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An Evidence-Based Systematic Review of Dream Water®
By the Natural Standard Research Collaboration

SYNONYMS/COMMON NAMES/RELATED SUBSTANCES

Dream Water®:

- 5-hydroxytryptophan (5-HTP), Dream Shot, Dream Water® Drink, Dream Water® Shot, gamma-aminobutyric acid (GABA), I Dream of Kiwi, Lullaby Lemon, melatonin, Snoozeberry.

Gamma-aminobutyric acid (GABA):

- 4-amino butyric acid, aminalon, GABA, GABA(A) receptors, GABA(B) receptors, GABA-enriched defatted rice-germ, GABA-enriched fermented milk product (FMG), GABA-enriched soybean, GABA-enriched tempeh-like fermented soybean (GABA-tempeh), GABA-transaminase (GABA-T), GABA transporter (GAT), gamma-amino butyric acid (GABA), gammalon, glutamate, glutamic acid decarboxylase (GAD), *Lactobacillus brevis* GABA100, Pharma-GABA, picamilon (nicotinyl-g-aminobutyric acid), succinic semialdehyde dehydrogenase (SSADH), γ-aminobutyric acid.
- **Note**: Gamma-aminobutyric acid (GABA) should not be confused with gamma-hydroxybutyric acid (GHB), an analog of GABA that also functions as a neurotransmitter in the brain (1). While it may be used to treat alcohol addiction, GHB itself carries a risk of abuse (2). GHB is often used recreationally and is commonly known as the "date rape" drug.

5-Hydroxytryptophan (5-HTP):

- *Griffonia simplicifolia* (syn. *Bandeiraea simplicifolia* Benth.), L-5-HTP, L-5-hydroxytroptophan, Natrol® 5-HTP, Natural Factors® 5-HTP, oxitriptan, Tript-OH®, tryptophan.
- **Note**: 5-HTP ($C_{11}H_{12}N_2O_3$) should not to be confused with tryptophan ($C_{11}H_{12}N_2O_2$).

Melatonin:

- 5-Methoxy-N-acetyltryptamine, 6-sulfatoxymelatonin, acetamide, agomelatine, aMT6s, antioxidant, BMS-214778, beta-methyl-6-chloromelatonin, CAS 73-31-4, hypnotic, indole, luzindole, mel, MEL, melatonine, MLT, MT, N-acetyl-5-methoxytryptamine, N-2-(5-methoxyindol-3-ethyl)-acetamide, neurohormone, ramelteon (CAS 196597-26-9, TAK-375).

CLINICAL BOTTOM LINE

Brief Background:

- **Dream Water®**: Dream Water® is a brand of noncaloric functional products that are marketed as dietary supplements to safely promote relaxation and enhance sleep. Introduced in late 2009 after two years of research and development, Dream Water® products contain a propriety formulation of naturally occurring substances that are commonly used for their purported anxiolytic (calming) and sleep-promoting effects: gamma-aminobutyric acid (GABA), melatonin, and 5-hydroxytryptophan (5-HTP).
- **Gamma-aminobutyric acid (GABA)**: GABA is a nonprotein amino acid that is the principle inhibitory neurotransmitter in the mammalian central nervous system (3). Most of the immediate synaptic inhibitory effects of GABA are mediated by the GABA(A) class of ligand-gated ion channel receptors; thus, many pharmacological agents (including alcohol and psychoactive drugs)

exert anxiolytic, analgesic, anticonvulsant, and sedative effects by modulating GABA(A) receptor activity (4) or by blocking its reuptake (5).

- For many dietary supplements that are used widely for enhancing memory and reducing insomnia, the effects may be achieved through modulating endogenous GABA. These include 5-HTP, hop (*Humulus lupulus*), kava (*Piper methysticum*), lemon balm (*Melissa officinalis*), passion flower (*Passiflora* spp.), skullcap (*Scutellaria* spp.), and valerian (*Valeriana officinalis*) (6).
- A vast body of research has been devoted to the pharmacological effects of endogenous GABA and agents that mimic or potentiate the effects of GABA, including drugs and herbs. In the 1970s and 1980s, synthetic GABA (called aminalon in Russia and gammalon in Japan) was examined as a treatment for various disorders (including autonomic, cardiovascular, and neurological disorders).
- Because endogenous GABA has known relaxant effects (7), supplemental GABA is commonly taken to promote relaxation and as a sleep aid. GABA has also been shown to increase growth hormone (GH) secretion in humans when taken orally; thus, GABA is popularly used as a body building supplement.
- **5-Hydroxytryptophan (5-HTP)**: 5-HTP is the precursor of the neurotransmitter serotonin. It is obtained commercially from the seeds of the plant *Griffonia simplicifolia*.
- 5-HTP has been suggested as a treatment for many conditions such as stress, anxiety, panic attacks, and pain. Anxiolytic effects of various dietary supplements, including 5-HTP, have been discussed in a review (6). It has also been suggested that 5-HTP reduces carbohydrate cravings and controls appetite.
- There is some research to support the use of 5-HTP in treating cerebellar ataxia, headache, depression, psychiatric disorders, and fibromyalgia, and as an appetite suppressant or weight-loss agent. There is also some evidence from clinical case studies that 5-HTP may improve sleep.
- **Melatonin**: Endogenous melatonin is an indole neurohormone produced in the brain by the pineal gland, from the amino acid tryptophan (8), and day-night changes in synthesis are regulated by serotonin N-acetyltransferase (9). The synthesis and release of melatonin are stimulated by darkness and suppressed by light, suggesting the involvement of melatonin in circadian rhythm and regulation of diverse body functions. Levels of melatonin in the blood are highest prior to bedtime.
- Melatonin acts on MT(1) and MT(2) melatonin receptors located in the hypothalamic suprachiasmatic nuclei, the site of the body's master circadian clock. Melatonin may reset disturbed circadian rhythms and can promote jet lag recovery and other circadian rhythm sleep disorders, including delayed sleep phase syndrome and work shift sleep disorder (10; 11).
- Administration of exogenous melatonin has been used for a variety of medical conditions, most notably for disorders related to sleep, such as jet lag, delayed sleep phase syndrome (DSPS), and insomnia, for which there exists an ample body of research.
- Many of melatonin’s proposed therapeutic or preventive uses are based on its antioxidant activity (12-47).
- New pharmacological agents that block the effects of melatonin are in development, such as BMS-214778 or luzindole, and may have uses in various disorders (48-50).

Expert Opinion and Historic/Folkloric Precedent:

- **Gamma-aminobutyric acid (GABA)**: GABA is likely safe to use for short-term, low-dose treatments. The prevailing expert opinion is that the known effects of endogenous GABA in neural tissues are generally not replicated with exogenous GABA supplementation because it does not cross the blood-brain barrier. However, some clinical studies have shown oral GABA supplementation to reduce anxiety (51; 52) and improve sleep (51).
- Because many mood disorders have been associated with low plasma levels of GABA (53), supplementation with exogenous GABA has been suggested for disorders such as anxiety and depression (54).
- As a food additive, GABA (PharmaGABA™ produced by Pharma Foods International Co. Ltd., Kyoto, Japan) has a Generally Recognized as Safe (GRAS) notice on file with the United States Food and Drug Administration (FDA).
- **5-Hydroxytryptophan (5-HTP)**: There has been recent interest in the use of 5-HTP as a precursor therapeutic agent to increase serotonin production.
- 5-HTP has orphan drug status for the treatment of post-anoxic myoclonus (Lance-Adams syndrome), a rare complication of successful cardiopulmonary resuscitation.
- Naturopathic practitioners have recommended taking 50-100mg of 5-HTP three times daily for antidepressant effects. It is recommended that 5-HTP be taken at night to reduce daytime drowsiness.
- **Melatonin**: Melatonin is widely recommended for various sleep disorders and for prevention of jet lag. In addition, it is used in conditions believed to be associated with low levels of endogenous melatonin, such as aging, sleep disorders in children, and affective disorders. It has also garnered attention as possibly playing a role in or serving as a treatment for chronic inflammatory diseases (55), cancer (56), and hypertension (57), as well as an antioxidant therapy to counter aging and a variety of metabolic diseases (58).
- A review by Bjorvatn and Pallesen outlined how to estimate circadian rhythm based on a careful patient history and use this estimate to administer melatonin or light to treat delayed sleep phase disorder, advanced sleep phase disorder, free-running, irregular sleep-wake rhythm, jet lag disorder and shift work disorder (59).

Brief Safety Summary:

Dream Water®:

- **Likely safe**: When used in recommended doses by healthy adults who are not pregnant or nursing.
- **Possibly safe**: When used under medical supervision by adults taking medications with no known interactions with the components of Dream Water®.
- **Note**: The manufacturer warns against use by children or pregnant or nursing women due to the lack of safety information, and driving or operating machinery after taking Dream Water®. It is not recommended to take more than one dose in any 24hr period.

Gamma-aminobutyric acid (GABA):

- **Likely safe**: When ingested in amounts that are biosynthesized in plant foods. These may include fava beans (60), tomatoes (61; 62), sunflower (63), soybeans (64), GABA-enriched rice (65); or in fermented foods such as cabbage (kimchi) (66; 67), fermented milk (68), and fermented fruit juice (69).
- **Possibly safe**: When used in recommended oral doses for short-term supplementation. In clinical studies, oral GABA has been well tolerated (68; 70-72); side effects have been mostly minor.

5-Hydroxytryptophan (5-HTP):

- **Possibly Safe**: When used orally and short-term (up to one year) in recommended doses for cerebellar disorders (73) or depression (74). When used orally and short-term (up to 90 days) in

recommended doses for fibromyalgia (75); (up to four months) in recommended doses for headache (76); (up to 12 weeks) in recommended doses for obesity (77); (up to 12 weeks) in recommended doses for psychiatric disorders (78). When 5-HTP 4.5mg/kg daily is used in children for up to four months for headache (79).

Melatonin:

- **Likely safe**: When used orally for up to two years at a dose of 5mg daily (80).
- **Possibly safe**: When used in doses up to 40mg for short periods of time. When beta-methyl-6-chloromelatonin is used orally at doses up to 100mg based on a study in eight healthy men; some minor side effects were noted, but causality is unclear (81).

DOSING/TOXICOLOGY

General:

- Doses may be based on those most commonly used in available trials, or on historical practice. However, with natural products it is often not clear what the optimal doses are to balance efficacy and safety. Preparation of products may vary from manufacturer to manufacturer, and from batch to batch within one manufacturer. Because it is often not clear what the active component(s) of a product is, standardization may not be possible, and the clinical effects of different brands may not be comparable.

Standardization:

- There is no well-known standardization for gamma-aminobutyric acid (GABA), 5-hydroxytryptophan (5-HTP), or melatonin. For melatonin, experts note that many brands contain impurities that cannot be characterized, as well as dissimilar amounts of actual hormone. In 2002, Consumer Lab evaluated 18 melatonin-containing supplements (15 quick-release and three time-release products), of which 12 were melatonin-only products. It was reported that 16 of the 18 products contained between 100-135% of the claimed amount of melatonin, one rapid-release product contained only 83% of the claimed amount of melatonin, and another rapid-release product contained a small amount of lead (slightly more than 0.5mcg per daily recommended serving size of melatonin). Among the 12 melatonin-only products that "passed" these standards are: Nature's Bounty® Melatonin 1mg and 3mg tablets, Puritan's Pride® Inspired by Nature® Melatonin 3mg tablets, Twinlab® Melatonin Caps, Highest Quality, Quick Acting 3mg tablets.

Dosing:

Adult (age ≥18):

Oral:

- **Dream Water®:**
- **General**: Dream Water® is available in 8oz "drink" doses and 2.5oz "shot" doses. Exceeding one dose in a 24hr period is not recommended.

- **Gamma-aminobutyric acid (GABA):**

- **General**: Secondary sources suggest taking 250-500mg GABA three times daily on an empty stomach or taken only at bedtime (as GABA may induce sleepiness). Doses should not exceed 750mg, as higher amounts may induce anxiety and insomnia.
- **Insomnia**: GABA is popularly used in oral doses of 500-1000mg before sleep.
- **Relaxation/stress/anxiety**: For relaxant effects, GABA is popularly used at 750mg daily in up to three divided doses.
- Healthy Japanese volunteers received an acute dose of 200mL distilled water with 100mg GABA produced by lactic acid bacteria fermentation (Pharma-GABA, Pharma Foods International Co., Japan) (52).
- An oral dose of 50mg GABA in normal female volunteers was associated with "lack of alertness" (82).

- **5-Hydroxytryptophan (5-HTP):**
- **General**: Most randomized, controlled trials have administered 5-HTP at low doses and for short durations. However, case series have demonstrated tolerability at doses as high as 1,600mg daily (83) or 16mg/kg daily over 12 months (73). In one study it was recommended to initiate therapy at low doses (50mg three times daily) and increase the dosage gradually to minimize side effects such as nausea (84). Enteric-coated tablets are recommended to increase absorption and minimize gastrointestinal side effects (85). Secondary sources have recommended 50-100mg three times daily
- **Sleep disorders**: Oral loading with 5-HTP has been used to treat the REM fragmentation in a group of alcoholics who were abstinent following acute ethanol withdrawal (86).

- **Melatonin:**
- **General**: Melatonin is available in doses ranging from 0.5mg (500mcg) to 10mg. Dosing has not been clearly established for melatonin, as it is believed that responses to oral melatonin may vary widely among different individuals. Some experts recommend starting at lower doses of melatonin (less than 1mg) and adjusting the dose, either lower or higher, within the manufacturer recommended doses. Many experts maintain that timing of melatonin supplementation may be more critical than the dose level, and recommend that doses be taken one to three hours before desired sleep time.
- **Anxiety (preoperative)**: Melatonin treatment delivered either singly or in combination with other sedatives prior to surgery has been studied in dosages ranging from three to 10mg and/or 0.1 to 0.5mg/kg (47; 87-91).
- **Circadian rhythm entraining (in blind persons)**: A dose of 5mg delivered daily has been studied (92). A dose of 0.5mg daily under a regimen lasting 26-81 days has also been investigated (93).
- **Delayed sleep phase syndrome (DSPS)**: Melatonin was most commonly administered daily in the hours preceding the desired sleep period for durations of two weeks to three months (94-99). Dosages ranged from 0.3mg up to 6mg; however, the most frequent dose was 5mg.
- **Insomnia (elderly)**: Studies have evaluated melatonin taken by mouth, daily, at and up to 120 minutes prior to bedtime for insomnia in the elderly (100-106). Compared to placebo and fast-release melatonin, sleep maintenance and initiation were improved following a two-month treatment using 1mg sustained-release melatonin treatment (103; 104). Treatment was most often administered for several weeks though some studies continued for several months (107; 108). Low doses (0.1 to 0.3mg taken nightly) appear to be as equally effective as higher doses (three to 5mg nightly) (109).
- **Jet lag**: Melatonin is usually started on the day of travel (close to the target bedtime at the destination), then taken every 24 hours for several days. Various doses have been used and studied, including low doses between 0.1-0.5mg (110; 111), a more common dose of 5mg (110-118), and higher doses of 6-8mg (119; 120). Overall, 0.5mg appears to be slightly less effective

than 5mg for improvement of sleep quality and latency (121), although this area remains controversial and other research suggests no statistically significant differences (119; 122). Slow-release melatonin may not be as effective as standard (quick release) formulations (111) for sleep onset, but may be more effective for sleep maintenance. If the dose is taken too early in the day, it may result in excessive daytime sleepiness and greater difficulty adapting to the destination time zone. Formulations were rarely specified; however, one study reported using Circadin®, a pharmaceutical grade time-released formulation of melatonin (Neurim Pharmaceuticals, Tel Aviv, Israel).

- **REM sleep behavior disorder**: One study administered 3-9mg of melatonin daily (123). A case report of one patient reported a 3mg dose (124).
- **Sleep disturbance**: Studies have evaluated 3mg of melatonin taken nightly by mouth for four weeks (125), as well as 9mg daily for 22-35 months (126) in patients with Alzheimer's disease. One study examined a 3mg evening dose of melatonin (127), while another employed a flexible dose regimen with a mean dose of 5.4mg in hospitalized and ill patients (128). Varying regimens have been studied with dosages ranging from 2.5mg to 10mg and treatment duration from three weeks to 35 months in patients with Alzheimer's disease (AD) (125; 126; 129-131). One study examined a 5mg dose of melatonin administered in combination with light exposure for 10 weeks in patients with AD (132). One study used 3mg for four weeks in patients with asthma (133). Regimens in individuals with depression include: 0.5mg daily at 1700h for six days, 2mg nightly before bedtime for three weeks, 3mg for 21 days at bedtime, and 5mg daily for two weeks followed by 10mg for another two weeks (126; 134-136). Studies have evaluated 3mg and 10mg of melatonin taken nightly by mouth in individuals with bipolar disorder (137). Another study administered melatonin for four weeks in conjunction with fluoxetine (138). One study administered five or 50mg of melatonin for two weeks in patients with Parkinson's disease (139), while another used 3mg daily one hour before bedtime for four weeks (140). Study durations ranged from 15 days to 12 weeks with doses of 3-12mg in individuals with psychiatric disorders (137; 141-144). Melatonin was administered daily, generally before the desired rest period. Two doses (five and 10mg) have been documented for the treatment of sleep disturbance related to tuberous sclerosis complex (145; 145).
- **Sleep enhancement in healthy people**: Doses studied ranged from 0.3 to 75mg (120; 146-157). Melatonin was generally administered daily in the evening hours immediately preceding the desired rest period, though some studies investigated the effect of earlier dosing on nighttime sleep (158; 159), as well as day time naps (160). Most studies occurred over the course of several days, while some ranged to multiple weeks (161; 162).
- **Work shift sleep disorder**: Regimens studied included doses which ranged from 1.8mg to 10mg and were generally administered daily prior to daytime sleep following a night shift schedule (11; 163-172).

Children (age <18):

- Not recommended due to lack of sufficient data.

Pregnancy & Lactation:

- **Dream Water®**: Not recommended for use in pregnant or lactating women due to lack of sufficient data.
- **Gamma-aminobutyric acid**: Not recommended due to lack of sufficient data.
- **5-Hydroxytryptophan (5-HTP)**: Not recommended due to lack of sufficient data.
- **Melatonin**: Not recommended due to lack of sufficient data.

