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### 2021 Summary Report on Symptomatic Neuroinflammation

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### **Abstract**

Neuropsychiatric disorders and neurocognitive impairment are the hallmark findings in neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, and other brain pathologies. A growing compendium of studies has also suggested that common neuropsychiatric disorders such as major depression, bipolar disorder, and schizophrenia could be considered as neuroinflammatory conditions. Identifying the mechanism responsible for precipitating these conditions has not been fully elucidated, but it appears to be due to an elevation in oxidative stress that induces the brain's microglia to release pro-inflammatory cytokines.

The neuroprotective and neuroregenerative ability of specific nutraceutical products has been advanced in the scientific research literature for decades. The ability of select nutraceuticals to significantly reduce the production of damaging free radicals is reflected in the reduction of glial production of proinflammatory cytokines. Put together, diminishing the level of oxidative stress represented by reactive oxygen and nitrogen species, can protect the sensitive neuro-circuitry of the brain, and allow for healing with recovery of function.

This 2021 summary report highlights the outcome of treatment in 237 individuals who had their biomarker panel evaluated by an expert analytical AI laboratory program which generated a treatment protocol based upon measured neurosteroids and neuroactive steroids. Concurrent to the replenishment of any deficient steroids, a blended nutraceutical product was used to address oxidative stress and to reduce the production of pro-inflammatory chemistry.

### Introduction

The Millennium Health Centers, Inc. began its erudition program in 2004 looking at the effects of traumatic and non-traumatic injuries on the brain's production of neurosteroids as well as neuroactive steroids, those hormones produced outside the brain. Thanks to the meticulous work of French chemist and endocrinologist Dr. Etienne-Emile Baulieu, we became aware of the brain's ability to synthesize its own steroid hormones (neurosteroids) within glial cells from cholesterol and that these neurosteroids are identical in structure as those made in the body by our endocrine glands (neuroactive steroids) (5,6). Additionally, the bench sciences were expanding our understanding of these steroid hormones as having pleiotropic effects beyond their stereotypical "sex hormone" classification. Many were being found to influence inflammatory systems based upon cytokines and chemokines (7), to enhance immunity with increases in CD4+ and CD8+ cells (8), and to improve the removal of damaging Amyloid Beta by upregulating Neprilysin's transport of it out of cells (9). Thereafter, our patient care focus became one of





improving levels of both neurosteroids and neuroactive steroids as a means of generating clinical improvement.

Nevertheless, we kept on asking the question of "How does trauma cause the loss of neurosteroids and/or neuroactive steroids?" Reviewing the scientific literature in conjunction with our clinical findings, it became apparent that inflammation was a by-product of both traumatic and non-traumatic events and was responsible for the disruption of numerous biomolecular processes that influence cognitive and emotional well-being (10,11). So, around 2015 we changed from our initial theory that neurotrauma caused hormonal deficiencies that allows for neuroinflammation to go unchecked thereby altering the brain's chemistry (12), to our present hypothesis that neurotrauma begets neuroinflammation that basically induces a phenotypic change in Microglial cells causing chronic release of inflammatory cytokines which increase ROS (13), decreases NO, increases peroxynitrite (14), inactivates enzymes, damages mitochondrial energy production (ATP) (15), loss of gated ion channels, inhibits neurotransmitters, and impedes pre- and post-synaptic communication, damages the blood brain barrier, and increases the occurrence of neuropsychiatric and somatic complaints (16,17,18).

### The Millennium's Approach to Assessment and Treatment

Each program candidate completes a comprehensive historical inventory containing all the standard data points in addition to requesting history of exposures to all forms of trauma (service and civilian related). Additionally, a subjective psychological and physical inventory is taken. The laboratory assessment uses the Millennium's Biomarker Panel-2436 which consists of 28 tests that are readily available in major commercial clinical laboratories (Access Medical Labs, Quest, and LabCorp.) Once the laboratory results are obtained, they are processed by the Millennium-TBI Office Assistant (MOA), an expert-Al system which provides for a multi-tiered, cross-correlational analysis of the results in real-time.

