**Sentra PM™ Product Information**

**Indications**

*Sentra PM* is intended for use in management of sleep disorders associated with depression. *Sentra PM* is a medical food that must be used under the active or 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.¹

Normal patterns of sleep and waking are regulated by neurotransmitters that alter electrical activity in specific areas of the brain. A loss of coordinated activity between sleep-active and wake-active neurons disrupts the circadian rhythms that control the sleep-wake cycle. Difficulty falling asleep, staying asleep, and early morning awakening are the sleep parameters that are most sensitive to abnormalities in circadian rhythm and are the most common sleep disorders associated with depression, affecting approximately 70-80% of depressed patients. Disruption of the sleep-wake cycle by dysregulation of circadian rhythms can be attributed to imbalances in glutamate, acetylcholine, serotonin, and gamma-aminobutyric acid (GABA). Patients with depression-related sleep disorders benefit from increased availability of these neurotransmitters to re-establish homeostasis. *Sentra PM* is designed to provide a balance of neurotransmitters with well-defined roles in sleep parameters sensitive to circadian rhythm.

**Ingredients**

*Sentra PM* is a proprietary blend of neurotransmitter precursors (choline bitartrate, glutamate, and 5-hydroxytryptophan); polyphenolic antioxidants (hawthorn berry, cocoa); an amino acid uptake stimulator (gingko biloba); activators of amino acid utilization (acetyl-L-carnitine, glutamate, cocoa powder); and an adenosine antagonist (cocoa powder). Each of the neurotransmitters or neurotransmitter precursors included in the formulation has been specifically selected based on scientific support for their roles in the physiological processes that regulate sleep-wake cycles and circadian rhythm. These roles are summarized in this monograph in the section *Scientific Support for Use of Sentra PM in Sleep Disorders Associated with Depression*. The other ingredients in the formulation 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,

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

**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 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 neurotransmitters, which is especially important for processes that are controlled by circadian rhythm which are sensitive to timing of neurotransmitter release 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. Ingestion of large quantities of amino acids also contributes to an increased risk of adverse effects. In addition, when large amounts of amino acids are delivered simultaneously to tissues, the membrane transport receptors are quickly saturated, which reduces the fractional amino acid uptake resulting in an attenuation of the tissue response to the supplemental amounts. Improving metabolic efficiency in uptake and utilization of neurotransmitter precursors by target neurons using *Targeted Cellular Technology* allows ingestion of smaller amounts of amino acids to elicit the same response as the larger amounts, making daily dosing more feasible and reducing the potential for tolerance. Unlike pharmaceutical products which are not innate components of the processes regulating sleep, 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 and other nutrients for patients with depression-associated sleep disorders. These patients require additional amounts of glutamate, choline, and tryptophan to support synthesis of the neurotransmitters, GABA, acetylcholine and serotonin, respectively, which are active in circadian processes that govern sleep. Under normal physiological conditions, glutamate is metabolized as a nonessential amino acid because endogenous synthesis is sufficient to satisfy metabolic demand. When needs are altered such as in sleep disorders, the usual rate of synthesis is no longer sufficient and glutamate become conditionally essential, requiring that a supplemental amount be consumed. Choline and carnitine are also considered nonessential nutrients under normal conditions because de novo synthesis can provide sufficient amounts, but they become conditionally essential when metabolic demand is increased as in sleep disorders and supplemental amounts must be obtained from the diet.

In contrast to amino acids 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 to be divided among multiple pathways of utilization. Tryptophan is a precursor not only of serotonin, but also of the coenzymes nicotinamide adenine dinucleotide (NAD+) and nicotinamide adenine dinucleotide phosphate (NADP) (Figure 1). In addition, serotonin is utilized as a precursor of melatonin so that an increased demand for melatonin will further increase the requirement for tryptophan. The competition between these and other metabolic pathways for the limited supply of tryptophan restricts the amount of serotonin, and thus of melatonin, that can be produced from supplemental amounts of the amino acid. To overcome this limitation, *Sentra PM* provides 5-hydroxytryptophan, which is the immediate precursor of serotonin in the pathway of conversion from tryptophan. 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, *Sentra PM* conserves the existing supply of the amino acid for other uses, thus improving metabolic efficiency.
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, the requirement for glutamate increases because additional amounts are needed to support GABA synthesis as well as to maintain activity of glutamatergic neurons. 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 important biological 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 glutamate, *Sentra PM* improves metabolic efficiency by ensuring that there are adequate amounts of both neurotransmitters available while conserving the supply of glutamine for other uses.
Both choline and carnitine are considered nonessential nutrients under normal physiological conditions because they can be synthesized in sufficient amounts to meet usual metabolic demand. A steady supply of choline is also available from breakdown of phosphatidylcholine (lecithin), an abundant phospholipid found in cell membranes which can serve as a reservoir of choline to meet short-term needs. If cholinergic activity is sustained at high levels over time, the demand for acetylcholine will eventually exceed the amount of choline that can be supplied by de novo synthesis or from the membrane phospholipid pool, and additional choline must be consumed from exogenous sources. **Sentra PM** provides supplemental choline to prevent an acetylcholine deficiency when demands for the neurotransmitter are increased.

