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## GABAdone™ Product Information

### Indication

**GABAdone** is intended for use in sleep disorders involving difficulty in falling asleep, maintaining sleep, falling back to sleep after awakening at night, feeling tired upon awakening, and snoring.

**GABAdone** is a medical food that must be used under the active and ongoing supervision of a physician. Medical foods are developed to address the different or altered physiologic requirements that may exist for individuals who have distinctive nutritional needs arising from metabolic disorders, chronic diseases, injuries, premature birth, and other medical conditions, as well as from drug therapies.<sup>1</sup>

Normal patterns of sleep and waking are regulated by neurotransmitters that alter electrical activity in specific areas of the brain. Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter of the central nervous system and the primary neurotransmitter involved in the homeostatic regulation of sleep. Patients with sleep disorders characterized by disrupted patterns of sleep and wakefulness benefit from increased availability of GABA, in addition to glutamate, serotonin, and acetylcholine, to re-establish homeostasis. **GABAdone** is designed to provide a balance of neurotransmitters that have well-defined roles in the modulation of the sleep cycle.

### Ingredients

**GABAdone** is a proprietary blend of neurotransmitter precursors (glutamate, 5-hydroxytryptophan, and choline bitartrate), neurotransmitters (GABA and glutamate), polyphenolic antioxidants (grape seed extract), an amino acid uptake stimulator (gingko biloba), activators of amino acid utilization (glutamate, cocoa powder), and an adenosine antagonist (cocoa powder). Each of the neurotransmitters or precursor amino acids included in the formulation has been specifically selected based on scientific support for their roles in the physiological processes involved in the sleep/wake cycle. These roles are summarized in this monograph in the section *Scientific Support for Use of GABAdone in Sleep Disorders*. The other ingredients in the formulation are functional components of the *Targeted Cellular Technology*™ system.

All of the ingredients included in **GABAdone** are classified as generally recognized as safe (GRAS) by the United States Food and Drug Administration (FDA). To qualify for GRAS status, a substance that is added to a food, including a medical food, has to be supported by data demonstrating that it is safe when consumed in the amounts obtained from these foods as they are typically ingested or prescribed.

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<sup>1</sup> As defined in the guidelines issued by the Center for Food Safety and Nutrition, United States Food and Drug Administration (FDA).

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### **Targeted Cellular Technology™**

**GABAdone** has been formulated using *Targeted Cellular Technology*, an integrated molecular system that facilitates the uptake and utilization of neurotransmitter precursors by target cells within the nervous system. This 5-component system consists of (1) specific neurotransmitter precursors; (2) a stimulus for the neuronal uptake of these precursors by specific neurons; (3) an adenosine antagonist that blocks the inhibitory effect of adenosine on neuronal activity (adenosine brake); (4) a stimulus to trigger the release of the required neurotransmitters from targeted neurons; and (5) a mechanism to prevent attenuation of the precursor response, a well known phenomenon associated with precursor administration.

Use of *Targeted Cellular Technology* improves the metabolic efficiency of neurotransmitter synthesis, thereby reducing the amounts of amino acid precursors needed to correct neurotransmitter imbalances. Use of *Targeted Cellular Technology* also insures that the appropriate amounts of neurotransmitter precursors are delivered to the target neurons with the appropriate timing. As such, *Targeted Cellular Technology* synchronizes the fluctuating demand for neurotransmitters with the availability of the precursor supply, which is especially important for processes that are controlled by circadian rhythms such as the sleep/wake cycle.

Previous attempts to provide an exogenous source of precursor amino acids in the quantities required to support neurotransmitter synthesis for individuals with specific needs necessitated that large amounts of these amino acids be added to the formulations. For patients whose requirements were considerably higher than normal, the amounts of exogenous amino acids that were needed were not practical to consume on a daily basis. In addition, ingestion of large amounts of amino acids increased the risk of adverse effects and the potential for attenuation of the response. Improving metabolic efficiency in uptake and utilization of neurotransmitter precursors by target neurons with Targeted Cellular Technology allows ingestion of smaller amounts of amino acids to elicit the same response, thus making daily dosing more feasible and reducing the potential for tolerance. Unlike pharmaceutical sleep aids which are not innately involved in the sleep process, and thus may lose their effectiveness in a relatively short period of time, the effectiveness of **GABAdone** is not attenuated.

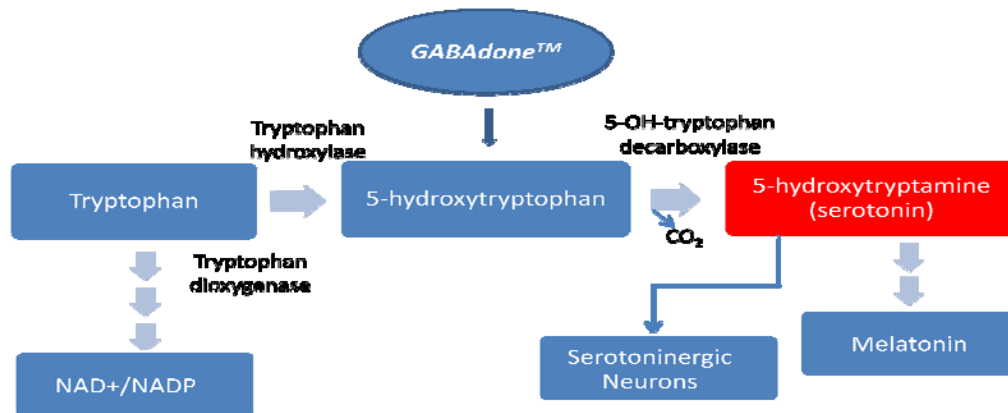
### **Metabolism**

**GABAdone** is a source of amino acids and other nutrients designed for patients with certain types of sleep disorders. These patients require additional amounts of glutamate, tryptophan, and choline to support synthesis of the neurotransmitters, gamma-aminobutyric acid (GABA), serotonin (5-hydroxytryptamine) and acetylcholine, respectively, which are active in the processes that govern sleep and wakefulness. Under normal physiological conditions, glutamate and choline are metabolized as nonessential amino acids because endogenous synthesis is sufficient to satisfy metabolic demand. When needs are altered as in some types of sleep disorders, the usual rate of

synthesis is no longer sufficient and these amino acids become conditionally essential, requiring that an additional amount be consumed. Choline is considered a nonessential nutrient under normal conditions, but becomes conditionally essential in sleep disorders when metabolic demand is increased.

In contrast to glutamate, tryptophan is an essential amino acid in that it must always be consumed from exogenous sources, as the enzymes required for its synthesis are absent in humans. Because it is an essential amino acid, the amount consumed determines the amount available which is divided among the multiple pathways of utilization. In addition to serotonin, tryptophan is a precursor of the coenzymes nicotinamide adenine dinucleotide (NAD<sup>+</sup>) and nicotinamide adenine dinucleotide phosphate (NADP) (Figure 1). The competition between these and other metabolic pathways for the limited supply of tryptophan restricts the amount of serotonin that can be produced from supplemental amounts of the amino acid. To overcome this limitation, **GABAdone** provides 5-hydroxytryptophan, which is the immediate precursor of serotonin in the conversion pathway (Figure 1). The availability of this intermediate circumvents the limiting step in serotonin synthesis and lessens the dependence of serotonin levels on the amount of tryptophan consumed. By facilitating production of serotonin without requiring large amounts of tryptophan as a precursor, **GABAdone** conserves the existing supply of the amino acid for other uses, thus improving metabolic efficiency.