The AI system contains subroutines that consider the influence of medication and supplements on these laboratory results to avoid either over or under reading of the labs. This AI system helps to standardize the interpretation of laboratory results as well as to provide a consistent recommendation for treatment based upon the results. In essence, the MOA is a complex neural network trained by machine learning to advance the abilities of any healthcare provider in relation to hormone replacement therapies affected by trauma as well as in the normal aging process – Age Management Medicine.

Based upon the individualized MOA reports, 237 candidates were provided with a customized treatment protocol that was recommended by the expert-Al system. Treatment recommendations might have included specific hormone replenishment protocols inclusive of Testosterone, Estrogen, Pregnenolone, Progesterone, Growth Hormone, DHEA, 7-Keto DHEA, Vitamin D3, Cortisol, and Thyroid hormones (T4/T3). Additionally, medication such as Clomiphene citrate might be offered before the use of testosterone or estrogen products in order to encourage the individual's own endocrine system to provide these hormones. This was also true with the recommendation for use of secretagogues such as Secretropin or DynaTropin to improve one's innate growth hormone production.

Finally, a group of three nanoliposomal nutraceutical products were used to address neuroinflammation, mitochondriogenesis, and energy production (ATP) they were Clear Mind & Energy, Brain Care II and B is for Brain. Each product was used singularly or in combination over a 16-year period in a clinical environment prior to being released.





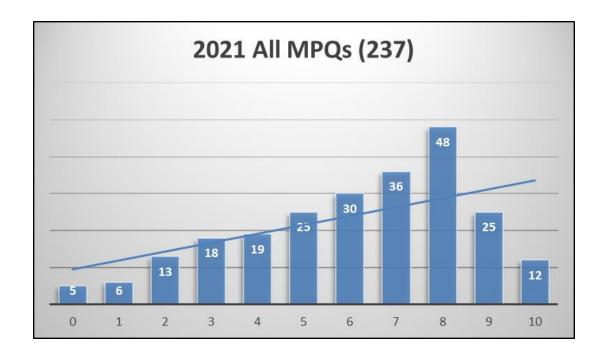
### **Ongoing Assessment**

Since 2010, a self-assessment tool called the Monthly Program Questionnaire (MPQ) has been filled-out and submitted every 30 days by program participants. The MPQ asks questions about psychological, physiological, and physical functioning while on their treatment protocol. There are a total of 25 questions which are scored between a zero and 10 indicating the level of improvement in a particular area. The graphs that follow represent the final MPQ scores obtained from all 237 clients as of December 31, 2021.

### **Results**

Two hundred thirty-seven individuals completed their initial assessment and subsequent monitoring laboratory testing while on their treatment protocol. Each provided a minimum of 6 separate MPQs over the course of the year adhering to a submission every 30 days. The participants were comprised of 81 military (51.9%), 75 civilians (48.1%) of which 7 had a chemically exacerbated neurotrauma due to the use of the drug finasteride. The average age of the participants was 41.7 years (range was 21 – 76yrs), 9 females (5.8%) and 147 males (94.2%).

### A. Over-All Results







### **B.** Active Military and Veteran Results

Of the 81 Military (active and veterans), 51 (62.96%) were exposed to one or more blast wave traumas (BWT) with 37 (72.6%) of those having had loss of consciousness. There were 55 (67.9%) participants having depression as a chief complaint, anxiety in 64 (79%), and migraines in 40 participants (49.4%).