Acetyl-L-carnitine increases the efficiency of the response to increased demand for acetylcholine by enhancing synthesis of the neurotransmitter. Acetyl-L-carnitine also influences other aspects of neurotransmitter function such as modulation of neurotrophic factors and neurohormones, synaptic morphology, and synaptic transmission of multiple neurotransmitters (1). 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 cholinergic activity as well as its other roles in neurotransmission.

**Dosage**

The recommended dose of *Sentra PM* is 1 or 2 capsules taken at bedtime. One or 2 capsules may also be taken during the night if awakened and unable to fall back to 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. At the doses of *Sentra PM* recommended for depression-related sleep disorders, the amounts of each ingredient consumed based on body weight are presented in Table 1.

**Table 1. Sentra PM Composition**

<table>
<thead>
<tr>
<th>Ingredient [Select]</th>
<th>mg/kg body weight¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>choline bitartrate</td>
<td>1.0 – 7.7</td>
</tr>
<tr>
<td>L-glutamate</td>
<td>0.4 – 3.1</td>
</tr>
<tr>
<td>5-hydroxytryptophan (griffonia seed, 95% w/w)</td>
<td>0.2 – 1.9</td>
</tr>
<tr>
<td>Acetyl-L-carnitine</td>
<td>0.3 – 0.9</td>
</tr>
<tr>
<td>grape seed extract</td>
<td>0.2 – 1.5</td>
</tr>
<tr>
<td>cocoa powder</td>
<td>0.2 – 1.5</td>
</tr>
<tr>
<td>Hawthorn berry</td>
<td>0.1 – 0.4</td>
</tr>
</tbody>
</table>

¹Dosing range of [1 to 2] capsules

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 use of *Sentra PM* with the drug 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 *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. All of 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.

**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>Protects against oxidative cell damage from exposure to free radicals</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>Cholinergic</td>
<td>Neurons that secrete choline</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>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</td>
</tr>
<tr>
<td>GABAergic</td>
<td>Neurons that secrete gamma-aminobutyric acid</td>
</tr>
<tr>
<td>Glutamatergic</td>
<td>Neurons that secrete glutamate</td>
</tr>
<tr>
<td>Inhibitory Neurotransmitters</td>
<td>Mediators of neural signals that slow the rate of transmission through hyperpolarization of postsynaptic membranes; inhibit responsiveness to a stimulus</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Hormone synthesized from serotonin which increases or decreases in response to neurotransmitter signals initiated by changes in light exposure and transmitted to the suprachiasmatic nucleus</td>
</tr>
<tr>
<td>Monoaminergic</td>
<td>Neurons that secrete monoamine neurotransmitters such as norepinephrine and dopamine; serotoninergic neurons are classified as monoaminergic</td>
</tr>
<tr>
<td>Neurotransmitter</td>
<td>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</td>
</tr>
<tr>
<td>NREM Sleep</td>
<td>Period of non-rapid eye movement sleep; a period in the sleep cycle comprising 4 stages that are differentiated by characteristic brain electrical activity</td>
</tr>
<tr>
<td>Phosphotidylcholine</td>
<td>A phospholipid component of cell membranes that can serve as a reservoir of choline; also called lecithin</td>
</tr>
<tr>
<td>Raphe Nucleus</td>
<td>Mesencephalic nucleus which includes the hypothalamic tract which links ganglion cells to the suprachiasmatic nucleus</td>
</tr>
<tr>
<td>REM Sleep</td>
<td>Rapid eye movement sleep; the period of the sleep cycle that normally follows NREM sleep which is characterized by rapid eye movements</td>
</tr>
<tr>
<td>Restorative Sleep</td>
<td>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</td>
</tr>
<tr>
<td>Term/Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Reticular Formation</td>
<td>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</td>
</tr>
<tr>
<td>Serotonergic</td>
<td>Neurons that secrete serotonin</td>
</tr>
<tr>
<td>Sleep Stages</td>
<td>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.</td>
</tr>
<tr>
<td>Suprachiasmatic Nucleus (SCN)</td>
<td>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-photic stimuli.</td>
</tr>
<tr>
<td>Targeted Cellular Technology™</td>
<td>A patent pending 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 activity</td>
</tr>
</tbody>
</table>

