**Sentra PM® Product Information**

**Indication**

*Sentra PM* is intended for use in management of sleep disorders associated with fibromyalgia and depression. *Sentra PM* is a medical food that must be used under the active or ongoing supervision of a physician. Medical foods are intended 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 associated with inflammation and other medical conditions, as well as from pharmaceutical therapies.

Normal patterns of sleep and waking are regulated by neurotransmitters which alter electrical activity in specific areas of the brain. A loss of coordinated activity between sleep-active and wake-active neurons disrupts the circadian rhythm of the sleep-wake cycle and of autonomic nervous system activity during the transitions between sleep and waking. Disturbances in sleep patterns resulting from circadian phase shifts and disordered autonomic function are associated with imbalances in neurotransmitters which modulate these activities. Nearly all patients with fibromyalgia and approximately 70-80% of depressed patients experience some type of sleep disorder. Difficulty falling asleep, staying asleep, and early morning awakening are the most common sleep disturbances associated with these conditions. Patients with these types of sleep disorders benefit from increased availability of glutamate, acetylcholine, and serotonin to restore homeostasis. *Sentra PM* is designed to provide a balance of neurotransmitters with well-defined roles in regulation of the sleep-wake cycle.

**Ingredients**

*Sentra PM* is a proprietary blend of neurotransmitters and neurotransmitter precursors (choline bitartrate, 5-hydroxytryptophan, L-glutamate); activators of precursor utilization (acetyl-L-carnitine, L-glutamate, cocoa powder); stimulator of precursor uptake (ginkgo biloba); polyphenolic antioxidants (cocoa powder, grape seed extract, hawthorn berry); an adenosine antagonist (cocoa powder); and an inhibitor of the attenuation of neurotransmitter production associated with precursor administration (grape-seed extract). The neurotransmitters and neurotransmitter precursors have been specifically selected based on scientific support for their roles in regulation of the sleep-wake cycle through modulation of circadian rhythms and autonomic nervous system activity. These roles are summarized in this monograph in the section *Scientific Support for Use of Sentra PM in Management of Sleep Disorders Associated with Fibromyalgia and Depression*. The other ingredients in the formulation are involved in neurotransmitter metabolism or are functional components of the *Targeted Cellular Technology®* system.

All of the ingredients included in *Sentra PM* 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

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

**Targeted Cellular Technology®**

*Sentra PM* 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 patented 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 precursors needed to correct neurotransmitter imbalances. Use of *Targeted Cellular Technology* also ensures that the appropriate amounts of neurotransmitter precursors are delivered to the target neurons with the appropriate timing. As such, *Targeted Cellular Technology* synchronizes the availability of the precursor supply with the fluctuating demand for the corresponding neurotransmitters, which is especially important for processes which are modulated by circadian rhythms and are therefore sensitive to the timing of synthesis and release of neurotransmitters such as acetylcholine, serotonin, nitric oxide, and histamine (1-4).

Previous attempts to provide an exogenous source of precursor amino acids and other biogenic amines in the quantities required to support neurotransmitter synthesis for individuals with specific needs necessitated that large amounts of 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. Moreover, ingestion of large quantities of amino acids increases the potential for adverse effects. Metabolic efficiency is also decreased when large amounts of amino acids are delivered to the cells at one time because intestinal membrane transport receptors would be rapidly saturated resulting in a reduction in fractional amino acid absorption and thus attenuation of the tissue response to the supplemental amounts provided. 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 as larger amounts, 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 *Sentra PM* is not attenuated.

**Metabolism**

*Sentra PM* is a source of amino acids, biogenic amines, and other nutrients formulated for patients with sleep disorders associated with fibromyalgia and depression. These patients require additional amounts of glutamate, choline, and tryptophan to restore homeostasis. Under normal physiological
conditions, these nutrients are considered nonessential because endogenous synthesis is sufficient to satisfy metabolic demand. When needs are altered by conditions that increase metabolic demand, the usual rate of synthesis is no longer sufficient and these nutrients become conditionally essential, requiring that supplemental amounts be consumed.

Tryptophan/5-hydroxytryptophan. In contrast to nutrients which are nonessential under normal conditions, tryptophan is an essential amino acid that 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 of tryptophan consumed determines the amount available for utilization by multiple pathways. Tryptophan is a precursor of the neurotransmitter serotonin, as well as of the coenzymes nicotinamide adenine dinucleotide (NAD⁺) and nicotinamide adenine dinucleotide phosphate (NADP) (Figure 1). Since serotonin is further utilized as a precursor of melatonin, an increase in melatonin synthesis will impose a need for additional tryptophan. The competition between these and other metabolic pathways for the supply of tryptophan available restricts the amount of serotonin and thus melatonin that can be produced from supplemental amounts of the amino acid.

Figure 1. Competing Pathways of Tryptophan Metabolism

To overcome this limitation, Sentra PM provides 5-hydroxytryptophan, an intermediate metabolite in the pathway of tryptophan conversion to serotonin, thus bypassing the rate-limiting step dependent on tryptophan availability (5-6) (Figure 2). Unlike tryptophan, this intermediate cannot be shunted into production of niacin or protein which eliminates competition by other metabolic pathways for the amount available (6). Consequently, an increase in 5-hydroxytryptophan lessens the dependence of serotonin levels on the amount of tryptophan consumed. By facilitating production of serotonin without requiring consumption of large amounts of tryptophan, Sentra PM ensures that adequate amounts of serotonin are produced without compromising synthesis of other important compounds derived from tryptophan, thus improving metabolic efficiency.
**Glutamate.** As a nonessential amino acid, glutamate is not normally dependent on exogenous sources, thus metabolic competition for this amino acid develops only under conditions of increased demand. For individuals with sleep disorders associated with fibromyalgia and depression, the requirement for glutamate is increased to maintain activity of glutamatergic neurons as well as to provide a precursor for production of GABA. Under normal conditions, glutamate can be supplied by several sources including deamination of glutamine; however, glutamate synthesis competes for glutamine with other pathways that utilize it as a precursor of a number of cellular compounds such as the antioxidant glutathione (γ-glutamylcysteinylglycine), purines, pyrimidines, and urea (Figure 3). 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 glutamate, **Sentra PM** improves metabolic efficiency by ensuring that there are adequate amounts of both neurotransmitters available while conserving the supply of glutamine for its other uses.

**Figure 3. Competing Pathways of Glutamate Metabolism**

*Sentra PM®*
Choline. Both choline and carnitine are considered nonessential nutrients under normal physiological conditions. When the demand for choline is increased to supply additional precursor for synthesis of acetylcholine, supplemental amounts of choline are needed. Acetylcholine is produced from choline in an acetylation reaction catalyzed by choline acetyltransferase with acetyl coenzyme A (CoA) as the acetyl group donor (Figure 4).

**Figure 4. Biosynthesis of Acetylcholine**

![Biosynthesis of Acetylcholine](image)

The primary source of choline normally utilized in the synthesis of acetylcholine is phosphatidylcholine (lecithin), a membrane phospholipid which serves as a reservoir to supply choline for short-term needs (Figure 5). When the demand for acetylcholine exceeds the amount of choline that can be supplied by hydrolysis of phosphatidylcholine from membrane pool, dietary choline becomes an increasingly more important source. *Sentra PM* provides additional amounts of choline to meet the increased needs for acetylcholine when demand is elevated over an extended time period. By supplying an exogenous source of choline, *Sentra PM* prevents the depletion of membrane phosphatidylcholine and thus preserves the structural integrity of the cell.

**Figure 5. Sources of Acetylcholine**

![Sources of Acetylcholine](image)

Carnitine. The efficiency of the metabolic response to an increased demand for acetylcholine is enhanced by acetyl-L-carnitine (Figure 6). Acetyl-L-carnitine promotes the synthesis of acetylcholine and
influences neurotransmitter activity by effects on neurotrophic factors and neurohormones, synaptic morphology, and synaptic transmission of multiple neurotransmitters (7-8). Sufficient amounts of acetyl-L-carnitine can normally be produced from acetylation of carnitine, an amino acid derived from lysine and methionine; however, as essential amino acids, lysine and methionine are utilized by multiple competing pathways and cannot sufficiently accommodate a sustained increase in demand for carnitine. **Sentra PM** provides acetyl-L-carnitine to ensure that an adequate supply of acetylcholine is available to support increased cholinergic activity without compromising amounts needed for its other roles in neurotransmission.