INTERACTIONS

GABA/Herb/Supplement Interactions:

- **5-HTP**: 5-HTP is a precursor to serotonin, which is known to potentiate GABAergic effects (173).
- **L-Arginine**: In electrophysiological experiments, L-arginine increases membrane currents induced by exogenous GABA (174). The clinical relevance of this interaction is unclear.
- **Magnesium**: In electrophysiological experiments, magnesium potentiates GABAergic synaptic currents mediated by GABA(A) receptors (175). Theoretically, magnesium may increase the effects of GABA supplementation, but the clinical relevance of this potential interaction is unclear.
- **Phosphatidylserine**: Phosphatidylserine (PS) supplementation appears to increase the uptake of intraperitoneally administered GABA into nerve terminals by over 40% (176), and PS been shown to potentiate the anticonvulsant effects of equal amounts of exogenous GABA administered to rats (177). Thus, clinical studies have examined GABA-PS for the treatment of epilepsy (71; 178).
- **Tea**: Tea has been shown to enhance the GABA(A) receptor response (179). However, some tea components have been shown to inhibit the GABA(A) receptor response in cultured cells (180), and may thus counter the effects of exogenous GABA.
- **Valerian**: The anxiolytic effects of valerian are potentiated by GABAergic mechanisms (181). In rats, administration of valerian extracts with exogenous GABA (3.6mcg/kg) led to increased anxiolytic effects (182).
- **Vitamin B6**: Some GABA supplements are formulated to include vitamin B6, which purportedly decreases drowsiness induced by GABA.
- **Zinc**: In electrophysiological experiments, zinc inhibits GABAergic synaptic currents, presumably through allosteric modulation of GABA(A) receptor gating (183). Theoretically, zinc may reduce the effects of GABA supplementation, but the clinical relevance of this potential interaction is unclear.

5-HTP/Herb/Supplement Interactions:

- **Magnesium**: Magnesium is involved in the conversion of 5-HTP to serotonin. Concomitant use may increase serotonin levels.
- **Melatonin**: In theory, L-tyrosine, adenosyl-L-methionine, tryptophan, vitamin B6, chromium, melatonin, niacin, SAMe, St. John's wort, herbs and supplements with monoamine oxidase inhibitor (MAOI) activity, and magnesium may increase the effects associated with 5-HTP.
- **Niacin**: Niacin is involved in the conversion of 5-HTP to serotonin. Concomitant use may in theory increase serotonin levels.
- **SAMe**: When used in combination with SAMe, 5-HTP may result in additive effects (anecdotal).
- **Vitamin B6**: Vitamin B6 is involved in the conversion of 5-HTP to serotonin. Theoretically, concomitant use may increase serotonin levels.

MECHANISM OF ACTION

Pharmacology:

Dream Water®:

- **Constituents**: Dream Water® products contain a propriety formulation of gamma-aminobutyric acid (GABA), melatonin, and 5-hydroxytryptophan (5-HTP), a sweetener (sucralose), and artificial coloring. All Dream Water® products are certified kosher and produced by methods consistent with good manufacturing practice (GMP) guidelines.
- **General**: The purported anxiolytic and sleep-promoting effects of Dream Water® may be attributed to its active constituents (GABA, melatonin, and 5-HTP).

Gamma-aminobutyric acid:

- **General**: Gamma-aminobutyric acid (GABA) was originally identified as a natural bacterial fermentation product of decaying material (184). It has since been found to be a metabolic product of numerous organisms, including bacteria, yeast and other fungi, algae, and plants (185).
- Several studies have examined growth conditions that maximize GABA biosynthesis and accumulation in plant foods, such as fava beans (60), tomatoes (61; 62), sunflower (63), and soybeans (64). Transgenic rice expressing a seed-specific glutamate decarboxylase (GAD) gene has been developed to produce GABA-enriched rice (65). GABA has also been produced in various food products through fermentation by certain strains of lactic acid bacteria, such as *Lactobacillus brevis* GABA100 (69) or *Lactobacillus casei* strain Shirota and *L. lactis* YIT 2027 (68).
- As a neurotransmitter, the inhibitory effects of GABA are mediated by GABA(A) and GABA(B) receptors (186). Many GABAergic drugs target the ligand-gated chloride channels of the GABA(A) receptors.
- **Anxiolytic effects**: Although endogenous GABA has well established relaxant effects (7), the effects of exogenous GABA are not as clear. When administered orally or systemically, it does not efficiently cross the blood brain barrier (185). An oral dose of 50mg GABA in normal female volunteers was associated with "lack of alertness" (82). On the other hand, intravenous doses of GABA (0.1 to 1.0mg/kg) have been shown to induce anxiety, dysphoria, and mood disturbance in a dose-dependent manner in both normal volunteers and euthymic bipolar patients (187).
- **Sleep-promoting effects**: The GABA(A) receptors have an established physiological role in sleep. Many sedative pharmacological agents used to treat insomnia, such as zolpidem (Ambien®), target the GABA(A) receptors (188). GABA agonists appear to exert sleep-promoting effects at the hypothalamus, a region of the brain associated with sleep (189). However, the therapeutic use of GABA has not been conclusively demonstrated for enhancing or promoting sleep. This is due in part to the fact that GABA does not efficiently cross the blood-brain barrier (185).

5-Hydroxytryptophan (5-HTP):

- **General**: Serotonin (5-HT) is a neurotransmitter synthesized centrally from precursors; tryptophan, an essential amino acid, is converted to produce 5-hydroxytryptophan (5-HTP) via tryptophan hydroxylase, which is subsequently decarboxylated to serotonin (5-HT). Therefore, 5-HTP can elevate extracellular serotonin levels. This tight relationship of 5-HTP with serotonin has yielded interesting correlations, including the inhibition of both focal and generalized seizures by 5-HTP (190) and improved locomotor function and survival in a mouse model of amyotrophic lateral sclerosis (ALS) (191). Based on animal study, systemic administration of 5-HTP allowed frontal cortical serotonin response to stress (192). In animals, 5-HTP increased serotonin in all five brain areas; physiological effects were dependent on whether mice were SERT -/- (exaggerated serotonin syndrome behaviors) or SERT +/+ (193).
- Several studies have shown that 5-HTP induces an increase in plasma cortisol (194-197). The increase in cortisol has been blocked by administration of ritanserin, a $5\text{-HT}_2/5\text{-HT}_{1C}$ antagonist. Thus, the increase in cortisol may be mediated by a serotonergic mechanism (196).
- **Calming effects**: Preclinical studies using 5-HTP were included in a meta-analysis of animal studies investigating the effects of agents used to modulate levels of serotonin on symptoms of aggression (198). It was determined that increased serotonin did have an inhibitory effect on aggression in certain strains of animals.
- **Sleep-promoting effects**: In animals, intraperitoneal 5-HTP at dark onset increased non-rapid eye movement sleep (199).

Melatonin:

- **General**: Melatonin acts on MT(1) and MT(2) melatonin receptors located in the hypothalamic suprachiasmatic nuclei, the site of the body's master circadian clock (10). In animal experimental models, melatonin has antidopaminergic effects; repeated administration of melatonin may modify the plasticity of behaviors mediated by central dopaminergic systems (200).
- Time of melatonin administration is important. When administered orally in the morning, melatonin delays circadian rhythms, but advances circadian rhythms when administered in the afternoon or early evening (201).
- Multiple studies performed to date on the functions of endogenous melatonin have utilized exogenous melatonin, often at high doses. However, the most reliable data are obtained at low doses of exogenous melatonin (about 300mcg), at which plasma levels are within a physiological range (202-205). It is not entirely clear what relationships exist between melatonin secretion and pharmacological effects observed at higher concentrations (202-205).
- While measuring endogenous melatonin, some authors have not found a link between melatonin secretion and the sleep-waking cycle in humans (206). It has been suggested by some that natural sleep is largely determined by a functioning circadian system without melatonin involvement (202-205).
- **Sleep-promoting effects**: Melatonin, administered either day or night in doses beyond the physiological range, appears to elicit a hypnotic effect. Exogenous melatonin exerts hypnotic effects primarily when circulating levels of endogenous melatonin are low (152). Even very low doses can cause sleep when ingested before endogenous melatonin onset (147; 154; 158; 159; 207), although some studies have failed to confirm this finding (149). Melatonin has been shown to decrease the amount of anesthesia required during surgery (89; 91; 208; 209). Melatonin seems to potentiate the effects of gamma-aminobutyric acid (GABA) and benzodiazepines, and quality of sleep may be improved with a combination of melatonin and benzodiazepines (210). Melatonin may interact directly with the GABA-benzodiazepine-chloride ion channel (211; 212), but not with the benzodiazepine receptor (213). As seen in functional magnetic resonance imaging, melatonin may play a role in priming sleep-associated brain activation patterns in anticipation of sleep (214).
- Randomized clinical trials have demonstrated some effect of melatonin on circadian rhythm entraining (215-217) and that endogenous circadian rhythmicity influences autonomic control of HR and that the timing of these endogenous rhythms can be altered by extended sleep/rest episodes and associated changes in photoperiod, as well as by melatonin treatment (218) with no evidence of changes in the duration of endogenous melatonin secretion or pituitary/gonadal hormones (219). In blind individuals, disturbances of sleep and sleep-related neuroendocrine patterns can be caused by the absence of light cues. In individuals who are completely blind, a single administration of a pharmacological dose (5mg) of melatonin can improve sleep function by synchronizing the inhibition of pituitary-adrenal activity with central nervous sleep processes (92).
- Exogenous melatonin is able to shift circadian rhythms, as well as endogenous melatonin secretion and core body temperature (220-223). Light appears to be a stronger regulator of circadian rhythm than melatonin itself (201; 224-230). The time of administration of melatonin is of critical importance since it may cause both phase-delay and phase-advance. For phase-delay, melatonin should be administered in the early morning; for phase-advance, melatonin should be administered one to two hours before 2100 hours (201).

Pharmacodynamics/Kinetics:

- **Dream Water®**: According to the manufacturer, the onset of action for Dream Water® is approximately 30 minutes after ingestion.
- **Gamma-aminobutyric acid (GABA)**: GABA is synthesized in tissues (both neural and non-neural) by the enzyme glutamic acid decarboxylase (GAD) (186). GAD is present in many tissues besides the brain (such as liver, kidney, pancreas, testis, ova, erythrocytes, and the gastrointestinal tract), and synthesizes GABA from glutamic acid. Systemic GABA does not cross the blood-brain

barrier efficiently; thus, virtually all of the GABA found in the brain is synthesized *in situ* by GAD (231). Outside of the central nervous system, GABA is synthesized by gut bacteria (232).

- GABA is catabolized by the enzymes GABA-transaminase (GABA-T) and succinic semialdehyde dehydrogenase (SSADH) (186). GABA-T is widely distributed and catalyzes GABA degradation via transamination to succinic semialdehyde (SSA), which is further catabolized to succinate by SSADH. Succinate is then able to enter the tricarboxylic acid cycle (TCA).
- Outside of the central nervous system, GABA is primarily catabolized in the liver (232). In liver failure, the blood-brain barrier becomes more permeable to GABA and may lead to hepatic encephalopathy (232).
- The synaptic effects of GABA are terminated upon its reuptake into nerve terminals or nearby cells. This is mediated by GABA transporter (GAT) proteins, of which there are five known subtypes: GAT1, GAT2, GAT3, betaine/GABA transporter 1, and rB16a (233). Inhibition of GABA uptake is the mechanism of action for some anticonvulsant and anxiolytic agents. Tiagabine (Gabatril®), a selective GAT1 inhibitor, is currently available in the United States as an anticonvulsive (5).
- **5-Hydroxytryptophan (5-HTP)**: 5-HTP is well absorbed after oral administration; gastrointestinal absorption is consistent with first order kinetics (84). The time from administration of 5-HTP with carbidopa to maximum measured 5-HTP plasma concentration is one to two hours (84; 234). In animals, 5-HTP (but not serotonin) induced the development of microvilli in the gut epithelium (235). 5-HTP specifically induced actin remodeling and decreased phosphorylation of extracellular signal-regulated kinase (ERK) in the gut.
- 5-HTP crosses the blood-brain barrier; the brain concentration of 5-HTP can be increased by the administration of carbidopa, which diminishes the peripheral conversion to serotonin (236; 237). In the dose range of 150-600mg daily, combined with 150mg carbidopa, the concentration of 5-HTP in plasma increases, according to linear kinetics (84; 236).
- In a study of healthy Asian males, L-5-hydroxytryptophan (L-5HTP) increased cortisol AUC (0-3 hours), and a 200mg dose of L-5HTP significantly augmented the prolactin and cortisol response AUC (0-3h) to 20mg oral citalopram (238).
- In a patient with non-communicating hydrocephalus and HIV-1 infection, 5-HTP levels were higher in cerebrospinal fluid extracted from different sites of the cerebral cavity than cerebrospinal fluid extracted from patients with non-communicating hydrocephalus but no HIV-1 infection (239). In animals, 5-HTP increased serotonin in all five brain areas (193).
- 5-HTP is the immediate precursor of serotonin. 5-HTP is converted to serotonin by aromatic-L-amino-acid decarboxylase (240; 241). Metabolites of 5-HTP include 5-HT and 5-hydroxyindoleacetic acid (5-HIAA).
- The half-life of 5-HTP is reported to be 2-4 hours (84; 242; 243). 5-HTP is eliminated renally. In humans, 5-HTP increased serotonin excretion in some subjects (244).
- **Melatonin**: When administered in gelatin capsules, melatonin reaches peak levels after 60-150 minutes (350 to 10,000 times higher than nighttime concentration) (202-205).
- Melatonin can be monitored by its serum metabolite, 6-sulphatoxymelatonin by radioimmunoassay (202-205), and in saliva (202-205), although melatonin concentrations measured in saliva do not consistently reflect absolute concentrations in blood (202-205).
- Melatonin secretion increases after the onset of darkness, peaks in the middle of the night (between 2 and 4 am) then gradually decreases (202-205). Pharmacological effects appear to depend on the time of administration. Research shows that the time-delay between administration and maximal effect varies linearly from 220 minutes at noon, to 60 minutes at 9pm (202-205).
- The calculated oral bioavailability of melatonin is three to 76 percent (202-205). Some foods, such as oats, sweet corn, rice, ginger, tomatoes, bananas, and barley, contain small amounts of melatonin and may increase melatonin levels (202-205). Melatonin can be delivered transdermally in humans (202-205), or transmucosally to mimic physiological activity (202-205). Melatonin is highly lipophilic (202-205) and readily passes through the blood brain barrier (202-205).

- Melatonin is primarily inactivated by 6-hydroxylation within the liver, followed by conjugation and excretion as the sulfate or glucuronide. First-pass hepatic metabolism is extensive (up to 60% of oral dose) (202-205). 6-sulphatoxymelatonin is an inactive metabolite of melatonin (202-205), In patients with liver cirrhosis, melatonin levels are elevated compared to controls (202-205).
- Up to 85% of 6-hydroxymelatonin sulfate is excreted in urine; 6-sulphatoxymelatonin levels during melatonin treatment correlate with a normal circadian rhythm of excretion (202-205). In normal children, total 6-sulfatoxymelatonin excretion ranged from 11.1 to 40.2mcg (mean 19.0mcg, SD 7.4mcg) (202-205).
- The physiologic half-life of melatonin is approximately 30-60 minutes (202-205). Nutritional supplements do not appear to mimic the physiologic release of melatonin, as dissolution testing has ranged from 4-12 hours (202-205), with controlled release formulations available (202-205).

HISTORY

- **Dream Water®**: Dream Water® was launched on December 7, 2009 by Sarpes Beverages after two years of research and development. The non-caloric flavored products are composed of a proprietary formula that includes gamma-aminobutyric acid (GABA), melatonin, and 5-hydroxytryptophan (5-HTP). The Dream Water® 8oz. product retails for $2.49 per bottle or $30 for a pack of 12. The 2.5oz Dream Water® shot, designed to be suitable for airline travel, retails for $2.99 per bottle.
- Dream Water® first became available in the Duane Reade drug store chain in New York City and expanded to North Carolina, South Carolina, and Georgia in early 2010 with Sam's Mart as the distributor. In March 2010, Dream Water® became available in GNC locations in New York City.
- **Gamma-aminobutyric acid (GABA)**: GABA was reportedly first synthesized in 1883 (245) and was identified as a bacterial fermentation product of decaying material in 1910 (184). It has since been found to be a metabolic product of numerous organisms, including bacteria, yeast and other fungi, algae, and plants (185). GABA naturally occurs in a number of fermented food products, including fermented cabbage (kimchi) (66; 67), fermented milk (68), and fermented fruit juice (69).
- In 1950, several independent studies identified large quantities of GABA in the mammalian brain (246-248). Glutamate was determined to be the precursor to GABA (248). By the late 1950s, it became apparent that GABA served some important neurophysiological function (185).
- By the 1970s, endogenous GABA was widely recognized as the primary mediator of inhibitory synaptic responses in the nervous system of animals (249). In the 1970s and 1980s, synthetic GABA (called aminalon in Russia and gammalon in Japan) was examined as a treatment for various disorders.
- GABA has recently gained interest as a dietary supplement in a wide variety of uses. Several functional foods enriched in GABA are currently available. These include GABA-rich soy sauce, GABA rice, and GABA-supplemented beverages. Several studies have aimed to maximize GABA biosynthesis and accumulation in plant foods, such as fava beans (60), tomatoes (61; 62), sunflower (63), and soybeans (64). Transgenic rice expressing a seed-specific glutamate decarboxylase (GAD) gene has been developed to produce GABA-enriched rice (65).
- **5-Hydroxytryptophan**: 5-HTP is extracted from the seed of the African *Griffonia simplicifolia* plant. This method of isolation is in contrast to L-tryptophan, which is produced by bacterial fermentation. 5-HTP has been used clinically since the 1970s, and has become widely available over the counter in the past several years.
- **Melatonin**: The pineal gland, which secretes melatonin, was originally defined as the "seat of the soul" by Descartes (250) It was not until the early 1900s that physicians indentified the pineal gland as belonging to the endocrine system. Aaron Lerner, a dermatologist from Yale, and his team of researchers discovered melatonin in 1958 when investigating its treatment potential for vitiligo (251).

- Melatonin's sedative properties emerged from research in the 70s and 80s, leading to its widespread use in the treatment of sleep disorders.
- Melatonin's popularity grew dramatically in the United States following 1995 reports of its ability to promote sleep and alleviate jet lag, perhaps its best known application.
- Synthetic melatonin is sold in the United States as a dietary supplement. Small amounts of melatonin occur naturally in some foods such as bananas and rice. Some authors suggest that this categorization interferes with standardization and quality improvement of melatonin.