**Mechanism of Action**

Understanding the mechanism of action of *Sentra PM* in the management of sleep disorders associated with depression requires a brief overview of the physiology of sleep and the role of circadian rhythm in regulation of the sleep-wake cycle. Sleep is an active process consisting of 2 phases that are differentiated by brain electrical activity on an electroencephalogram (EEG). During non-rapid eye movement (NREM) sleep, 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 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. In patients with depression, EEG recordings show changes in brain wave activity indicative of rapid onset REM sleep with a shortened period of slow-wave restorative sleep (2).

The sleep-wake cycle is regulated by neurotransmitters, which are amino acids or amino acid derivatives that 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 cholinergic receptors are located.

The cycling between periods of sleep and wakefulness is controlled by the synchronized activity between sleep-active or sleep-promoting neurotransmitters (GABA) and wake-active or wake-promoting neurotransmitters (serotonin, acetylcholine, and glutamate). These neurotransmitters transmit signals generated by the interactions between an ultraviolet light stimulus and photoreceptor cells in the retina or by nonphotic signals originating from metabolic factors such as changes in blood glucose levels to the suprachiasmatic nucleus (SCN), the biological clock which controls the circadian-dependent processes of wakefulness, body temperature, and mood (3). The SCN consists of 2 pin-sized structures situated in the hypothalamus above the point at which the optic nerves cross comprising more than 20,000 neurons rich in serotoninergic activity (4-10). Depending upon the specific signal received by the SCN, a message is sent to the pineal gland which turns melatonin production on or off (11-12). 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 (2).

The coordinated activity between sleep-active and wake-active neurons is integral to regulation of the sleep-wake cycle by the SCN. A decrease in light exposure promotes the withdrawal of acetylcholine, serotonin, and glutamate from the reticular formation which is 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. Many sleep disorders are the result of disruption of normal circadian rhythm by desynchronization of the activities of these neurons due to imbalances in GABA, acetylcholine, serotonin, and glutamate (7, 9, 13-22). 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 (23).

Scientific Support for Use of Sentra PM in Sleep Disorders

The effectiveness of Sentra PM in the management of sleep disorders is supported by an extensive body of experimental and clinical data which has identified specific roles for each of the ingredients in regulation of the sleep-wake cycle through circadian effects. Sentra PM is formulated to insure availability of the appropriate balance of neurotransmitters involved in circadian-dependent parameters of sleep. Because amino acid or other nutrient precursor uptake by specific neurons is concentration-dependent, intakes must be sufficient to maintain blood concentrations at high enough levels to drive the rapid rate of uptake needed when the activities of these neurons are elevated (24-28). Moreover, the enzymes that synthesize neurotransmitters are found only in neurons, thus the concentration-dependent rate of precursor uptake by these tissues is the limiting factor in neurotransmitter production. The balance of neurotransmitters released is important because neurotransmitter functions are highly interrelated and regulated by multiple feedback loops; therefore, deficiencies in any one may influence the activities of the others and thus the response to photic or nonphotic stimuli (13, 29-30).

The transition from waking to sleep is the result of a coordinated inhibition of multiple arousal systems in response to secretion of GABA (4-5, 13, 31-33). 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 (34-39). 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 (6, 39). 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 (14, 32). The activation of GABAergic neurons by decreased light exposure and sleep deprivation also suggests a dependence of sleep homeostasis on GABA production and release (5, 36).

The transition from sleep to waking is initiated by an increase in activity of the wake-active serotonergic (serotonin secretors) neurons 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 (4, 6, 13-17, 29, 31-44). Glutamatergic neurons (glutamate secretors) which are
widely distributed in the brain are also involved in the initiation and maintenance of the waking state (34, 45-46). Acetylcholine and glutamate promote arousal by depolarization of hypocretin- or orexin-secreting neurons in the perifomical lateral hypothalamus which control arousal, a heightened state of alertness, while GABA and serotonin inhibit arousal by hyperpolarization of these neurons (13, 29, 33-34, 47-48).

