Endorphinate®

FOR THE RELIEF OF EMOTIONAL AND PHYSICAL DISTRESS

I. THE PROBLEM

Nearly everyone suffers from emotional and physical *distress*[1]. For many people this is a serious daily problem, experienced as anxiety, panic, anger, depression, addiction, distractibility, or pain. For others, their distress is less frequent or severe, with concerns regarding excessive worries and fears, frustration and irritability, low mood, cravings, or bodily aches. While these problems may reflect symptoms of a more serious medical disorder, such as diabetes, hormonal imbalances, or cardiac conditions, which need to be ruled out, for most of us, this emotional and physical *distress* is triggered by our difficulty handling life's *stresses*. Furthermore, this distress clearly interferes with the quality of our life, relationships, and productivity.

Current treatment for emotional and physical distress, including anxiety, depression, addiction, distractibility, and pain is *insufficient* for a number of important reasons:

1. Most people are hesitant to turn to psychiatrists to "treat" these concerns since they do not see themselves as "crazy" or having a "mental disorder."
2. In fact, most of them actually do not have a serious "mental disorder," which would be required for a prescription psychiatric medication.
3. Even when a "mental disorder" is diagnosed and medication is prescribed, most people find that psychiatric drugs produce noxious side effects[2-4], including cognitive and psychomotor impairments, weight gain/loss, sexual dysfunction, drug dependence and tolerance, as well as, ironically, *increased* anxiety, irritability, depression, addiction, and even suicidal tendencies.

4. Most psychiatric medications for anxiety, depression, distractibility, addiction, and pain have limited clinical benefits, ranging from 10-20% improvement over placebo, and do not effectively reduce emotional and physical distress for most people[5,6,].
5. More and more people are turning to over-the-counter formulations, from Seredyn® to 5 Hour Energy®, and are willing to spend tens of billions of US dollars on supplements[7]. Unfortunately, these popular products tend to trigger either excessive sedation and cognitive impairments or agitation and anxiety as well as mood and energy swings. They also have little-to-no scientific basis or clinical testing and often have limited effectiveness[8].

Limited efficacy, compliance, and access, serious side effects and the social stigma of psychiatric treatment for emotional and physical distress, indicate a clear need for a completely new approach to resolving this wide-spread problem.

II. OUR SOLUTION

Rather than rely on outdated psychiatric models and medications based on science from decades ago, or on unscientific and unproven nutritional supplements, Pondera scientists have used the groundbreaking discoveries, over years of systematic published neuroscience research on the brain's stress processing neural networks, to develop an innovative method to relieve a wide variety of emotional and physical distress concerns[9,10].

Evidence suggests that imbalances in stress-related neurotransmitter levels and receptor signaling may be responsible, at least in part, for a wide variety of previously considered distinct distress syndromes, including anxiety, depression, distractibility, addiction, and pain[11-13]. Pondera's distress relief Endorphinate® supplements are the first in-kind nutraceuticals that have been developed specifically to restore healthy balance to the stress centers of the brain, including the endorphin and dopamine neurotransmitter systems[10,14].

Our patented formulations are based on scientifically developed combinations of *Generally Recognized as Safe* (GRAS) natural plant extracts, vitamins, and amino acids, and are available in the United States without prescription. Moreover, they have been well tested over several years in clinical populations and have been shown to provide remarkable

benefits for a wide variety of emotional and physical distress conditions[10,14]. In contrast to other popular supplements on the market, our formulations have been clinically tested to produce minimal to no side effects[10,14]. Moreover, they uniquely produce a balanced integration of enhanced calm and comfort with increased energy and mental clarity[10,14].

III. ENDORPHINATE®

A. Pre-Marketing Clinical Study

Our line of Endorphinate® nutraceuticals are our lead products for the relief of emotional and physical distress[14]. Prior to their launch in early 2012, the formulations were clinically tested with 203 participants (121 females, 82 males, ages 14-85) suffering from a wide variety of distress-related symptoms and conditions including chronic anxiety and agitation, obsessions and compulsions, cravings and addictions, anger and irritability, low energy and mood, distractibility and hyperactivity, as well aches and pains[10].