REVIEW OF THE EVIDENCE: DISCUSSION

Gamma-aminobutyric acid: Relaxation/stress/anxiety

- **Summary**: Although endogenous gamma-aminobutyric acid (GABA) has known relaxant effects (7), exogenous GABA may not be similarly effective because when administered orally or systemically, it does not efficiently cross the blood brain barrier (185). An oral dose of 50mg GABA in normal female volunteers was associated with "lack of alertness" (82). On the other hand, intravenous doses of GABA (0.1 to 1.0mg/kg) have been shown to induce anxiety, dysphoria, and mood disturbance in a dose-dependent manner (187).
- **Evidence**: Abdou et al. conducted two studies to examine the effect of orally administered GABA on relaxation and immune parameters during stress (52). One study was a randomized, placebo-controlled study of eight healthy volunteers (five males and three females, 25-20 years of age) with a history of acrophobia. The subjects were randomly assigned to receive either GABA treatment (dose unclear; presumed to be the same as in the accompanying study) or placebo in a single-blind fashion. Subjects then crossed a suspended pedestrian bridge to induce stress. Standardization, adverse effects, dropouts, and interactions were not discussed. In a previous unpublished study, GABA treatment significantly increased immunoglobulin A (IgA) levels in saliva; thus, salivary IgA was measured to indicate relaxation, stress, and immunity response. Mean IgA levels were determined and subjected to statistical analysis by unpaired Student's t-test. In the placebo group, salivary IgA levels were significantly lower in the middle and end of the bridge. However, in the GABA group, IgA levels were slightly lower in the middle of the bridge and significantly higher at the end of the bridge ($p<0.05$). The results suggested that GABA interferes with stress-induced reduction in immune parameters, and may even increase immunity. Weaknesses of this study include unclear methods of randomization, single-blind format, and lack of description of withdrawals.
- Another study by Abdou et al. was a controlled equivalence trial (52). Healthy Japanese volunteers of normal weight (n=13, seven males and six females, 21-35 years of age) participated in the study. Subjects did not have preexisting behavioral or medical conditions. The subjects refrained from food, water, or tobacco use two hours before the study. The treatment consisted of either 200mL distilled water only (control), or 200mL distilled water with either 100mg GABA produced by lactic acid bacteria fermentation (Pharma-GABA, Pharma Foods International, Japan) or 200mg L-theanine. Each subject received all three treatments separated by seven-day intervals. Standardization, adverse effects, dropouts, and interactions were not discussed. Five-minute electroencephalogram (EEG) recordings were acquired from resting subjects before and after (0, 30, and 60 minutes) each treatment. Mean alpha and beta waves (which are indicative of arousal, relaxation, concentration, stress, and anxiety) were calculated, and statistical analysis was done using unpaired Student's t-test. Compared to control, 100mg GABA significantly increased alpha waves but decreased beta waves ($p<0.05$). L-theanine treatment also increased alpha waves and decreased beta waves, but to a lesser extent than GABA. The authors concluded that GABA (sourced naturally from lactic acid bacteria fermentation) could reduce stress and improve concentration within one hour of administration. Caveats of this study were lack of randomization, double-blinding, or discussion of dropouts.

- An unpublished study conducted by Pharma Foods International (Kyoto, Japan) tested the effects of GABA on salivary markers of stress (reviewed in (51)). Thirteen volunteers were subjected to the same pedestrian bridge in the study by Abdou et al. (52). Subjects who were given an acute dose of 200mg natural-source GABA showed a 20% decrease in salivary levels of chromagranin A (an adrenal stress marker) compared to baseline values, whereas control subjects showed a 20% increase in salivary chromagranin A.

Gamma-aminobutyric acid: Sleep enhancement

- **Summary**: The GABA(A) receptors have an established physiological role in sleep; many sedative pharmacological agents used to treat insomnia, such as zolpidem (Ambien®), target the GABA(A) receptors (188). GABA agonists appear to exert sleep-promoting effects at the hypothalamus, a region of the brain associated with sleep (189). However, few studies have studied the therapeutic use of GABA for enhancing or promoting sleep. This is due in part to the fact that GABA does not cross the blood-brain barrier (185).
- **Evidence**: In an unpublished study conducted by Pharma Foods International (Kyoto, Japan), 100mg of natural-source GABA was shown to reduce sleep latency by 20% and increase deep sleep time by 20% (reviewed in (51)).

5-HTP: Relaxation/stress/anxiety

- **Summary**: Although 5-HTP has been proposed as a possible treatment for anxiety disorders, there are very few studies in humans. More research is needed to determine whether 5-HTP is an effective treatment for certain types of anxiety disorders and what dose may be safe and effective. The relaxing effects of 5-HTP, as well as other supplements with potential anxiolytic or mild relaxation properties, were discussed in a review by Weeks (6).

5-HTP: Sleep enhancement

- **Summary**: In animals, intraperitoneal 5-HTP at dark onset increased non-rapid eye movement sleep (199). There is insufficient evidence regarding the use of 5-HTP for sleep disorders. Additional studies are needed before a conclusion can be drawn.
- **Evidence**: Petre-Quadens et al. conducted a case series to determine the effect of 5-HTP on polygraphic total night sleep electroencephalographic (EEG), electro-oculographic (EOG) and electromyographic (EMG) recordings in six infants with Downs' syndrome (252). The infants received oral 5-HTP for periods extending from 12 to 36 months and the doses were adapted to the infants' ages and tolerance levels. Compared with normal age-related infants, the eye-movement (EM) density was significantly decreased in the non-treated infants with Downs' syndrome. In the 5-HTP-treated patients, the results in two were within the limits for normal age-related infants. Thus it was suggested that 5-HTP failed to induce any long-term differences in the EM frequencies. The authors suggested that long-lasting results included an increase in muscle tone and an improvement of motor behavior. This study is limited by lack of randomization, blinding, and control groups.
- Zarcone et al. conducted a case series to examine the effect of oral loading with 5-HTP on REM fragmentation in a group of alcoholics who were abstinent following acute ethanol withdrawal (86). Decreased fragmentation was found in the majority of subjects. In subjects with a low baseline REM efficiency (greater fragmentation), 5-HTP appeared to offer greater benefit vs. subjects who were less impaired initially. It was suggested that 5-HTP loading may partially reverse the decrement of serotonin observed during ethanol withdrawal. This study is limited by lack of randomization, blinding, and control groups.
- Two schizophrenic boys (ages seven and nine years) were selectively deprived of rapid eye movement (REM) sleep for two nights (253). Both patients were given oral 5-HTP in a dosage of 3mg/kg daily for eight days during which a second REM deprivation and recovery was studied. It was found that both subjects had a significantly greater amount of REM time during the post-

deprivation period as compared to baseline (p=0.029; p=0.014, respectively). This study is limited by lack of randomization, blinding, and control groups.

- **Select combination study (not included in Evidence Table)**: Shell et al. conducted a randomized placebo-controlled study to examine the effect of a combination amino acid formula (Gabadone™; containing 5-HTP as well as other amino acids) in 18 patients with sleep disorders (254). The main endpoints were sleep latency and duration of sleep as measured by daily questionnaires, as well as sleep quality as determined using a visual analog scale, and autonomic nervous system function as determined by heart rate variability analysis using 24-hour electrocardiographic recordings. Gabadone™ resulted in a decrease in the time to fall asleep (32.3 minutes vs. 19.1 minutes after treatment; p=0.01). There was no effect in the placebo group. The difference between the groups was statistically significant. The duration of sleep also significantly improved in the Gabadone™ group vs. the placebo group (p=0.01).
- **Case report**: Leu-Semenescu et al. published a case report involving the sleep and sleep-wake rhythms in a 28 year old man with a genetic deficiency in sepiapterin reductase leading to a combined deficit of serotonin and dopamine (255). The sleep, sleep-wake rhythms, CSF neurotransmitters, and melatonin profile in this patient were examined. Results were also reported after treatment with 5-HTP or levodopa. Before treatment, it was indicated that the patient had mild hypersomnia with long a sleep time (704 minutes), ultradian sleep-wake rhythm (sleep occurred every 11.8 ± 5.3 hours), organic hyperphagia, attention/executive dysfunction, and no depression. Supplementation with 5-HTP normalized serotonin metabolism in the CSF, reduced sleep time to 540 minutes, normalized his eating disorder and the melatonin profile, restored a circadian sleep-wake rhythm (sleep occurred every 24 hours), and improved cognition.

Melatonin: Jet lag

- **Note**: Due to the quantity of melatonin research, the Evidence Discussion paragraphs are limited to meta-analyses, systematic reviews, and clinical trials with strong methodological design.
- **Summary**: Several randomized, placebo-controlled human trials suggest that melatonin taken by mouth, started on the day of travel (close to the target bedtime at the destination) and continued for several days, reduces the number of days required to establish a normal sleep pattern, diminishes the time it takes to fall asleep ("sleep latency"), improves alertness, and reduces daytime fatigue. Melatonin has been used in combination with zaleplon, zopiclone, and temazepam to compare the drugs' hypnotic effects, and to observe drowsiness levels (120). Other research has attempted to determine optimal formulations in preparation for travel (256). Further well-designed trials are necessary to confirm these findings, to determine optimal dosing, and to evaluate use in combination with prescription sleep aids.
- **Systematic reviews**: Buscemi et al. conducted a systematic review of the efficacy and safety of exogenous melatonin in managing secondary sleep disorders and sleep disorders accompanying sleep restriction, such as jet lag and shiftwork disorder (257). Thirteen electronic databases were searched. Reference lists of relevant reviews, as well as a random sample of included studies, were reviewed. Abstracts of meetings of Associated Professional Sleep Society abstracts (1999 to 2003) were also searched. Medline and Embase were searched again in 2004 to identify more recent published studies. Randomized controlled trials were assessed using the Jadad Scale and criteria by Schulz et al. and non-randomized controlled trials by the Downs and Black checklist. One reviewer extracted data and another reviewer verified the data extracted. The inverse variance method was used to weight studies and the random effects model was used to analyze data. A range of doses were used in the various studies. The duration of administration varied from days to weeks. Dosage and duration of melatonin administration described a considerable amount of heterogeneity across studies. *Efficacy*: Nine trials (427 participants) (11; 111; 114; 118; 154; 167-169; 172) were included in the efficacy analysis for secondary sleep disorders. The median quality score was 4 out of 5 (Jadad score). There was no evidence that melatonin had an effect on sleep onset latency in people who had sleep disorders accompanying sleep restriction (-1.0 (-2.3 to 0.3) min). *Sleep onset latency*: Six randomized controlled trials with 97 participants showed no

evidence that melatonin had an effect on sleep onset latency in people with secondary sleep disorders (weighted mean difference -13.2 (95% confidence interval -27.3 to 0.9) min). *Safety*: Ten studies (487 participants) were included in the safety analysis. The most commonly reported adverse events were headaches, dizziness, nausea, and drowsiness. The occurrence of these outcomes was similar for melatonin and placebo.

- Herxheimer et al. conducted a systematic review to assess the effectiveness of oral melatonin taken in different dosage regimens for alleviating jet lag after air travel across several time zones (121; 258). Cochrane Controlled Trials Register, MEDLINE, EMBASE, PsychLit and Science Citation Index were searched electronically, and the journals 'Aviation, Space and Environmental Medicine' and 'Sleep' were searched by hand. Citation lists of relevant studies for other relevant trials were also searched. Principal authors of relevant studies were asked about unpublished trials. Randomized trials were included that analyzed airline passengers, airline staff or military personnel. Treatments compared oral melatonin with placebo or other medications. Outcome consisted of subjective rating of jet lag or related components, such as subjective well-being, daytime tiredness, onset and quality of sleep, psychological functioning, duration of return to normal, or indicators of circadian rhythms. Ten trials met the inclusion criteria (111; 113; 115-117; 119; 122; 259-261). All compared melatonin with placebo; one in addition compared it with a hypnotic, zolpidem. Nine of the trials were of adequate quality to contribute to the assessment; one had a design fault and could not be used in the assessment. Reports of adverse events outside trials were found through MEDLINE, 'Reactions Weekly', and in the WHO UMC database. Nine of the ten trials found that melatonin, taken close to the target bedtime at the destination (10pm to midnight), decreased jet lag from flights crossing five or more time zones. Daily doses of melatonin between 0.5 and 5mg are similarly effective, except that people fall asleep faster and sleep better after 5mg than 0.5mg. Doses above 5mg appear to be no more effective. The relative ineffectiveness of 2mg slow-release melatonin suggests that a short-lived higher peak concentration of melatonin works better. Based on the review, the number needed to treat (NNT) is 2. The benefit is likely to be greater the more time zones are crossed, and less for westward flights. The timing of the melatonin dose is important: if it is taken at the wrong time, or early in the day, it may cause sleepiness and delay adaptation to local time. The incidence of other side effects was reportedly low. Case reports suggest that people with epilepsy and patients taking warfarin may experience harm from melatonin.
- Paul et al. conducted a repeated measures, controlled crossover trial of 30 subjects to explore the effectiveness of lower doses of zopiclone and melatonin in inducing early circadian sleep and how the treatments impact the performance of aircrew (120). The subjects were given capsules of a placebo, 2mg sustained-release melatonin (Circadin®, a pharmaceutical grade time-released formulation of melatonin made by Neurim Pharmaceuticals in Tel Aviv, Israel), or zopiclone 5mg, all with an identical appearance. Objective measures include: sleep latency, wake after sleep time, total sleep time, time taken to get to sleep, number of awakenings, and time spent awake after having fallen sleep, using wrist actigraphy (Precision Control Design, Fort Walton Beach, FL). Fatigue, sleep quality and mood, drug effects/side effects, and amount of any alcohol ingested were measured subjectively using a self-reported questionnaire (using 7-point Likert scales). According to the actigraphic data, subjects slept longer while using melatonin ($p< 0.02$) and zopiclone ($p<0.005$) compared to placebo. Melatonin ($p<0.01$) and zopiclone ($p<0.003$) decreased sleep latency. Compared to placebo, subjects woke up less after having fallen asleep when taking melatonin ($p<0.004$) and zopiclone ($p<0.01$). Relative to placebo, subjects spent less time awake after sleep onset while taking melatonin ($p<0.01$) and zopiclone ($p<0.05$). There was no statistically significant difference between melatonin and zopiclone in total sleep time, time taken to get to sleep (latency), number of awakenings, or time spent awake after having fallen asleep. Subjects found it easier to fall asleep on melatonin ($p<0.0001$) and zopiclone ($p<0.001$) when compared to placebo. Relative to the placebo group, subjects woke up less and reported it easier to fall back asleep after awakening when using melatonin ($p<0.005$ and $p<0.0003$ respectively) and zopiclone ($p<0.001$ and $p<0.0003$ respectively). The quality of sleep was improved in the

melatonin (p<0.0003) and zopiclone (p<0.0004) groups compared to placebo. All of these findings were statistically significant. However, no statistically significant difference was shown between the zopiclone and melatonin groups in difficulty getting to sleep, reported number of awakenings, difficulty returning to sleep after awakening, or quality of sleep. Limitations of this study include a lack of a power calculation, randomization, adequate description of blinding process, and intention-to-treat analysis, as well as sub-optimal study design, length of study (just one dose, one day), and statistical interpretation. It is questionable whether these results can be extrapolated to the general population, as the sample was from an aircrew and predominantly male. Standardization, allergies/adverse effects, toxic effects, and interactions were not discussed.

Melatonin: Delayed sleep phase syndrome (DSPS)

- **Note**: Due to the quantity of melatonin research, the Evidence Discussion paragraphs are limited to meta-analyses, systematic reviews, and clinical trials with strong methodological design.
- **Summary**: Delayed sleep phase syndrome is a condition that results in delayed sleep onset, despite normal sleep architecture and sleep duration. Several randomized controlled studies have reported improvements in sleep latency. Non-randomized clinical trials have also been conducted (94; 99) and, overall, the results agree with those observed in the RCTs.
- **Meta-analysis**: Buscemi et al. conducted a systematic review to evaluate the efficacy and safety of exogenous melatonin in the management of primary sleep disorders (262). A number of electronic databases were searched. Bibliographies of included studies were searched by hand, and relevant reviews were included. Randomized controlled trials were eligible for the efficacy review, and controlled trials were eligible for the safety review. One reviewer extracted data, while the other verified extracted data. The Random Effects Model was used to analyze data. Fourteen randomized controlled trials were relevant to the efficacy review, encompassing 279 participants (95; 100-103; 109; 128; 146; 148; 150; 263-266). Melatonin decreased sleep onset latency (weighted mean difference [WMD]: -11.7 minutes; 95% confidence interval [CI]: -18.2, -5.2); it was decreased to a greater extent in people with delayed sleep phase syndrome (WMD: -38.8 minutes; 95% CI: -50.3, -27.3; N=2) compared with people with insomnia (WMD: -7.2 minutes; 95% CI: -12.0, -2.4; N=12). There was no evidence of adverse effects of melatonin. The researchers concluded that there is evidence to suggest that melatonin is not effective in treating most primary sleep disorders with short-term use (4 weeks or less); however, additional large-scale randomized controlled trials are needed before firm conclusions can be drawn. There is some evidence to suggest that melatonin is effective in treating delayed sleep phase syndrome with short-term use.
- **Evidence**: Rahman et al. conducted a randomized, double-blind, crossover, placebo-controlled trial to examine the hypothesis that exogenous melatonin (5mg) can attenuate depressive symptomatology in Delayed Sleep Phase Syndrome patients (267). A total of 20 patients (13 males aged 35.6 ± 14.0 years and seven females aged 30.8 ± 12.4 years) with an established diagnosis of DSPS participated in the study. Subjects were excluded if there was a presence of other sleep disorders, shift work, under 16 years old, alcohol or drug abuse, current use of psychotropic medications or any other form of medication affecting melatonin secretion, receiving active behavioral treatment or with severe psychiatric and neurological disorders. Subjects were randomly allocated to the melatonin treatment group or placebo group. Each subject was given 5mg daily of either melatonin or placebo capsule between 19:00 and 21:00. The total duration of the study was nine weeks. Before the randomization, a two-night sleep study was conducted to establish the baseline. After the second night of study and randomization, treatment continued for four weeks followed by a one-week washout period before treatment crossover. Two-night sleep studies were later conducted again on day 27 and 28 (the first four-week treatment) and on day 62 and 63 (the second four-week treatment). Each group received the treatment of melatonin or placebo capsule between 19:00 and 21:00 daily. Subjects were primarily assessed by clinical interviews, psychometric evaluation for depression (Center for Epidemiologic Studies Depression Scale and Hamilton Depression Rating Scale-17), and overnight polysomnographic sleep studies

(carried out at baseline and at the end of melatonin and placebo treatments). Melatonin secretion rhythm (measured by urinary 6-sulphatoxymelatonin level) was also conducted to determine circadian phase. Significant decreases ($p<0.05$) in HDRS-17 and CES-D scores after melatonin treatment were observed in Group I (DSPS patients with comorbid depressive symptoms; n=8) while placebo treatment had no effect on either score. Changes in Group II (DSPS patients without comorbid depressive symptoms; n=12) were not significant. The sleep onset latency was significantly reduced ($p=0.03$) in the melatonin treatment arm compared to both placebo and baseline in Group I. Polysomnographic findings in Group II indicated significant advance ($p=0.03$) in sleep onset latency in the melatonin treatment arm compared to placebo and baseline. The Circadian profile of DSPS patients with marked depressive symptoms showed abnormal pattern of endogenous melatonin secretion on placebo treatment, however, DSPS patients without depression showed normal melatonin production. This was a well-designed study; however, it should be noted that the study population was small.