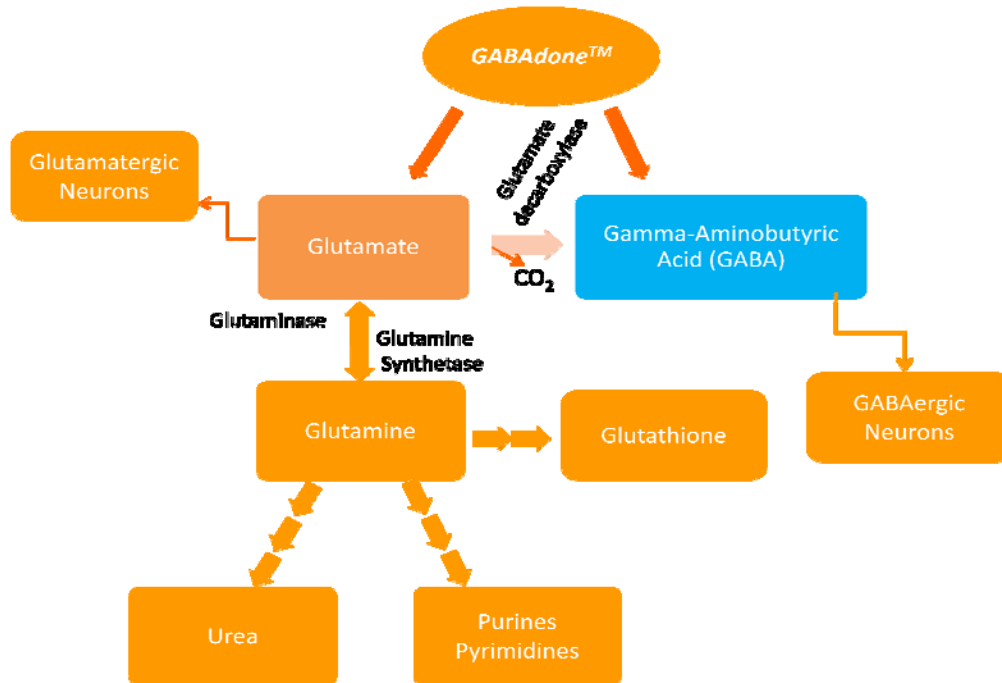
**Figure 1. Competing Pathways of Tryptophan Metabolism**



In contrast to tryptophan, the supply of glutamate is not normally dependent on exogenous sources, thus metabolic competition for glutamate develops only under conditions of increased demand. For individuals with sleep disorders, the requirement for glutamate is higher than normal because additional amounts are needed to support GABA synthesis and to sustain glutamatergic activity. Under normal physiological conditions, glutamate can be supplied by several sources including deamination of glutamine; however, glutamine is also utilized as a precursor for synthesis of other compounds such as glutathione, purines, pyrimidines, and urea (Figure 2). These competitive

demands for glutamine limit the amount of glutamate, and thus the amount of GABA available to function as neurotransmitters. As a source of both GABA and glutamate, **GABAdone** improves metabolic efficiency by insuring that there are adequate amounts of both neurotransmitters while conserving the supply of glutamine for other uses.

**Figure 2. Competing Pathways for Utilization of Glutamate**



Choline is considered a nonessential nutrient under normal physiological conditions because it can be supplied in sufficient amounts to meet usual metabolic demand. Choline is a precursor of acetylcholine which is formed by the action of choline acetyltransferase in an acetylation reaction with acetyl coenzyme A (CoA) as the acetyl group donor. Under steady-state conditions, choline acetyltransferase is not completely saturated in the brain; therefore, the rate of acetylcholine synthesis is determined by the amount of free choline and acetyl CoA available. The primary source of choline under usual conditions is the membrane phospholipid phosphatidylcholine (lecithin), the most abundant phospholipid in the body. The ready availability of membrane phosphatidylcholine ensures that there is normally a steady supply of choline available to support acetylcholine synthesis. Choline can also be synthesized using lysine as a precursor with methionine, folate, vitamin B<sub>12</sub>, and pyridoxine as cofactors, but this pathway contributes only minor amounts of choline to the body pool. When the demand for acetylcholine exceeds the amount of choline that can be supplied from the membrane phospholipid pool, dietary choline becomes an increasingly more important substrate for synthesis of acetylcholine. **GABAdone** provides additional amounts of choline to meet increased needs for acetylcholine which prevents depletion of membrane phosphatidylcholine and protects the structural integrity of the cell.

## **Dosage**

The recommended dose of **GABAdone** is 1 or 2 capsules taken at bedtime. An additional dose may be taken during the night if the patient awakes and finds it difficult to resume sleep. As with any medical food, the best dosing protocol should be determined by assessment of individual needs. At the doses of **GABAdone** recommended to initiate sleep and promote restfulness, the amounts of each ingredient consumed based on body weight are presented in Table 1.

**Table 1. Ingredients in GABAdone Ingested From Recommended Doses**

<b>Ingredient</b>	<b>mg/kg body weight<sup>1</sup></b>
δ-aminobutyric acid (GABA)	1.5 – 12.0
choline bitartrate	1.0 – 7.7
L-glutamate	0.4 – 3.1
5-hydroxytryptophan (griffonia seed, 95% w/w)	0.2– 1.9
Gingko biloba	0.18 – 0.4
grape seed extract	0.2 – 1.5
cocoa powder	0.2 – 1.5

<sup>1</sup>Amounts consumed over the dosing range of 1 to 2 capsules daily

Patients who are taking pharmaceutical agents to initiate and maintain sleep may continue to take these medications with **GABAdone** prior to retiring. If the combination of the drug and **GABAdone** is effective in promoting restorative sleep, then the drug dosage may be further tapered to lower levels under medical supervision. The experience of restorative sleep can be clinically confirmed by the absence of morning grogginess, daytime fatigue, or memory loss upon awakening.

## **Side Effects**

As with any amino acid therapy, headache, nausea, or dry mouth may be experienced in some people after beginning treatment with **GABAdone**. These symptoms are mild and temporary, and readily managed by increasing fluid intake. The development of side effects from **GABAdone** can be minimized by careful titration of the dosage. All of the ingredients in **GABAdone** are regularly consumed in amounts normally found in foods or dietary supplements; therefore development of an adverse reaction to **GABAdone** is not expected.

## **Abbreviations and Definition of Terms**

The definitions for the abbreviations and terms referenced in this monograph are summarized in Table 2.

Table 2. Abbreviations and Definitions of Terms

Term/Abbreviation	Definition
Antioxidant	Protects against oxidative cell damage from exposure to free radicals
Circadian Rhythm	A 24-hour cycle of physiological, biochemical, and behavioral processes controlled by the suprachiasmatic nucleus in the hypothalamus
Excitatory Neurotransmitters	Mediators of neural signals that accelerate the rate of transmission through depolarizing postsynaptic neuronal membranes resulting in increased responsive to a stimulus or reduced responsiveness to a stimulus through stimulation of inhibitory mechanisms
GABAergic	Neurons that secrete gamma-aminobutyric acid
Inhibitory Neurotransmitters	Mediators of neural signals that slow the rate of transmission through hyperpolarization of postsynaptic membranes; inhibit responsiveness to a stimulus
Melatonin	Hormone synthesized from serotonin which increases or decreases in response to changes in light exposure that established circadian rhythms
Monoaminergic	Neurons that secrete monoamine neurotransmitters such as norepinephrine and dopamine; serotonergic neurons are classified as monoaminergic
Neurotransmitter	Secreted by presynaptic neurons in response to an action potential generated by a stimulus, binds to postsynaptic neurons which alters their membrane properties resulting in transmission of a signal down the neural pathways to a specific center in the brain which interprets the signals to initiate a response
NREM Sleep	Period of non-rapid eye movement sleep; a period in the sleep cycle comprising 4 stages that are differentiated by characteristic brain electrical activity
Raphe Nucleus	Mesencephalic nucleus which includes the hypothalamic tract which links ganglion cells to the suprachiasmatic nucleus
REM Sleep	Rapid eye movement sleep; the period of the sleep cycle that normally follows NREM sleep which is characterized by rapid eye movements
Restorative Sleep	Occurs during the late stages of non-REM sleep (Stage III and IV); period during which levels of growth hormone and rates of protein synthesis and rejuvenation of cellular processes, specifically immune function, occur
Reticular Formation	A component of the reticular activating system consisting of a large network of connected tissue nuclei within the brainstem that regulates vital functions, maintains wakefulness, and supports consciousness; also includes the cerebral cortex
Serotonergic	Neurons that secrete serotonin
Sleep Stages	Four distinct periods of non-REM sleep differentiated by changes in brain wave patterns and distinguished by differences in muscular activity, vital signs, and responsiveness to external stimuli.
Suprachiasmatic Nucleus (SCN)	Two pin-sized structures comprising 20, 000 neurons located in the hypothalamus above the point at which the optic nerves cross; controls circadian rhythm in response to signals from light-induced and non-photoc stimuli
Targeted Cellular Technology™	A patent pending process that facilitates endogenous production, uptake, and utilization of neurotransmitter precursors.
Ventrolateral Preoptic (VLPO)	Area of the rostral hypothalamus rich in GABAergic activity

### **Mechanism of Action**

Understanding the mechanism of action of **GABAdone** in the management of sleep disorders requires a brief overview of the physiology of sleep. Sleep is an active process consisting of 2 phases that are differentiated by brain electrical activity on an electroencephalogram (EEG).