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 (4, 44, 49). Acetylcholine concentrations fluctuate from high levels while awake to lower levels during slow-wave Stage IV sleep returning to higher levels during REM sleep (34). 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 (16, 34, 43, 49-50). 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 (48). A more rapid onset of REM sleep and a reduction in restorative sleep are characteristic of sleep abnormalities in depressed mood states indicating abnormalities in cholinergic activity.

Serotonergic activity is highest during periods of waking, slows during NREM sleep, and is virtually silent in REM sleep (20, 39, 48, 60). Sleep is initiated and sleep latency is decreased at times of low serotonergic activity (52). 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 (11, 14, 18, 53). Altered serotonin production and activity have been linked to disturbances in sleep patterns that contribute to sleep apnea, snoring, and depression-associated sleep disorders (20, 37, 53-54).

The overlapping pattern of changes in neurotransmitter levels over the sleep cycle is indicative of the complexity of the interactions among them (15, 17, 45, 55). 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 (35). The subsequent decrease in serotonergic activity lifts the inhibition on the specific cholinergic activity that promotes REM sleep (39). 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 Sentra PM is presented in Table 3.
### Table 3. Roles of the *Sentra PM* Ingredients in Depression-Associated Sleep Disorders

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Effector Molecule</th>
<th>Function</th>
<th>Role in Neurotransmitter Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-OH-tryptophan</td>
<td>Serotonin</td>
<td>Excitatory neurotransmitter</td>
<td>Primary modulator of circadian rhythm; transmits nonphotic signals to the SCN; precursor of melatonin (6, 15, 18, 20, 39)</td>
</tr>
<tr>
<td>Choline</td>
<td>Acetylcholine</td>
<td>Inhibitory (midbrain reticular formation) and Excitatory (basal forebrain) neurotransmitter</td>
<td>Withdrawn from the reticular formation in response to decreased light exposure; 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 (13, 16, 34, 43, 48-50)</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Glutamate, GABA</td>
<td>Excitatory neurotransmitter</td>
<td>Affects circadian rhythm through transmission of light signals from photoreceptor cells in the retina to the SCN; moderates serotoninergic activity to preserve REM sleep (4-6, 13-14, 31-39)</td>
</tr>
<tr>
<td>Acetyl-L-carnitine</td>
<td>Acetyl-L-carnitine</td>
<td>Precursor uptake stimulator</td>
<td>Enhances production of acetylcholine and phospholipids (56)</td>
</tr>
<tr>
<td>Cocoa Powder</td>
<td>caffeine</td>
<td>Adenosine antagonist</td>
<td>Increases neuronal activity by competitively binding to adenosine receptors which disinhibits the “adenosine brake” (57-59)</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 (60-62)</td>
</tr>
<tr>
<td>Hawthorn Berry</td>
<td>Flavonoids, oligomeric proanthocyanidins, triterpene acids</td>
<td>Antioxidant</td>
<td>Preserves receptor membrane integrity (63)</td>
</tr>
</tbody>
</table>
Nutritional Requirements of Depression-Associated Sleep Disorders

The nutrient requirements of most interest for patients with sleep disorders associated with depression are those which function as neurotransmitters involved in regulation of the sleep-wake cycle through effects on circadian rhythm (23). These nutrients are glutamate, tryptophan, and choline which are precursors of GABA, serotonin, and acetylcholine, respectively. The therapeutic effects of many drugs approved for treatment of sleep disorders and of depression involve manipulation of brain levels of serotonin indicating that imbalances in this neurotransmitter and the neurotransmitters that associated with changes in serotonergic activity contribute to alterations in sleep patterns related to depression and supports the benefits of consuming additional amounts of neurotransmitters and nutrient precursors to restore this balance (13, 22, 55, 61-62, 64-75).

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 (76). 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 degree of coordination of activity among various neurotransmitters underscores the importance of balance in the availability of the precursor amino acids required for synthesis of these neurotransmitters (64-67, 71-72).

The presence of a disease with underlying pathology that involves imbalances in neurotransmitters will increase the requirements for certain amino acids and other nutrient precursors to restore homeostasis (55, 64-82). As blood levels of these nutrients rise in response to increased intakes, the concentration-dependent rate of precursor uptake by target neurons is increased, making more substrate available for neurotransmitter production and subsequent release (83-85). 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 serotonergic neurons (83-84). By affecting both the production and release of neurotransmitters, changes in dietary intakes of precursor amino acids can influence the physiological functions that are dependent on these neurotransmitters (24-28, 30, 65-68, 77, 79).