**Figure 6. Biosynthesis of Acetylcarnitine**

The need for carnitine is increased for synthesis of acetylcarnitine to meet the demand for additional acetyl groups to support the increased production of acetylcholine when cholinergic activity is high (Figure 7). Acetyl-L-carnitine is synthesized from carnitine in a reaction similar to acetylcholine synthesis from choline which involves the transfer of an acetyl group from acetyl CoA in an acetylation reaction catalyzed by carnitine acetyltransferase. Sufficient amounts of acetyl-L-carnitine can normally be produced from carnitine, but when the rate of cholinergic activity is elevated over extended periods, the demand for acetyl-L-carnitine cannot be met by endogenous synthesis alone. **Sentra PM** provides additional acetyl-L-carnitine to sustain an increased rate of acetylcholine synthesis and enhance its activity when the rates of cholinergic-mediated activities are increased.

**Figure 7. Role of Acetyl-L-Carnitine in the Biosynthesis of Acetylcholine**

In addition to its role as an acetyl group donor in the synthesis of acetylcholine, acetyl-L-carnitine also facilitates uptake of acetyl groups by cholinergic neurons. This role involves a membrane transport mechanism similar to that utilized for acetyl group transport in the pathway of fatty acid oxidation. In this pathway, acetylcarnitine serves as a membrane transport carrier of acetyl CoA groups which are released
in the cytoplasm as endproducts of β-oxidation to undergo further oxidation by the tricarboxylic acid cycle in the mitochondria.

**Dosage**

The recommended dose of *Sentra PM* is 1 or 2 capsules taken at bedtime. An additional dose of 1-2 capsules may also be taken during the night if the patient awakes and finds it difficult to resume sleep. *Sentra PM* must always be taken with water on an empty stomach at least 30 minutes before or after eating. As with any medical food, the best dosing protocol should be determined by assessment of individual needs.

There are no known interactions between *Sentra PM* and any medication.

Patients who are taking pharmaceutical agents to initiate and maintain sleep may continue to take these medications with *Sentra PM* prior to retiring. If the combination of the drug and *Sentra PM* 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.

The amounts of each ingredient consumed at the recommended doses of *Sentra PM* are presented in Table 1.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>mg/kg body weight¹</th>
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<tbody>
<tr>
<td>Choline bitartrate</td>
<td>3.6 – 9.1</td>
</tr>
<tr>
<td>L-glutamate</td>
<td>0.6 – 1.4</td>
</tr>
<tr>
<td>5-hydroxytryptophan (griffonia seed, 95% w/w)</td>
<td>0.4 – 0.9</td>
</tr>
<tr>
<td>Acetyl-L-carnitine</td>
<td>0.6 – 1.4</td>
</tr>
<tr>
<td>Cocoa powder</td>
<td>1.0 – 2.5</td>
</tr>
<tr>
<td>Grape seed extract</td>
<td>0.3 – 0.7</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>0.4 - 0.9</td>
</tr>
<tr>
<td>Hawthorn berry</td>
<td>0.2 - 0.5</td>
</tr>
</tbody>
</table>

¹Dosing range of 1 to 2 capsules daily

**Side Effects and Contraindications**

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

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

<table>
<thead>
<tr>
<th>Term/Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant</td>
<td>Molecules or enzyme systems that inhibit injury to cells from reactive oxygen or nitrogen species</td>
</tr>
<tr>
<td>Autonomic Nervous System</td>
<td>Part of the efferent division of the peripheral nervous system but includes visceral afferent neurons; motor component comprises two-neuron system of preganglionic (myelinated) and postganglionic (unmyelinated) neurons; divided structurally and functionally into parasympathetic and sympathetic nervous systems</td>
</tr>
<tr>
<td>Biogenic amine</td>
<td>Biologically active substance that contains an amine group but does not ave the characteristic structure of an amino acid, i.e., alpha carbon binding both an amino and carboxyl group</td>
</tr>
<tr>
<td>Cholinergic</td>
<td>Neurons that synthesize, package, and release choline</td>
</tr>
<tr>
<td>Circadian Rhythm</td>
<td>A 24-hour cycle of physiological, biochemical, and behavioral processes controlled by the suprachiasmatic nucleus in the hypothalamus</td>
</tr>
<tr>
<td>Depression</td>
<td>A mood state characterized by unrelenting feelings of sadness and despair</td>
</tr>
<tr>
<td>Excitatory Neurotransmitters</td>
<td>Molecules released from presynaptic cells at terminal nerve endings which transmit action potentials to adjacent neurons by depolarization of postsynaptic cell membranes resulting in a decreased stimulus threshold for firing which increases the frequency and rate of transmission of action potentials</td>
</tr>
<tr>
<td>GABAergic</td>
<td>Neurons that synthesize, package, and release gamma-aminobutyric acid (GABA)</td>
</tr>
<tr>
<td>Glutamatergic</td>
<td>Neurons that synthesize, package, and release glutamate</td>
</tr>
<tr>
<td>Inhibitory Neurotransmitters</td>
<td>Molecules released from presynaptic cells at terminal nerve endings which transmit action potentials to adjacent neurons by hyperpolarization of postsynaptic cell membranes resulting in an increased stimulus threshold for firing which decreases the frequency and rate of transmission of action potentials</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Hormone synthesized from serotonin which is regulated by the suprachiasmatic nucleus in response to changes in light exposure</td>
</tr>
<tr>
<td>Monoaminergic</td>
<td>Neurons that synthesize, package, and release monoamine neurotransmitters such as norepinephrine and dopamine; serotoninergic neurons are monoaminergic</td>
</tr>
<tr>
<td>Neurotransmitter</td>
<td>Amino acids, biogenic amines, and other molecules that facilitate communication between the peripheral nervous system, spinal cord, and brain by generating a series of action potentials which are transmitted between neurons</td>
</tr>
<tr>
<td>Term/Abbreviation</td>
<td>Definition</td>
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<tr>
<td>NMDA Receptor</td>
<td>N-methyl-D-aspartate receptor; subfamily of glutamatergic receptors which require a co-agonist for activation; mediates events that are critical components of pathological and/or prolonged pain states</td>
</tr>
<tr>
<td>NREM Sleep</td>
<td>Non-rapid eye movement period of the sleep cycle; comprises 4 stages differentiated by brain electrical activity</td>
</tr>
<tr>
<td>Parasympathetic Nervous System</td>
<td>Component of the autonomic nervous system which functions to conserve and restore energy reserves; synaptic transmission mediated by cholinergic receptors; opposes the activity of the sympathetic nervous system; increases during sleep and subsides with waking</td>
</tr>
<tr>
<td>Raphe Nucleus</td>
<td>Mesencephalic nucleus which includes the hypothalamic tract that links ganglion cells to the suprachiasmatic nucleus</td>
</tr>
<tr>
<td>REM Sleep</td>
<td>Rapid eye movement period of the sleep cycle; normally follows NREM sleep</td>
</tr>
<tr>
<td>Restorative Sleep</td>
<td>Period during the late stages of non-REM sleep (Stage III and IV ) when levels of growth hormone and rates of protein synthesis are increased and rejuvenation of cellular processes occur</td>
</tr>
<tr>
<td>Reticular Formation</td>
<td>A component of the reticular activating system which regulates vital functions, maintains wakefulness, and supports consciousness; consists of a large network of connected tissue nuclei within the brainstem; includes the cerebral cortex</td>
</tr>
<tr>
<td>Serotonergic</td>
<td>Neurons that synthesize, package, and release serotonin (5-hydroxytryptamine)</td>
</tr>
<tr>
<td>Sleep Stages</td>
<td>Four distinct periods of NREM sleep differentiated by changes in brain wave patterns and distinguished by differences in muscular activity, vital signs, and responsiveness to external stimuli.</td>
</tr>
<tr>
<td>Suprachiasmatic Nucleus (SCN)</td>
<td>Bilaterally-paired nuclei in the hypothalamus situated above the point where the optic nerves cross; integrates and synchronizes information from peripheral oscillators that respond to temporal changes in environmental and internal cues such exposure to light, hormone levels, hunger, and body temperature and then signals circadian time to the rest of the body</td>
</tr>
<tr>
<td>Sympathetic Nervous System</td>
<td>Component of the autonomic nervous system which functions to mobilize energy reserves; synaptic transmission mediated by cholinergic and adrenergic receptors; opposes the activity of the parasympathetic nervous system; responsive to stress; activity decreases during sleep and increases with waking</td>
</tr>
<tr>
<td>Targeted Cellular Technology®</td>
<td>A patented process that facilitates endogenous production, uptake, and utilization of neurotransmitter precursors.</td>
</tr>
<tr>
<td>Ventrolateral Preoptic (VLPO)</td>
<td>Area of the rostral hypothalamus rich in GABAergic neurons which promote NREM sleep</td>
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**Mechanism of Action**

*Sentra PM* has been formulated to provide a balance of neurotransmitters that have well-defined roles in regulation of the sleep-wake cycle.