During non-REM (NREM), brain wave patterns progress through 4 distinct stages beginning with the fast, medium-amplitude alpha waves that characterize the waking state. In the transition from wakefulness to light sleep (Stages I and II), the pattern of alpha waves is interspersed with medium-velocity, high-amplitude theta waves. This wave pattern eventually shifts to large, high amplitude, slow-moving delta waves indicating the onset of deep sleep or slow-wave sleep (Stages III and IV). Eye movements during light sleep are slow and further diminish with progression into deep sleep when they become nearly undetectable or cease completely. The transition out of NREM sleep to REM (rapid eye movement) sleep is characterized by a shift in brain electrical activity to desynchronized, low-voltage, fast waves accompanied by rapid and jerky eye movements that signal the beginning of REM sleep.

The progression through each stage of NREM sleep into REM sleep comprises a sleep cycle, which is repeated at 90-110 minute intervals. The first period of REM sleep begins 70 to 90 minutes after initiation of non-REM sleep. During the first few sleep cycles, the time spent in REM sleep is relatively short compared with the time spent in deep sleep. As the duration of sleep increases, the amount of time spent in the REM period is extended while the amount spent in deep sleep is shortened. Just prior to awakening, nearly all of the sleep cycle consists of Stage II and REM sleep. On average, a healthy adult spends approximately 20% of time in REM sleep, 50% in Stage II NREM sleep, and 30% divided between Stages I, III, and IV NREM sleep. Restorative sleep occurs during the deep sleep stages III and IV when there is an increase in growth hormone levels and metabolic activities associated with cellular rejuvenation.

The sleep-wake cycle is regulated by neurotransmitters, amino acids or amino acid derivatives which function as mediators of physiological responses to physical, chemical, or electrical stimuli. The interaction of one or more of these stimuli with specialized receptors in various tissues generates a particular type of signal which is converted to an electrical impulse that is propagated over a neural pathway or pathways to specific centers in the brain where it is processed. These impulses are relayed by neurotransmitters secreted from the terminal endings of presynaptic neurons into the synaptic cleft where they bind to receptors on postsynaptic neurons.

Neurotransmitter binding changes the receptor membrane potential and depending upon the electrochemical properties of the neurotransmitter, will either accelerate or inhibit transmission of the electrical impulse. Excitatory neurotransmitters such as glutamate or serotonin depolarize the membrane which lowers the stimulus threshold for neuronal firing, thereby increasing the frequency and rate of signal transmission. Inhibitory neurotransmitters such as GABA hyperpolarize the membrane which raises the stimulus threshold resulting in a reduction in the frequency and rate of signal transmission. Acetylcholine can exhibit both excitatory and inhibitory effects on neuronal membranes depending upon the area of the brain where the receptors are located.

The primary signals that control sleep and waking are generated by interactions between ultraviolet light and photoreceptor cells in the retina. A decrease in light exposure promotes withdrawal of

acetylcholine, serotonin, and glutamate from the reticular formation accompanied by increased GABA in the cerebral cortex. Nonphotic signals originating from metabolic factors such as changes in blood glucose levels that are mediated primarily by serotonin can also influence the sleep cycle. Brain electrical activity is altered by changes in levels of neurotransmitters to wave patterns associated with drowsiness and initiation of NREM sleep.

### **Scientific Support for Use of GABAdone in Sleep Disorders**

**GABAdone** is formulated to insure availability of the appropriate balance of neurotransmitters involved in the sleep process. Adequate intakes of precursor amino acids are critical to maintaining blood concentrations at levels high enough to drive a rapid rate of neuronal uptake (1-5). Since the enzymes that synthesize neurotransmitters are found only in the neurons, the concentration-dependent rate of precursor uptake is limiting to neurotransmitter production. The balance of neurotransmitters is important because their interrelationships are regulated by multiple feedback loops; therefore low levels of any one may influence the activities of the others and thus the net response (6-8).

The transition from waking to sleep is the result of a coordinated inhibition of multiple arousal systems in response to secretion of gamma-aminobutyric acid (GABA) (6, 9-13). Almost all of the sleep-active or sleep-promoting neurons in the brain are GABAergic (GABA secretors) and concentrated in the median preoptic nucleus and ventrolateral preoptic (VLPO) area of the rostral hypothalamus (14-19). NREM sleep is promoted by GABAergic cells in the VLPO region whereas REM sleep is promoted in the areas adjacent to the VLPO. Lesions in the GABAergic-rich anterior hypothalamus have been associated with severe insomnia and fragmented sleep (19-20). Sleep deficits caused by damage to these areas of the brain can be reversed by electrical, thermal, or chemical stimulation indicating that decreased GABAergic activity contributes to disruptions in sleep patterns (12, 21). The activation of GABAergic neurons by sleep deprivation also suggests a dependence of sleep homeostasis on GABA production and release (10, 16).

The transition from sleep to waking is initiated by an increase in activity of wake-active or wake-promoting neurons. These neurons consist of serotonergic (serotonin secretors) neurons originating in the dorsal raphe nucleus, cholinergic (acetylcholine secretors) neurons in the brainstem and basal forebrain, and monoaminergic (norepinephrine and dopamine secretors) neurons in the rostral pons, midbrain, and posterior hypothalamus (6-7, 9, 11-12, 14-15, 17, 19, 11-29). Glutamatergic neurons (glutamate secretors) which are widely distributed in the brain are also involved in the initiation and maintenance of the waking state (14, 30-31). Interactions between the wake-active neurons and hypocretin or orexin-secreting neurons in the perifornical lateral hypothalamus that control arousal, a heightened state of alertness, sustains a long consolidated awake period (6, 32-33). Acetylcholine and glutamine promote arousal by depolarization of these neurons while GABA and serotonin inhibit arousal by hyperpolarization of these neurons (7, 13-14, 33).

Normal patterns of sleep and waking reflect the synchronized activity between sleep-active and wake-active neurons (9-10, 34). This activity is integrated with circadian rhythms which are controlled by the suprachiasmatic nucleus (SCN), 2 pin-sized structures comprising more than 20,000 neurons rich in serotonergic activity which are situated in the hypothalamus above the point at which the optic nerves cross (20, 35-37). Sleep disorders reflect a loss of coordinated activity between sleep-active and wake-active neurons associated with circadian rhythms that can be attributed to imbalances in the activities of GABA, acetylcholine, serotonin, and glutamate (6, 21-22, 25-26, 34, 36, 38-42). Each of these neurotransmitters is involved in transmission of signals generated by light or nonphotic stimuli to the SCN. Glutamatergic neurons transmit light-induced signals directly from the retina by way of the retinohypothalamic tract while GABAergic neurons transmit light-induced signals using the indirect pathway of the geniculohypothalamic tract (23). Serotonergic neurons are the primary transmitters of nonphotic signals to the SCN. Depending upon the specific signal received, the SCN sends a message to the pineal gland to increase or decrease melatonin production (43-44).

During sleep, specific patterns of brain electrical activity are modulated by coordinated changes in neurotransmitter levels which regulate the duration of each stage and the timing of transitions between stages (9, 29, 45). Acetylcholine concentrations fluctuate from high levels while awake to lower levels during slow-wave Stage IV sleep returning to higher levels during REM sleep (14). Cholinergic activity stimulates delta waves in the transition from deep slow-wave sleep to REM sleep, increases the duration of stage IV and stage V sleep, and increases the frequency and duration of REM sleep (14, 25, 28, 45-46). Release of acetylcholine is also associated with increased theta wave activity during the transition from the early to the later stages of the sleep cycle (33).

Serotonergic activity is highest during periods of waking, slows during NREM sleep, and is virtually silent in REM sleep (19, 33, 40, 47). Sleep is initiated and sleep latency is decreased at times of low serotonergic activity (48). During sleep, the highest levels of serotonin are observed within several hours of onset before declining in the transition from NREM to REM sleep. Fluctuations in serotonin levels reflecting both the amount released and timing of the release are closely associated with circadian rhythm and the neuronal systems that inhibit arousal (21, 38, 43, 49). Altered serotonin production and activity have been linked to disturbances in sleep patterns that contribute to sleep apnea, snoring, and depression-associated sleep disorders (17, 40, 49-50).