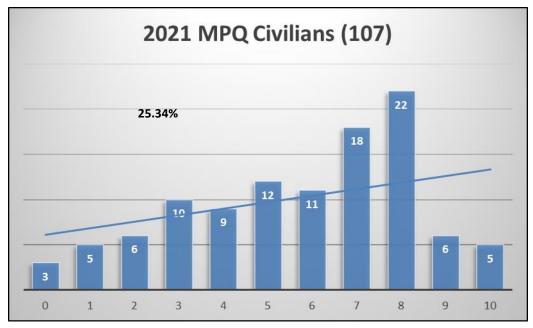
### C. Civilian MPQ Results

Of the 75 civilians, 28 (37.3%) experienced loss of consciousness, 49 (65.3%) had depression, 45 (60%) anxiety, and 31 (41.3%) had migraines. Over-all, in the civilian group, they experienced a 50% or greater improvement in 74.66% of the cases, while 25.34% experiencing less than 50% improvement.





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### The Millennium Protocol and Tinnitus

In December 2020, I was called by Dr. Eric and asked if there was anything that could be done for his annoying tinnitus that he had for years. He explained that during the daytime, its presence was tolerable due to his work activities that acted as a distraction, so he kept his mind off of it. Although during the night when all things went quiet, the noise dominated. I suggested that he take our Brain Care 2 product pre-breakfast and again pre-dinner for 2 weeks and then get back to me.

At about 2 weeks, I received this email from Dr. Eric; "Hey Dr. Gordon! Just following up on the Brain Care 2 modification you suggested to the protocol. You bumped me up to do Brain Care 2 pre-breakfast and pre-dinner for 2 weeks. I just completed the 2-week period and will return to pre-breakfast only as I was doing before if you give the go ahead. The tinnitus has definitely improved to the point where it is not noticeable most times of the day and just barely even at night when everything is quiet. I love the results! "I picked up the phone and Eric and I had an incredible conversation about his tinnitus and overall well-being.

My response was to review the scientific literature about Tinnitus. What I found were the generally accepted causes for tinnitus that included hearing loss, sudden or recurrent noise trauma, as well as neurotrauma. Isn't inflammation or neuroinflammation a potential form of neurotrauma too? Additionally, it appeared that if tinnitus was present for more than a year, it was considered permanent.

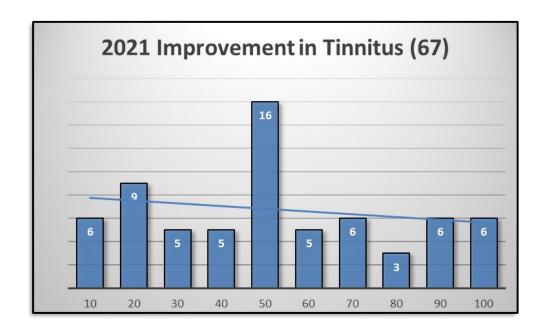
In January 2021, Andrew Marr and I reunited in Austin Texas to be guests on the Joe Rogan Experience (1589). At that time, I shared with Andrew the Dr. Eric and Tinnitus story and asked him how his tinnitus was doing. Of note, while Andrew was in the Green Berets he developed a fondness of blowing things up and also became an explosives technician (EOD). During his enlistment, he was exposed to





hundreds of explosions and then one major one that ended his military career. I asked him how was his tinnitus to which he responded; it disappeared almost a year earlier (a little after Brain Care II was released). In my state of amazement, I repeated his answer and then asked, "why didn't you tell me?" to which he responded, "You never asked!" Since January 2021, I have been asking everyone and have incorporated a question about Tinnitus in to the 2021 MPQ.

There are 67 participants that responded to the question, "Since starting your treatment protocol, how much has your tinnitus (ringing in the ears) improved? The average improvement was 52.09% within a 6-to-12-month window. When we compared over-all MPQ improvement to reduction in level of Tinnitus, they were inversely related.