**Mechanism of neurotransmitter activity.** Neurotransmitters are amino acids, biogenic amines, or amino acid derivatives which function as mediators of physiological responses to physical, chemical, or electrical stimuli. Neurotransmitters are released from storage vesicles in presynaptic neurons in response
to action potentials at the distal nerve endings where they bind to receptors on postsynaptic neurons (Figure 8). Neurotransmitter binding alters the resting membrane potential of postsynaptic neurons generating an action potential which is transmitted to the terminal ending of the neuron where the sequence of electrochemical events is repeated until the signal reaches specific processing centers in the brain. The same mechanism of neurotransmitter-mediated electrochemical events is involved in transmission of output from the brain to target effector tissues or organs, and in transmission of signals originating within different regions of brain over the internal circuits between these regions.

**Figure 8. Neurotransmitter Activity in Presynaptic and Postsynaptic Neurons**

The rate of signal transmission between presynaptic and postsynaptic neurons in the central and peripheral nervous systems is dependent on the chemical nature of the neurotransmitter involved (9). Excitatory neurotransmitters released from presynaptic nerve terminals depolarize postsynaptic cell membranes which lowers the stimulus threshold for firing and increases the frequency and rate of transmission. Inhibitory neurotransmitters have the opposite effect of hyperpolarizing postsynaptic membranes which raises the stimulus threshold and decreases the frequency and rate of transmission. Although neurotransmitters can be classified as excitatory or inhibitory based on the primary effects they have on resting membrane potentials, these classifications do not always predict the response of the effector tissue or organ. Excitatory neurotransmitters can suppress a response by activation of inhibitory mechanisms and inhibitory neurotransmitters can activate a response by suppression of these mechanisms. Imbalances caused by deficiencies in one or more of the excitatory and inhibitory neurotransmitters, or changes in their binding affinities to postsynaptic receptors, will determine the intensity and duration of the signals transmitted (10-14).

**General roles of neurotransmitters.** The primary neurotransmitters involved in regulation of the sleep/wake cycle are glutamate, GABA, serotonin, and acetylcholine (15). Glutamate is the major excitatory neurotransmitter of the central nervous system and GABA is the primary inhibitory neurotransmitter. Serotonin functions as an excitatory neurotransmitter while acetylcholine exhibits both excitatory and inhibitory effects in the central and peripheral nervous systems depending upon the specific type and location of the cholinergic receptors. Imbalances caused by deficiencies in one or more of the excitatory and inhibitory neurotransmitters, or changes in their binding affinities to postsynaptic
receptors, will determine the intensity and duration of the signals generated and thus the response to these signals (10-14, 16). Most hypnotic drugs act by increasing the sensitivity of GABA receptors while most stimulants act by increasing the release or inhibiting the reuptake of serotonin or other monoamines (17-22).

The sleep cycle. Sleep is an active process consisting of 2 phases that are differentiated by brain electrical activity on an electroencephalogram (EEG). During NREM (non-rapid eye movement) sleep, brain wave patterns progress through 4 distinct stages beginning with the fast, medium-amplitude alpha waves that characterize the waking state then shifting to theta and delta waves as sleep progresses. The transition from wakefulness to light sleep (Stages I and II) is characterized by the appearance of medium-velocity, high-amplitude theta waves interspersed with alpha waves which eventually shift to large, high amplitude, slow-moving delta waves that signal the onset of deep sleep or slow-wave sleep (Stages III and IV). The transition from NREM to REM (rapid eye movement) sleep is marked by a shift in brain electrical activity to desynchronized, low-voltage, fast waves. The corresponding pattern of eye movements consists of slow movements during light sleep becoming nearly undetectable or completely absent in deep sleep. The appearance of rapid, jerky eye movements is a hallmark of REM sleep.

The progression through each stage of NREM sleep to the end of REM sleep comprises a sleep cycle, which repeats at 90-110 minute intervals. The first period of REM sleep is initiated 70 to 90 minutes after the onset of non-REM sleep. During the first few sleep cycles, the time spent in REM sleep is short relative to the period of deep sleep. As sleep duration 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 is spent in Stage II and REM sleep. A healthy adult spends an average of approximately 20% of time asleep in the REM period and 50% in Stage II with the remaining time divided between the other stages of NREM sleep. Restorative sleep occurs during deep sleep (Stages III and IV) when growth hormone levels are elevated and the metabolic activities associated with cellular rejuvenation are increased. Patients with depression show changes in brain wave activity on EEG recordings that are indicative of rapid onset REM sleep and shortened periods of slow-wave restorative sleep (23). In patients with fibromyalgia, alpha-wave activity, which is dominant during waking and light sleep, intrudes into the delta-wave period of deep sleep when restorative processes occur (10). Total sleep time, sleep efficiency, and a heightened state of arousal are associated with the alpha-delta pattern of brain wave activity observed associated with fibromyalgia.

The suprachiasmatic nucleus (SCN) and circadian patterns. The sleep/wake cycle follows a circadian pattern that is closely coordinated with the activity of the autonomic nervous system. Circadian-dependent processes are regulated by input from the hypothalamus to the suprachiasmatic nucleus (SCN). The SCN consists of bilaterally-paired nuclei comprising more than 20,000 neurons with a high concentration of serotoninergic receptors situated in the hypothalamus above the point where the optic nerves cross (10-14, 19-21). The SCN is the master clock which integrates and synchronizes input from peripheral oscillators responding to temporal changes in environmental and internal cues such light exposure, hormone levels, hunger and body temperature, and then signals circadian time to the autonomic nervous system and the rest of the body (10, 24-26). Diurnal balance in the functions of autonomic-innervated organs are therefore regulated by neurotransmitters which transmit circadian information to the SCN (27-28).
Neurotransmitter relationship to SCN activity. Acetylcholine, glutamate, and GABA are involved in transmission of signals generated by changes in light exposure while serotonin is the primary neurotransmitter involved in transmission of signals generated by nonphotic stimuli from peripheral oscillators (12-13, 19, 26, 28-29). The pineal gland responds to acetylcholine-mediated SCN output by either ramping up or shutting down melatonin production resulting in a corresponding increase or decrease in drowsiness (21-22). Circulating melatonin levels increased 10-fold during sleep (13). In depressed mood states, the normal increase in melatonin observed with diminishing light exposure is delayed and sensitivity to light-induced melatonin suppression is heightened suggesting a phase shift in circadian processes in these disorders (23).

The SCN organizes opposing signals from the anatomically-separate sympathetic and parasympathetic neurons in the brainstem and paraventricular nucleus of the hypothalamus to determine autonomic output from the brain (24-25). Acetylcholine is the primary neurotransmitter responsible for propagation of signals by the autonomic nervous system and the only neurotransmitter involved in signal transmission by the parasympathetic nervous system (9, 24, 30-31). Cholinergic activity follows a circadian pattern which reflects the sensitivity of acetylcholine to changes in light with levels increasing in response to light exposure and decreasing with diminishing light. Consequently, cholinergic neurons would be expected to play a prominent role in mediating the diurnal pattern of autonomic activity observed during sleep and wakefulness (13, 19).