The overlapping pattern of changes in neurotransmitter levels over the sleep cycle is indicative of the complexity of the interactions among them (22, 26, 30, 51). Local release of GABA in areas of high serotonergic activity inhibits the serotonin-mediated effects that sustain brain activity during waking periods and explains the decrease in serotonin levels noted during REM sleep (15). The subsequent decrease in serotonergic activity lifts the inhibition on the specific cholinergic activity that promotes REM sleep (19). The inhibitory effects of cholinergic activity in the midbrain

reticular formation promote a restful wake state and REM sleep whereas its excitatory effects in the basal forebrain promote vigilance.

A summary of the roles of each of the ingredients in **GABAdone** is presented in Table 3.

**Table 3. Roles of the GABAdone Ingredients in the Sleep Process**

<b>Ingredient</b>	<b>Effector Molecule</b>	<b>Function</b>	<b>Role in Neurotransmitter Metabolism</b>
<b>GABA</b>	GABA	Inhibitory neurotransmitter	Homeostatic regulation of sleep; coordinates inhibition of multiple arousal systems; modulates circadian rhythms through transmission of light signals from photoreceptor cells in the retina to the SCN; moderates serotonergic activity to preserve REM sleep (6, 9-21)
<b>5-OH-tryptophan</b>	Serotonin	Excitatory neurotransmitter	Sustains waking and inhibits arousal; promotes a normal sleep-wake cycle as the major modulator of circadian rhythm; transmits nonphotic signals to the SCN; precursor of melatonin (19-20, 22, 38, 40)
<b>Choline</b>	Acetylcholine	Inhibitory and Excitatory neurotransmitter	Elicits theta and delta wave patterns which control initiation of sleep and frequency and duration of REM sleep, respectively; promotes REM sleep in the midbrain reticular formation and vigilance in the basal forebrain (6,14, 25, 28, 33, 45-46)
<b>Glutamate</b>	Glutamate GABA	Excitatory neurotransmitter	Transmits signals generated light directly from photoreceptor cells in the retina to the SCN through the retinohypothalamic tract (14, 30)
<b>Gingko biloba</b>		Stimulates amino acid uptake by neurons	Modulates presynaptic choline uptake and acetylcholine release (52-53)
<b>Cocoa Powder</b>	caffeine	Adenosine antagonist	Increases neuronal activity by competitively binding to adenosine receptors which disinhibits the “adenosine brake” (54-56)
<b>Grape seed extract</b>	Polyphenols	Antioxidant	Preserves receptor membrane integrity and prevents attenuation of responses to neurotransmitter precursors (57-59)

### **Nutritional Requirements of Sleep Disorders**

The nutrient requirements of greatest interest for patients with sleep disorders are those involved in regulation of the sleep/wake cycle functioning either as neurotransmitter precursors or neurotransmitters. These nutrients consist of choline and the amino acids, 5-hydroxytryptophan, glutamate, and GABA. The fact that the therapeutic effects of the majority of pharmaceuticals

approved for treatment of sleep disorders involve manipulation of brain levels of serotonin and GABA suggests that imbalances in these neurotransmitters contribute to altered sleep patterns. (6, 42, 51, 58-71).

The concept that nutrient requirements are modified by disease has been recognized for more than 30 years, and is supported by studies which have shown changes in plasma, urinary, and tissue levels of nutrients associated with abnormalities in physiological endpoints reflective of a particular pathology (72). These requirements can be estimated by identifying the level of intake at which alterations in specific physiological responses are normalized, indicating that the balance between intake and metabolic demand has been restored. The high degree of coordination of neurotransmitter activities supporting the cyclical nature of the sleep and waking processes underscores the importance of balance in availability of the nutrient precursors required for synthesis of these neurotransmitters (19, 60-63, 73-74).

Diseases that are characterized by imbalances in neurotransmitters require higher intakes of specific nutrient precursors to promote increased production of these neurotransmitters (51, 60-78). The increase in blood levels of these nutrients associated with higher intakes will stimulate the rate of neuronal uptake thereby increasing availability of substrates for the enzymes involved in neurotransmitter synthesis. Intake of nutrient precursors not only influences neurotransmitter synthesis, but it also influences neurotransmitter release (79-81). The appearance of increased amounts of the primary metabolite of serotonin, 5-hydroxyindolacetic acid, in cerebrospinal fluid following administration of 5-hydroxytryptophan confirms that increased amounts of serotonin are not only produced but are also released by the neurons (79-80). By having effects on both the production and release of neurotransmitters, dietary intakes of nutrient precursors also influence the physiological functions dependent on them (1-5, 8, 61-64, 73, 75).

Low blood tryptophan levels have been associated with decreased brain serotonin concentration and disturbances in the sleep-wake cycle indicating an increased need for tryptophan to correct the serotonin deficiency associated with these disturbances (1-3, 8, 39, 44, 64-65, 82-86). Low levels of serotonin accompanied by low levels of 5-hydroxytryptophan in patients with sleep disorders also implicate inadequate tryptophan intake that may be secondary to increased metabolic demand which may also be contributing to disturbances in sleep patterns (82-84). Imbalances in serotonin production and release may be further complicated if tryptophan metabolism is also altered in the disorder (72, 87).

In addition to tryptophan, low blood levels of choline and GABA have been noted in patients with sleep disorders indicating that the requirements for these nutrient precursors are not being met at current levels of intake (51, 81-82, 84, 88-89). Low dietary intake of choline has been associated with sleep apnea syndromes and disorders of restorative sleep (60, 73, 90). The insensitivity of acetylcholine and serotonin to circulating levels of GABA observed in patients with sleep disorders

suggests impaired control of the normal sleep/wake cycle which may be related to imbalances among these neurotransmitters resulting from inadequate intakes of nutrient precursors (11, 19, 51).

A summary of support for increased requirements of specific nutrients in patients with sleep disorders is found in Table 4.

**Table 4. Observations Supporting Increased Nutrient Requirements in Sleep Disorders**

Nutrient	Biochemical and Physiologic Observations	Clinical Observations
<b>GABA</b>	Low blood and brain levels	Insomnia, fragmented sleep
<b>Tryptophan</b>	Low blood levels; low blood 5-hydroxytryptophan and serotonin levels; increased serotonin metabolites in cerebrospinal fluid with tryptophan supplementation	Sleep apnea, snoring, depression-associated sleep disorders
<b>Choline</b>	Low blood choline levels; decreased parasympathetic autonomic nervous system function	sleep apnea syndromes and disorders of restorative sleep
<b>Glutamate</b>	Reduced blood glutamate and GABA	Similar to GABA deficiency

### **Clinical Validation of GABAdone for Use in Sleep Disorders**

A large body of experimental and clinical data supports a relationship between the intake of nutrient precursors and production of corresponding neurotransmitters and clinical outcomes (4-5, 8, 11, 38-39, 47, 60-66, 75-78, 91). Changes in levels of a neurotransmitter in the blood and/or its metabolites in cerebrospinal fluid following ingestion of a precursor reflect uptake and utilization of the nutrient by target cells, thus confirming biological availability and clinical utility of the supplemental nutrient when ingested from a medical food (23, 60, 63-65, 75, 77-78, 88).