- Mundey et al. conducted a randomized double-blind placebo-controlled trial of 22 subjects to test the effectiveness of melatonin to advance the timing of sleep and circadian phase in individuals with delayed sleep phase syndrome (DSPS) (96). Subjects received 0.3 (N=5) or 3mg (N=4) melatonin or placebo (N=4) capsules taken for a period of four weeks, between 1.5 and 6.5 hours before dim light melatonin onset. The primary outcomes included the circadian phase shift markers dim-light melatonin onset (DLMO) and timing of the fitted nocturnal temperature minimum, measured both objectively and subjectively. Actigraphs (Actiware-Sleep, Mini Mitter Co., Inc, Bend, Ore) measured objective sleep outcomes. Subjective outcomes (bed/lights-out times from sleep-diary) were compared to actigraphy data to calculate secondary outcome sleep latency. During the baseline week and on the fourth week of treatment, sleep onset, sleep offset, sleep efficiency, and sleep latency averages were calculated. The circadian phase of endogenous melatonin progressed in the groups after taking both doses of melatonin. Compared to baseline, advances (average time in hours±SD) in dim light melatonin onset (1.75±0.89; $p<0.001$) and timing of the fitted nocturnal temperature minimum (1.63±1.79; $p<0.05$) were noted in the melatonin groups. There was a strong correlation between the size of the phase advance in dim-light melatonin onset and the time that the subjects took the melatonin. The earlier the time of melatonin administration, the more effective it was ($r2=0.94$; $p<0.0001$). There was a correlation, although weak, between the time at which the subjects took the melatonin and change in sleep time. Limitations of this study include a lack of a power calculation, intent to treat analysis, and between groups comparison. This study was supported by the Northwestern Drug Discovery Program and by AG00810. Standardization, adverse effects, toxic effects, and interactions were not discussed.
- Kayumov et al. conducted a randomized, double-blind, placebo-controlled crossover trial to investigate the effects of exogenous melatonin delayed sleep phase syndrome (264). Twenty-two patients with delayed sleep phase syndrome received either placebo or melatonin (5mg) daily for four weeks; these patients underwent a one-week washout period, and then were given the other treatment for an additional four weeks. Two consecutive overnight polysomnographic recordings were performed on three occasions: at baseline (before treatment), after four weeks of melatonin treatment, and after four weeks of placebo treatment. In the 20 patients who completed the study, sleep onset latency was reduced while subjects were taking melatonin as compared with both placebo and baseline. There was no evidence that melatonin altered total sleep time (as compared with baseline total sleep time), but there was a significant decrease in total sleep time while patients were taking placebo. Melatonin did not result in altered scores on subjective measures of sleepiness, fatigue, or alertness when administered at different times of the day. After an imposed conventional sleep period (from 24:00 to 08:00), subjects taking melatonin reported being less sleepy and fatigued than they did while taking placebo. No adverse effects of melatonin were noted.
- Nagtegaal et al. conducted a double-blind, placebo-controlled, crossover trial to determine the importance of dim light melatonin onset in patients suffering from DSPS (97). Thirty patients with

DSPS received melatonin 5mg during two weeks in a double-blind setting and two weeks in an open setting successively or interrupted by two weeks of placebo. The study's impact was assessed by measurements of the 24-hour curves of endogenous melatonin production and rectal temperature (N=14), polysomnography (N=22), actigraphy (N=13), sleep log (N=22), and subjective sleep quality (N=25). Mean dim light melatonin onset (± SD), before treatment, occurred at 23.17 hours (±138 min). Melatonin was administered five hours before the individual dim light melatonin onset. After treatment, the onset of the nocturnal melatonin profile was significantly advanced by approximately 1.5 hours. During melatonin use, actigraphy showed an advance of sleep onset and polysomnography and a decrease in sleep latency. Sleep architecture was not influenced. During melatonin treatment, patients reported feeling more refreshed in the morning. The researchers concluded that dim light melatonin onset of patients suffering from DSPS is important both for diagnosis and therapy.

Melatonin: Insomnia (elderly)

- **Note**: Due to the quantity of melatonin research, the Evidence Discussion paragraphs are limited to meta-analyses, systematic reviews, and clinical trials with strong methodological design.
- **Summary**: Mean excretion of 6-sulfatoxymelatonin (a metabolite of melatonin) has been found to be lower in patients aged 55 years or older with insomnia than patients of the same age or younger (268). Several randomized controlled studies (RCT) have reported improvements in insomnia in the elderly with melatonin supplementation. Non-randomized clinical trials have reported similar results (107; 269).
- **Evidence**: Luthringer et al. conducted a randomized, double-blind, sleep laboratory phase II study to investigate the effects of prolonged-release melatonin (PRM) on sleep and daytime performance in patients with insomnia (270). Subjects were 40 patients aged 55 years or older with primary insomnia, as defined by the fourth revision of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association. Patients with other sleeping disorders (related to breathing disorders or restless leg/periodic leg movements), a history of severe cardiac or neurologic disorders, or those who took sedative hypnotics in the preceding month were excluded from this study. Patients were treated with a nightly single-blinded placebo for two weeks. They were then randomized in a double-blind fashion to either prolonged release melatonin (PRM) 2mg or placebo two hours before bedtime for three weeks. Following the double-blind randomization, a withdrawal period in which no drugs were given was conducted for three weeks. Eleven patients in each treatment group reported adverse events; however, none were considered to be treatment-related. Sleep was assessed objectively using polysomnography, all-night electroencephalography spectral analysis, and subjective questionnaires (the Leeds Sleep Evaluation Questionnaire, LSEQ). Daytime psychomotor performance was objectively assessed using the Leeds Psychomotor Tests battery. At the end of the double-blind treatment period, the PRM treatment group had significantly shorter sleep onset latency (nine minutes; p=0.02) compared to placebo group. The PRM group also had significantly better Critical Flicker Fusion scores (p=0.008), without negative effects on sleep structure and architecture. Based on the LSEQ questionnaire, quality of sleep was significantly improved in the PRM group (p=0.004), but not in the placebo group. More patients in the PRM group reported substantial improvement in sleep quality at home compared to placebo (50% vs. 15%; p=0.018), as well. However, there was no significant difference in objective measures of sleep quality between the groups. The authors concluded that nightly treatment with PRM effectively induced sleep and improved perceived quality of sleep. It should be noted that this study was funded by the manufacturer of the melatonin supplement used in the study.
- Garfinkel et al. conducted a crossover, randomized controlled trial of 15 elderly subjects who complained of long-term insomnia and were receiving different medications at baseline to measure 6-sulphatoxymelatonin levels, and to assess the effect of controlled-release melatonin on sleep hygiene (102). Participants received tablets of 2mg controlled-release melatonin (Circadin, Neurim Pharmaceuticals) or a placebo. Sleep variables were measured for three consecutive nights

at the end of the three-week treatment periods; averages were taken. Wrist actigraphs (Somnitor, Neurim Pharmaceuticals, Tel Aviv, Israel) assessed sleep-wake patterns. Indicators for sleep quality were assessed in the subjects for three nights in a row. The authors did not specifically state the primary outcome; latency is assumed. Latency (time between bedtime and sleep onset), efficiency (total time asleep as a percentage of total time in bed), total sleep time (time spent asleep after sleep onset), and wake after sleep onset (WASO; accumulated time awake after sleep onset) were assessed. 6-sulphatoxymelatonin excretion, onset, and peak time, were also measured. Compared to the melatonin group, the placebo group exhibited a longer latency period. The mean sleep latency was 19 [SE 5; range 3-49] minutes in the melatonin group compared to the placebo period 33 [SE 7] minutes, but the decrease was not statistically significant ($p=0.088$). Sleep efficiency in the melatonin period showed an increase (83 [SE 4] %), when compared to the placebo period (75 [SE 3] %) ($p<0.001$). Wake after sleep onset in the melatonin period was 49 [SE 14] minutes, and 73 [SE 13] minutes in the placebo group ($p<0.001$). Melatonin did not significantly affect total sleep time ($p=0.49$). It was hypothesized that, due to the short half life of melatonin, the controlled-release melatonin is helpful for sleep maintenance. Limitations of this study include a lack of a power calculation and explanation of randomization. Toxic effects, standardization, and interactions were not discussed.

- Dawson et al. conducted a randomized, double-blind, placebo-controlled, crossover trial of 12 elderly patients to assess the effect of exogenous melatonin on age-related sleep maintenance insomnia (101). Subjects were over 55 years of age (mean = 65.67 years, SEM = 1.68) and had all been suffering from sleep maintenance insomnia for at least six months. Subjects were treated with either 0.5mg transbuccal (delivered via a patch placed on the gums) melatonin or a placebo at 1900h for two sessions of four consecutive nights, at least three days apart. Nightly urine samples were assayed for the melatonin metabolite 6-sulfatoxy-melatonin. Body temperature was measured continually from 2100 to 0700h. Subjects self-selected lights-out times, and sleep was assessed using standard polysomnographic (PSG) measures. Outcome measures included polysomnographic recordings (EEG, EMG, EOG) and associated variables (total sleep time, sleep onset latency, REM onset latency, early morning awake, percentage time awake, sleep efficiency, stage changes in sleep period, time of sleep onset, and wake after sleep onset) and body temperature (rectal probe). Analysis revealed that, compared to the placebo, transbuccal melatonin administration significantly reduced core body temperature ($p<0.05$) but had no positive, statistically significant effect on any PSG measure of sleep quality. This study found no statistically significant effect of 0.5mg transbuccal in treating age-related sleep maintenance insomnia. The authors speculate that both the dose size and timing may have influenced the negative result. This study was well designed and characterized, although interactions, allergies and adverse effects, as well as dropouts, were not discussed.

- Haimov et al. conducted a clinical trial to investigate the effects of melatonin replacement therapy on melatonin-deficient elderly insomniacs (103; 104). The study comprised a running-in, no-treatment period and four experimental periods. During the second, third and fourth periods, subjects were administered tablets for seven consecutive days, two hours before desired bedtime. The tablets were either 2mg melatonin administered as sustained-release or fast-release formulations, or an identical-looking placebo. The fifth period, which concluded the study, was a 2-month period of daily administration of 1mg sustained-release melatonin two hours before desired bedtime. During each of these five experimental periods, sleep-wake patterns were monitored by wrist-worn actigraphs. Analysis of the first three one-week periods revealed that a one-week treatment with 2mg sustained-release melatonin was effective for sleep maintenance (i.e. sleep efficiency and activity level) of elderly insomniacs, while sleep initiation was improved by the fast-release melatonin treatment. The authors stated that sleep maintenance and initiation were further improved following the 2-month, 1mg sustained-release melatonin treatment, indicating that tolerance had not developed. After cessation of treatment, sleep quality deteriorated.
- Lemoine et al. conducted a randomized, double-blind, placebo-controlled, parallel study to assess the efficacy and safety of melatonin in improving quality of sleep and morning alertness in patients aged 55 years or older (105). The study began with a two-week, single-blind, run-in phase with placebo treatment followed by an evaluation. Those who met eligibility were randomized to receive placebo or prolonged release (PR) melatonin 2mg for three weeks. Subjects were instructed to take the medication daily after the evening meal, between one and two hours before bedtime, preferable between 2100 and 2200 hours. Prolonged-release melatonin significantly improved quality of sleep ($p=0.047$), quality of sleep ratings ($p=0.003$) and morning alertness ($p=0.002$) compared with placebo. The authors suggested that the improvements in quality of sleep and morning alertness were linked, indicating a beneficial treatment effect on the restorative value of sleep. Rebound insomnia or withdrawal effects were not found upon treatment discontinuation. Adverse effects were mild. Randomization and blinding were not described.
- Wade et al. conducted a randomized, double-blind, placebo-controlled study to evaluate whether or not treatment with prolonged release (PR)-melatonin (2mg) would improve quality of sleep and next day alertness in older patients with primary insomnia (106). A total of 354 patients were randomized to treatment (177 to active medication and 177 to placebo). Of the 354 patients entering the active phase of the study, 20 failed to complete visit 3 (eight melatonin; 12 placebo). A total of 334 patients comprised the full analysis set. Participants entered a two-week run-in period followed by a three-week treatment period, with either PR-melatonin 2mg or placebo. Patients were instructed to take one tablet per day two hours before bedtime. Improvements were noted in quality of sleep and morning alertness (26% vs. 15%; $p=0.014$). A statistically significant and clinically relevant shortening of sleep latency to the same extent as most frequently used sleep medications was also found (-24.3 vs.-12.9 minutes; $p=0.028$). Quality of life also improved ($p=0.034$). Blinding was not described.
- Valtonen et al. investigated the effects of melatonin-rich night-time milk on sleep and activity in institutionalized elderly patients in two long-term randomized, double-blind, placebo-controlled studies (108). Study 1: Seventy patients receiving various medications for chronic illnesses participated in the crossover study. The subjects were divided into two groups (I and II). Group I (N=31) used night milk (experimental) for eight weeks and normal commercial milk (placebo) for eight weeks with a washout period of one week in between. Group II (N=31) started with normal daytime milk for eight weeks and switched to night milk after the washout period. Each subject drank about 0.5L of milk daily. The study was performed between March and July. Based on subjective evaluation, quality of sleep was good during the whole study. Almost all scores were between 8 and 10 (10 = most restful). No difference in sleep quality was found between night milk and normal milk periods for Group I, but for Group II, which consumed night milk, sleep quality decreased during the later period ($p<0.01$). Sleep quality was reduced towards the summer, indicating a seasonal effect that was more evident in subjects with severe dementia. The seasonal

effect was statistically significant. Study 2: Since the subjective evaluation in Study 1 was too limited and the parameter most strongly related to season (light and melatonin) was nocturnal activity, another study was organized. Eighty-one subjects participated in the study. They consumed milk regularly. The participants in Study 2 were divided into three groups. Group III (N=23) started by consuming night milk for eight weeks and then, after a washout period of one week, consumed normal daytime milk for another eight weeks. Group IV (N=26) started with normal milk for eight weeks and changed to night milk after the washout period. Group V (N=32), living in another rest-home, consumed normal daytime milk during the whole experiment and served as a control group for evaluating the effect of season. The study was performed between October and February. For Group III, sleep quality was rated significantly ($p< 0.001$) higher during the normal milk period. There were no changes in morning or evening activity, and no effect of night milk. In Group IV, sleep quality, morning activity and evening activity increased ($p<0.001$) when night milk was consumed. In Group V, sleep quality was slightly better ($p< 0.05$) when night milk was consumed. No differences were observed between the periods in morning or evening activity, which may indicate no seasonal effect in activity. Randomization, blinding, and dropouts were not described.

- Zhdanova et al. conducted a randomized, double-blind, placebo-controlled trial to determine if melatonin at various doses can restore sleep in the elderly population (109). Thirty subjects participated and completed the study. They received a placebo on alternate (odd numbered) weeks throughout the study, starting with the first "run-in" week, thus providing washout periods between and after active treatments. During the second week and thereafter on each even-numbered treatment week, subjects received melatonin (0.1mg, 0.3mg, or 3.0mg) mixed with microcrystalline cellulose or the placebo (cellulose) daily, administered for four days at home and then for three days as inpatients in a research center. Melatonin or placebo capsules were ingested half an hour before each subject's fixed bedtime. Treatments were separated by one-week washout periods. Sleep data were obtained by polysomnography on the last three nights of each treatment period. The physiologic melatonin dose (0.3mg) restored sleep efficiency ($p<0.0001$), acting principally in the middle third of the night; it also reportedly elevated plasma melatonin levels ($p<0.0008$) to normal. The pharmacologic dose (3.0mg), like the lowest dose (0.1mg), also improved sleep; however, it induced hypothermia and caused plasma melatonin to remain elevated into the daylight hours. Although control subjects, like insomniacs, had low melatonin levels, their sleep was unaffected by any melatonin dose.

Melatonin: Sleep disorders (children with behavioral, developmental, psychological, and intellectual disorders)

- **Note**: Due to the quantity of melatonin research, the Evidence Discussion paragraphs are limited to meta-analyses, systematic reviews, and clinical trials with strong methodological design.
- **Summary**: Several randomized controlled studies have reported melatonin use in children with various neuro-psychiatric disorders, including mental retardation, autism, psychiatric disorders, visual impairment, or epilepsy. Non-randomized clinical trials have also been conducted (271-284) and, overall, the results agree with those observed in the RCTs. Well-designed controlled trials in select patient populations are needed before a conclusion can be made.
- **Systematic review**: Phillips et al. conducted a systematic review to assess randomized control trial evidence for the use of melatonin in children with neurological and developmental problems (285). Randomized clinical trials were identified of children (up to 18 years of age) with any type of neurological disorder or neurodevelopmental disability and associated sleep disturbance, where oral melatonin was used and compared to placebo. Sustained release formulations were excluded. Three studies (N=35 children) met inclusion criteria (277; 286; 287). Two studies reported time to sleep onset and showed a decrease ($p<0.05$) in this specific outcome where melatonin was compared with a placebo (277; 287). There was no significant effect of melatonin compared with a placebo on the other outcome measures of total sleep time, night-time awakenings, and parental opinions.
- Bendz et al. conducted a systematic review of the safety and efficacy of melatonin for the alleviation of insomnia in children with attention-deficit/hyperactivity disorder (ADHD) (288). Criteria for inclusion were English-language articles and human studies conducted in children with ADHD and administering melatonin for the treatment of insomnia. Databases searched included: MEDLINE (1948-August 2009), EMBASE (1950-August 2009), and Scopus (1960-August 2009). Search terms were melatonin, attention-deficit/hyperactivity disorder (ADHD), pediatric, insomnia, sleep disorder, and sleep. A total of four studies were found (272; 289-291). Doses ranged from 3mg to 6mg of oral melatonin. Tjon Pian Gi et al. conducted a one year open-label study (N=120). Van der Heijden et al. conducted a four week randomized controlled trial (N=105). Hoebert et al. conducted a three year follow-up to the Van der Heijden trial (N=94). Weiss et al. conducted a six month crossover study (N=28). Tjon Pian Gi et al. reported one case of restless sleep. Van der Heijden et al. reported mild adverse effects including headache, hyperactivity, dizziness and abdominal pain. Also, a two year safety follow-up showed bedwetting, abnormal feces and drowsiness. Hoebert et al. had 20% of patients (n=19) report adverse effects, all of which were not serious and did not involve new cases of epilepsy. After discontinuation, there were no reports of withdrawal symptoms or dependence. Weiss et al. reported mild to moderate adverse effects, except for one report of severe migraine. Tjon Pian Gi et al. examined sleep onset. Van der Heijden et al. measured sleep parameters including sleep onset, total sleep time, and sleep latency as well as specific core problems including anger, sleep, and attention. Hoebert et al. measured relapse rates of sleep onset insomnia after discontinuation of melatonin using subjective questionnaires filled out by parents. Weiss et al. measured sleep latency and also implemented a sleep hygiene regimen using actigraphy and somnolog measures. Tjon Pian Gi et al. concluded that, at short-term evaluation, sleep onset was significantly improved (median increase 135 min, n=24), which was then sustained at the long-term evaluation (n=13). Van der Heijden et al. reported significant improvements in sleep parameters (sleep onset, total sleep time, sleep latency, DLMO) and specific core problems (anger, sleep, attention). Hoebert et al. reported that 92% (n=60) of subjects experienced a delay in sleep onset, although, overall, 90% (n=85) of parents believed melatonin to be an effective treatment for SOI in their children with ADHD, 71% (n=67) thought daytime behavior improved, and 61% (n=57) thought mood improved. Weiss et al. determined that those who responded well to melatonin therapy did not have a significant improvement with continued treatment. In most studies, sleep onset was improved by 0.5-2 hours, sleep duration was improved by 0.33-1 hour, and sleep latency was improved by approximately 20 minutes. The review was well-conducted; however, there is an overall lack of well-designed

studies related to melatonin use. The available studies were limited by small sample sizes and variable outcome measures.