At sleep onset, parasympathetic functions are activated while sympathetic functions are suppressed. The elevated level of parasympathetic activity observed during sleep begins to subside prior to waking in parallel to the increase in sympathetic activity (32). Parasympathetic activity slows heart rate resulting in decreased metabolic activity which conserves energy for restorative functions. The role of the SCN in regulation of autonomic functions during sleep suggests an association between imbalances in neurotransmitters that modulate circadian rhythms and the pathology of sleep disorders which are characterized by poorly coordinated autonomic nervous system activity (24, 33-36).

Scientific Support for Use of Sentra PM in Management of Sleep Disorders Associated with Fibromyalgia and Depression

The use of Sentra PM in the management of sleep disorders associated with fibromyalgia and depression is supported by experimental and clinical data which have identified specific roles for each ingredient in modulation of pain, mood, and the sleep-wake cycle. Sleep disorders are strongly predictive of pain and fatigue which are symptoms shared by both fibromyalgia and depression indicating that there may be a common mechanism underlying the sleep disturbances associated with these conditions (37).

Neurotransmitter balance in regulation of the sleep-wake cycle. Imbalances in neurotransmitters which mediate circadian control of the sleep-wake cycle and patterns of autonomic nervous system activity during sleep and waking may be involved. The relatively lower levels of brain serotonin associated with fibromyalgia and depression may be indicative of the dysregulation of circadian rhythms underlying the sleep disturbances and the poorly coordinated autonomic nervous system activities observed in these conditions (32, 38-40). Many sleep disorders arise from the disruption of normal
circadian patterns due to imbalances in serotonin as well as GABA, acetylcholine, and glutamate which are involved in transmission of circadian input to the SCN (14, 20, 41-50).

Commonly used drugs that modify sleep patterns through effects on neurotransmitter release and receptor activity but do not restore neurotransmitter balance will alter other aspects of the sleep cycle that can interfere with restorative sleep (51). Benzodiazepines increase the efficiency of synaptic transmission of GABA which reduces sleep latency, but also abolish REM sleep and slow-wave NREM sleep which decreases the period of restorative sleep (18). Selective serotonin reuptake inhibitors (SSRIs), the class of antidepressants which includes fluoxetine and sertraline, increase sleep latency but also decrease REM and slow-wave sleep (52). Most hypnotic drugs act mainly by increasing the sensitivity of GABA receptors and drugs that promote wakefulness act mainly by stimulating release or inhibiting reuptake of serotonin and other monoamines (18, 53-55).

**Neurotransmitter activity during the sleep/wake cycle.** The cycling between periods of sleep and wakefulness is controlled by the synchronized activity between sleep-active neurotransmitters (GABA) and wake-active neurotransmitters (serotonin, acetylcholine, and glutamate). Desynchronization of the wake-promoting effects of glutamate and acetylcholine with the sleep-promoting effects of GABA disrupts the normal circadian rhythms which modulate the sleep-wake cycle and the balance in parasympathetic and sympathetic nervous systems activities during sleep and waking periods (13-14, 19-20, 40, 44). Coordination of the activity between sleep-active and wake-active neurotransmitters is essential to regulation of the sleep-wake cycle by the SCN. A decrease in light exposure stimulates the withdrawal of acetylcholine, serotonin, and glutamate from the reticular formation accompanied by increased GABAergic activity in the cerebral cortex. These changes shift brain electrical activity to wave patterns associated with drowsiness and initiation of NREM sleep. Experimental manipulation of the sleep-wake cycle in healthy volunteers has revealed a dependence of sleep latency, sleep efficiency, and REM sleep propensity on circadian phase (56).

During sleep, specific patterns of brain electrical activity are modulated by changes in neurotransmitter levels which regulate the duration of each stage and the timing of transitions between stages (11, 51, 57). Acetylcholine concentrations fluctuate from high levels while awake to lower levels during slow-wave Stage IV sleep and begin to increase again during REM sleep (51). Cholinergic activity stimulates delta waves in the transition from deep slow-wave sleep to REM sleep, increases the duration of Stage IV sleep, and increases the frequency and duration of REM sleep (44, 57-60). 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 (58). A more rapid onset of REM sleep and a reduction in restorative sleep are characteristic of sleep abnormalities in depressed mood states suggesting abnormalities in cholinergic activity. In fibromyalgia, the intrusion of alpha wave patterns into delta wave sleep indicates an abnormal transition between sleep stages related to the availability of acetylcholine (37).

**GABA.** The asymmetry of the relationship between wakefulness and sleep wherein the period of wakefulness is more likely to be extended than shortened relative to the period of sleep indicates that these states are mediated by different neurotransmitter systems (10). The transition from waking to sleep is mediated by the coordinated inhibition of multiple arousal systems in response to activation of
GABAergic neurons (11-12, 41, 51, 61-62). Almost all of the sleep-active or sleep-promoting neurons in the brain are GABAergic and concentrated in the median preoptic nucleus and ventrolateral preoptic (VLPO) area of the rostral hypothalamus (15, 17, 25-26, 29 58). NREM sleep is promoted by GABAergic neurons 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 (13, 26). 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 (42, 62). The activation of GABAergic neurons by decreased light exposure and sleep deprivation also suggests a dependence of sleep homeostasis on GABA production and release (12, 29).

**Neurotransmitter activity in sleep to waking transition.** The transition from sleep to waking is initiated by an increase in activity of the wake-active serotoninergic neurons in the dorsal raphe nucleus, cholinergic neurons in the brainstem and basal forebrain, and monoaminergic (norepinephrine and dopamine secretors) neurons in the rostral pons, midbrain, and posterior hypothalamus (11, 13, 15, 17, 25-26, 29, 41-44, 58, 60-66). In the SCN, glutamate mediates the synchronization of circadian clocks to environmental cues through the process of entrainment which involves activation of its N-methyl-D-aspartate (NMDA) receptor (26). Glutamatergic neurons which are widely distributed in the brain are also active in the initiation and maintenance of the waking state (9, 58, 67). Patients with fibromyalgia who experience sleep disturbances have significantly higher blood glutamine levels than controls suggesting that an increase in glutamate availability may be a factor in this disorder (30, 68).

**Glutamate.** Interactions between glutamate and acetylcholine have been identified in mediation of many neurological functions including sleep and arousal (30, 62, 69-73). Glutamatergic neurons in the central nervous system are concentrated in areas of high cholinergic activity. Under conditions where glutamatergic receptor activity is inhibited, cholinergic transmission is stimulated and its receptors upregulated in the hypothalamus (30). Both neurotransmitters initiate and maintain arousal in the perifomical lateral hypothalamus and both promote vigilance in the basal forebrain through effects on hypocretin- or orexin-secreting neurons which mediate neuroendocrine control of arousal (62, 71-74). Stimulation of arousal is mediated by glutamate and acetylcholine through depolarizing effects that increase release of hypocretin or orexin (42, 58, 61-62, 71) and opposed by GABA and serotonin through hyperpolarizing effects that inhibit release. Acetylcholine also enhances glutamatergic activity as a coagonist in activation of the glutamate-dependent NMDA receptor (30).

**Acetylcholine.** Acetylcholine concentrations normally vary over the sleep/wake cycle from high levels observed during periods of waking to low levels during slow-wave Stage IV sleep and return to higher levels during REM sleep (58). Increased cholinergic activity is associated with an increase in theta wave patterns which characterizes the transition from early to later stages of the sleep cycle (60). It also increases delta wave patterns that mark the transition from deep slow-wave sleep to REM sleep, extends the time spent in Stage IV and Stage V sleep, and increases the frequency and duration of REM sleep (32, 41, 51, 63, 65, 75-76).