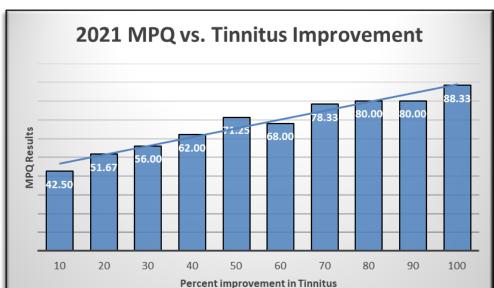


Tinnitus Graph 1: Improvement in tinnitus symptoms over a 6–12-month time frame; the amount of reduction in tinnitus intensity and presence.





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Tinnitus Graph 2: Improvement in Tinnitus directly correlates with the participants overall improvement as indicated by their MPQ Scores.

### **Treatment**

The Millennium Health Centers, Inc., has had the opportunity to assess and treat over 3,500 individuals from both military and civilian communities since 2004. During this time, we have added and subtracted a number of treatment protocol options that did not provide the level of improvement desired for continued use. Additionally, and as stated above, the paradigm of replenishing neurosteroids and neuroactive steroids as the mainstay of treatment, was modified based upon a greater understanding of the causation for loss of these important steroids, namely inflammation. As our treatment protocol focused more on inflammation, we saw a trend of quicker and more sustainable improvement in many of the patients' symptomatic complaints and a diminished use of prescription medication.

Furthermore, we removed the urgency to acutely supplement with growth hormone and testosterone by first addressing the causation for the loss of production and release of these important hormones. A number of articles have appeared reporting the effects of neuroinflammation on a number of pathways that lead to the production of Testosterone and Growth Hormone. In fact, inflammation can be seen as the great disruptor of all important biochemical pathways that generate not only the brain's neurosteroids, but also neurotransmitters and enzymes. Therefore, treatment that reduces inflammation has led to the improvement in measurable levels of these and other hormones.

When reduction of inflammation is associated with sub-optimal improvement in one's free testosterone level, we will add a **SERMS** to help increase the patient's hypothalamic production of gonadotropin releasing hormone (GnRH) before using an injectable testosterone. Inflammation reduces





the hypothalamic production of GnRH so that the signal to the pituitary gland to release follicle stimulating hormone (FSH) and luteinizing hormone (LH) is greatly reduced (19). The finding on laboratory testing will be low FSH and LH along with a low peripheral free testosterone level. Using any form of testosterone will further diminish the hypothalamic-pituitary-gonadal circuitry's ability to regulate testosterone production (negative feedback affect). This also holds true for growth hormone.

### Summary

The outcome report for 2021 has been following an annual trendline of progressive improvement over the prior years since 2018. We are attributing this to the addition to the Millennium's treatment protocol of products such as Clear Mind & Energy added in March of 2017, Brain Care II added in May 2019, and B is for Brain added in February 2020. These three products (**Tri-Pak or Brain Rescue 3**) have become our core approach to treatment where each product addresses a tactic for helping the brain reestablish a neuropermissive environment conducive to healing. The main focus is on the inflammation precipitated by trauma and complimented with an array of nutraceutical components addressing mitochondrial function with ATP production. The more energy produced the more efficient the brain can function to restore biochemical processes that have been damaged by the change in the neurochemical environment precipitated by inflammation. <a href="https://www.millenniumhealthstore.com">www.millenniumhealthstore.com</a>

Year-by-year, we have shown progressive improvement in both neuropsychiatric and neurocognitive functioning. These are commonly represented by improvement in social habits, family unity, diminished medication, educational advancement, emotional stability, greater joy, and happiness in life.

#### Recommendations

The Millennium Health Centers, Inc, since 2004 has offered a comprehensive laboratory assessment utilizing the Millennium Biomarker panel (MBM panel) to direct the diagnoses and treatment of each client. This has been considered our flagship approach. In 2020, with our three core products available, we started testing their effectiveness without the benefits of initially drawing the MBM panel. Our initial group were active Marines from Camp Pendleton, California to which we added another group of veteran Marines. The final count of participants was 25 individuals, of which 65% (16) had a 50% to 100% improvement within 90 days over 20 points of assessment.