The participants took one of our nutraceutical formulations for a minimum of two months up to the entire 26 months of the clinical research project. Most of these participants had already been in intensive psychotherapy and many had either previously tried or were concurrently on psychiatric medications including anxiolytic, anti-depressant, stimulant, and pain medication as well as a variety of herbal nutraceuticals[10].

In contrast to most psychiatric drugs and popular over-the-counter stress relief products, side effects were rare and minor, and disappeared within a day or two. Moreover, the clinical benefits were remarkable. As measured by the Distress Dysfunction Inventory (DDI), *all* of the 203 participants reported increased calm and well-being as well as concentration and attention, while more than 90% of them experienced an increase in emotional, relationship, sexual, work, and spiritual satisfaction. Nearly 90% of the participants reported increased physical comfort, while 75% of them experienced increased energy and motivation[10].

More than 90% of the participants, who suffered from emotional distress, anxiety, obsessions and compulsions, depressed mood, anger and irritability, as well as restlessness and agitation prior to commencing the endorphinergic formulation, experienced a reduction in symptoms at the end of the study.

The same level of benefits were reported by sufferers of physical distress, aches and pains, as well as concerns about motivation, energy, concentration, and attention. Similarly, more than 90% of the participants suffering from sleep, sexual, weight, and body image concerns as well as food, alcohol, and drug cravings reported at least some improvement from taking the endorphinergic formulation. Finally, nearly 90% of those suffering from memory concerns and 80% of those suffering from gastrointestinal concerns experienced at least some improvement in these problems. These anonymous, quantified DDI findings were consistent with clinical observations of these individuals by experienced psychotherapists as well as reports from family members and the participants themselves[10].

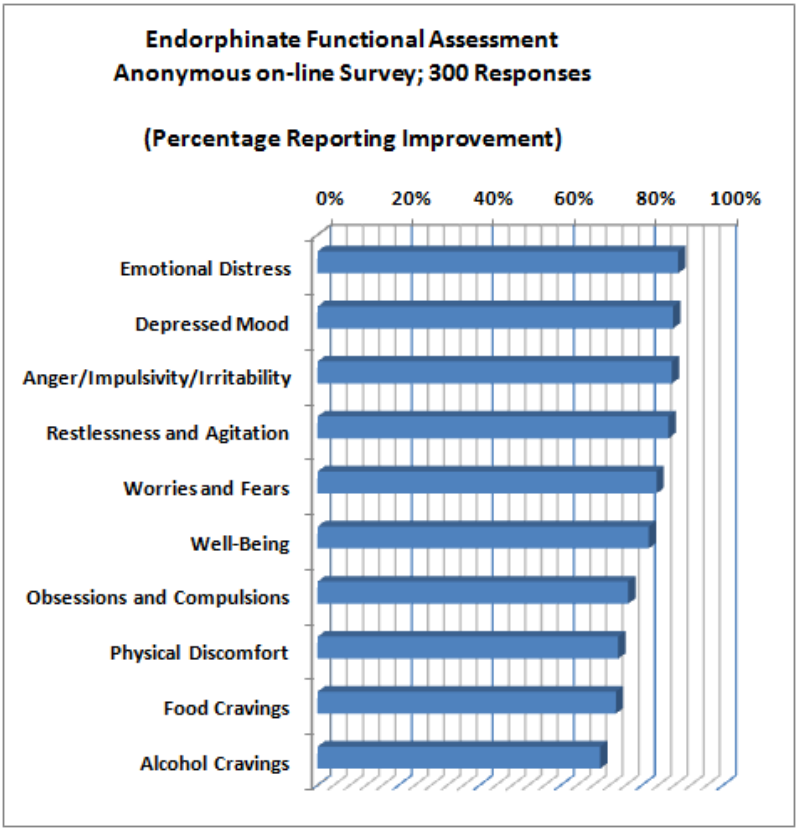
Most participants, regardless of their neuropsychiatric diagnosis, experienced this comprehensive set of emotional and physical distress relief benefits from our nutraceutical formulations. These nutraceuticals provided a safe method to *simultaneously* enhance calm, comfort, well-being, mental clarity, positive mood, energy, as well as adaptive emotional, cognitive, behavioral, and physiological functioning. Obviously, simply taking these nutraceuticals did not typically resolve all of life's problems, but they clearly helped most of them feel better and engage in their lives more adaptively as well as more effectively and thoughtfully work through their life challenges and stresses.