- **Evidence**: Weiss et al. conducted a randomized, double-blind, placebo-controlled, crossover trial to evaluate the efficacy of sleep hygiene and melatonin treatment for initial insomnia in children with attention-deficit/hyperactivity disorder (ADHD) (291). Twenty-seven stimulant-treated children (6-14 years of age) with ADHD and initial insomnia (>60 minutes) received sleep hygiene intervention and were administered melatonin 5mg. Each treatment period was 10 days, followed by a 5-day washout period with placebo. Sleep hygiene reduced initial insomnia to less than 60 minutes in five cases, with an overall effect size in the group of 0.67. A reduction in initial insomnia of 16 minutes with melatonin relative to placebo was observed ($p<0.01$), with an effect size of 0.6. The effect size of the combined sleep hygiene and melatonin intervention from baseline to 90 days post-trial was 1.7, with a mean decrease in initial insomnia of 60 minutes. Improved sleep had no demonstrable effect on ADHD symptoms. This trial was well-designed.
- Wirojanan et al. conducted a four week, randomized, double blind, placebo-controlled, crossover trial to determine the efficacy of melatonin on sleep problems in children with autistic spectrum disorder (ASD) and fragile X syndrome (FXS) (292). The experiment was conducted on eighteen subjects (16 boys, 2 girls) between 2 and 15.3 years of age who were diagnosed with ASD (either autism or pervasive developmental disorder [PDD-NOS]) or fragile X syndrome (FXS) or a combination of both. Participants were given 3mg melatonin or placebo to take orally at bedtime. The placebo was provided by the Twinlab Corporation to look similar to the melatonin capsule. The study medication was given 30 minutes prior to bedtime over the two week treatment arm followed by a one week washout period. Lastly, the participants crossed over to the alternate treatment for an additional two weeks. There were six dropouts from a total of 18 enrolled. Three participants were excluded, even though they finished the study because their caregivers did not complete the sleep diary or the Actiwatch data was unreadable. Two participants were excluded since they failed to wear the Actiwatch during one of the treatment arms. Also, a family was excluded due to study protocol violation and an incomplete sleep diary. Objective sleep variables, including sleep-onset time (actual time participant fell asleep), total length of sleep duration, sleep-onset latency time (time from bedtime to sleep onset time), as well as the number of times the participant woke were obtained from actigraphy and the subjective daily sleep diary, which was completed by the parents or caregivers. A small device worn around the wrist or ankle, the Actiwatch, measured gross motor activity in one minute intervals. Total night sleep duration tended to be longer (mean increase 21 minutes) in the melatonin arm, but was not statistically significant, ($p= 0.057$). Sleep latency time tended to be shorter (mean decrease 28 minutes 5 seconds) in the melatonin arm but was not significant ($p=0.10$). Sleep-onset time was significantly earlier (mean decrease of 42 minutes) for participants ($p=0.0017$) during melatonin treatment compared with placebo when using a parametric test. Number of nighttime awakenings was not significantly lower in the melatonin group ($p=0.73$). The study was well designed albeit with a small participant size.
- Braam et al. conducted a randomized, double-blind, placebo-controlled trial to evaluate the effectiveness of melatonin in patients with intellectual disabilities, measuring dim light melatonin onset and the influence of melatonin on endogenous melatonin rhythm (293). The trial consisted of a baseline and qualification period followed by a four-week treatment period. During the treatment period, subjects (N=51) received melatonin 5mg or placebo at bedtime. Individuals younger than six years received 2.5mg of melatonin. Compared with placebo treatment, during melatonin treatment mean sleep latency decreased 29 minutes ($p<0.01$), mean sleep onset increased 34 minutes ($p<0.01$) and mean total sleep time increased 48 minutes ($p<0.05$). The mean number of night wakings per night decreased ($p<0.05$). There was no change in lights out time, number of nights with night wakings per week and sleep offset time compared with baseline. There was a correlation between baseline dim light melatonin onset and the change in dim light melatonin onset between baseline and week four in the melatonin group ($p<0.001$). This trial was well designed.

- Wasdell et al. conducted a randomized, double-blind, placebo-controlled crossover trial to determine the efficacy of controlled-release (CR) melatonin in the treatment of delayed sleep phase syndrome and impaired sleep maintenance of children with neurodevelopmental disabilities, including autistic spectrum disorders (98). Fifty-one children (age range 2-18 years) who did not respond to sleep hygiene intervention were enrolled. Fifty patients completed the crossover trial and 47 completed the open-label phase. Participants received controlled release (CR) melatonin 5mg followed by a 3-month open-label study during which the dose was gradually increased until the therapy showed optimal beneficial effects. Sleep characteristics were measured by a caregiver who completed somnologs and wrist actigraphs. Clinician ratings of severity of the sleep disorder and improvement from baseline, along with caregiver ratings of global functioning and family stress were also obtained. Recordings of total night-time sleep and sleep latency showed an improvement of approximately 30 minutes ($p<0.001$). Similarly, improvement was observed in clinician and parent ratings. There was additional improvement in the open-label somnolog measures of sleep efficiency and the longest sleep episode in the open-label phase. This study was well designed.
- van der Heijden et al. conducted a randomized, double-blind, placebo-controlled trial to investigate the effects of melatonin treatment on sleep, behavior, cognitive performance, and quality of life in children with attention-deficit/hyperactivity disorder (ADHD) and chronic sleep onset insomnia (289). A total of 105 medication-free children, ages six to 12 years received melatonin three or 6mg fast-release tablets (depending on body weight) or placebo for four weeks. Primary outcome parameters were actigraphy-derived sleep onset, total time asleep, and salivary dim light melatonin onset. Sleep onset advanced by 26.9 ± 47.8 minutes with melatonin and delayed by 10.5 ± 37.4 minutes with placebo ($p<0.0001$). There was an advance in dim light melatonin onset of 44.4 ± 67.9 minutes in melatonin and a delay of 12.8 ± 60.0 minutes in placebo ($p<0.0001$). Total time asleep increased with melatonin (19.8 ± 61.9 minutes) as compared to placebo (-13.6 ± 50.6 minutes; $p=0.01$). There was no statistically significant effect on behavior, cognition, and quality of life, and significant adverse events did not occur. Randomization and blinding were not described.
- Garstang et al. conducted a randomized, double-blind, placebo-controlled, crossover trial to evaluate the effects of melatonin in autistic children with sleep disorders (294). Eleven children (between 4-16 years old) with autism received 5mg or placebo for four weeks. There was a washout period of one week between each of the treatment periods. Seven children completed the trial. Melatonin reduced sleep latency, number of night wakings and increased the total sleep time. Sleep latency was 2.6 hours (95% CI: 2.28-2.93) at baseline, 1.91 hours (95% CI: 1.78-2.03) with placebo and 1.06 hours (95% CI: 0.98-1.13) with melatonin. Wakings per night were 0.35 (95% CI: 0.18-0.53) baseline, 0.26 (95% CI: 0.20-0.34) with placebo and 0.08 (95% CI: 0.04-0.12) with melatonin. Total sleep duration was 8.05 hours (95% CI: 7.65-8.44) baseline, 8.75 hours (95% CI: 8.56-8.98) with placebo and 9.84 hours (95% CI: 9.68-9.99) with melatonin. Blinding was not described in this study.
- Coppola et al. conducted a randomized, double-blind, placebo-controlled crossover trial to assess the efficacy of melatonin in children, adolescents and young adults with wake-sleep disorder and mental retardation (some of the patients were on chronic anticonvulsant therapy for epileptic seizures) (295). Twenty-five patients (16 males, nine females), ages ranging from 3.6 to 26 years (mean 10.5 years), all affected with mental retardation mostly with epileptic seizures, received either fast-release melatonin (3mg at bedtime) or placebo in phase 1 for four weeks. After a crossover period of one week, each patient entered the four-week second phase of the study. EEG, side effects and blood levels of concomitant adverse effects were monitored in all patients at baseline and at the end of each melatonin or placebo 1-month phase of the study. At the end of the second phase, responders to melatonin entered an open-label phase of two months. The analysis of all the sleep logs revealed that melatonin improved sleep latency ($p=0.019$). Melatonin did not significantly alter the number of nocturnal awakenings ($p=0.768$) or total time of diurnal sleep

(p=1). Melatonin was well tolerated in all patients and no side effects were reported. Randomization and blinding were not described.

- Niederhofer et al. conducted a randomized, double-blind, placebo-controlled trial to determine whether depressed nocturnal melatonin levels and insomnia are associated, and whether various melatonin doses restore sleep in mentally retarded subjects (296). Twenty adolescents received a placebo on alternate (odd numbered) weeks throughout the study, starting with the first "run-in" week, thus providing washout periods between and after active treatments. During the second week and thereafter on each even-numbered treatment week, subjects received melatonin (0.1mg or 0.3mg) or the placebo daily (half-hour before bedtime) for seven days. Sleep was improved by all three melatonin doses, with the 0.3mg dose causing the greatest effect ($p<0.0001$). The authors reported that melatonin had no behavioral, dose-related effects on total sleep time; and number of awakenings.
- Jan et al. conducted a randomized, double-blind, crossover trial to compare the effectiveness of fast-release and controlled-release melatonin and to establish the most effective dose in children with chronic and severe sleep disorders (297). In the initial study, controlled-release melatonin was administered to 16 multi-disabled children (4-21 years of age) with severe sleep-wake disorders. They were already treated with fast-release melatonin for more than three months, then the 16 subjects were randomized to receive either controlled- or fast-release melatonin, each for 11 days and the drugs were crossed over. A washout period was not utilized. The fast-release dose was the same as before the study. The controlled-release formulation was 50% of the fast-release dose. Improvements in sleep patterns were noted in 11 of the children. The controlled-release formulation had no clear advantage over the fast-release melatonin in five children. Following this initial study, 42 other patients on fast-release melatonin were permitted to change to controlled-release preparation in an open study design. The average final controlled-release melatonin dose in the 42 patients was 5.7mg (2-12mg). Fast-release melatonin was found to be most effective for delayed sleep onset; controlled release formulations were more beneficial for sleep maintenance. Randomization was not described.
- Gupta et al. conducted a double-blind, randomized, placebo-controlled study in epileptic children, aged three to 12 years to evaluate the effect of add-on melatonin on the sleep behavior in epileptic children on sodium valproate monotherapy using a parental questionnaire (298). Of the 31 patients, 16 randomly received add-on melatonin, whereas 15 received add-on placebo. The authors reported that the questionnaire showed good internal consistency in the patient population (Cronbach's alpha = 0.83). The percentage decrease in the median total sleep score was 24.4 (range 0.0-34.9) in the valproate + melatonin group compared with 14.0 (range -2.2-18.8) in the valproate + placebo group, the difference being statistically significant ($p<0.05$). The median percentage decrease in the parasomnias score was 60 (range 0.0-70.8) in the valproate + melatonin group compared with 36.4 (range 0.0-63.2) in the valproate + placebo group, the difference being statistically significant ($p<0.05$). There was no statistically significant difference between the percent decrease in the daytime drowsiness scores and sleep fragmentation scores. Parent-child interaction subscale scores were not significantly different between age groups. The age at onset of seizures and the type of seizures did not correlate significantly to the total sleep scores.
- Dowling et al. conducted a randomized, controlled trial to examine whether the addition of melatonin to bright-light therapy enhances the efficacy in treating rest-activity (circadian) disruption in institutionalized patients with Alzheimer's disease (AD) (132). Fifty subjects (mean age 86) with AD received one hour of morning light exposure (≥2,500 lux in gaze direction) Monday to Friday for 10 weeks and 5mg melatonin (LM, N=16) or placebo (LP, N=17) in the evening. Control subjects (N=17) received usual indoor light (150-200 lux). Nighttime sleep variables, day sleep time, day activity, day:night sleep ratio, and rest-activity parameters were determined using actigraphy. Linear mixed models were employed to test the primary study hypotheses. No statistically significant differences in nighttime sleep variables were found between groups. At the end of the intervention, the LM group showed improvement in daytime somnolence as indicated by a reduction in the duration of daytime sleep, an increase in daytime

activity, and an improvement in day:night sleep ratio. The LM group also evidenced an increase in rest-activity rhythm amplitude and goodness of fit to the cosinor model. The authors conclude that light treatment alone did not improve nighttime sleep, daytime wake, or rest-activity rhythm and that light treatment plus melatonin increased daytime wake time and activity levels and strengthened the rest-activity rhythm.

Melatonin: Insomnia (adults)

- **Note**: Due to the quantity of melatonin research, the Evidence Discussion paragraphs are limited to meta-analyses, systematic reviews, and clinical trials with strong methodological design.
- **Summary**: Patients with insomnia appear to have decreased melatonin secretion and treatment with exogenous melatonin may offer some benefit (Attenburrow, 1996 54 /id}. Most human trials have been small and brief in duration (often single-dose studies). However, the weight of scientific evidence does suggest that melatonin decreases the time it takes to fall asleep ("sleep latency"), increases the feeling of "sleepiness," and may increase the duration of sleep. Melatonin may also aid in inducing daytime sleep (299).
- **Meta-analysis**: Brzezinski et al. conducted a meta-analysis of randomized, double-blinded trials of varying design to assess the effects of exogenous melatonin on sleep (300). A total of 17 studies were included (95; 102; 104; 109; 131; 147; 149; 150; 154; 156; 157; 160; 269; 301-304). Subjects included varied widely, representing insomniacs (naturally occurring and artificially induced), schizophrenics, Alzheimer's disease patients, and healthy volunteers. Age and sex distributions also varied from study to study. Authors report dosages ranged from 0.3 to 80mg of melatonin delivered orally. One study administered melatonin intravenously (50mg). The therapy schedule also varied from study to study, ranging from multiple times over one experimental session to one treatment daily for up to two months. Included studies employed only adult subjects. Allergies, adverse and toxic effects, as well as interactions were not discussed. Dropouts were also not discussed. Outcome measures included sleep onset latency, total sleep duration, and sleep efficiency. Analysis revealed melatonin treatment significantly reduced sleep onset latency by 4.0min (95% CI: 2.5-5.4), increased sleep efficiency by 2.2% (95% CI: 0.2-4.2), and increased total sleep duration by 12.8min (95% CI: 2.9-22.8). Since 15 of the 17 studies included enrolled healthy subjects or people with no relevant medical condition other than insomnia, the analysis was also done including only these 15 studies. The sleep onset results were changed to 3.9 min (95% CI: 2.5-5.4), sleep efficiency increased to 3.1% (95% CI: 0.7-5.5), and sleep duration increased to 13.7 min (95% CI: 3.1-24.3). This study suggests a small but statistically significant increase in sleep onset latency, sleep efficiency, and total sleep duration in response to melatonin treatment as measured via meta-analysis of a number of studies of varying design; however, the disparate nature of the included research makes pooling of data and objective comparison of results somewhat difficult.
- **Systematic review**: Morera et al. conducted a review to evaluate whether melatonin may be considered as an alternative for the treatment of insomnia (305). A computerized search spanning a 33-year period was performed and 93 articles were collected. Melatonin, pineal gland and insomnia were used as key words. Of the 93 articles collected, 85 were excluded because they were reviews or were not directly related to the research topic. A total of 111 insomniac patients were treated with melatonin in eight articles. 60% of the patients reported an improvement in sleep quality. Objective sleep measures also improved; there was a decrease in the sleep latency time and the number of awakenings (62% and 50% of patients respectively) after melatonin treatment.
- **Evidence**: Tzischinsky and Lavie conducted a crossover, placebo-controlled, double-blind trial of eight men in a 7/13 ultra-short sleep/wake paradigm (following an overnight sleep deprivation) to assess the efficacy of melatonin on inducing sleep (159). All subjects were men with an average age of 27.06 ± 3.7 years. Subjects were administered the Technion Sleep questionnaire and the Horne and Ostberg questionnaire prior to experimentation to exclude sleep disturbances and/or extreme morning or evening types. During the sessions, subjects were administered a pill at four different times (12:00, 17:00, 19:00, and 21:00). In four of the sessions, three of the pills were

placebo and one contained 5mg of melatonin. Melatonin administration was varied according to a Latin Square design. During a fifth session, all pills administered were placebo. Four of the subjects received the all-placebo trial during the first experimental session, while the other four received it in the last. Outcome measures included polysomnographic recordings (EEG), oral temperature, and subjective reports of sleepiness. Subjects receiving melatonin at 12:00, 17:00, 19:00, and 21:00 experienced significant effects of treatment ($p<0.1$, $p<0.003$, $p<0.0001$, $p<0.004$), trial ($p<0.0001$, $p<0.008$, $p<0.0001$, $p<0.0001$), and a significant interaction trial x treatment ($p<0.03$, $p<0.01$, $p<0.0001$, $p<0.001$) respectively. Wilcoxon tests revealed significant drops in oral temperature following administration of melatonin at all times except 2100. This study suggests an increase in sleep propensity in subjects ingesting melatonin prior to the desired rest period; however, it is somewhat limited by the homogeneity of the population used (adult males of a narrow age range).