The clinical benefit of a medical food can be validated by changes in biological, physiological, and clinical endpoints following administration to individuals with a specific disease or disorder. For example, a medical food which provides supplemental arginine is clinically validated in individuals with low blood arginine levels by increases in blood arginine levels (biological availability) and nitric oxide production (physiological change) accompanied by an improvement in an associated functional parameter (FEV1) (clinical response) following administration. Similarly, if an individual with a sleep disorder shows an increase in serotonin levels after administration of a medical food containing tryptophan or 5-hydroxytryptophan (biological availability) and increased serotonin metabolites in cerebrospinal fluid (physiological change) associated with improvement in sleep patterns (clinical response), then the clinical benefit of the medical food is validated. Improvement in sleep latency from 120 to 10 minutes following consumption of 2000 mg of 5-

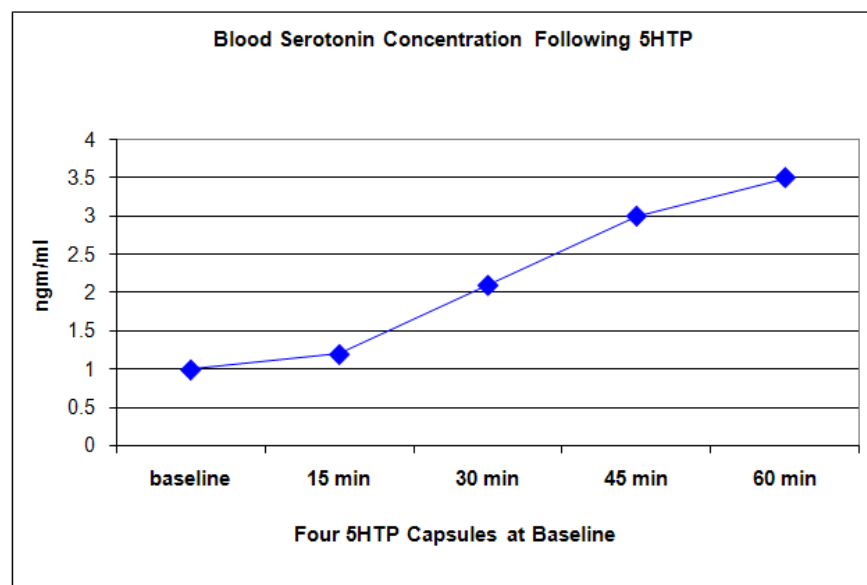
hydroxytryptophan would support the requirement for an additional allowance of tryptophan by individuals having difficulty falling asleep and maintaining sleep.

**GABAdone** provides balanced amounts of GABA, serotonin, acetylcholine, and glutamate in a formulation using Targeted Cellular Technology to control the timing of their release. If sufficient amounts of these neurotransmitters are not available, or their release is not well-synchronized with circadian rhythm, restorative sleep will not occur (10, 19-20, 36, 60). Commonly used drugs that modify sleep patterns through effects on neurotransmitter release and receptor activity, but do not influence neurotransmitter balance, may alter other aspects of the sleep cycle that interfere with restorative sleep (11). Benzodiazepine drugs increase the efficiency of synaptic transmission of GABA which reduces sleep latency, but also abolish REM sleep and stages IV and V of NREM sleep (67). Most hypnotic drugs act by increasing the sensitivity of GABA receptors whereas drugs that promote wakefulness act by stimulating release or inhibiting reuptake of serotonin and other monoamines (67-70).

#### *Biological Availability*

The biological availability of 5-hydroxytryptophan, the source of serotonin in **GABAdone**, has been demonstrated by observed changes in blood serotonin levels within 15 minutes of ingestion of 2000 mg of 5-hydroxytryptophan (Figure 3). These levels continued to increase and were more than 3-fold higher than baseline levels at 60 minutes, confirming that 5-hydroxytryptophan was being utilized to increase production of serotonin.

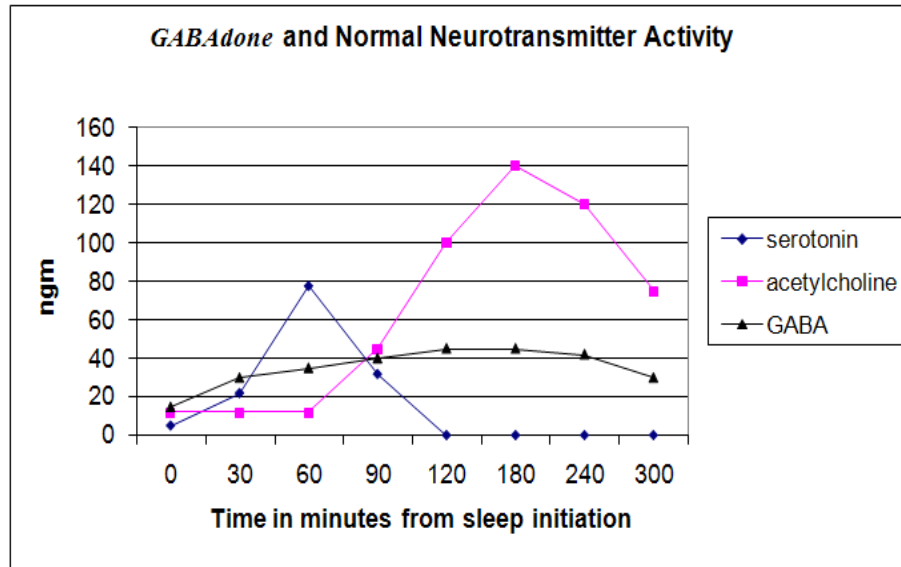
**Figure 3. Effect of 5-Hydroxytryptophan Supplementation on Blood Serotonin Levels**



### Physiological Response

Figure 4 depicts the pattern of changes observed in the blood levels of serotonin, acetylcholine, and GABA following consumption of **GABAdone** at the recommended 2 capsule dose. These data confirm that the levels of neurotransmitters obtained from **GABAdone** or from the precursors in the formulation change over the sleep cycle in patterns consistent with the corresponding endogenous neurotransmitters.

**Figure 4. Physiological Response to GABAdone Administration**



### Clinical Response

A number of clinical trials performed with **GABAdone** have demonstrated favorable effects on initiation of sleep, frequency of snoring, and duration of restorative sleep. These trials include:

- 2 open-label trials of effects on induction and maintenance of sleep and frequency of snoring
- 8 open label trials of effects on awakening in the middle of the night
- 1 randomized, double-blind, placebo-controlled trial of effects on timing and quality of sleep.

#### *A Randomized Placebo-Controlled Trial of an Amino Acid Preparation on Timing and Quality of Sleep*

The effects of **GABAdone** on timing and quality of sleep were examined in a randomized, double-blind, placebo-controlled trial in 18 subjects > 18 years of age with a history of self-reported deficiency of restorative sleep. The primary exclusion criteria were current use of sleep medications, known endocrine disease, or previous treatment with **GABAdone**. Subjects who met all eligibility criteria were randomized to treatment with 2000 mg/d (2 capsules) of **GABAdone** or

to placebo for a 1-week period and instructed to maintain their current sleep routine for the duration of the study. The primary clinical outcome variables were time to fall asleep and sleep quality scores based on both visual analogue and Likert numeric scales. In addition, activation of parasympathetic nervous system function was assessed by a repeat 24-hour ECG on the 6th day and again on the night of the 7th day of the treatment period using Heart Rate Variability analysis, a method that has been validated in patients with sleep disorders. Parasympathetic system activation is associated with normal sleep patterns and is considered to be an objective indicator of restorative sleep and reduced snoring.

The results from this study are displayed in Figures 5 through 8. Statistically significant improvements from baseline in time to fall asleep ( $p=0.01$ ) (Figure 5), hours of sleep (Figure 6) ( $p=0.01$ ), number of awakenings during the night ( $p<0.01$ ) (Figure 7), and morning grogginess as an indicator of restorative sleep and reduction in snoring ( $p=0.01$ ) were demonstrated in subjects treated with **GABAdone** compared with placebo (Figure 8). These findings of improvements in the disruptions in sleep examined in this study were confirmed by a statistically significant increase in parasympathetic nervous system activity in subjects treated with **GABAdone** (Figure 9). None of these parameters were changed by statistically significant amounts in the placebo group.