**Serotonin.** Increased serotoninergic activity is associated with wakefulness fluctuating in parallel with circadian patterns and inversely with neurotransmitter systems that inhibit arousal (22, 42, 46, 77). Sleep
is initiated and sleep latency is decreased at times of low serotoninergic activity (75). Activity is highest during periods of waking, slow during NREM sleep, and virtually silent in REM sleep (26, 48, 59, 78). During sleep, peak serotonin levels are observed in the first hours following onset and the lowest levels are reached in the transition from NREM to REM sleep. Altered patterns of serotonin production and release have been linked to disturbances in the sleep process which contribute to sleep apnea and snoring, and may also be linked to disruption in the balance of autonomic nervous system activities associated with these sleep disorders (25, 32, 48, 77, 79). Genetic evidence of an abnormal serotonin transporter which has been reported in depression as well as in fibromyalgia may explain the relatively lower levels of brain serotonin observed in patients with these conditions (32).

**Neurotransmitter interactions.** The pattern of changes in the amounts and activities of different neurotransmitter systems over the sleep cycle reflects the complexity of the interactions between them (2, 43, 45, 67). Local release of GABA in areas of the brain where serotoninergic activity is concentrated inhibits the serotonin-mediated effects which maintain brain activity during waking periods and underlies the low levels of serotonin activity observed during REM sleep (15). The decrease in serotoninergic activity induced by increased GABA concentration releases cholinergic neurons from the inhibitory effects of serotonin thereby facilitating the transition from NREM to REM sleep (26). Cholinergic activity during waking periods is mediated by the inhibitory effects of acetylcholine in the midbrain reticular formation which promote a restful state and the excitatory effects in the basal forebrain which promote vigilance.

**Acetyl-L-carnitine.** Acetyl-L-carnitine enhances cholinergic activity by promoting the synthesis of acetylcholine and by its own cholinomimetic effects (7, 35). By increasing the availability of acetylcholine, acetyl-L-carnitine acts similarly to cholinesterase inhibitors except that it promotes acetylcholine synthesis instead of inhibiting its hydrolysis. Although the exact mechanism by which acetyl-L-carnitine enhances acetylcholine synthesis by cholinergic neurons has not been identified, it may be similar to the mechanism that stimulates uptake of acetyl CoA by the mitochondria. Cholinergic activity may be further enhanced by acetyl-L-carnitine through effects that block the postsynaptic inhibitor potential of cholinergic receptors. Acetyl-L-carnitine also directly influences synaptic transmission by a mechanism which is independent of acetylcholine involving neurotrophic factors, neurohormones, synaptic morphology, and the coordination of the activities of multiple neurotransmitters (8).

A summary of the roles of each of the ingredients in *Sentra PM* is presented in Table 3.
### Table 3. Roles of *Sentra PM* Ingredients in Sleep Disorders Associated with Fibromyalgia and Depression

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Effector Molecules</th>
<th>Effects</th>
<th>Roles</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-OH-tryptophan</td>
<td>Serotonin</td>
<td>Excitatory neurotransmitter</td>
<td>Promotes wakefulness; initiates sleep and decreases sleep latency; primary modulator of circadian rhythms; transmits nonphotic signals to the SCN; precursor of melatonin; regulates autonomic function through effects on circadian rhythms; inhibits activity of cholinergic neurons which facilitate the transition from NREM to REM sleep</td>
</tr>
<tr>
<td>Choline</td>
<td>Acetylcholine</td>
<td>Inhibitory neurotransmitter</td>
<td>Decreases in the reticular formation in response to decreased light exposure; elicits delta wave patterns which increases the frequency and duration of REM sleep; elicits theta waves which initiates sleep; promotes REM sleep in the midbrain reticular formation and vigilance in the basal forebrain; primary neurotransmitter of the autonomic nervous system</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Glutamate</td>
<td>Excitatory neurotransmitter</td>
<td>Active in initiation and maintenance of the waking state; modulates circadian rhythms by transmission of light signals from photoreceptor cells in the retina to the SCN; mediates synchronization of circadian clocks to environmental cues through the NMDA receptor; interacts with acetylcholine; stimulates arousal through depolarizing hypocretin (orexin) neurons</td>
</tr>
<tr>
<td>Glutamate</td>
<td>GABA</td>
<td>Inhibitory neurotransmitter</td>
<td>Primary sleep-active neurotransmitter; promotes NREM and REM sleep; coordinates inhibition of multiple arousal systems; modulates circadian rhythms through transmission of light signals from photoreceptor cells in the retina to the SCN; promotes homeostasis of the sleep cycle; inhibits serotonergic activity; inhibits arousal through hyperpolarizing hypocretin (orexin) neurons</td>
</tr>
<tr>
<td>Acetyl-L-carnitine</td>
<td>Acetyl-L-carnitine</td>
<td>Precursor uptake stimulator, cholinomimetic agent</td>
<td>Enhances production of acetylcholine; blocks the postsynaptic inhibitor potential of cholinergic receptors; directly stimulates cholinergic synaptic effects; influences synaptic transmission by effects on neurotrophic factors, neurohormones and synaptic morphology; coordinates the activities of multiple neurotransmitters</td>
</tr>
<tr>
<td>Cocoa Powder</td>
<td>Caffeine</td>
<td>Adenosine antagonist</td>
<td>Binds to adenosine receptors to disinhibit the adenosine brake which promotes the inhibitory effect of adenosine on neuronal activity (80-81)</td>
</tr>
<tr>
<td>Ginkgo Biloba</td>
<td>Stimulates amino acid uptake by neurons</td>
<td>Modulates presynaptic choline uptake and acetylcholine release (82-83)</td>
<td></td>
</tr>
<tr>
<td>Grape seed extract</td>
<td>Polyphenols</td>
<td>Antioxidant</td>
<td>Preserves receptor membrane integrity and prevents attenuation of responses to neurotransmitter precursors (84-88)</td>
</tr>
<tr>
<td>Ingredient</td>
<td>Effector Molecules</td>
<td>Effects</td>
<td>Roles</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>-------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Hawthorn Berry</td>
<td>Flavonoids, oligomeric proanthocyanidins, triterpene acids</td>
<td>Antioxidant</td>
<td>Preserves receptor membrane integrity (89)</td>
</tr>
</tbody>
</table>

**Nutritional Requirements of Sleep Disorders Associated with Fibromyalgia and Depression**

The nutritional requirements of most interest to patients with sleep disorders associated with fibromyalgia and depression are nutrients or dietary factors which function as neurotransmitters or precursors of neurotransmitters that modulate circadian effects on the sleep-wake cycle and autonomic nervous system activity (56). As precursors of serotonin and acetylcholine, tryptophan and choline are especially important to these patients as is glutamate which functions not only as a neurotransmitter but also as a precursor of GABA. **Sentra PM** is formulated with balanced amounts of glutamate, choline, 5-hydroxytryptophan, and the neuromodulator acetyl-L-carnitine to optimize circadian-dependent processes using *Targeted Cellular Technology* to control the timing of the release of these ingredients.

**Neurotransmitter balance.** Balance in the production and release of neurotransmitters is important to neurotransmission because it is the highly integrated functions and complexity of the multiple feedback loops between them that determine the net input received by the brain. These interactions explain why an imbalance in the intake of a nutrient or dietary factor which supports the synthesis or activity of any one neurotransmitter can influence the activities of the others, potentially inducing absolute and relative deficiencies (41, 43, 63, 90). The therapeutic effects of many drugs approved for treatment of sleep disorders and depression involve manipulation of brain levels of serotonin indicating that imbalances in this neurotransmitter and the neurotransmitters that respond to changes in serotonergic activity contribute to alterations in sleep patterns manifested in these conditions, and supports the benefits of consuming additional amounts of these neurotransmitters and nutrient precursors to restore balance (2, 18, 41, 50, 53-55, 91-97).

**Nutrient requirements in disease.** 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 specific pathologies (98). These requirements can be estimated by determining the level of intake at which a physiological response is improved indicating that the balance between intake and metabolic demand has been favorably modified. The nature of the pathological characteristics of a disease will determine the relative amounts of nutrients needed to restore balance between intake and demand (91, 97-105). The degree of coordination between the activities of different neurotransmitters is an important consideration in assessing the amounts of dietary precursor needed (91-96, 106).