This long-term pre-marketing study demonstrated the remarkable clinical benefits of our nutraceutical formulations across a wide variety of neuropsychiatric disorders. The findings from this clinical study were published in the *Journal of Behavioral and Brain Science* in September 2013[10].

B. Post-Marketing Survey Study

Given the remarkable clinical efficacy and safety of our nutraceutical formulations, the Endorphinate® product line was launched in early 2012. Their benefits were rapidly recognized, including leading mind/brain experts such as Dr. Deepak Chopra from the Chopra Center, and Dr. Rudolph Tanzi from Harvard Medical School[14]. In February 2012, Deepak Chopra publicly endorsed Endorphinate® for daily stress relief on the Dr. Oz Show[14], which gained international interest in our products, and led to our current branding: Deepak Chopra Endorphinate®. Thousands of people around the world began to use Endorphinate® on a daily basis.

Given Pondera's commitment to science and clinical research, we conducted an anonymous on-line survey, using the DDI, for anyone using Endorphinate® daily for at least one week. The data compilation from the first 300 participants who completed the survey demonstrated a set of benefits almost as remarkable as that experienced under clinical supervision[14]. As seen in the chart below, more than 80% of the participants experienced significant relief from emotional distress, worries and anxieties, depressed mood, anger and irritability, as well as restlessness and agitation. Similarly, around 75% of the participants reported a reduction in obsessions and compulsions as well as food and alcohol cravings[14]. Therefore, it became clear from this independent study, as well as numerous on-line testimonials that Endorphinate® products are therapeutic in both clinical and general populations.



IV. NEUROSCIENCE OF ENDORPHINATE®

Pondera's neuroscientists have devoted the past three decades to researching the pain and stress pathways in the central nervous system, and have discovered a safe and effective method to reduce the emotional and physical distress signals of the brain[9]. While the endogenous opioid system has generally been associated with regulation of pain[15,16], it also modulates the experience of distress and appears to play a central role in many psychiatric and neurodevelopmental disorders[11-13].

Our scientific team, led by Dr. Stanley M. Crain, Professor of Neuroscience at Albert Einstein College of Medicine, using sophisticated neurophysiological and biochemical analyses in nerve tissue cultures, discovered the "bimodal" nature of opioid receptors[17,18]. They determined that whereas opioid receptors are normally in an *inhibitory* mode, thereby producing pain and stress *relief* when triggered by *endogenous* opioids (i.e., endorphins) or *exogenous* opioids (e.g., morphine), they can also be in an *excitatory* mode, which literally stimulates the *opposite* effect, that is, *increased* pain and distress[9].

Agents that enhance the production of endorphins, such as caffeine, typically produce increased pain sensitivity as well as anxiety and agitation[19,20], due to excessive excitatory opioid receptor signaling[9]. Dr. Crain's exciting breakthrough came when he discovered specific agents that switch opioid receptors from the *excitatory* (*distress*) to *inhibitory* (*relief*) mode, such as ultra-low-dose opioid antagonists (e.g., naltrexone)[21] and sulfate-enhancing substances (e.g., magnesium sulfate)[22].