- Wyatt et al. conducted a randomized, placebo-controlled, double-blind, parallel-group design trial to investigate the effects of melatonin on sleep latency and sleep efficiency in sleep episodes initiated across a full range of circadian phases (155). Subjects were healthy, young adults aged 18-30 (male, N=15; female, N=11). Treatment consisted of pharmaceutical grade melatonin obtained from Regis Technologies (Morton Grove, IL); dose was either 0.3 or 5mg delivered orally and administered 30 minutes prior to each 6.67-hour sleep episode during forced desynchrony from endogenous circadian rhythm. All subjects received placebo capsules during the first and last three days of the protocol. Outcome measures included polysomnographic recordings (EEG), sleep time and latency, core body temperature, and stage-distribution of sleep. Analysis revealed both doses of melatonin improved polysomnographically determined sleep efficiency from 77% in the placebo group (0.3mg = 84%, 5.0mg = 83%; all $p<0.05$) for sleep episodes occurring during circadian phases when endogenous melatonin was absent (EM-). However, this remained below the average sleep efficiency of 88% observed during sleep episodes scheduled during the circadian night, when endogenous melatonin was present (EM+). Comparisons within the three drug groups showed that all had statistically significant, lower sleep efficiency during EM- versus EM+ (all $p<0.05$). Melatonin did not affect sleep initiation, core body temperature, or relative stage-distribution of sleep in a statistically significant manner. This study reports an increase in sleep efficiency in response to melatonin treatment when administered outside of the increased endogenous melatonin phase of the body's natural circadian rhythm. Although no children or elderly were included, this study was thorough and well characterized.
- Paul et al. conducted a double-blind, placebo-controlled crossover study to compare the sleep-inducing power of four medications (zopiclone, zaleplon, melatonin, and temazepam) (120). There were nine men and 14 women, ages 21-53 years, who were assessed for psychomotor performance before and for seven hours after ingestion of a single dose of placebo, zaleplon 10mg, zopiclone 7.5mg, temazepam 15mg, or time-released melatonin 6mg. Subjects wore polysomnographic electrodes to record total sleep and sleep latency during 4-minute periods with eyes closed immediately before and after each psychomotor test sequence. Subjective drowsiness was assessed by questionnaire. There were drug x trials interactions for zaleplon, zopiclone, and temazepam for total sleep, sleep latency, and subjective drowsiness. More sleep, shorter sleep latency, and more drowsiness occurred immediately after psychomotor testing compared to before testing for all medications. Melatonin did not cause any sleep prior to psychomotor testing sessions, but caused sleep and reduced sleep latency after psychomotor test sessions from 1 3/4 hours to 4 3/4 hours post-ingestion. The authors reported the sleep-inducing power of the medications before psychomotor testing as zopiclone > zaleplon > melatonin > temazepam. The corresponding effect after psychomotor testing was reported to be zopiclone > melatonin > zaleplon > temazepam.
- Pinto et al. conducted a placebo-controlled, double-blind trial of 40 young adult males using two different criteria for sleep onset (10 min. of uninterrupted sleep and first three epochs of uninterrupted stage 1 sleep) to assess the effect of melatonin on inducing the onset of sleep (162). All subjects were men with an average age of 28 ± 5 years. Subjects were administered 10mg of melatonin or a placebo every day for 28 days one hour prior to sleep (10pm). Outcome measures

included polysomnographic recordings (EEG, EOG in both eyes, and EMG in both legs). Analysis revealed a statistically significant decrease in sleep latency ($p<0.05$) using one criterion (10 minutes of uninterrupted sleep). The study is also somewhat limited by the homogeneity of the population used (adult males of a narrow age range).

- Cajochen et al. conducted a randomized, placebo-controlled, double-blind crossover trial of eight healthy, young men to assess the effect of melatonin on subjective and objective measures of sleepiness (158). Eight male students (average age in experiment 1: 27±4 years old; experiment 2: 24.8±3.5 years old) were paid to participate in the study. The study comprised two separate experiments during which melatonin was either administered at 1800h or 1300h. Each subject participated in two consecutive treatment periods which comprised one day with placebo and one day of treatment with melatonin, in randomized order. Volunteers reported at 1500h (exp. 1) or 0900h (exp. 2) each day to the chronobiology laboratory for the eight hour experimental period. Subjects remained awake throughout experimentation. Toxic or interaction effects were not discussed. Dropouts were also not specifically addressed; however, data were reported for all eight subjects in both experiments. Outcome measures included half-hourly self-ratings of fatigue and mood obtained on 100mm visual analogue scales (VAS) as well as subject-completed Åkerstedt Sleepiness Symptoms Check Lists (ASSC) and Åkerstedt Sleepiness Scales (ASS). Furthermore, EEG, EOG, EMG, and ECG recordings were also made. Saliva was collected in parallel for analysis of melatonin. Analysis revealed a significant increase in subjective sleepiness as rated on the VAS, ASSC, and ASS in experiment 1. The ANOVAs for all three scales separately revealed a significant interaction term 'treatment*time' (VAS, $p<0.02$; ASSC, $p<0.04$; ASS, $p<0.001$). Following treatment, self-rated sleepiness on the ASS remained higher than after placebo from 1930h for the remainder of the evening ($p<0.05$). In experiment 2, melatonin administration increased subjective sleepiness as rated on the ASS ($p<0.05$) but not on the other two scales (VAS and ASSC). Statistical analysis of EEG data showed that the theta/alpha band (5.25-9Hz) was significantly higher following melatonin treatment as compared to placebo ($p<0.05$). Further analysis of the temporal relationship between melatonin concentrations, subjective sleepiness, and theta/alpha activity in the waking EEG revealed both subjective sleepiness and EEG power center points as significantly different from the melatonin center point ($p<0.002$). In addition, the subjective sleepiness center point occurred 23.4 minutes later than the EEG power center point ($p<0.002$). Testing of the relationship between melatonin levels and the amount of increase in subjective and objective fatigue as measure in the waking EEG showed no statistically significant correlations between subjective fatigue and the area under the melatonin curve (AUC) but showed statistically significant, negative correlations between the center point of subjective sleepiness and melatonin AUC ($p<0.05$). The authors concluded that this study presents evidence that daytime administration of melatonin causes an acute and strong effect on subjective and objective measures of sleepiness, though these findings are somewhat limited by the homogeneity of the subject population.
- Satomura et al. conducted a randomized, single-blind, placebo-controlled trial to assess the presence or absence of hypnotic action by administering exogenous melatonin during the day when secreted levels of melatonin are low compared to triazolam (153). Seven male college students were included in the study. Hypnotic action, effects on rectal temperature and dose dependency by daytime administration were assessed. Melatonin (1mg, 3mg, 6mg), triazolam 0.125mg, or placebo (lactose) was administered at 1330 hours; however the duration and frequency were not described. Exogenous melatonin (1mg, 3mg, and 6mg) significantly increased total sleep time and sleep efficiency compared to placebo ($p<0.05$). Melatonin 6mg was observed to demonstrate hypnotic effects that were nearly equal to those of triazolam at 0.125mg. Rectal temperature was decreased at melatonin 1mg and 3mg; however, the hypothermic action of triazolam and melatonin 6mg were not observed to be different in a statistically significant manner. Drop-outs, randomization, and blinding were not described.
- Kunz et al. conducted a randomized, double-blind, placebo-controlled trial to the effects of exogenous melatonin on disturbed REM sleep in humans (151). Fourteen subjects were assigned

to be treated with melatonin 3mg daily for four weeks (study 1). After a 3- to 5-day washout period, patients treated with melatonin in study 1 received placebo in study 2, and patients treated with placebo in study 1 received melatonin in study 2 for a four-week period. The results of the study show that melatonin was more effective than placebo: patients on melatonin experienced significant increases in REM sleep percentage (baseline/melatonin, 14.7/17.8 vs. baseline/placebo, 14.3/12.0, $p<0.010$) and improvements in subjective measures of daytime dysfunction, as well as clinical global impression score. Melatonin did not shift circadian phase or suppress temperature but did increase REM sleep continuity and promote decline in rectal temperature during sleep. Dropouts were not described.

- Nave et al. conducted a placebo-controlled, double-blind trial of 12 young adults to assess the combined effect of melatonin of two different dosages and pre-sleep dosage intervals on the onset and length of sleep of an early evening nap (152). Subjects were all students with an average age of 24.6 ±2.7 years, following more or less the same daily schedule and were given one of the following treatments: placebo and placebo, placebo and 3mg melatonin (or in the reverse order), placebo and 6mg melatonin (or in the reverse order). Outcome measures included polysomnographic recordings, sleep time and latency, and questionnaires probing subjective sleep experience. Analysis revealed a decrease in sleep latency ($p<0.0054$) and an increase in sleep time ($p<0.0001$) in all drug conditions. Additionally, all conditions exhibited an increase in stage 2 sleep time ($p<0.0054$). The authors neglect to discuss their particular methodology for polysomnographic recording and how they determined sleep time and onset latency from these recordings.
- Ellis et al. conducted a randomized, double-blind, placebo-controlled trial to evaluate the hypnotic action of melatonin in subjects with psychophysiological insomnia (148). Melatonin 5mg or placebo was taken at 2000 hours for a one-week period. Effects on sleep and wakefulness were monitored by visual analogue scale and interview. Bedtime, sleep onset time, estimated total sleep and wake time, as well as self-rated sleep quality, were not altered by melatonin, and estimates of next-day function did not change. The period of melatonin treatment was retrospectively correctly identified by eight of 15 subjects. Seven of 15 subjects reported that sleep had subjectively improved with active treatment.
- MacFarlane et al. conducted a conducted a double-blind, placebo-controlled, crossover study to evaluate the effects of melatonin on total sleep time and daytime alertness in patients with chronic insomnia (161). Patients (N=13) were administered melatonin 75mg per night or placebo at 2200 hours daily for 14 consecutive days. An increase in the subjective assessment of total sleep time and daytime alertness was demonstrated with melatonin but not with placebo. However, seven of the 13 patients reported that the active treatment had no effect on subjective feelings of well-being.

Melatonin: Insomnia (children)

- **Note**: Due to the quantity of melatonin research, the Evidence Discussion paragraphs are limited to meta-analyses, systematic reviews, and clinical trials with strong methodological design.
- **Summary**: Several randomized clinical trials have shown benefits of melatonin in children with insomnia. Non-randomized clinical trials have also been conducted (306; 307) and, overall, the results agree with those of randomized controlled trials (RCTs). A review of the effects of melatonin on sleep-wake disorders in children and adolescents was published by Jan et al. in 1999 (308). More well-designed studies are needed before a conclusion can be made.
- **Evidence**: Smits et al. conducted a randomized, placebo-controlled, double-blind trial to investigate the effect of melatonin treatment on health status and sleep in children with idiopathic sleep-onset insomnia (266). Sixty-two children, six to 12 years of age, who suffered for more than one year from idiopathic chronic sleep-onset insomnia, received either 5mg melatonin or placebo at 1900 hours. The study consisted of a one-week baseline period, followed by a four-week treatment. Health status was measured with the RAND General Health Rating Index (RAND-GHRI) and Functional Status II (FS-II) questionnaires. Lights-off time, sleep onset, and wake-up time were recorded in a diary, and endogenous dim light melatonin onset was measured in saliva.

The total scores of the RAND-GHRI and FS-II improved significantly more during melatonin treatment compared to placebo. The magnitude of change was much higher in the melatonin group than in the placebo group, with standardized response means for the RAND-GHRI of 0.69 versus 0.07 and for the FS-II of 1.61 versus 0.64. Melatonin treatment also significantly advanced sleep onset by 57 minutes, sleep offset by nine minutes, and melatonin onset by 82 minutes, and decreased sleep latency by 17 minutes. Lights-off time and total sleep time did not change.

- Smits et al. conducted a double-blind, placebo-controlled trial to establish the efficacy of melatonin treatment in childhood sleep onset insomnia (265). Forty elementary school children, six to 12 years of age, who suffered for more than one year from chronic sleep onset insomnia received 5mg melatonin or placebo. The study consisted of a one-week baseline, consecutively followed by a four-week treatment period. The study's impact was assessed by measurements of lights-off time, sleep onset, and wake-up time, recorded in a diary (N=33). Sleep onset was also recorded with an actigraph (N=25). Endogenous dim light melatonin onset was measured in saliva (N=27). Sustained attention was evaluated with the Bourdon-Vos reaction time test (N=36). In the melatonin group, mean (95% CI) lights-off time advanced 34 (6-63) minutes, diary sleep onset 63 (32-94) minutes, actigraphic sleep onset 75 (36-114) minutes, and melatonin onset 57 (24-89) minutes; total sleep time increased 41 (19-62) minutes. The change during the four-week treatment period differed between the treatment groups significantly as to lights-off time, diary and actigraphic sleep onset, sleep duration, and melatonin onset. There were no statistically significant differences between the treatment groups in the change of sleep latency, wake-up time, and sustained attention reaction times. Mild headache occurred in two children during the first two days of the melatonin treatment. Eighteen months after the start of the trial, in 13 of the 38 children who could be followed up, melatonin treatment was stopped because their sleep problem was solved, and in one child because sleep was not improved. Twelve children used melatonin 5mg, the other 1mg to 2.5mg. One child developed mild generalized epilepsy four months after the start of the trial.
- Van der Heijden combined the data of two randomized controlled trials (N=110, between 6-12 years) to investigate the efficacy of melatonin by pretreatment dim light melatonin onset in children with chronic sleep onset insomnia (309). Sleep was actigraphically estimated, and saliva collected, at baseline and in the third week of a four-week treatment period with 5mg melatonin or placebo at 1800 or 1900 hours. Primary outcome measures were pre- to post-treatment changes in dim light melatonin onset (DeltaDLMO), sleep onset (DeltaSO), sleep latency (DeltaSL), and total sleep duration (DeltaTSD). Melatonin advanced DLMO with +1:12 h ($p<0.001$), SO with +0:42 h ($p=0.004$), SL decreased with 25 min ($p=0.019$), and TSD did not change significantly, as compared with placebo. In the melatonin-treated group, but not in the placebo-treated group, pretreatment DLMO was related to DeltaDLMO [$F(1, 29) = 7.28$, $p=0.012$] and DeltaSO [$F(1, 25) = 7.72$, $p=0.010$]. The time interval between treatment administration and pretreatment DLMO (INT) was only related to DeltaSO [$F(1,26) = 5.40$, $p=0.028$]. The researchers conclude that the results suggest that in children with sleep onset insomnia, the efficacy of early evening melatonin to advance sleep onset and endogenous melatonin onset increases the later the pretreatment DLMO is administered.

Melatonin: Preoperative sedation / anxiolysis

- **Note**: Due to the quantity of melatonin research, the Evidence Discussion paragraphs are limited to meta-analyses, systematic reviews, and clinical trials with strong methodological design.
- **Summary**: A small number of studies have compared melatonin with placebo and standard drugs (benzodiazepines) for sedation and anxiety reduction prior to general anesthesia for surgery. Melatonin has also been suggested as a treatment for delirium following surgery (310). Non-randomized clinical trials have also been conducted (311) and, overall, the results agree with those observed in the randomized controlled trials (RCT). However, due to weaknesses in the design and reporting of the available research, better studies are needed before a clear conclusion can be drawn.

- **Evidence**: Caumo et al. conducted a randomized, double-blind, placebo-controlled study to test whether premedication with melatonin (N-acetyl-5-methoxytryptamine) is as effective as clonidine premedication, and if both are more effective than placebo, in reducing postoperative pain and anxiety and enhancing postoperative clinical recovery (312). Patients were included if they were 19 to 60 years old, classified as class I or II (normal healthy patient or mild systemic disease) according to the American Society of Anesthesiologists (ASA) grading system, and scheduled to undergo total abdominal hysterectomy for myomatosis. Patients were excluded if they had contraindications to regional anesthesia, history of congestive heart failure or valvular heart disease, renal or hepatic disease, body mass index (BMI) greater than 25 kg/m2, or a history of or positive screening for current psychiatric disorder. Depending on the treatment group, patients received 5mg oral melatonin (N=20), 100mcg oral clonidine (N=19), or an oral placebo tablet (N=20). During the first 72 hours after the total abdominal hysterectomy, all participants received 2.5mg morphine, with a 10-minute lockout, and a maximum dose of 30mg per four hours via a patient controlled analgesia (PCA) pump. If the pain was unrelieved, then the dose was increased by 0.8mg until pain control was achieved. The night before and one hour before total abdominal hysterectomy, participants received either 5mg melatonin tablet, 100mcg clonidine tablet, or a placebo tablet. Thirty-six hours after surgery, melatonin and placebo groups received a dose of placebo while the clonidine group received another dose of 100-mcg oral clonidine. Sixty-three patients were randomly assigned to one of three groups and received preoperative intervention, but four were excluded from analysis. One patient's surgery was cancelled, one withdrew for an unknown reason, one submitted to myomectomy, and one failed epidural anesthesia. There was a reduction in morphine consumption in the melatonin-treated subjects, which authors stated may be explained by evidence from animal studies that show interactions between opioid peptides and the analgesic effects of melatonin. The primary outcomes were intensity of postoperative pain up to 72 hours after surgery, assessed using the subjective 10-cm visual analog scale (VAS), and analgesic consumption, measured by morphine consumption objectively registered using a patient controlled analgesia (PCA) pump. A statistically significant difference was observed between the treatment groups (melatonin and clonidine) and placebo groups on the levels of postoperative pain ($p<0.05$) during the first 48 hours after surgery. There was no statistical difference ($p>0.05$) between VAS scores in the melatonin and clonidine treatment groups. Morphine consumption showed a significant reduction over time, independent of treatment group ($p=0.00$), and was not affected by the interaction between time and treatment ($p=0.07$). Beneficial reductions in postoperative morphine consumption from the anxiolytic effect of melatonin and clonidine were more evident in highly anxious patients than those only mildly anxious. There was a significant decrease of postoperative anxiolysis ($p=0.03$) in the melatonin and clonidine group from 6, 24, and 48 hours. In patients experiencing high anxiety six hours after surgery (high anxiety subgroup), the incidence of postoperative moderate to intense pain was lower in both melatonin and clonidine groups than in placebo. However, the incidence of postoperative pain in the low anxiety group was similar in the melatonin, clonidine, and placebo groups. For patients with higher levels of anxiety, the NNT to prevent moderate to intense pain during the first 24 hours postoperatively was 1.52 (95% CI, 1.14 to 6.02) and 1.64 (95% CI, 1.29 to 5.93) in the melatonin and clonidine groups, respectively, compared with the placebo. For the participants with mild levels of anxiety, the NNT to prevent moderate to intense pain during the first 24 hours postoperatively in the melatonin and clonidine groups compared with placebo-treated was 15.71(95% CI, 2.53 to ∞) and 63 (95% CI, 2.28 to ∞), respectively. The authors acknowledged that pharmacological response to sedatives is related to gender, age, and surgery type. Therefore, data obtained in this study cannot be extrapolated to other surgeries or different populations easily.
- Ismail et al. conducted a prospective, randomized, placebo-controlled, double blind study on patients undergoing cataract surgery to assess the effects of oral melatonin on pain, anxiety, and intraocular pressure (IOP) (313). Subjects were 40 patients (all aged greater than 60) with an American Society of Anesthesiologists (ASA) physical status I-III, scheduled to undergo cataract

surgery with intraocular lens implantation using topical anesthesia for the procedure. The exclusion criteria included any of the following: autoimmune disease, diabetes, epilepsy, depression, leukemia, nystagmus, deafness, concurrent use of analgesic or sedative drugs regularly, allergy to study medications and those unable to tolerate Shioetz tonometer measurements. Subjects received a melatonin 10mg tablet or a placebo tablet by mouth. Each treatment arm consisted of 20 subjects, with a total of 40 participants. A one-time dose was administered 90 minutes prior to cataract surgery. Mean arterial pressure (MAP) decreased significantly after melatonin premedication. No hypotension or bradycardia requiring intervention was reported in either group. However, after melatonin administration, IOP decreased significantly; this drop was maintained to the end of surgery. No incidence of hypoxia or intraoperative complications was noted. One individual taking melatonin complained of dizziness, and another patient taking placebo suffered nausea. Primary subjective outcomes were reduction in anxiety and pain scores measured using the verbal anxiety score (VAS) and the verbal pain score (VPS), respectively. Secondary objective outcomes included intraocular pressure (IOP), mean arterial blood pressures (MAP), heart rate (HR), and peripheral oxygen saturation values (measured before medication administration, three times during the operation and three times after surgery had commenced, and once before discharge). Anxiety scores decreased significantly in the melatonin treatment arm preoperatively ($p=0.04$), and intraoperatively ($p=0.005$) compared to the placebo group. Pain scores and analgesia administration were also significantly lower in the melatonin group ($p=0.007$). Subjects treated with melatonin had significantly decreased IOP, which was maintained until the end of surgery ($p<0.001$). MAP was also decreased significantly in the melatonin group.