**Figure 5. Changes in Time to Fall Asleep with GABAdone vs Placebo**

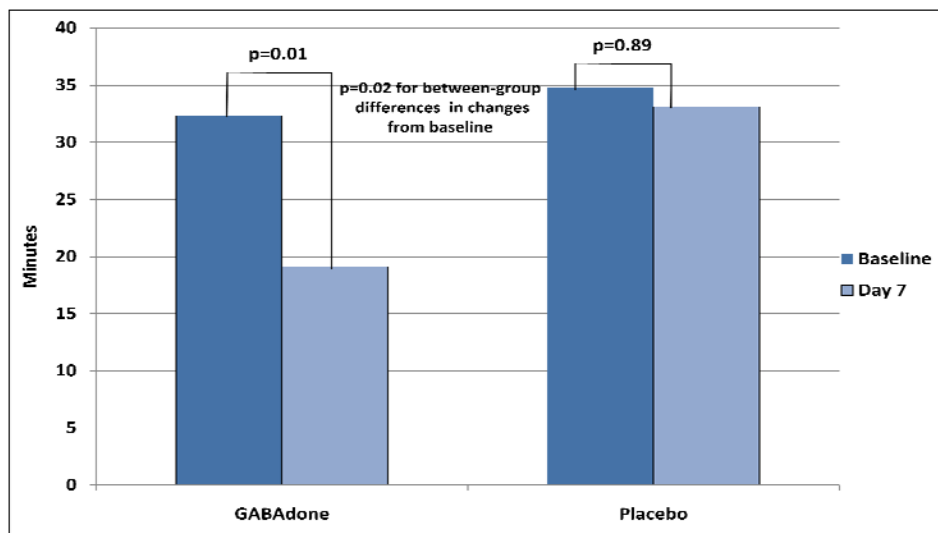


Figure 6. Changes in Hours Slept with GABAdone vs Placebo

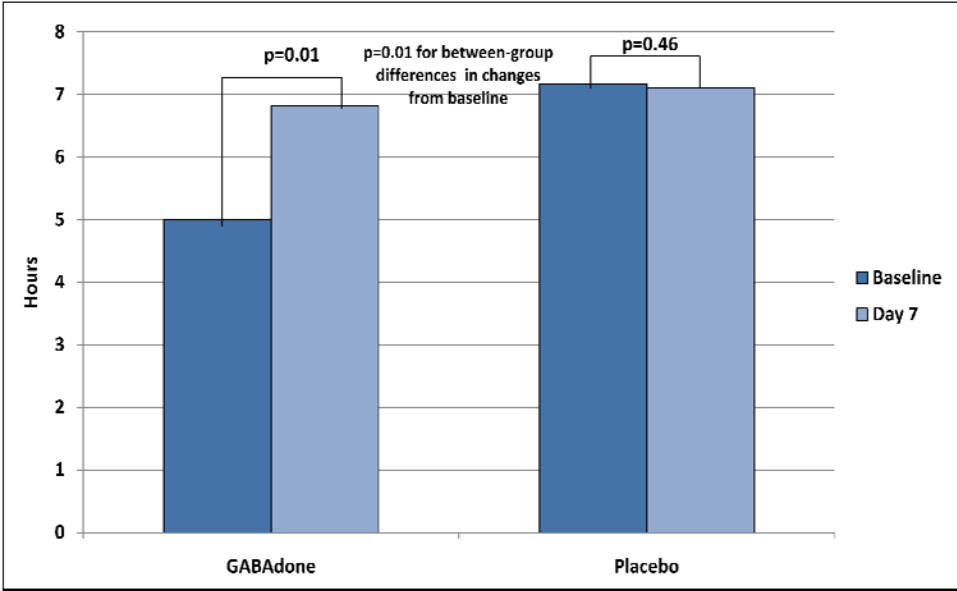
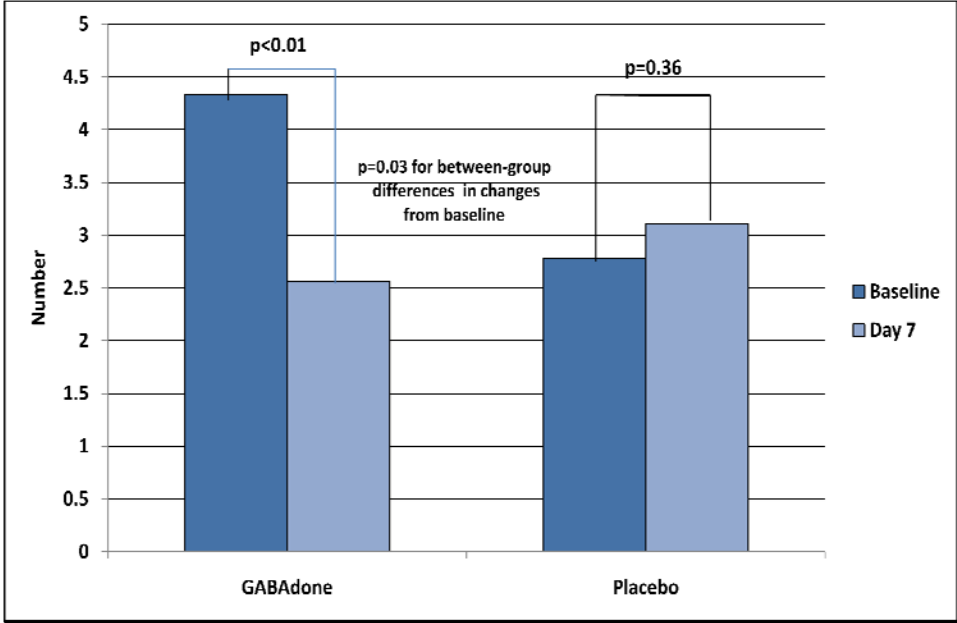
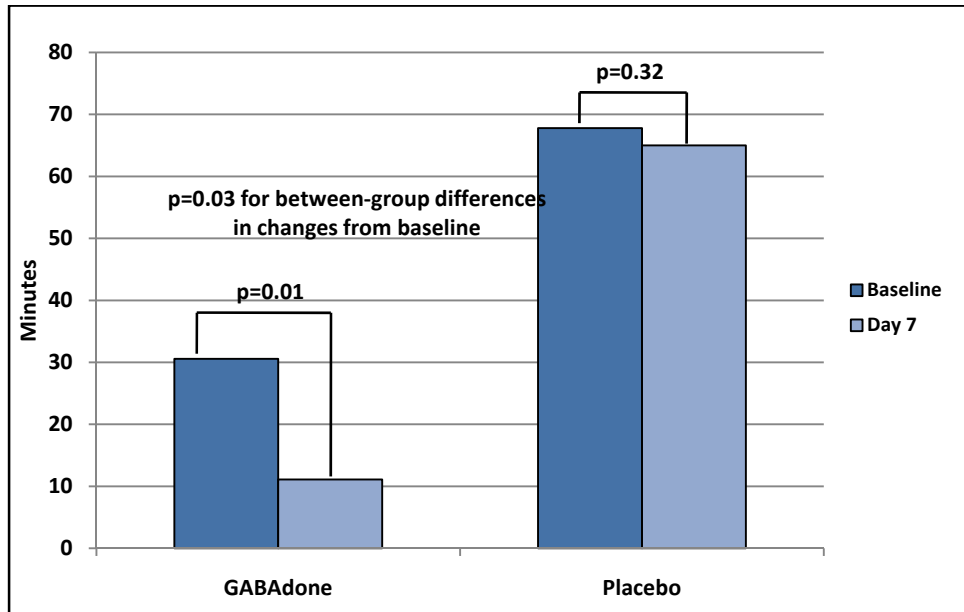


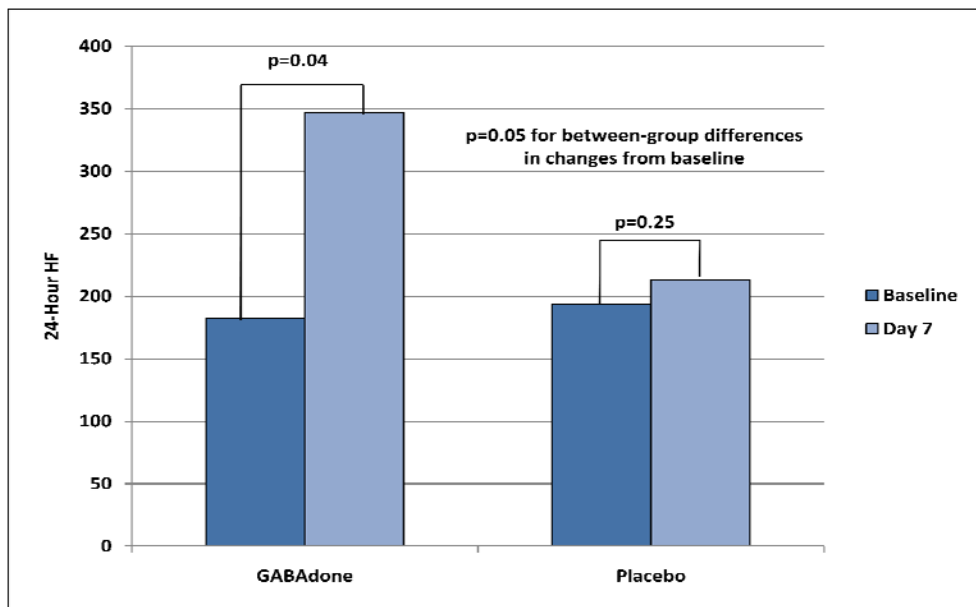
Figure 7. Changes in Number of Awakenings with GABAdone vs Placebo



**Figure 8. Changes in AM Grogginess with GABAdone™ vs Placebo**



**Figure 9. Changes in Parasympathetic Activity with GABAdone vs Placebo**



Compared with baseline, subjects in the **GABAdone** treatment group showed a mean decrease of approximately 40% in time to fall asleep, a mean increase of approximately 2 hours in the hours slept, a mean decrease in frequency of awakenings from 4 times to 3, and a mean decrease of 64% in minutes of morning grogginess. None of the corresponding mean changes in the placebo group was increased by > 5% of baseline values.

