleukin-7 (IL-7)	Bone marrow stromal cells	Primary function in adaptive immunity; stimulates pre-B cells and thymocyte development and proliferation
Interleukin-8 (IL-8)	Macrophages, endothelial cells	Primary function in adaptive immunity; chemoattracts neutrophils and T lymphocytes; regulates lymphocyte homing and neutrophil infiltration
Interleukin-10 (IL-10)	Macrophages, some T-helper cells	Inhibitor of activated macrophages and dendritic cells; decreases inflammation by inhibiting T_H1 cells and release of IL-12 from macrophages
Interleukin-12 (IL-12)	Macrophages, dendritic cells	Enhances NK cell cytotoxicity in innate immunity; induces T_H1 cell differentiation in adaptive immunity
Type I interferons (IFN-α, IFN-β)	Macrophages, fibroblasts	Inhibit viral replication, activate NK cells, and increase expression of MHC-I molecules on virus-infected cells
Interferon-γ (IFN-γ)	NK cells, $CD4^+$ and $CD8^+$ T lymphocytes	Activates macrophages in both innate immune responses and adaptive cell-mediated immune responses; increases expression of MHC-I and -II and antigen processing and presentation
Tumor necrosis factor-α (TNF-α)	Macrophages, T cells	Induces inflammation, fever, and acute-phase response; activates neutrophils and endothelial cells; kills cells through apoptosis
Chemokines	Macrophages, endothelial cells, T lymphocytes	Large family of structurally similar cytokines that stimulate leukocyte movement and regulate the migration of leukocytes from the blood to the tissues
Granulocyte-monocyte CSF (GM-CSF)	T cells, macrophages, endothelial cells, fibroblasts	Promotes neutrophil, eosinophil, and monocyte maturation and growth; activates mature granulocytes
Granulocyte CSF (G-CSF)	Macrophages, fibroblasts, endothelial cells	Promotes growth and maturation of neutrophils consumed in inflammatory reactions
Monocyte CSF (M-CSF)	Macrophages, activated T cells, endothelial cells	Promotes growth and maturation of mononuclear phagocytes

CSF, colony-stimulating factor; NK, natural killer; T_H1, T-helper type 1; T_H2, T-helper type 2; MHC, major histocompatibility complex.