The outcome of this open study (not blinded) showed us that the treatment protocol utilizing the Brain Rescue 3 protocol could identify a population of traumatized and symptomatic individuals and improve their condition in a relatively short time frame (90days). Used as a screening tool, the Brain Rescue 3 protocol could identify those individuals that would need to have a more comprehensive assessment with performing the Millennium's Biomarker panel. (Nutraceutical MPQ @ www.TBIHELPNOW.org/the-science)





Furthermore, since June 2021, we have started looking at two pre-laboratory, nutraceutical treatment protocols identified as:

**Phase 1 Protocol**: Brain Care 3, one sachet pre-breakfast for 90 days.

<u>Phase 2b Protocol</u>: Brain Care 3, one sachet pre-breakfast. Brain Care 2, one sachet pre-dinner. Then 15-30min after dinner, 50-100mg of Pregnenolone, 25mg-50mg of DHEA (males) or 15mg-25mg of DHEA (females), and 125mcg-250mcg Vitamin D3.

### Conclusion

The scientific literature abounds with research that has been performed over decades addressing the biochemical changes that impact our psychiatric health and cognitive abilities. Currently, there are volumes of research associating neuroinflammation with psychiatric conditions such as depression and anxiety while advanced neuroinflammation is associated with neurodegeneration presenting as Alzheimer's, Parkinson's, Multiple Sclerosis, and Amyotrophic Lateral Sclerosis.