The between-group differences in changes from baseline to Day 7 were statistically significant for time to fall asleep ( $p=0.02$ ), hours slept ( $p=0.01$ ), number of awakenings ( $p=0.03$ ), and morning grogginess ( $p=0.01$ ). These changes were associated with a statistically significant increase of approximately 48% in parasympathetic activity in the **GABAdone** treatment group ( $p=0.04$ ). The change in parasympathetic activity in the placebo group was <10% of baseline and not statistically significant.

The results of this study support a clinical benefit for individuals with sleep disorders involving difficulty in falling asleep, maintaining sleep, resuming sleep after awakening, feeling tired upon awakening, and snoring with **GABAdone**.

### **Selected References**

1. Turner EH, Loftis JM, Blackwell AD. Serotonin a la carte: supplementation with the serotonin precursor 5-hydroxytryptophan. *Pharmacol Ther* 2006;109:325-338.
2. Wurtman RJ. Dietary treatments that affect brain neurotransmitters. Effects on calorie and nutrient intake. *Ann N Y Acad Sci* 1987;499:179-90.
3. Wurtman RJ, Hefti F, Melamed E. Precursor control of neurotransmitter synthesis. *Pharmacol Rev* 1980;32:315-335.
4. Fernstrom JD. Effects of precursors on brain neurotransmitter synthesis and brain functions. *Diabetologia* 1981;20 Suppl:281-289.
5. Fernstrom JD, Fernstrom MH. Tyrosine, phenylalanine, and catecholamine synthesis and function in the brain. *J Nutr* 2007;137:1539S-1547S.
6. Szymusiak R, McGinty D. Hypothalamic regulation of sleep and arousal. *Ann N Y Acad Sci* 2008;1129:275-286.
7. Szymusiak R, McGinty D, Fairchild MD, Jenden DJ. Sleep-wake disturbances in an animal model of chronic cholinergic insufficiency. *Brain Res* 1993;629:141-145.
8. Meyers S. Use of neurotransmitter precursors for treatment of depression. *Altern Med Rev* 2000;5:64-71.
9. Gaillard JM. Neurochemical regulation of the states of alertness. *Ann Clin Res* 1985;17:175-184.
10. McGinty D, Szymusiak R. The sleep-wake switch: A neuronal alarm clock. *Nat Med* 2000;6:510-511.
11. Mendelson WB. Neurotransmitters and sleep. *J Clin Psychiatry* 2001;62 Suppl 10:5-8.

12. Szymusiak R. Magnocellular nuclei of the basal forebrain: substrates of sleep and arousal regulation. *Sleep* 1995;18:478-500.
13. McCormick DA. Neurotransmitter actions in the thalamus and cerebral cortex. *J Clin Neurophysiol* 1992;9:212-223.
14. Cape EG, Jones BE. Effects of glutamate agonist versus procaine microinjections into the basal forebrain cholinergic cell area upon gamma and theta EEG activity and sleep-wake state. *Eur J Neurosci* 2000;12:2166-2184.
15. Gallopin T, Fort P, Eggermann E et al. Identification of sleep-promoting neurons in vitro. *Nature* 2000;404:992-995.
16. Gvilia I, Xu F, McGinty D, Szymusiak R. Homeostatic regulation of sleep: a role for preoptic area neurons. *J Neurosci* 2006;26:9426-9433.
17. Horner RL. Is there a rationale in modulating brainstem neurons in obstructive sleep apnea and is it clinically relevant? *Sleep* 2000;23 Suppl 4:S179-S181.
18. Johnston GA. Medicinal chemistry and molecular pharmacology of GABA(C) receptors. *Curr Top Med Chem* 2002;2:903-913.
19. Markov D, Goldman M. Normal sleep and circadian rhythms: neurobiologic mechanisms underlying sleep and wakefulness. *Psychiatr Clin North Am* 2006;29:841-853.
20. Fuller PM, Gooley JJ, Saper CB. Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. *J Biol Rhythms* 2006;21:482-493.
21. Seifritz E. Contribution of sleep physiology to depressive pathophysiology. *Neuropsychopharmacology* 2001;25:S85-S88.
22. Carlsson A. Interaction between dopaminergic and serotonergic systems. *Clin Neuropharmacol* 1992;15 Suppl 1 Pt A:616A-617A.
23. Choi SJ, Patil V, Fernstrom JD. 5,7-Dihydroxytryptamine: regional brain concentrations following intraventricular administration to rats. *Neurochem Res* 2001;26:1145-1149.
24. Espana RA, Scammell TE. Sleep neurobiology for the clinician. *Sleep* 2004;27:811-820.
25. Gillin JC, Salin-Pascual R, Velazquez-Moctezuma J, Shiromani P, Zoltoski R. Cholinergic receptor subtypes and REM sleep in animals and normal controls. *Prog Brain Res* 1993;98:379-387.
26. Guha M, Biswas S, Poddar MK. Possible involvement of central cholinergic-serotonergic interaction in natural sleep. *Methods Find Exp Clin Pharmacol* 1988;10:243-245.

27. Muzur A, Pace-Schott EF, Hobson JA. The prefrontal cortex in sleep. *Trends Cogn Sci* 2002;6:475-481.
28. Vazquez J, Baghdoyan HA. Basal forebrain acetylcholine release during REM sleep is significantly greater than during waking. *Am J Physiol Regul Integr Comp Physiol* 2001;280:R598-R601.
29. Cudeiro J, Rivadulla C, Grieve KL. A possible role for nitric oxide at the sleep/wake interface. *Sleep* 2000;23:829-835.
30. Hasselmo ME, Fehlau BP. Differences in time course of ACh and GABA modulation of excitatory synaptic potentials in slices of rat hippocampus. *J Neurophysiol* 2001;86:1792-1802.
31. Thomas RJ. Excitatory amino acids in health and disease. *J Am Geriatr Soc* 1995 November;43(11):1279-89.
32. Tamakawa Y, Karashima A, Koyama Y, Katayama N, Nakao M. A quartet neural system model orchestrating sleep and wakefulness mechanisms. *J Neurophysiol* 2006;95:2055-2069.
33. Cape EG, Jones BE. Differential modulation of high-frequency gamma-electroencephalogram activity and sleep-wake state by noradrenaline and serotonin microinjections into the region of cholinergic basal ganglia neurons. *J Neurosci* 1998;18:2653-2666.
34. Turek FW, Dugovic C, Zee PC. Current understanding of the circadian clock and the clinical implications for neurological disorders. *Arch Neurol* 2001;58:1781-1787.
35. Moore RY. Suprachiasmatic nucleus in sleep-wake regulation. *Sleep Med* 2007;8 Suppl 3:27-33.
36. Silver R, Lesauter J. Circadian and homeostatic factors in arousal. *Ann N Y Acad Sci* 2008;1129:263-274.
37. Benarroch EE. Suprachiasmatic nucleus and melatonin: reciprocal interactions and clinical correlations. *Neurology* 2008;71:594-598.
38. Huwig-Poppe C, Voderholzer U, Backhaus J, Riemann D, Konig A, Hohagen F. The tryptophan depletion test. Impact on sleep in healthy subjects and patients with obsessive-compulsive disorder. *Adv Exp Med Biol* 1999;467:35-42.
39. Fernstrom JD. Effects of the diet and other metabolic phenomena on brain tryptophan uptake and serotonin synthesis. *Adv Exp Med Biol* 1991;294:369-376.
40. Jouvet M. Sleep and serotonin: an unfinished story. *Neuropsychopharmacology* 1999;21:24S-27S.
41. Nitz D, Siegel J. GABA release in the dorsal raphe nucleus: role in the control of REM sleep. *Am J Physiol* 1997;273:R451-R455.