Moreover, in a series of induced pain hot water mouse-tail flick studies, Dr. Crain discovered that the increased pain sensitivity typically seen when an *Endorphin Enhancer* (e.g., caffeine) is administered alone was completely reversed and converted to remarkable *pain relief* simply by adding an *Opioid Receptor Switcher* (e.g., magnesium sulfate)[23]. These preclinical studies provided significant evidence that excessive opioid receptor *excitatory* signaling is responsible for *heightened* pain sensitivity, whereas pain *relief* is produced when these receptors are switched to an *inhibitory* mode[23]. Furthermore, they demonstrated, for the first time, that the pain relieving power of endorphins could be unmasked by combining an Endorphin Enhancer with an Opioid Receptor Switcher[9].

Pondera neuroscientists subsequently conducted a series of clinical studies with 60 healthy volunteer participants, using a cold pressor pain induction paradigm[24] (in which participants were asked to keep their hand in ice-cold water for as long as possible), in an attempt to replicate these preclinical studies in humans[10]. Our findings paralleled the animal studies and revealed the potent pain and distress relief benefits of *endorphinergic* formulations, which combine an Endorphin Enhancer with an Opioid Receptor Switcher[10].

For the *nutraceutical* formulations, Endorphin Enhancers included caffeine, a cAMP-PDE inhibitor, known to stimulate the production of endorphins indirectly through the inhibition of PDE (thereby increasing cAMP, which enhances endorphin levels), and forskolin, which directly increases cAMP and, therefore, endorphin levels[9,23]. Increasing cAMP also stimulates dopamine production, which is important in reward and stress pathways as well[25]. Opioid Receptor Switchers initially included magnesium sulfate and n-acetyl cysteine (NAC), both of which are known to increase sulfates[26] and, therefore, switch opioid receptors from an excitatory to an inhibitory mode[9,22]. NAC also has neuroprotective benefits when dopamine levels are increased[27].

When administered alone, Endorphin Enhancers (e.g., caffeine or forskolin) produced an average 12% *reduction* in pain tolerance (i.e., participants became *more sensitive* to pain). In contrast, a placebo actually *increased* pain tolerance by 7%, similar to the effect of Opioid Receptor Switchers (e.g., magnesium sulfate or NAC) administered alone. However, when an Opioid Receptor Switcher was combined with an Endorphin Enhancer, its pain sensitizing effect was eliminated and shifted to a dramatic 18% *increase in* pain tolerance[10].

In fact, this increased pain tolerance was similar to that of low-dose opioid pain medication (e.g., oxycodone) in the same induced pain "cold pressor paradigm[24,28]. However, while both opioid pain medications and our endorphinergic formulations reduce *reactivity* to pain (i.e., increase participants' ability to keep their hands submerged in ice-cold water), opioid pain medications tend to also reduce their ratings of the pain level[24]. Therefore, the induced pain studies revealed the remarkable benefit of our endorphinergic nutraceutical formulations to become *less reactive to painful (i.e., stressful) stimuli*, without significantly altering pain sensations or

producing the noxious side effects typically experienced with opioid medications.

Moreover, our clinical observations of the *emotional* state of the participants during the induced pain paradigm revealed unexpected, dramatic, and meaningful changes in the *distress* they experienced when facing this stress-inducing situation. When participants were administered this endorphinergic formulation, a remarkable reduction in emotional and physical distress – including anxiety and agitation as well as anger and irritability – was evident in the majority of participants, especially those who initially were the most apprehensive about the stressful protocol[10].

Most participants, when given the combination of an Endorphin Enhancer (e.g., caffeine or forskolin) and an Opioid Receptor Switcher (e.g., NAC or magnesium sulfate), were clearly more relaxed and calmer with a greater sense of well being and a more adaptive approach to the stress-induced "cold pressor" paradigm. In discussing their experience, it became clear that the participants' higher pain tolerance when given the endorphinergic formulation was generally due to their *reduced emotional and physical distress*, despite the stressful nature of the situation, rather than a significant decrease in their ability to sense painful stimuli[10].