Diseases with pathologies that involve imbalances in neurotransmitters will increase the requirements for certain amino acids and other dietary precursors to restore homeostasis (2, 68, 91-96, 104-109). For most of these amino acids and dietary precursors, uptake by target neurons is a concentration-driven process;
therefore, intakes must be sufficient to increase the extracellular to intracellular concentrations to levels high enough to drive a rapid rate of uptake (92, 94, 110-113). The rate of precursor uptake by target neurons is important to neurotransmitter synthesis because the enzymes involved are found only in these neurons and thus the amount of substrate available is the limiting factor in neurotransmitter production (110-111). As blood levels of dietary precursors rise in response to increased intakes, the concentration-driven rate of precursor uptake by target neurons is increased, making more substrate available for neurotransmitter production and subsequent release (92, 102, 114-115). Changes in intakes of dietary precursors of these neurotransmitters will therefore influence physiological responses by affecting neurotransmitter availability (4, 93, 99-100, 102-103, 110, 115-119).

A large body of peer-reviewed published data supports the basis for increased requirements of tryptophan (46, 90, 99, 102, 112, 114, 120-125), glutamate (126-127), and choline (105, 128-135) in conditions which depend on neurotransmitter balance. (90-96, 99, 103-104, 106-107, 111, 120, 136). Patients who show decreased blood levels of certain amino acids despite maintaining their usual protein intake may have needs for these amino acids that are selectively increased as a result of specific physiological requirements associated with their disease (67). This observation may be explained by the competitive demands for certain amino acids by different metabolic pathways which decrease the supply of neurotransmitters available to function in the sleep process (Refer to the section Metabolism in this monograph).

**Nutrient effects on neurotransmitter availability.** Certain physiologic and biochemical mechanisms must exist in order for nutrient consumption to affect neurotransmitter synthesis (110). These conditions are listed below. The extent to which neurotransmitter synthesis in any particular aminergic neuron is affected by changes in precursor availability will vary directly with the firing frequency of the neuron. Consequently, precursor administration can produce selective physiologic effects by enhancing neurotransmitter release from some but not all of the neurons potentially capable of utilizing the precursor for the particular effect. It is also useful in predicting when administering the precursor might be useful for support of a normal physiologic process, or for addressing an increased need due to intrinsically-altered or externally-modified factors.
Conditions that Support Effects on Dietary Precursors of Neurotransmitter Synthesis

1. Absence of significant feedback control of plasma precursor levels
2. Ability of plasma precursor levels to control influx into or efflux from the central nervous system
3. Presence of a low-affinity (unsaturated) transport system mediating the flux of precursor between blood and brain
4. Low-affinity kinetics of enzyme that initiates conversion of precursor to neurotransmitter
5. Lack of in vivo end-product enzyme inhibition by the neurotransmitter

Requirement for tryptophan/5-hydroxytryptophan. Patients with fibromyalgia exhibit significantly lower plasma levels of tryptophan and total essential amino acids compared with controls (68). 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 (22, 47, 54-55, 68, 79, 88, 90, 95, 106, 110, 112-113, 115, 120-121, 126, 137-140). The low levels of serotonin accompanied by low 5-hydroxytryptophan levels in patients with sleep disorders also implicate the presence of a tryptophan deficiency secondary to increased metabolic demand which may also be contributing to disturbances in sleep patterns (113, 121, 126, 138, 140). Imbalances in serotonin production and release may be further complicated if tryptophan metabolism is also altered in the disorder (98, 113, 140-141). Abnormalities in tryptophan metabolism have been identified in the pathophysiology of both depression and fibromyalgia (124, 142-143).

In conditions where tryptophan metabolism is altered, intake of 5-hydroxytryptophan, the metabolic intermediate in the conversion pathway of tryptophan to serotonin, would be a more effective approach for restoring balance in serotonin levels than administration of tryptophan (Figure 1). (See section on Metabolism in this monograph). Therapeutic administration of 5-hydroxytryptophan has been shown to be effective in treating a wide variety of conditions that involve serotonergic activity including depression and insomnia (6). Oral 5-hydroxytryptophan is well-absorbed with approximately 70% of the dose measured in blood following intake. This molecule crosses the blood-brain barrier and effectively increases central nervous system synthesis of serotonin. The appearance in cerebrospinal fluid of increased amounts of 5-hydroxyindolacetic acid, the primary metabolite of serotonin, following oral administration of 5-hydroxytryptophan confirms that supplemental intake of the metabolic intermediate not only increases production of serotonin but that it is released by serotonergic neurons (102, 114, 116). By affecting both the production and release of various neurotransmitters, changes in intakes of precursor nutrients and dietary factors can influence the physiological functions dependent on these neurotransmitters (91-94,97, 99, 100, 103, 106-107, 111-112, 144).
Nutrient deficiencies in sleep disorders. In addition to tryptophan, low blood levels of choline and GABA have been noted in patients with sleep disorders indicating that the needs for choline and glutamate are not being met at the current levels of intakes of these patients (2, 113, 115, 121, 126, 130). A dietary deficiency of choline has been associated with sleep apnea syndromes and disorders of restorative sleep (91, 107, 145). Plasma levels of glutamate have been found to be a highly significant discriminatory variable for identifying patients with major depression (146). 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 their nutrient precursors (2, 26, 51).

Requirement for choline. Acetylcholine is produced in the terminal endings of cholinergic neurons and in regions of the brain where choline acetyltransferase is concentrated. Under steady state conditions, the brain enzyme is not completely saturated, thus the rate of acetylcholine production is driven by the availability of choline and acetyl CoA (115, 147). Dietary choline is the primary contributor to plasma choline levels accounting for a greater proportion of the plasma concentration than de novo synthesis (126, 130-131, 140, 148). The rate of choline transport across the blood brain barrier is increased by an amount proportional to the increase in serum concentration and is followed by an increase in the release of acetylcholine from cholinergic neurons (115). In the brain, most of the free choline is phosphorylated to phosphatidylcholine (lecithin) in order to moderate the rate of acetylcholine synthesis in the presence of increased availability of precursor; however, the appearance of choline in cerebrospinal fluid confirms that there is a pool of free choline in the brain (149-150).

Membrane reserves. Incorporation of choline into membrane phosphatidylcholine provides a ready reserve of precursor for acetylcholine synthesis over periods of short duration (149). Under steady state conditions, most of the choline utilized for acetylcholine synthesis is obtained from hydrolysis of membrane phosphatidylcholine (149, 151-153). Dietary choline becomes an increasingly more important source of precursor over prolonged periods as membrane phosphatidylcholine is depleted. If a supplemental source is not provided at this time, cell membrane function will be compromised causing apoptosis (105, 131, 132, 135, 149, 151, 153-155).

Blood and urine levels. Since changes in choline levels in the blood and urine correspond to changes in dietary choline intake, measurements of choline levels in these body fluids have been used to evaluate choline status following dietary deficiency or augmentation. Low blood levels of choline indicate that the requirements for the dietary precursors are not being met at current levels of intake (113, 115, 129, 149). Serum choline levels are more responsive to supplementation with dietary choline than to a choline deficiency with increases of as much as 52% observed with supplementation compared with decreases of 20% observed with a choline-deficient diet (99, 149).

Central nervous system concentrations. Although serum choline levels are decreased by a choline-free diet, brain choline levels remain relatively stable indicating that the brain is given metabolic priority at the expense of other tissues when the amount of free choline available is limited (150). Brain phosphatidylcholine levels decrease in parallel with the decrease in serum choline which further suggests that brain choline concentration is maintained within narrow limits at the expense of larger tissue pools of
phosphatidylcholine and other phospholipid precursors (serine and ethanolamine) (129, 149). Data from an experimental study in rats showed that brain choline concentration increased within 5 hours following oral administration of choline chloride (150). The consumption of a choline-free diet for 7 days lowered serum choline and brain phosphatidylcholine concentration suggesting that choline kinase, the controlling enzyme in phospholipid synthesis, is unsaturated with substrate in vivo and thus may serve as a modulator of the response of brain choline concentrations to alterations in the supply of circulating choline.