- Samarkandi et al. conducted a randomized, double-blind, placebo-controlled trial to compare the perioperative effects of different doses of melatonin and midazolam in children (90). Seven groups of children (N=15 in each) received one of the following premedicants. Midazolam 0.1, 0.25 or 0.5mg/kg(-1) orally, melatonin 0.1, 0.25 or 0.5mg/kg(-1) orally, each mixed in 15mg/kg(-1) acetaminophen, or placebo only (15mg/kg(-1) acetaminophen). Anxiety and temperament were evaluated before and after administration of the study drug, on separation from parents and on the introduction of the anesthesia mask. At week two postoperatively, the behavior of the children was measured by the Post Hospitalization Behavior Questionnaire. Melatonin or midazolam each in doses of 0.25 or 0.5mg/kg(-1) were equally effective as premedicants in alleviating separation anxiety and anxiety associated with the introduction of the anesthesia mask. The use of melatonin was associated with a lower incidence ($p=0.049$) of excitement at 10 minutes postoperatively, and a lower incidence ($p=0.046$) of sleep disturbance at week two postoperatively than that observed with midazolam and control groups. No postoperative excitement was noted in the melatonin groups at 20, 30 and 45 min. The authors conclude that melatonin was not only as effective as midazolam in alleviating preoperative anxiety in children, but it was also associated with a tendency towards faster recovery, lower incidence of excitement postoperatively and a lower incidence of sleep disturbance at week 2 postoperatively.
- Acil et al. conducted a randomized, double-blind, placebo-controlled trial to compare the perioperative effects of melatonin and midazolam given in premedication, on sedation, orientation, anxiety scores and psychomotor performance (87). Sixty-six patients undergoing laparoscopic cholecystectomy received melatonin 5mg, midazolam 15mg, or placebo, 90 min before anesthesia, sublingually. Sedation, orientation and anxiety were quantified before premedication, 10, 30, 60 and 90 min after premedication; and 15, 30, 60 and 90 min after admission to the recovery room. Neurocognitive performance was evaluated at these times, using the Trail Making A and B and Word Fluency tests. Patients who received premedication with either melatonin or midazolam had a significant increase in sedation and decrease in anxiety before operation compared with controls. After operation, there was no difference in sedation scores of all groups. However, 30, 60 and 90 min after premedication, the melatonin and midazolam groups exhibited a poorer performance in Trail Making A and B tests compared with placebo, there were no statistically significant differences among the groups in terms of neuropsychological performance after the operation.

Amnesia was notable only in the midazolam group for one preoperative event. The authors conclude that melatonin premedication was associated with preoperative anxiolysis and sedation without postoperative impairment of psychomotor performance.

Melatonin: Sleep disorders (secondary)

- **Note**: Due to the quantity of melatonin research, the Evidence Discussion paragraphs are limited to meta-analyses, systematic reviews, and clinical trials with strong methodological design.
- **Summary**: Melatonin may improve sleep disturbances in a wide range of patients, including those in the intensive care unit (ICU) and with Alzheimer's disease (126; 129; 314-316), as well as those with psychiatric disorders (317) and end-stage renal disease (318). Several published cases report improvements in sleep patterns in young people with damage to the pineal gland area of the brain due to tumors or surgery (319-322). Melatonin has also been proposed as a possible therapy for asynchronization, a disease condition produced by exposure to light during nighttime hours (323), and melatonin in combination with clomethiazole in circadian rhythm sleep disorder in elderly patients with dementia (324). Preliminary research suggests that melatonin may improve sleep in patients with asthma. Melatonin has been suggested for the improvement of sleep patterns in patients with depression, although research is limited in this area (126; 134; 138; 325; 326). Due to very limited study to date, a recommendation cannot be made for or against the use of melatonin in Parkinsonism (327) or Parkinson's disease (328-330). There is limited study of melatonin given to patients with sleep disturbances associated with bipolar disorder (such as insomnia or irregular sleep patterns) (137; 141; 331). A review of the use of alternative treatments (including melatonin) in pediatric bipolar disorder concluded that more research is warranted and necessary (332). There is limited study of melatonin for improving sleep latency (time to fall asleep) in patients with schizophrenia (143; 304). Sleep disturbances in blind children have been associated with delays in nocturnal secretion of melatonin (333). Although melatonin has been shown to improve sleep in a number of contexts, not all trials have been positive. Depending on the particular condition, melatonin may or may not be an effective sleep aid.
- **Meta-analysis (patients with intellectual disability)**: Braam et al. conducted a meta-analysis to investigate whether melatonin is effective for sleep problems in individuals with intellectual disabilities (334). The databases PubMed, Medline and Embase were searched for randomized controlled trials (written in English) that used melatonin as a treatment intervention for individuals with a diagnosis of intellectual disabilities. Search criteria under the heading of developmental problems included "intellectual disability," "developmental disability," "learning disorder," "mental retardation," and "neurodevelopmental disability." Furthermore, for inclusion, studies had to contain quantitative data on one of the following measures: sleep latency, total sleep time, or number of wakes per night. Nine studies were found to meet inclusion criteria (98; 277; 277; 286; 287; 293-295; 335). Doses used ranged from 0.5mg to 9mg, with regimens lasting from 32 to 73 days (inclusive of washout periods). Of the nine included studies, only four specified the formulation of melatonin used. McArthur et al. and both studies by Braam et al. used immediate release melatonin, whereas the Wasdell et al. study used a combination immediate release (1mg)/ extended release (4mg) melatonin product. Analysis of the included trials revealed that melatonin treatment was found to decrease median time to sleep by 34 minutes ($p<0.001$), increase median length of sleep by 50 minutes ($p<0.001$), and decrease median night time wakes ($p=0.024$). The mean quality of included studies was 25.28 out of a scale of 32. The two reviewers had an intraclass correlation of 0.90. No substantial effect on publication bias was observed. Overall most adverse effects were small with rates comparable to placebo. It should be noted that, of the nine included trials, five had less than ten subjects. Also, none of the studies compared the same developmental disabilities.
- **Systematic review (in patients with autism)**: Rossignol et al. conducted a systematic review of the literature for novel and emerging treatments for Autism Spectrum Disorders (ASD), among which melatonin was identified (336). The studies included regarding melatonin were (98; 271; 282; 292; 294; 337-344). Studies were gathered via a systematic search through PubMed and

Google Scholar (1966 to April 2009), using the search terms autism, autistic, pervasive, or PDD in all languages in combination with a list of identified treatments. The list of treatments was developed by drawing on the Autism Research Institute, review articles, and the author's knowledge of the relevant literature. Regimens from the included studies ranged from 0.75mg to 10mg administered over two weeks to two months. Reported adverse effects included morning drowsiness, nighttime awakening, increased enuresis, and excitement before going to sleep. Experimental measures consisted of blood melatonin concentrations, nighttime urinary excretion of 6-sulphatoxymelatonin, total night sleep, length of sleep, sleep-wake rhythm, sleep pattern, sleep latency, night time awaking, sleep onset time, and seizure occurrences. The Jan et al. study reported that fast-release melatonin improved sleep in over 80% of the children, without any adverse effects or tolerance observed in the retrospective study that recruited children with chronic sleep disorders and a neurologic or developmental disability (including an unspecified number with autism). Hayashi et al. observed prolonged total night sleep and improved the sleep-wake rhythm in a case study. Ishiyaki et al. reported that melatonin administered at bedtime led to improvements in sleep in 84% of participants. Paavonen et al. stated that melatonin significantly improved sleep patterns and decreased sleep latency ($p<0.002$) in children with Asperger's syndrome. Giannotti et al. stated that melatonin significantly improved sleep ($p < 0.001$) without any adverse effects in autistic children with sleep disorder, although sleep problems returned when melatonin therapy was stopped (and improved again when melatonin was reintroduced). These improvements were still present at both 12- and 24-month follow-ups. In a retrospective study, Andersen et al. reported that 85% of participating children experienced improvements in sleep. In the same study, only one child had worsening of sleep with melatonin and three other children had mild adverse effects. Wasdel et al. stated that melatonin therapy improved the length of sleep ($p<0.01$) and sleep latency ($p<0.01$) in children with a neurodevelopmental disorder and sleep problems. Garstang et al. reported significant improvement on sleep latency by nearly 0.9 hours ($p<0.05$), decreased nighttime awakenings ($p<0.05$), and increased sleep duration by 1.1 hours ($p<0.05$) in 11 ASD children. Finally, Wirojanan et al. stated that the use of melatonin in children with autism and/or fragile X syndrome increased mean sleep duration ($p=0.02$), sleep latency ($p=0.0001$), and sleep onset time ($p=0.02$). The authors concluded that promising treatments for ASD include melatonin, antioxidants, acetylcholinesterase inhibitors, naltrexone and music therapy, which all received a Grade A according to their evidence-based guideline (based on the availability of 2 or more randomized controlled trials or 1 or more systematic reviews).

- **Systematic review (patients with Alzheimer's disease)**: Jansen et al. conducted a systematic review to assess the clinical efficacy and safety of melatonin in the treatment of manifestations of dementia or cognitive impairment (345). The Cochrane Dementia and Cognitive Improvement Group's Specialized Register was searched for trials involving melatonin on 5 October 2005. The search terms used were "melatonin" and "n-acetyl-5-methoxytryptamine." The review included randomized controlled trials that compared orally administered melatonin in any dosage with a control group, and analyzed effects on cognitive, behavioral (excluding sleep), and/or affective disturbances of people with dementia of any degree of severity. Two to three reviewers independently assessed the retrieved articles for relevance and methodological quality, and extracted data from the selected studies. Statistically significant differences in changes in outcomes from baseline to end of treatment between the melatonin and control groups were examined. Each study was summarized using a measure of effect (e.g. mean difference) and meta-analyses were conducted when appropriate. Three studies met the inclusion criteria (125; 130; 131). This review revealed non-statistically significant effects from the pooled estimates of MMSE cognitive, and ADAS cognitive change scores. Individual study estimates for treatment effect demonstrated a statistically significant improvement for melatonin compared with placebo in behavioral and affective symptoms as measured by the ADAS non-cognitive scale in a study of 20 patients, and the Neuropsychiatric Inventory (NPI) following treatment with 2.5mg daily (SR) melatonin, but not with 10mg daily (IR) melatonin in a larger study of 157 patients. The remainder

of the treatment effects for affect, behavior, and activities of daily living were non-statistically significant.

- **Evidence (patients with depression)**: Serfaty et al. conducted a randomized double-blind, placebo-controlled trial to determine if exogenous melatonin can act as a sleep promoter and antidepressant in patients with major depressive disorder (MDD) (346). Patients aged 18-65 years were included in the trial if they were diagnosed with major depressive disorder (MDD) and experienced early-morning wakings. Subjects (33 patients diagnosed with major depressive disorder early-morning waking) were administered melatonin (6mg slow-release at bedtime) or placebo for four weeks in addition to any pre-existing treatment for depression. Patients were excluded if they had delusions, hallucinations, suicidal ideation, or a recent change in psychotropic medication within the last four weeks. Actigraphy, sleep diaries, and the Leeds Sleep Evaluation Questionnaire were used as measures of sleep quality. Two subjective questionnaires, the Beck Depression Inventory (BDI) and the 21-item Hamilton Depression Rating Scale (HDRS), were used to measure depression. Of the 33 participants, 31 completed the trial; two dropped out immediately because they felt better. Sleep diary data indicated a shortened time to get to sleep ($p=0.03$); however, this was not specific to melatonin. LSEQ scores revealed a significant improvement in sleep based on time getting to sleep and quality of sleep for the whole group (not specific to melatonin). There was no correlation between subjective and objective measures of sleep. The BDI and HDRS questions relating to sleep showed no significant differences in sleep between the melatonin and placebo group. Overall, HDRS scores showed a significant change with time ($p<0.01$). However, this was not related to any one group and was considered an overall decrease. BDI scores showed an insignificant difference between melatonin and placebo (2.03, 95% CI:-6.30 to 2.25), in favor of melatonin. It should be noted that the study was conducted over a three year three month period with different patients undergoing the four-week randomization throughout this time. The trial stated that 17 people would be required in each group (total of 34) in order to power the trial adequately; however, this standard was not met. It should also be noted that participants were allowed to continue any current antidepressive medication, whose effects on these findings are difficult to quantify.
- **Evidence (post-operative)**: Gögenur et al. conducted a placebo-controlled, randomized clinical trial to determine whether postoperative melatonin administration would improve sleep quality, fatigue, and general well-being in patients undergoing elective ambulatory laparoscopic cholecystectomy (347). Subjects were patients scheduled for elective outpatient laparoscopic cholecystectomy with an American Society of Anesthesiologists (ASA) physical status classification I–III. Exclusion criteria were: pre-existing sleep disorders, treatment with hypnotics or psychotropic drugs (including opioids) within a week of admission, daily analgesic treatment, treatment with beta-blockers, or ongoing treatment with Coumadin derivates. Patients were instructed to take treatment (either a 5mg melatonin capsule or placebo) at bedtime for three nights following discharge. Five patients were excluded from the study post-enrollment. Patients who experienced a complicated recovery or were changed to an open procedure were dropped. Self-reported sleep quality was assessed by questionnaire and sleep diary. The time and duration of daytime naps were also recorded. Self-reported discomfort was evaluated using questions concerning level of fatigue, general well-being, and pain. These parameters were also measured on a visual analogue scale (VAS). Assessments were made preoperatively and for three days postoperatively. No significant differences between the melatonin group and the placebo group were observed when comparing postoperative sleep quality, total sleep duration, number of night awakenings, night awakening duration, number of daytime naps, and nap duration. Sleep latency in the melatonin group was significantly reduced as compared to placebo on postoperative night one ($p<0.05$), but was not significantly reduced on other postoperative nights. This was a well-developed and well executed-study. The authors acknowledge the possibility of suboptimal dosing.
- **Evidence (elderly with sleep or behavioral disorders)**: Garzon et al. conducted a prospective randomized, double blind, placebo-controlled, crossover trial to examine the efficacy of melatonin

on sleep and behavioral disorders in the elderly (348). A total of 22 participants (7 men and 15 women) over 65 years of age were recruited from several community health centers in Seville, Spain. Subjects were included if they were healthy, aged 65 or older, and diagnosed with insomnia or transient sleep disorders related to emotional stress. Subjects were excluded if they had secondary sleep disorders, autoimmune diseases, tumors, dementia, psychosis or other severe mental disorders, advanced, severe or unstable medical diseases or currently enrolled in another experimental protocol. Subjects receiving hypnotic drug therapy were not excluded. Melatonin (5mg) or placebo (lactose) was given at bedtime (around 11pm) seven days a week for eight weeks. Subjects then underwent a two week washout period before crossover treatment for another eight weeks. The overall study duration was 18 weeks. Four participants did not complete the study. The causes for dropouts included missing more than two days of participation, an adverse event that was determined to be unrelated to the study, and diagnosis of a severe disease. Participants were assessed throughout the two phases (eight weeks each) with the Northside Hospital Sleep Medicine Institute (NHSMI) test for sleep disorder. Yesavege Geriatric Depression Scale (GDS) and Goldberg Anxiety Scale (GAS) were also used. Subjects' ability to discontinue hypnotic drugs was evaluated as well. NHSMI test results showed improved sleep quality in the melatonin group ($p<0.005$) compared to both baseline and placebo. Nine out of 14 subjects were able to discontinue hypnotic drug therapy (benzodiazepine) during both the melatonin and placebo treatment period. The GDS and GAS also revealed significant improvements in depression ($p=0.043$) and anxiety ($p=0.009$) measurements after melatonin therapy compared to baseline or placebo. It should be noted that concomitant use of other sedatives may have affected the results of this study.

- **Evidence (patients with cystic fibrosis)**: de Castro-Silva et al. conducted a randomized, double-blind, placebo-controlled study to evaluate the effects of exogenous melatonin on sleep and inflammation in cystic fibrosis (349). Subjects (N=19) were clinically stable patients with a confirmed diagnosis of cystic fibrosis, and free of infection or hospitalization in the last 30 days. Subjects were excluded for co-morbidities (including diabetes mellitus), or use of hypnotic-sedative drugs. Subjects received identical melatonin (3mg) or placebo capsules. Prior to supplementation, patients were monitored to acquire baseline (day zero to day six) objective and subjective measures (questionnaire) of sleep. They were then randomized into the melatonin or placebo group wherein they received treatment two hours before bedtime for three weeks. Primary outcome measures were nitrite and isoprostane levels (to test stress and inflammation on lung tissue) measured from exhaled breath condensate (EBC) using spirometry and sleep-wake patterns measured using actigraphy. Secondary outcome measures included subjective sleep questionnaires to evaluate global sleep quality (Pittsburgh Sleep Quality Index) and excessive daytime sleepiness (Epworth Sleepiness Scale). After treatment, patients in the melatonin group showed significant improvements in sleep efficiency (SE) ($p=0.01$) and a trend toward shorter sleep latency ($p=0.08$). Nitrite levels were significantly reduced after treatment with melatonin ($p=0.01$); a significant reduction was not seen in the placebo group ($p=0.43$). It should be noted that data from one patient was excluded from analysis without explanation.
- **Evidence (in hemodialysis patients)**: Koch et al. conducted a randomized, double-blind, placebo-controlled, crossover study in 20 patients to investigate the effects of melatonin on sleep-wake rhythm in patients on hemodialysis (350). Patients included in this study were between 18 and 85 years of age and on stable hemodialysis for more than three months. Patients were excluded if they had previously used melatonin, current use of hypnotics that could not be discontinued, or if they had severe psychological or neurological disease. Patients received either 3mg melatonin daily or placebo daily at 10pm. In the first six weeks, melatonin 3mg tablets or placebo tablets were taken every night. In the second six weeks, treatments were reversed. All patients received 3mg tablets for the last six weeks (no washout was included due to the short half-life of melatonin). Four patients dropped out of the original 24 patients enrolled. Two patients died, one terminated his dialysis, and one was excluded due to noncompliance. The Dutch sleep disorders questionnaire was used to determine sleep-wake characteristics and patients kept a log of their sleep-wake

schedule for one week at baseline, after five, and after eleven weeks. Patients needed a median of 44.5min (CI 50±78 min) to fall asleep with placebo treatment and 15.5min (CI 33.6 ± 66min, p=0.002) after melatonin treatment. Sleep efficiency increased from 67.3% with placebo to 73.1% with melatonin (p=0.01). Actual sleep time increased from 377min with placebo to 388 min with melatonin (p=0.003), and sleep fragmentation decreased from 4.5 to 3.1 (p=0.007). Patients reported less time needed to fall asleep on nights of daytime dialysis (p=0.003) and the nights without daytime dialysis (p=0.04) when using melatonin instead of placebo. An increase in sleep time was seen on nights after daytime dialysis (p=0.01) with melatonin. Wake periods during the nights were significantly fewer on nights after dialysis (p=0.03) and nights without daytime dialysis (p=0.03). Limitations of this study include the reliance on subjective reporting.