From these preclinical and clinical studies, we realized that we had discovered a remarkably safe and effective method to reduce emotional and physical distress. The endorphinergic nutraceutical formulation clearly improved a person's ability to adaptively handle life's *stresses* without becoming overly *distressed*. Sensory, cognitive, and motor functions remained intact, in contrast to most psychiatric and pain medications, which is critical in maintaining our ability to respond effectively to life's stresses and challenges.

Therefore, we began the next step in our research program, which was to evaluate the safety and efficacy of our endorphinergic formulation in clinical populations for the relief of emotional and physical distress, including anxiety, depression, anger, distractibility, and addiction, as well as to enhance energy, mental clarity, positive mood, and functioning.

A series of clinical case studies were done using our core endorphinergic formulation, including one or more Endorphin Enhancers (caffeine and/or forskolin) together with one or more Endorphin Enhancers (NAC and/or

magnesium sulfate). During this clinical testing, we discovered that l-theanine[29], a natural amino acid in green tea, appeared to function as an Endorphin Enhancer, and was included in our final formulations. In addition, specific B-Vitamins (B-6, B-12, folate) were also added to certain formulations, as Synergistic Enhancers, since they are critical in the synthesis of stress-related neurotransmitters, including endorphins and dopamine.

We also did a systematic review of herbal adaptogens, which have been used for centuries to facilitate an ability to respond adaptively to life's stresses. While not as effective on their own, rhodiola rosea[30] and lemon balm[31] appeared to synergize with our core endorphinergic ingredients and were also included, as Synergistic Enhancers, in certain formulations. Finally, in order to maximize the efficacy of our formulation that targets pain and inflammation, we included extracts from natural anti-inflammatory agents[32], white willow bark and boswellia, to complement our core endorphinergic ingredients.

These clinical case studies were compelling and demonstrated the remarkable safety and efficacy of our final formulations for a wide variety of distress conditions, including, anxiety, depression, distractibility, addiction, and pain[10]. Not only did these formulations increase participants' ability to more adaptively handle life's stresses, but they also enhanced their overall well being, energy, mental clarity, and functioning. These nutraceutical formulations were then used in our pre-market clinical study, described earlier in this document.

V. ENDORPHINATE® PRODUCT LINE

The current Endorphinate® product line includes three formulations, each of which can be used alone or in combination[14]. For instance, many people benefit from taking Endorphinate® AR during the day for calming energy and then Endorphinate® CF in the evening for restful sleep. Endorphinate® (PR) can be used daily for chronic aches and pains or as needed for those already using another formulation daily. In this way, the three products in this nutraceutical line complement one another and provide a wide range of benefits.

Most people experience benefits from Endorphinate® within an hour. Given the restoration of balance in the stress pathways of the central nervous

system, the most comprehensive set of benefits develop over weeks of daily use.

A. Endorphinate® AR

Endorphinate® AR (Anxiety Relief) is our original formulation, which was developed to reduce emotional and physical distress including anxiety, depression, anger, and cravings. Endorphinate® AR has been shown to produce calm, comfort, and well being while simultaneously enhancing mental clarity and energy. Given its energizing benefits, most people use Endorphinate® AR daily upon awakening and mid-afternoon. Endorphinate® (AR) contains an Endorphin Enhancer (natural caffeine in the form of guarana and green tea), Opioid Receptor Switchers (NAC, magnesium sulfate, l-theanine), and Synergistic Enhancers: herbal adaptogens (lemon balm, rhodiola rosea), and B-vitamins (B-6, B-12, folate).