Other studies have confirmed that dietary choline can be utilized by central cholinergic neurons as a precursor of acetylcholine (150). An increase in plasma choline in response to choline supplementation promotes the expression of high affinity choline transporters on cholinergic neurons which regulate the synaptic availability of choline and facilitate the release of acetylcholine from these neurons (140, 149). Synaptic acetylcholine levels are regulated by a negative feedback mechanism in which accumulation of the neurotransmitter inhibits transporter activity on cholinergic neurons to prevent further uptake of choline. Anticholinergic drugs such as chlorpromazine, atropine, and cholinesterase inhibitors decrease acetylcholine release by inhibition of these transporters (151, 156-157).

**Dietary choline deficiency.** Clinical evidence of a human choline deficiency was first reported in adults receiving total parenteral nutrition (TPN) (158-159). These patients exhibited hepatic morphologic and aminotransferase abnormalities which were reversed by choline-supplemented TPN. The effects of inadequate choline intakes on physiological endpoints are rapidly observed. Clinical signs of deficiency were documented in men with otherwise normal nutritional status after consuming a choline-deficient diet for a period of < 2 weeks (133). Changes in blood and urine markers of organ dysfunction (muscle and liver enzymes) were also been reported in these men. Decreases in plasma levels of choline and phosphatidylcholine accompanied by elevated alanine aminotransferase, a biochemical marker of liver damage, and elevated creatine kinase, a biological marker of muscle damage, have also been observed with a dietary choline deficiency (105, 133, 160-162).

Muscle and liver damage are the most frequently observed signs of an inadequate intake of dietary choline. Fatty liver results from depletion of the phosphatidylcholine pool which limits membrane fatty acid transport leading to fat accumulation. The fragility of phospholipid-depleted membranes and apoptosis are the primary contributors to muscle damage in a choline deficiency (163). Catabolism of phosphatidylcholine drives cellular uptake of choline indicating that increased hydrolysis of the membrane phospholipid signals an increased demand for choline (149).

In addition to effects on liver and muscle function, dietary choline deficiency has also been associated with sleep apnea syndromes, disorders of restorative sleep, and memory disorders (77, 85, 104-105, 110-111, 115, 132, 164). Age-related memory loss was exacerbated by choline deficiency in rats and mice. In a double blind study conducted in normal college students, explicit memory measured by the number of trials in a serial-learning word test was improved after a single dose of 10 g of choline taken with 25 g phosphatidylcholine (165). Memory-enhancing effects were also observed in a randomized, double-blind, placebo-controlled trial conducted in adults with memory deficits but excluded dementia after supplementation with 1000 mg cytidine diphosphocholine (CDP-choline), a precursor of
phosphatidylcholine. The amounts of choline required to maintain cognitive function in humans is unknown and therefore must be individualized for each patient.

There is currently no recommended dietary allowance (RDA) for choline; however, based on a review of the available data, the Food and Nutrition Board of the Institute of Medicine has established 550 mg as an adequate intake level for adults, with an upper tolerable limit of 3000 to 3500 mg (166). Since the richest dietary sources of choline are eggs and high fat meats, many adults, particularly women and those who are on fat-restricted diets, are not consuming the recommended amounts (105). A high degree of individual variation in choline requirements may exist. In one study, 10% of subjects required 850 mg/d of choline to prevent clinical signs of muscle and liver damage.

**GABA deficiency syndrome.** Specific neurotransmitter deficiency syndromes related to inadequate intakes of dietary precursors have been identified for GABA and serotonin further supporting a link between requirements for nutrient precursors and production of sufficient amounts of the corresponding neurotransmitters. A syndrome characterized by a basic depressive state, sleep disorders, and other clinical symptoms has been attributed to a GABA deficiency based on the observation of a rapid reversal of these symptoms following administration of an enzyme inhibitor of GABA catabolism (167).

**Serotonin deficiency syndrome.** Several findings raise the possibility that inadequate intakes of tryptophan may be related to a brain serotonin deficiency in patients with fibromyalgia/fibrositis. An inverse relationship between blood tryptophan concentration and severity of musculoskeletal pain has been reported in patients with these conditions which was accompanied by significantly lower levels of serum tryptophan (p = 0.002) compared with healthy adults suggesting that a functional deficiency of serotonin may be involved in the pathology of this syndrome (168).

A possible link between inadequate intake of tryptophan and a serotonin deficiency is also supported by evidence of altered tryptophan metabolism associated with low tryptophan blood levels (169). A trend towards lower levels of plasma tryptophan was associated with a significantly lower tryptophan membrane transport ratio (p<0.01) in patients with primary fibromyalgia/fibrositis compared with controls indicating that insufficient amounts of tryptophan were reaching target tissues when plasma levels were below normal (168). A specific neuroendocrine response (i.e., prolactin release with tryptophan infusion) suggestive of postsynaptic serotonin receptor supersensitivity was associated with a 15 to 20% reduction in fasting total plasma tryptophan levels in 22 healthy subjects consuming a tryptophan-restricted diet (139). A serotonin deficiency has also been linked to glutamate intakes based on the relationship between plasma glutamate levels and major depression (145, 168).

**Requirement for carnitine.** Acetyl-L-carnitine supplements at doses of 1000-2000 g/d have also been shown to reduce fatigue associated with fibromyalgia and mild depression (dysthymia) after 8-24 weeks indicating that needs for carnitine were increased in these diseases (164, 170-172). The results of a double-blind placebo-controlled trial of patients with a clinical diagnosis of fibromyalgia who received supplemental acetyl-L-carnitine for a 10-week period revealed a statistically significant decrease from baseline in self-assessment of fatigue, tiredness upon awakening and sleep experience (120). These parameters were also significantly improved compared with controls.
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 of Sleep Disorders Associated with Fibromyalgia and Depression**

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Blood/Tissue/Urinary Levels</th>
<th>Clinical Observations and Associated Biochemical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tryptophan</td>
<td>Low blood and brain levels</td>
<td>Disturbances in the sleep/wake cycle; low blood 5 hydroxytryptophan and serotonin levels; low membrane transport ratio; postsynaptic serotonin receptor supersensitivity; sleep apnea, snoring; increased serotonin metabolites in cerebrospinal fluid following supplementation; serotonin deficiency</td>
</tr>
<tr>
<td>Choline</td>
<td>Low blood levels</td>
<td>Sleep apnea syndromes and disorders of restorative sleep; depression-associated sleep disorders; decreased transport across the blood brain barrier; decreased parasympathetic autonomic nervous system activity; documented human choline deficiency diseases; diminished responses to GABA and serotonin</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Low blood levels</td>
<td>Elevated blood glutamine; insomnia, fragmented sleep; loss of synaptic inhibition; seizures; GABA deficiency characterized by a basic depressive state, sleep disorders, and other clinical symptoms; loss of synaptic inhibition; seizures</td>
</tr>
<tr>
<td>Carnitine</td>
<td>Low plasma levels</td>
<td>Fatigue associated with mild depression (dysthymia) and fibromyalgia; acetylcholine deficiency; cholinergic deficits</td>
</tr>
</tbody>
</table>

**Clinical Validation of Sentra PM**

The relationship between intakes of dietary precursors and production of the corresponding neurotransmitters has been validated by observations of improvements in neurotransmitter-mediated clinical outcomes with supplemental intakes of these dietary factors (9, 54-55, 91, 99, 101, 103, 106, 111, 113-116, 120-121, 138-140, 146). A change in the levels of a neurotransmitter in the blood and/or its metabolites in cerebrospinal fluid following ingestion of a dietary precursor from a medical food reflect the uptake and utilization of the nutrient or dietary factor by target cells for synthesis of the neurotransmitter, thus demonstrating the biological availability of dietary precursors and the clinical utility of the medical food as a source of these precursors (63-64, 89, 91-93, 95, 98-99, 102-106, 116, 121, 125-126, 129, 131, 135, 140-141, 146, 150, 153-155, 164, 168-175).

The clinical benefits which may be obtained from medical foods can be validated by the observed changes in biological, physiological, and clinical endpoints following ingestion by individuals with specific conditions. If an individual with a chronic pain disorder ingesting a medical food containing 5-hydroxytryptophan and shows an increase in serum levels of the molecule following ingestion (biological availability) which is associated with increased concentrations of serotonin metabolites in cerebrospinal fluid (physiological response) and an improvement in pain measurement (clinical response), the clinical benefit of this medical food as a source of precursors for serotonin production has been 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.