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 (12, 19, 24-26, 30, 68-69,86-90). Low levels of serotonin accompanied by low levels of 5-hydroxytryptophan in patients with sleep disorders also implicate a tryptophan deficiency that may be secondary to increased
metabolic demand which may also be contributing to disturbances in sleep patterns (86-88). Imbalances in serotonin production and release may be further complicated if tryptophan metabolism is also altered in the disorder (76, 91).

In addition to tryptophan, low blood levels of choline and GABA have been noted in patients with sleep disorders indicating that the requirements for the precursor nutrients are not being met at current levels of intake (55, 85-86, 88, 92-93). A dietary deficiency of choline has been associated with sleep apnea syndromes and disorders of restorative sleep (64, 77, 94). 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 (31, 39, 55).

Acetyl-L-carnitine supplements have also been shown to reduce fatigue in mild depression (dysthymia) as well as a number of disorders including chronic fatigue syndrome, Alzheimer's Disease, and multiple sclerosis indicating that needs for this nutrient are increased in multiple pathologies affecting sleep and wakefulness (95-98).

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 Depression-Associated Sleep Disorders

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Biochemical and Physiologic Observations</th>
<th>Clinical Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tryptophan</td>
<td>Low blood levels; low blood 5-hydroxytryptophan and serotonin levels; increased serotonin metabolites in cerebrospinal fluid with tryptophan supplementation</td>
<td>Sleep apnea, snoring, depression-associated sleep disorders</td>
</tr>
<tr>
<td>Choline</td>
<td>Low blood choline levels; decreased parasympathetic autonomic nervous system function</td>
<td>Sleep apnea syndromes and disorders of restorative sleep; identification of human choline deficiency diseases</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Reduced blood glutamate and GABA</td>
<td>Insomnia, fragmented sleep</td>
</tr>
<tr>
<td>Carnitine</td>
<td>Reduced plasma carnitine levels</td>
<td>Fatigue associated with dysthymia, chronic fatigue syndrome, Alzheimer's Disease, and multiple sclerosis</td>
</tr>
</tbody>
</table>
Clinical Validation of *Sentra PM* for Use in Management of Depression-Associated Sleep Disorders

A large body of experimental and clinical data supports a relationship between intake of nutrient precursors, production of corresponding neurotransmitters, and associated clinical outcomes (27-28, 30, 64-70, 79-82, 99). Changes in levels of a neurotransmitter in the blood and/or its metabolites in cerebrospinal fluid following ingestion of the precursor nutrient 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 (40, 64, 67-69, 79, 81-82, 92).

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 when blood arginine levels increase following ingestion (biological availability) accompanied by an increase in nitric oxide production (physiological change) and subsequent 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.

*Sentra PM* provides balanced amounts of glutamate, choline, and 5-hydroxytryptophan 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 (5-6, 9, 23, 39, 64). 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 (31). 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 (71). 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 (71-74). In addition, selective serotonin reuptake inhibitors (SSRIs), the class of antidepressants that includes fluoxetine and sertraline, increase sleep latency and decrease REM and slow-wave sleep (100).
Biological Availability

The biological availability of 5-hydroxytryptophan, the source of serotonin in Sentra PM, 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 3 depicts the pattern of changes observed in the blood levels of plasma serotonin following consumption of Sentra PM at the recommended 2 capsule dose. These data confirm that the levels of neurotransmitters obtained from Sentra PM or from the precursors in the formulation change over the sleep cycle in patterns consistent with the corresponding endogenous neurotransmitters that support these responses.

Clinical Response

The effects of Sentra PM on sleep disorders associated with depression have been evaluated in several open-label clinical studies. The results from two of these studies demonstrated that Sentra PM was effective in inducing and maintaining sleep. Another study found that Sentra PM reduced the frequency of snoring while several others showed a reduction in awakenings during the night in patients who had previously experienced awakening with difficulty falling back to sleep.
Physiologic testing of autonomic nervous system function has been performed to assess effects on parasympathetic activity which is reduced 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. Patients with confirmed sleep disorders who were taking Sentra PM showed an improvement in parasympathetic activation as measured by heart rate variability analysis. The activation of parasympathetic nervous system function was assessed by a repeat 24-hour ECG using Heart Rate Variability analysis, which has been validated in patients with sleep disorders.

Selected References


14. Seifritz E. Contribution of sleep physiology to depressive pathophysiology. 


67. 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.