B. Endorphinate® PR

Endorphinate® PR (Pain Relief) combines the core endorphinergic formula of AR with natural anti-inflammatory ingredients in order to maximize relief of physical distress, including aches and pains. Endorphinate® PR has been shown to produce comfort, calm, well being, and energy, together with relief from mild-to-moderate aches and pains. Many people use Endorphinate® PR daily for chronic aches and pains as well as the relief of emotional distress, though others use it as needed for acute pain. Endorphinate® PR contains an Endorphin Enhancer (natural caffeine in the form of guarana and green tea), Opioid Receptor Switchers (NAC, magnesium sulfate, l-theanine), and Synergistic Enhancers: anti-inflammatory herbal extracts (white willow bark, Apres Flex®, a potent extract of boswellia), and B-vitamins (B-6, B-12, folate).

C. Endorphinate® CF

Endorphinate® CF (Caffeine-Free) was developed to reduce emotional and physical distress including anxiety, depression, anger, and cravings, without the energizing effects of the AR and PR formulations. Endorphinate® CF has been shown to produce calm, well being, and serenity. While this product is often used in the evening for restful sleep, it is not sedating, unlike most other “anxiety relief” and “sleep-inducing” herbs and nutraceutical formulations. Therefore, many people enjoy its calming

endorphinergic benefits, including relief from anxiety and cravings, throughout the day as well. Endorphinate® CF contains an Endorphin Enhancer (coleus forskolin), Opioid Receptor Switchers (NAC, magnesium sulfate, l-theanine), and Synergistic Enhancers: herbal adaptogens (rhodiola rosea, lemon balm).

VI. REGULATORY STATUS

All Endorphinate® products contain ingredients that are considered Generally Regarded as Safe (GRAS) and may be marketed as nutraceuticals or dietary supplements in the USA[33].

The key invention upon which all Endorphinate® products are based is covered by patents[28] (8,372,414 and 8,202,525) assigned to Pondera Biotechnologies. Pondera Biotechnologies has been assigned the registered trademark for Endorphinate®.

VII. MARKET ANALYSIS

There is a huge unmet need for nutraceuticals that can safely and effectively relieve emotional and physical distress, including the reduction of anxiety, depression, addictions, distractibility, and pain as well as the enhancement of well being, mental clarity, energy and an adaptive response to life's stresses. Tens of billions of US dollars are spent annually on dietary supplements to improve emotional and physical functioning[7]. Endorphinate® nutraceuticals are the only products on the market that are based on decades of scientific research on the stress pathways of the central nervous system. Moreover, only Endorphinate® has been shown to dramatically increase calm, comfort, and well-being, while ***simultaneously*** enhancing mental clarity and energy, as well adaptive response to life's stresses[10]. Therefore, our Endorphinate® product line is expected to take a significant share of this market with a strategic marketing and distribution program.

VIII. CURRENT DISTRIBUTION AND MARKETING

The Endorphinate® product line is currently available online through several websites, including Amazon.com, PonderaPharma.com, DeepakChopra.com, Chopra.com, and iHerb.com. The line is also available at selected healthcare centers, health food stores, and spas across the USA. (Our agreement with

Dr. Chopra permits, but does not require, that his name and endorsements be included on our label and associated with our marketing.)

IX. PARTNERSHIP AND LICENSING AGREEMENTS:

Pondera Pharmaceuticals is seeking partnership and licensing agreements in order to significantly expand the distribution, marketing, and sales of our Endorphinate® product line. Pondera is the sole owner of these patented formulations and has no obligation to, or contracts with, any third parties with regard to these patents.

For more information, please contact:

William E. Crain, President, CEO
Pondera Pharmaceuticals, Inc.
Pondera Biotechnologies, Inc.
www.ponderapharma.com

209 Chadsey Road
Pownal ME 04069
(207) 688-4494
william@ponderapharma.com

Endnotes:

[1] R. C. Kessler, P. A. Berglund, O. Demler, R. Jin, and E. E. Walters, "Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R)," Archives of Psychiatry, Vol. 62, No. 6, 2005, pp. 593-602.