- **Evidence (patients with intellectual disability)**: Braam et al. combined data from a pair of randomized controlled trials (293; 335) to examine the efficacy of melatonin in improving sleep and decreasing behavioral problems in persons with intellectual disabilities (ID) and chronic insomnia (351). Subjects were 66 patients with chronic insomnia with comorbid ID who had been referred to the investigators' sleep center by local general practitioners. Insomnia was defined as difficulty falling asleep (30 minutes or greater), waking up twice or more during the night for more than 45 minutes, or waking up five times for no less than 15 minutes each time, with these difficulties persisting for one year or longer. Patients with somatic or psychiatric causes of insomnia, previous use of melatonin, restless legs syndrome, liver or renal disease, chronic pain, sleep apnea, or those individuals younger than two years of age were excluded. Subjects received either melatonin (5mg for individuals six years of age and older and 2.5mg for those younger) or placebo (N=27 and 22, respectively) for four weeks (younger patients at 6pm, older patients at 7pm). Subjective outcome measures which were used to quantify challenging behavior included the Storend Gedragsschaal voor Zwakzinnigen (SGZ; Maladaptive Behavior Scale for the Mentally Retarded). Subjective measures which were used to quantify sleep problems included: times lights went out, time to actual sleep, total sleep time, and number and duration of night time wakes as logged by a sleep diary. Objective outcome measures included dim light melatonin onset (DLMO), which was set when salivary melatonin reached 4pg/mL. Out of the initial subject pool, one child was withdrawn due to unwillingness to submit to saliva sampling, and nine children in the placebo group and seven in the melatonin group were excluded due to incomplete sleep logs or SGZ scales. Melatonin therapy was found to significantly reduce mean SGZ-T ($p<0.003$) and M ($p<0.005$) scores, though V subscale scores were not (p=0.0617). Though clinical improvement was noted in individual items of the SGZ-A subscale, the mean score was not significantly changed (p=0.076). Melatonin treatment was also found to significantly improve a number of sleep parameters including sleep latency, number of wakes, duration of wakes, and total sleep time ($p<0.001$, 0.002, 0.034, and 0.043, respectively), as well as significantly advance DLMO ($p<0.001$). Time light out, however, was not significantly changed (p=0.697). Limitations of this study include reliance upon subjective measures of sleep and a small subject population. It should also be noted that although specific mention of an identical placebo is made, it is unclear if the study was double-blinded.
- **Evidence (hospitalized and medically ill patients)**: Ibrahim et al. conducted a randomized double-blind, placebo-controlled trial to examine the effects of nocturnal melatonin on nocturnal sleep in tracheostomized patients (127). Thirty-two ICU patients with tracheostomy who were not receiving continuous sedation were administered either oral melatonin (3mg) or placebo at 2000 h. Pre- and post-dosage blood samples on Days 1 and 3 were collected to confirm drug delivery. Primary outcome measure was number of hours of observed sleep at night, assessed by the bedside nurse. Secondary outcome measures included comparison of the incidence of agitation, assessed by score on the Riker Sedation-Agitation Scale, and requirement for sedatives or haloperidol to settle agitation. Pre-treatment melatonin levels in the two groups were similarly low: 4.8pg/mL (95% CI: 2.4-7.5) for melatonin versus 2.4pg/mL (95% CI: 1.6-3.2) for placebo (p=0.13). Post-treatment, melatonin levels increased in the melatonin group compared with the placebo group (3543pg/mL vs. 3pg/mL; $p<0.0001$). This finding was statistically significant.

However, subsequent observed nocturnal sleep was similar in the two groups: 240 minutes (range: 75-331.3) for melatonin versus 243.4 minutes (range: 0-344.1) for placebo (p=0.98). Observed diurnal sleep was also similar: 138.7 minutes (range, 50-230) with melatonin versus 104 minutes (range: 0-485) for placebo (p=0.42). The incidence of agitation was higher in the melatonin group versus placebo (31% vs. 7%; p=0.11); however this finding was not statistically significant. The requirement for extra sedation or use of haloperidol was slightly higher in the placebo group compared to the melatonin group (57% vs. 46%; p=0.56). This finding was also not statistically significant.

- Kemp et al. conducted a randomized double-blind, controlled crossover trial to compare melatonin (5mg) and amitriptyline (25mg) in a small sample of traumatic brain injury (TBI) patients presenting with chronic sleep disturbance (352). No differences in sleep latency, duration, quality or daytime alertness were found for either drug compared to baseline using significance testing. However, the authors reported that the effect sizes revealed some encouraging changes. Patients on melatonin reported improved daytime alertness compared to baseline. On amitriptyline, patients reported increased sleep duration compared to baseline.
- Andrade et al. conducted a randomized, double-blind, placebo-controlled trial to assess the effects of melatonin in medically ill patients with insomnia (128). Thirty-three medically ill patients were administered melatonin (N=18) or placebo (N=15) in a flexible dose regimen. The mean stable dose of melatonin was found to be 5.4mg. Melatonin significantly improved sleep onset, quality and depth of sleep, and increased sleep duration without producing drowsiness, early-morning "hangover" symptoms, or daytime adverse effects ($p<0.05$). Melatonin also contributed to freshness in the morning and during the day and improved overall daytime functioning ($0.05<p<0.10$). Benefits were most apparent during the first week of treatment.
- **Evidence (patients with asthma)**: Campos et al. conducted a randomized, double-blind, placebo-controlled study to examine the effects of melatonin on sleep disturbances in patients with asthma (133). Twenty-two consecutive women with asthma were randomized to receive melatonin 3mg (N=12) or placebo (N=10) for four weeks. Sleep quality and daytime somnolence were assessed by the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale, respectively. Pulmonary function was assessed by spirometry. Use of relief medication, asthma symptoms, and morning and evening peak expiratory flow rate were recorded daily. Melatonin treatment improved subjective sleep quality, as compared with placebo (p=0.04). No statistically significant difference in asthma symptoms, use of relief medication and daily peak expiratory flow rate, was found between groups.
- **Evidence (patients with Parkinson's disease)**: Medeiros et al. conducted a randomized placebo-controlled trial to evaluate the effect of melatonin on sleep and motor dysfunction in Parkinson's disease (PD) (140). Eighteen patients (Hoehn & Yahr I to III) from a PD clinic were included. Prior to treatment, baselines were assessed. Patients were then randomized to receive melatonin (3mg) or placebo one hour before bedtime for four weeks. On initial assessment, 14 patients (70%) showed poor quality sleep (PSQI > 6) and eight (40%) excessive daytime sleepiness (ESS > 10). Increased sleep latency (50%), REM sleep without atonia (66%), and reduced sleep efficiency (72%) were found on PSG. Eight patients had an apnea/hipopnea index greater than 15 but no severe oxygen desaturation was observed. Sleep fragmentation tended to be more severe in patients on lower doses of levodopa (p=0.07). Although melatonin improved subjective quality of sleep (p=0.03) as evaluated by the PSQI index, PSG abnormalities were not changed. Motor dysfunction was not improved by the use of melatonin. Undetected differences in motor scores and PSG findings may have been due to a small sample size and a type II error.
- Dowling et al. conducted a randomized double-blind, placebo-controlled trial to compare the effects of two doses of melatonin to placebo on sleep, daytime sleepiness, and level of function in patients with PD who complained of sleep disturbances (139). Forty patients completed the 10-week protocol. There was a two-week screening period, two-week treatment period, and one-week washout between treatments. Patients received 50mg melatonin or placebo. Nocturnal sleep was assessed by actigraphy and diaries, whereas daytime sleepiness and function were assessed by the

Epworth Sleepiness Scale (ESS), Stanford Sleepiness Scale (SSS), and General Sleep Disturbance Scale (GSDS). Repeated measures analysis of variance revealed an improvement in total nighttime sleep time during treatment compared to placebo. There was an improvement in subjective sleep disturbance, sleep quantity, and daytime sleepiness during the 5mg melatonin treatment compared to placebo as assessed by the GSDS.

- **Evidence (patients with psychiatric disorders)**: Suresh et al. conducted a randomized placebo-controlled trial to examine the effects of melatonin on insomnia in patients with schizophrenia (144). Stable DSM-IV schizophrenic outpatients (N=40) with initial insomnia of at least two weeks' duration were randomly assigned to augment their current medications with either flexibly dosed melatonin (3-12mg per night; N=20) or placebo (N=20). By use of a questionnaire, double-blind assessments of aspects of sleep functioning were obtained daily across the next 15 days. The modal stable dose of melatonin was 3mg. Relative to placebo, melatonin improved the quality and depth of nighttime sleep, reduced the number of nighttime awakenings, and increased the duration of sleep without producing a morning hangover ($p<0.05$). Subjectively, melatonin also reduced sleep-onset latency, heightened freshness on awakening, improved mood, and improved daytime functioning ($p<0.05$).
- Shamir et al. conducted a randomized placebo-controlled, double-blind crossover trial to evaluate the effect of melatonin on tardive dyskinesia in patients with chronic schizophrenia (142). Nineteen patients (eight men, 11 women), aged a mean ± SD 74.0±9.5 years with chronic DSM-IV schizophrenia of 31.3+±7.0 years' duration received slow-release melatonin, 2mg daily, or placebo for four weeks. After a two-week washout period, the patients were switched to the other treatment arm for an additional four weeks. The Abnormal Involuntary Movement Scale (AIMS) was administered at baseline, four weeks, six weeks, and 10 weeks. Regular administration of antipsychotic and other medications was kept unchanged throughout the study. Mean AIMS scores did not change significantly from baseline in either treatment arm. All patients completed the study, and there were no side effects or adverse events.
- Shamir et al. conducted a randomized double-blind, crossover trial to explore the neurobehavioral responses of patients with chronic schizophrenia to melatonin treatment using the first-night effect (FNE) as a marker (143). Fourteen patients with chronic schizophrenia were administered melatonin (2mg in a controlled-release formulation) or placebo for three weeks with a one-week washout between treatment periods. Polysomnography was performed during the last two consecutive nights of each treatment period. The following significant FNEs were observed with melatonin treatment: (1) rapid eye movement sleep latency was longer; (2) sleep efficiency was lower; and (3) the duration of wakefulness during sleep was lower on the first night than on the second night. These effects were not found when the patients received a placebo. The FNE manifested regardless of whether melatonin was administered before or after the placebo treatment period. The authors conclude that melatonin treatment exaggerates FNE in patients with chronic schizophrenia, thereby suggesting an improved ability of these patients to mobilize alertness in unfamiliar surroundings.
- **Evidence (patients with tuberous sclerosis)**: Hancock et al. conducted a randomized, double-blind, controlled, crossover trial to investigate the response to oral melatonin using two dose regimens in patients with sleep disorders associated with tuberous sclerosis complex (145). Eight outpatients with tuberous sclerosis complex and sleep disorder received either five or 10mg of melatonin. Sleep latency, total sleep time, number of awakenings, and seizure frequency were recorded in sleep and seizure diaries. No evidence of a dose effect between five and 10mg was seen with respect to any outcome measure. The authors concluded that a small beneficial effect of 10mg melatonin may have been missed and that an initial trial of 5mg melatonin is worth considering in patients with tuberous sclerosis complex and sleep disorder.
- O'Callaghan et al. conducted a randomized placebo-controlled, double-blind trial to examine the use of melatonin in patients with tuberous sclerosis complex who also have severe sleep problems (353). Seven patients with confirmed diagnoses of tuberous sclerosis and significant sleep disorder were recruited. Three outcome measures were employed: total sleep time, time to sleep onset, and

number of awakenings. Patients treated with melatonin had a small improvement in total sleep time (mean improvement 0.55 hours, $p<0.05$). They also tended to have an improvement in sleep-onset time but this did not reach statistical significance. Melatonin, in this trial, had no effect on sleep fragmentation. The authors conclude that melatonin does have a beneficial effect in prolonging the total sleep time of patients with tuberous sclerosis and sleep disorder, and that further trials are necessary to investigate the issues of optimal dosage, tolerance, and possible interactions with other medications.

Work shift sleep disorder

- **Summary**: Chronic circadian disturbance is thought to cause many of the health and social problems reported by shift workers. There are several studies of melatonin use in people who work irregular shifts, such as emergency room personnel (11; 166-169; 172; 354). Results are mixed, with some studies finding no statistically significant benefits, and others reporting benefits in sleep quality compared to placebo. Because most published trials are small, with incomplete reporting of design or results, additional research is necessary before a clear conclusion can be drawn.
- **Systematic review**: Buschemi et al. conducted a systematic review to review of the efficacy and safety of exogenous melatonin in managing secondary sleep disorders and sleep disorders accompanying sleep restriction, such as jet lag and shiftwork disorder (257). Searches were conducted from 1999 to 2003, with additional Medline and Embase searches in 2004. Randomized controlled trials were assessed by using the Jadad Scale and criteria by Schulz et al, and non-randomized controlled trials by the Downs and Black checklist. The inverse variance method was used to weight studies and the random effects model was used to analyze data. Dosage and duration (days to weeks) of melatonin administration described a considerable amount of heterogeneity across studies. *Efficacy*: Nine trials (427 participants) (11; 111; 114; 118; 154; 167-169; 172) were included in the efficacy analysis for secondary sleep disorders. The median quality score was 4 out of 5 (Jadad score). The authors reported that there was no evidence that melatonin had an effect on sleep onset latency in people who had sleep disorders accompanying sleep restriction (-1.0 (-2.3 to 0.3) min). *Sleep onset latency*: Six randomized controlled trials with 97 participants showed no evidence that melatonin had an effect on sleep onset latency in people with secondary sleep disorders (weighted mean difference -13.2 (95% confidence interval -27.3 to 0.9) min). *Safety*: Ten studies (487 participants) were included in the safety analysis. The most commonly reported adverse events were headaches, dizziness, nausea, and drowsiness. The occurrence of these outcomes was similar for melatonin and placebo.
- **Evidence**: Bjorvatn et al. conducted a randomized controlled crossover trial to evaluate the effects of bright light and melatonin on adaptation to night work on an oil rig in the North Sea (163). Seventeen persons working a schedule of two weeks on a 12-hour shift, with the first week on night shift and the second week on day shift (i.e., the swing shift schedule) participated. The shift workers received a placebo, melatonin (3mg, 1 hour before bedtime), or bright light (30-minute exposure, individually scheduled) during the first four days on the night shift and during the first four days on the day shift. Subjective and objective measures of sleepiness (Karolinska Sleepiness Scale and a simple serial reaction-time test) and sleep (diary and actigraphy) were recorded. Subjective measures indicated that melatonin modestly reduced sleepiness at work during the day shift and increased sleep by 15-20 minutes per day. Bright light gave values in between those of melatonin and the placebo, but with few statistically significant results. According to the authors, objective measures indicated that bright light improved sleep to a minor degree during the night shift. Side effects were reportedly low.
- Cavallo et al. conducted a double-blind, randomized, placebo-controlled crossover study to test whether melatonin reduces the deleterious effects of night shift work on sleep, mood, and attention in pediatric residents during night float rotation (164). Healthy second-year pediatric residents working two night float rotations were included in this study and took melatonin (3mg) or a placebo before bedtime in the morning after night shift; completed a sleep diary and an adverse-effects questionnaire daily; and completed the Profile of Mood States and the Conners Continuous

Performance Test three times in each study week to test mood and attention, respectively. Outcomes measures included standardized measures of sleep, mood, and attention. Twenty-eight residents completed both treatments; 17 completed one treatment (10 placebo, seven melatonin). Only one test for attention (the number of omission errors) was lower on melatonin (3.0 ± 9.6) than on placebo (4.5 ±- 17.5) (z = -2.12, p=0.03). This finding was statistically significant. But no statistically significant differences were found in measures of sleep, mood, and five of six measures of attention during melatonin and placebo treatment.

- Smith et al. conducted a placebo-controlled trial to determine whether melatonin had a soporific effect (171). Melatonin (N=18) and placebo (N=18) groups were formed by matching a melatonin participant with a placebo participant that had a similar baseline and final dim light melatonin onset (DLMO) (±1 h). Sleep log measurements of total sleep time (TST) and actigraphic measurements of sleep latency, TST, and three movement indices for the two groups were examined. Although melatonin was associated with small improvements in sleep quality and quantity, the differences were not statistically significant by analysis of variance. However, binomial analysis indicated that melatonin participants were more likely to sleep better than their placebo counterparts on some days with some measures. The authors concluded that the soporific effect of melatonin is small when administered prior to seven hours daytime sleep periods following night shift work.
- Sharkey et al. conducted a placebo-controlled, double-blind, crossover study to assess the effects of melatonin on shift-work (170). Subjects (N=21, mean age=27.0 ± 5.0 years) participated in two six-day laboratory sessions and took 1.8mg sustained-release melatonin 0.5h before the two daytime sleep episodes during one session, and placebo before the daytime sleep episodes during the other session. Polysomnography recorded sleep; the multiple sleep latency test (MSLT) and a computerized neurobehavioral testing battery evaluated sleepiness, performance, and mood during the night shifts. The authors reported that melatonin prevented the decrease in sleep time during daytime sleep relative to baseline, but only on the first day of melatonin administration. The authors reported that melatonin increased sleep time more in subjects who demonstrated difficulty in sleeping during the day. Melatonin had no effect on alertness on the MSLT, or performance and mood during the night shift. There were no hangover effects from melatonin administration. These findings may be limited by the short-duration and experimental design of this study.

FORMULARY: BRANDS USED IN CLINICAL TRIALS/THIRD-PARTY TESTING

Brands used in statistically significant clinical trials:

- Not applicable.

Brands shown to contain claimed ingredients through third-party testing:

- **Consumer Lab**: Not applicable.
- **Consumer Reports**: Not applicable.
- **Natural Products Association**: Not applicable.
- **NSF International**: Not applicable.
- **U.S. Pharmacopeia**: Not applicable.

U.S. equivalents of most commonly recommended European brands:

- Not applicable.

Select patents outside of the United States:

- Not applicable.

United States Patents:

- Not applicable.

ATTRIBUTION/MONOGRAPH CURRENCY

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