42. Marks GA, Roffwarg HP. The cholinergic influence upon rat dorsal lateral geniculate nucleus is dependent on state of arousal. *Brain Res* 1989;494:294-306.
43. Zimmermann RC, McDougale CJ, Schumacher M et al. Effects of acute tryptophan depletion on nocturnal melatonin secretion in humans. *J Clin Endocrinol Metab* 1993;76:1160-1164.
44. Bellingham MC, Ireland MF. Contribution of cholinergic systems to state-dependent modulation of respiratory control. *Respir Physiol Neurobiol* 2002;131:135-144.
45. Mallick BN, Kaur S, Saxena RN. Interactions between cholinergic and GABAergic neurotransmitters in and around the locus coeruleus for the induction and maintenance of rapid eye movement sleep in rats. *Neuroscience* 2001;104:467-485.
46. Landolt HP, Kelsoe JR, Rapaport MH, Gillin JC. Rapid tryptophan depletion reverses phenelzine-induced suppression of REM sleep. *J Sleep Res* 2003;12:13-18.
47. Yogman MW, Zeisel SH. Diet and sleep patterns in newborn infants. *N Engl J Med* 1983;309:1147-1149.
48. Leonard BE. Serotonin receptors and their function in sleep, anxiety disorders and depression. *Psychother Psychosom* 1996;65:66-75.
49. Lydic R, McCarley RW, Hobson JA. Serotonin neurons and sleep. I. Long term recordings of dorsal raphe discharge frequency and PGO waves. *Arch Ital Biol* 1987;125:317-343.
50. Joseph V, Pequignot JM, Van RO. Neurochemical perspectives on the control of breathing during sleep. *Respir Physiol Neurobiol* 2002;130:253-263
51. Brown DW. Abnormal fluctuations of acetylcholine and serotonin. *Med Hypotheses* 1993;40:309-310.
52. DeFeudis FV, Drieu K. Ginkgo biloba extract (EGb 761) and CNS functions: basic studies and clinical applications. *Curr Drug Targets*. 2000;1:25-58.
53. Nathan P. Can the cognitive enhancing effects of ginkgo biloba be explained by its pharmacology? *Med Hypotheses*. 2000;55:491-493.
54. Jacobson KA, Moro S, Manthey JA, West PL, Ji XD. Interactions of flavones and other phytochemicals with adenosine receptors. *Adv Exp Med Biol* 2002;505:163-71.
55. Sawynok J. Adenosine receptor activation and nociception. *Eur J Pharmacol* 1998 April 17;347(1):1-11.
56. Ribeiro JA, Sebastiao AM, de Mendonca A. Adenosine receptors in the nervous system: pathophysiological implications. *Prog Neurobiol* 2002 December;68(6):377-92.

57. Luceri C, Caderni G, Sanna A, Dolara P. Red wine and black tea polyphenols modulate the expression of cyclooxygenase-2, inducible nitric oxide synthase and glutathione- related enzymes in azoxymethane-induced f344 rat colon tumors. *J Nutr* 2002 June;132(6):1376-9.
58. Sovak M. Grape Extract, resveratrol, and its analogs: A Review. *J Med Food* 2001;4(2):93-105
59. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. *J Nutr* 2000 August;130(8S Suppl):2073S-85S.
60. Anderson GH, Johnston JL. Nutrient control of brain neurotransmitter synthesis and function. *Can J Physiol Pharmacol* 1983;61:271-281.
61. Fernstrom JD. Can nutrient supplements modify brain function? *Am J Clin Nutr* 2000;71:1669S-1675S.
62. Fernstrom JD. Dietary amino acids and brain function. *J Am Diet Assoc* 1994;94:71-77.
63. Fernstrom JD, Fernstrom MH. Monoamines and protein intake: are control mechanisms designed to monitor a threshold intake or a set point? *Nutr Rev* 2001;59:S60-S65.
64. Anderson IM, Mortimore C. 5-HT and human anxiety. Evidence from studies using acute tryptophan depletion. *Adv Exp Med Biol* 1999;467:43-55.
65. Arnulf I, Quintin P, Alvarez JC et al. Mid-morning tryptophan depletion delays REM sleep onset in healthy subjects. *Neuropsychopharmacology* 2002;27:843-851.
66. Conlay LA, Zeisel SH. Neurotransmitter precursors and brain function. *Neurosurgery* 1982;10:524-529.
67. Danneberg P, Weber KH. Chemical structure and biological activity of the diazepam. *Br J Clin Pharmacol* 1983;16 Suppl 2:231S-244S.
68. Musa MN. Sleep apnea following withdrawal of amitriptyline. *J Clin Pharmacol* 1988;28:1038-1039.
69. Nutt DJ, Malizia AL. New insights into the role of the GABA(A)-benzodiazepine receptor in psychiatric disorder. *Br J Psychiatry* 2001;179:390-396.
70. Stahmer SD. Pharmacodynamics of benzodiazepines. *S Afr Med J* 1985;Suppl:14-22.
71. Wurtman RJ. Nutrients affecting brain composition and behavior. *Integr Psychiatry* 1987;5:226-238.
72. *Modern Nutrition in Health and Disease*. 10th ed. Philadelphia: Lipincott Williams & Wilkin, 2006.
73. Fernstrom JD. Dietary precursors and brain neurotransmitter formation. *Annu Rev Med* 1981;32:413-425.

74. Wurtman RJ. When--and why--should nutritional state control neurotransmitter synthesis? *J Neural Transm Suppl* 1979;69-79.
75. Lehnert H, Wurtman RJ. Amino acid control of neurotransmitter synthesis and release: physiological and clinical implications. *Psychother Psychosom* 1993;60:18-32.
76. Zeisel SH. Dietary influences on neurotransmission. *Adv Pediatr* 1986;33:23-47.
77. Young SN, Teff KL. Tryptophan availability, 5HT synthesis and 5HT function. *Prog Neuropsychopharmacol Biol Psychiatry* 1989;13:373-379.
78. Young SN. Behavioral effects of dietary neurotransmitter precursors: basic and clinical aspects. *Neurosci Biobehav Rev* 1996;20:313-323.
79. Young SN, Gauthier S. Effect of tryptophan administration on tryptophan, 5-hydroxyindoleacetic acid and indoleacetic acid in human lumbar and cisternal cerebrospinal fluid. *J Neurol Neurosurg Psychiatry* 1981;44:323-328.
80. Young SN, Gauthier S. Tryptophan availability and the control of 5-hydroxytryptamine and tryptamine synthesis in human CNS. *Adv Exp Med Biol* 1981;133:221-230.
81. Ulus IH, Wurtman RJ. Choline increases acetylcholine release. *Lancet* 1987;1:624.
82. Leathwood PD. Tryptophan availability and serotonin synthesis. *Proc Nutr Soc* 1987;46:143-156.
83. Fernstrom JD, Wurtman RJ. Control of brain serotonin levels by the diet. *Adv Biochem Psychopharmacol* 1974;11:133-142.
84. Wurtman RJ. Effects of their nutrient precursors on the synthesis and release of serotonin, the catecholamines, and acetylcholine: implications for behavioral disorders. *Clin Neuropharmacol* 1988;11 Suppl 1:S187-S193.
85. Riemann D, Feige B, Hornyak M, Koch S, Hohagen F, Voderholzer U. The tryptophan depletion test: impact on sleep in primary insomnia - a pilot study. *Psychiatry Res* 2002;109:129-135.
86. Delgado PL, Charney DS, Price LH, Landis H, Heninger GR. Neuroendocrine and behavioral effects of dietary tryptophan restriction in healthy subjects. *Life Sci* 1989;45(24):2323-32
87. Bender DA. Biochemistry of tryptophan in health and disease. *Mol Aspects Med* 1983;6:101-197.
88. Wurtman RJ. Food consumption, neurotransmitter synthesis, and human behaviour. *Experientia Suppl* 1983;44:356-369.
89. Blusztajn JK, Liscovitch M, Mauron C, Richardson UI, Wurtman RJ. Phosphatidylcholine as a precursor of choline for acetylcholine synthesis. *J Neural Transm Suppl* 1987;24:247-259.

90. Veasey SC. Pharmacotherapies for obstructive sleep apnea: how close are we? *Curr Opin Pulm Med* 2001;7:399-403.
91. Lucki I. The spectrum of behaviors influenced by serotonin. *Biol Psychiatry* 1998;44:151-162.