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#### REFERENCES

- Giatti, S., Boraso, M., Melcangi, R. C., & Viviani, B. (2012). Neuroactive steroids, their metabolites, and neuroinflammation. *Journal of Molecular Endocrinology*, 49(3), R125–R134. https://doi.org/10.1530/JME-12-0127
- Charalampopoulos, I., Alexaki, V. I., Tsatsanis, C., Minas, V., Dermitzaki, E., Lasaridis, I., Vardouli, L., Stournaras, C., Margioris, A. N., Castanas, E., & Gravanis, A. (2006). Neurosteroids as endogenous inhibitors of neuronal cell apoptosis in aging. *Annals of the New York Academy of Sciences*, 1088, 139–152. https://doi.org/10.1196/annals.1366.003
- 3. Wilson, C. J., Finch, C. E., & Cohen, H. J. (2002). Cytokines and cognition--the case for a head-to-toe inflammatory paradigm. *Journal of the American Geriatrics Society*, 50(12), 2041–2056. https://doi.org/10.1046/j.1532-5415.2002.50619.x
- 4. Bodnar, C., Morganti, J., & Bachstetter, A. (2018). Depression following a traumatic brain injury: uncovering cytokine dysregulation as a pathogenic mechanism. *Neural Regeneration Research*, *13*(10), 1693. <a href="https://doi.org/10.4103/1673-5374.238604">https://doi.org/10.4103/1673-5374.238604</a>
- 5. Herbert, J. (2001). Neurosteroids: A New Regulatory Function in the Nervous System. *Journal of Psychiatry and Neuroscience*, 26(5), 421–422. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC167201/
- Hu, Z. Y., Bourreau, E., Jung-testas, I., Robel, P., & Baulieu, E.-E. (1987). Neurosteroids: Oligodendrocyte mitochondria convert cholesterol to pregnenolone. *Proceedings of the National Academy of Sciences*, 84(December), 8215–8219. https://doi.org/10.1073/pnas.84.23.8215
- Saraiva, M., & O'Garra, A. (2010). The regulation of IL-10 production by immune cells. Nature Reviews Immunology, 10(3), 170– 181. https://doi.org/10.1038/nri2711
- 8. Liva, S. M., & Voskuhl, R. R. (2001). Testosterone Acts Directly on CD4+ T Lymphocytes to Increase IL-10 Production. *The Journal of Immunology*, 167(4), 2060–2067. https://doi.org/10.4049/jimmunol.167.4.2060
- Yao, M., Nguyen, T. V. V., Rosario, E. R., Ramsden, M., & Pike, C. J. (2008). Androgens regulate neprilysin expression: Role in reducing β-amyloid levels. *Journal of Neurochemistry*, 105(6), 2477–2488. https://doi.org/10.1111/j.1471-4159.2008.05341.x
- Lurie, D. I. (2018). An integrative approach to neuroinflammation in psychiatric disorders and neuropathic pain. *Journal of Experimental Neuroscience*, 12, 1–11. <a href="https://doi.org/10.1177/1179069518793639">https://doi.org/10.1177/1179069518793639</a>
- 11. Eser, D., Schüle, C., Baghai, T. C., Romeo, E., & Rupprecht, R. (2007). Neuroactive steroids in depression and anxiety disorders: Clinical studies. *Neuroendocrinology*, 84(4), 244–254. https://doi.org/10.1159/000097879
- 12. Svetlov, S. I., Larner, S. F., Kirk, D. R., Atkinson, J., Hayes, R. L., & Wang, K. K. W. (2009). Biomarkers of blast-induced neurotrauma: Profiling molecular and cellular mechanisms of blast brain injury. In *Journal of Neurotrauma* (Vol. 26, Issue 6, pp. 913–921). https://doi.org/10.1089/neu.2008.0609
- 13. Ramlackhansingh, A. F., Brooks, D. J., Greenwood, R. J., Bose, S. K., Turkheimer, F. E., Kinnunen, K. M., Gentleman, S., Heckemann, R. A., Gunanayagam, K., Gelosa, G., & Sharp, D. J. (2011). Inflammation after trauma: microglial activation and traumatic brain injury. *Annals of Neurology*, 70(3), 374–383. https://doi.org/10.1002/ana.22455
- Li, J., Baud, O., Vartanian, T., Volpe, J. J., & Rosenberg, P. A. (2005). Peroxynitrite generated by inducible nitric oxide synthase and NADPH oxidase mediates microglial toxicity to oligodendrocytes. *Proceedings of the National Academy of Sciences of the United States of America*, 102(28), 9936–9941. https://doi.org/10.1073/pnas.0502552102
- Cornelius, C., Crupi, R., Calabrese, V., Graziano, A., Milone, P., Pennisi, G., Radak, Z., Calabrese, E. J., & Cuzzocrea, S. (2013). Traumatic Brain Injury: Oxidative Stress and Neuroprotection. *Antioxidants & Redox Signaling*, 19(8), 836–853. https://doi.org/10.1089/ars.2012.4981
- Réus, G. Z., Fries, G. R., Stertz, L., Badawy, M., Passos, I. C., Barichello, T., Kapczinski, F., & Quevedo, J. (2015). The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. *Neuroscience*, 300, 141–154. https://doi.org/10.1016/j.neuroscience.2015.05.018
- 17. Radtke, F. A., Chapman, G., Hall, J., & Syed, Y. A. (2017). Modulating Neuroinflammation to Treat Neuropsychiatric Disorders. BioMed Research International, 2017, 1–21. https://doi.org/10.1155/2017/5071786
- 18. Pall, M. L. (2010). The NO/ONOO- Vicious Cycle Mechanism as the Cause of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. In Chronic Fatigue Syndrome: Symptoms, Causes & Prevention (Issue 800, pp. 27–56). <a href="https://www.researchgate.net/publication/228471891">https://www.researchgate.net/publication/228471891</a> The NOONOO-Vicious Cycle Mechanism as the Cause of Chronic Fatigue SyndromeMyalgic Encephalomyelitis
- Sharif, A., Baroncini, M., & Prevot, V. (2013). Role of Glia in the Regulation of Gonadotropin-Releasing Hormone Neuronal Activity and Secretion. Neuroendocrinology, 98(1), 1–15. https://doi.org/10.1159/000351867