[2] N. Vgontzas and E. O. Bixler, "Benzodiazepine side effects: role of pharmacokinetics and pharmacodynamics," Pharmacology, Vol. 51, 1995, pp. 205-223.

[3] E. Cascade, A. H. Kalali and S. H. Kennedy, "Real-world data on SSRI antidepressant side effects," Psychiatry (Edgmont), Vol. 6, Vol. 2, 2009, pp. 16-18.

[4]C. I. Perez Benitez, et al, "Use of benzodiazepines and selective serotonin reuptake inhibitors in middle-aged and older adults with anxiety disorders: A longitudinal and prospective study," Am J Geriatr Psychiatry, Vol 16, No. 1, 2008, pp. 5-13.

[5] B. Dell'osso and M. Lader, "Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal," *European Psychiatry*, Vol 28, 2013, pp. 7-20.

[6] J. M. Kauffman, "Selective reuptake inhibitor (SSRI) drugs: More risks than benefits," *Journal of American Physicians and Surgeons,* Vol. 14, No. 1, 2009, pp. 7-12.

[7] M. Park, "Half of Americans use supplements," CNN Health, April 13, 2011. http://www.cnn.com/2011/HEALTH/04/13/supplements.dietary/

[8] C. Mar and S. Bent, "An evidence-based review of the 10 most commonly used herbs," *Western Journal of Medicine,* Vol. 171, 1999.

[9] S. Crain and S. M. Crain, "Endorphinergic attenuation of distress by concomitantly enhancing endogenous opioid release and switching opioid receptor signaling from an excessively excitatory to a normal inhibitory mode," Journal of Behavioral and Brain Science, Vol. 3, No. 7, 2013, pp. 497-508.

[10] S. Crain, M. A. Crain and S. M Crain, "Emotional and physical distress relief using a novel endorphinergic formulation," Journal of Behavioral and Brain Science, Vol. 3, No. 6, 2013, pp. 441-453.

[11] Merenlender-Wagner, Y. Dikshtein, and G. Yadid, "The β-endorphin role in stress-related psychiatric disorders," Current Drug Targets, Vol. 10, 2009, pp. 1096-1108.

[12] Merenlender-12S.C. Ribeiro, S. E. Kennedy, Y. R. Smith, C. S. Stohler, and J.-K. Zubieta, "Physical and emotional stress regulation through the endogenous opioid system and μ-opioid receptors," Progress in Neuro-Psychopharmacology & Biological Psychiatry, Vol. 29, 2005, pp. 1264-1280.

[13] A. L. O. Hebb, S. Laforest, and G. Drolet, "Chapter 4.9 "Endogenous opioids, stress, and psychopathology," Techniques in the Behavioral and Neural Sciences, Vol. 15, Part 1, 2005, pp. 561-583. In book series: Handbook of Stress and the Brain, Part 1: The Neurobiology of Stress, Eds. T. Steckler, N.H. Kalin & J.M.H.M Reul

[14] http://ponderapharma.com

[15] L. F. Tseng, "Mechanisms of β-endorphin-induced antinociception. In L. F. Tseng (Ed.), The Pharmacology of Opioid Peptides, Harwood Academia Publishers, United States, 1995, pp. 249-269.

[16] Parikh, A. Hamid, T. C Friedman, K. Nguyen, A. Tseng, P. Marquez, and K. Lufty, "Stress-induced analgesia and endogenous opioid peptides: the importance of stress duration," European Journal of Pharmacology, Vol. 650, No. 2-3, 2011, pp. 563-567.

[17] F. Shen and S. M Crain, " Dual opioid modulation of the action potential duration of mouse dorsal root ganglion neurons in culture," Brain Research, Vol. 491, No. 1, 1989, pp. 227-242.

