



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

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 aminalton 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



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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).

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