**Sentra PM** has been formulated with specific ratios of choline, glutamate, and acetyl-L-carnitine using **Targeted Cellular Technology** to control the timing of the release of each ingredient. If sufficient amounts of these nutrients are not available, or their availability is not well-synchronized with demand, imbalances in neurotransmitter activity may contribute to development of sleep disorders in patients with fibromyalgia and depression (20, 91, 95).

**Biological Availability**

The biological availability of 5-hydroxytryptophan, the source of serotonin in **Sentra PM**, has been demonstrated by changes in blood serotonin levels observed within 15 minutes of ingestion of 2000 mg of 5-hydroxytryptophan (Figure 9). By 60 minutes, serotonin levels were more than 3-fold higher than baseline levels confirming that 5-hydroxytryptophan was utilized to increase production of serotonin.

**Figure 9. Effect of 5-Hydroxytryptophan Supplementation on Blood Serotonin Levels**

![Figure 9](image)

Intestinal absorption of 5-hydroxytryptophan does not require the presence of a transport molecule, and is not affected by the presence of other amino acids (6). Oral doses of 5-hydroxytryptophan are well absorbed, with about 70 percent appearing in the bloodstream following ingestion. The precursor easily crosses the blood-brain barrier and effectively increases central nervous system synthesis of serotonin.

The bioavailability of 5-hydroxytryptophan was also confirmed by a clinical response to treatment observed following ingestion of 200 to 400 mg/d, the amounts delivered by **Sentra PM** at the recommended doses (176-177). In this study, bioavailability was evaluated in 50 patients with fibromyalgia in a double-blind, placebo-controlled, open-label study. After 90 days of treatment at these
doses of 5-hydroxytryptophan, all subjects showed statistically significant improvements in all of the clinical variables studied including quality of sleep and fatigue compared with baseline (P < 0.001).

**Physiological Response**

The effectiveness of **Sentra PM** in improving sleep quality in patients with sleep disorders has been assessed using autonomic function tests. These tests are indicators of the relative activities of the parasympathetic and sympathetic nervous systems during the sleep cycle, and thus can be used to evaluate the effectiveness of circadian rhythms in regulating autonomic balance. Because autonomic function cannot be consciously altered, these tests can be utilized as objective measures of restorative sleep and reduced snoring. Normal sleep patterns are characterized by activation of the parasympathetic nervous system at sleep onset. Without therapy, parasympathetic autonomic nervous system activity is stable with repetitive measurements.

Heart Rate Variability Analysis was used to assess parasympathetic activity in a study of patients with diagnostically-confirmed sleep disorders taking **Sentra PM**. This method, which has been validated in this patient population, analyzes heart rate from rr-intervals for each heartbeat measured by 24-hour ECG recordings using a complex mathematical formula (fast Fourier transform). This analysis allows bands that define total heart rate variability or autonomic function to be identified such as the HF band which is representative of parasympathetic activity. Patients with showed improvements in parasympathetic activation assessed by this method using repeat 24-hour ECG recordings with sleep disorder.

Parasympathetic activity was also assessed using Heart Rate Variability Analysis in a crossover study of 5 control subjects before taking **Sentra PM** and after taking **Sentra PM** for a 60-day period. Changes in parasympathetic activity between midnight and 5:00 AM were plotted against a normal pattern of change as depicted in Figure 10. These control subjects showed a normal pattern of change in parasympathetic activity which was similar in magnitude before and after taking **Sentra PM**. The results of this study indicated that **Sentra PM** does not alter the normal increase in parasympathetic activity observed during sleep by a statistically significantly amount in subjects who do not show an abnormal pattern at baseline. This observation is consistent with the pattern of parasympathetic activity that would be expected from a normal sleep pattern reflecting balanced activity of neurotransmitters that modulate circadian rhythms and thus autonomic balance.
Figure 10. Changes in Parasympathetic Activity by Heart Rate Variability Analysis in Normal Subjects after Taking Sentra PM

Compared with normal subjects, patients with fibromyalgia showed a different pattern of parasympathetic activity before and after taking Sentra PM (Figure 11). The increase in parasympathetic activity normally observed between midnight and 5 AM in controls was not seen in these patients prior to taking Sentra PM; however, a substantial increase was seen after taking Sentra PM. The results of Heart Rate Variability Analysis revealed a statistically significant difference in patterns of parasympathetic activity exhibited during sleep between patients with fibromyalgia and normal controls (P<0.001).

Figure 11. Changes in Parasympathetic Activity by Heart Rate Variability Analysis in Patients with Fibromyalgia after Taking Sentra PM
Clinical Response

The effects of *Sentra PM* on patterns of parasympathetic activity during sleep observed in patients with sleep disorders suggests that the effective doses of pharmaceutical sleep aids may be reduced when taken in combination with *Sentra PM*. To examine this possibility, a double-blind, placebo- and active-controlled, multicenter clinical trial comparing *Sentra PM* to low-dose trazodone was conducted in 111 patients at 10 sites. At low doses, trazodone is considered a poor hypnotic and modest antidepressant. In this study, sleep latency, quality of sleep, duration of sleep, morning (AM) grogginess, restorative sleep, and mood were assessed in subjects randomized to either placebo, trazodone + placebo, *Sentra PM* + placebo, or *Sentra PM* + trazodone. The results of this study support the use of *Sentra PM* as a medical food alone or in combination with a low dose pharmaceutical sleep aid. Clinically relevant improvements in sleep quality in this study observed in patients with fibromyalgia treated with trazodone indicated that the effectiveness of a low dosage of this medication was increased by *Sentra PM*. In addition, subjects treated with trazodone in combination with *Sentra PM* experienced a reduction in depression, a frequent side effect associated with low doses of this medication.

Figure 12 presents the results from assessment of sleep latency in this study. Statistically significant improvements were found in subjects who received either *Sentra PM* + placebo or *Sentra PM* + trazodone. In the *Sentra PM* + placebo group, time to sleep was reduced by almost 60 minutes compared with 20 minutes in the trazodone group. In the group of subjects treated with trazodone + placebo, sleep latency was not statistically significantly improved relative to placebo.

**Figure 12. Comparison of Sleep Latency in Patients with Fibromyalgia Receiving Sentra PM, Trazodone, or Sentra PM + Trazodone**

When quality of sleep was assessed by a Visual Analogue Scale (VAS), only subjects receiving *Sentra PM* + trazodone showed a statistically significant improvement from baseline \(P<0.05\) (Figure 13).
The results of the assessment of AM grogginess, an important component of sleep quality reflecting the frequency and duration of REM sleep, are presented in Figure 14. The duration of AM grogginess was increased by approximately 20 min in the group randomized to trazodone + placebo, compared with a 80 to 100 min decrease when trazodone was taken in combination with Sentra PM (P<0.001).

Figure 14. Comparison of Duration in Morning Grogginess in Patients with Fibromyalgia Receiving Sentra PM, Trazodone, or Sentra PM + Trazodone
**Sentra PM** taken alone or with trazodone also promoted statistically significant improvements in restorative sleep, a composite indicator of AM gogginess, AM memory, and feelings of fatigue (P<0.001) (Figure 15).

**Figure 15. Comparison of Change in Restorative Sleep in Patients with Fibromyalgia Receiving Sentra PM, Trazodone, or Sentra PM + Trazodone**

Although trazodone is believed to be an antidepressant at moderate to high dosages, increased feelings of depression were reported in patients in this study who had been treated with low doses (50 mg/d) of the medication (Figure 16). When taken at the same dose in combination with **Sentra PM**, a substantial reduction in feelings of depression was observed (P=0.01).
Figure 16. Comparison of Change in Depressed Mood in Patients with Fibromyalgia Receiving *Sentra PM*, Trazodone, or *Sentra PM* + Trazodone

<table>
<thead>
<tr>
<th>Change in VAS 10 pt. Scale</th>
<th>pla/pla</th>
<th>pla/tra</th>
<th>senpm/pl</th>
<th>senpm/tra</th>
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<td>pla=placebo</td>
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<td>senpm=SentraPM</td>
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Selected References


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