[18] M. Crain and K.-F. Shen, "Modulation of opioid analgesia, tolerance, and dependence by Gs-coupled, GM1 ganglioside-regulated opioid receptor functions," Trends in Pharmacologic. Science, Vol. 19, No. 9, 1998, pp. 358-365.

[19] M. A. Arnold, D. B. Carr, D. M. Togasaki, M. C. Pian, and J. B. Martin, "Caffeine stimulates release in blood but not in cerebrospinal fluid," Life Sciences, Vol. 31, No. 10, 1982, pp. 1017-1024. doi:org/10.1016/0024-3205(82)90174-6

[20] M. Veleber and D. I. Templer, "Effects of caffeine on anxiety and depression," Journal of Abnormal Psychology, Vol. 93, No. 1, 1984, pp. 120-122..

[21] S. M. Crain and K.-F. Shen, "Antagonists of excitatory opioid receptor functions enhance morphine's analgesic potency and attenuate opioid tolerance/dependence liability," Pain, Vol 84, No. 2-3, 2000, pp. 121-131.

[22] M. Crain and K.-F. Shen, "Neuraminidase inhibitor, oseltamivir blocks GM1 ganglioside-regulated excitatory opioid receptor-mediated hyperalgesia, enhances opioid analgesia and attenuates tolerance in mice," Brain Research, Vol 995, No. 2, 2004, pp. 260-266.

[23] S. M. Crain and K. F. Shen, "Low doses of cyclic AMP-phosphodiesterase inhibitors rapidly evoke opioid receptor-mediated thermal hyperalgesia in naïve mice which is converted to prominent analgesia by cotreatment with ultra-low-dose naltrexone," *Brain Research*, Vol. 1231, 2008, pp. 16-24.

[24] E. Eisenberg, A. Midbari, M. Haddad, and D. Pud, "Predicting the analgesic effect to oxycodone by 'static' and 'dynamic' quantitative sensory testing in healthy subjects," Pain, Vol 151, 2010, pp. 104-109.

[25] Dichter, C.A. Damiano, and J. S. Allen, "Reward circuitry dysfunction in psychiatric and developmental disorders and genetic syndromes: animal models and clinical findings." Journal of Neurodevelopmental Disorders, Vol. 4, No. 19, 2012, pp. 1-43.

[26] O. Dean, F. Giorlando, and M. Berk, "N-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action," Journal of Psychiatry and Neuroscience, Vol. 36, No. 2, 2011, pp. 78-86

[27] M. Berk, G. S. Malhi, L. J. Gray, and O. M. Dean, "The promise of N-acetylcysteine in neuropsychiatry," Trends in Pharmacological Science, Vol 34, No. 3, 2013, pp. 167-177

[28] Crain, W. Crain, S. M. Crain, and M. Crain, "Methods and compositions for treating distress dysfunction and enhancing safety and efficacy of specific medications. (US Patent No. 8,372,414; February 12, 2013)

[29] C. F. Haskell, D. O. Kennedy, A. L. Milne, K.A. Wesnes, A. B. Scholey, "The effects of l-theanine, caffeine and their combination on cognition and mood," Biological Psychology, Vol. 77, No. 2, 2008, pp. 113-122.

[30]Bystritsky, A., Kerwin, L., & Feusner, J. D. (2008). A Pilot Study of Rhodiola rosea (Rhodax®) for Generalized Anxiety Disorder (GAD). The Journal of Alternative and Complementary Medicine, 14(2), 175-180.

[31]D. O. Kennedy, W. Little, and A. B. Scholey, "Attenuation of laboratory-induced stress in humans after acute administration of Melissa officinalis (lemon balm)," Psychosomatic Medicine, Vol. 66, No. 4, 2004, pp. 607-613.

[32] J. C. Maroon, J. W. Bost, and Adara Maroon, "Natural anti-inflammatory agents for pain relief," Surgical Neurology International, Vol. 1, 2010.

[33] http://www.fda.gov/food/IngredientspackagingLabeling/GRAS