Sedation, Relaxation, and Regulation: The Clinical Application of Gamma-aminobutyric acid, Niacin, and Melatonin for the Treatment of Insomnia

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Abstract *Insomnia is a common problem seen in clinical practice. It has been defined as unsatisfactory sleep that impacts daily functioning, and for diagnostic purposes can be separated into acute insomnia (i.e., less than 30 days), or chronic insomnia (i.e., greater than or equal to 30 days). The majority of insomnia cases are associated with other medical conditions, giving rise to a more appropriate diagnosis of "comorbid insomnia." The work-up of chronic insomnia is described. Improving sleep habits should be the foundation of a program designed to correct insomnia, especially if it is considered chronic. The author has been experimenting clinically with a variety of orthomolecular substances for over 15 years, and has found a specific combination of three orthomolecules to be particularly effective for many cases of acute or chronic insomnia. This approach is called, "SRR," which refers to the use of gamma-aminobutyric acid, niacin, and prolonged-release melatonin to promote sedation, relaxation, and regulation, respectively. A brief description of each of these orthomolecules is included, as well as appropriate prescribing information. Other clinical considerations are described to assist clinicians in managing insomnia.*

Introduction

Insomnia, as defined by the American Academy of Sleep Medicine, is unsatisfactory sleep that impacts daytime functioning.[1] The DSM-IV describes the essential features of insomnia disorder as: a predominant complaint of insomnia lasting for at least one month and causing significant distress or daytime impairments in social, occupational or other sectors of daily life.[2-4] Insomnia affects more than two-thirds of all adults in any given year, and some 2-6% of them use medication to facilitate sleep.[5] Individuals having insomnia suffer from increased morbidity and mortality due to cardiovascular disease and psychiatric disorders, making insomnia a major public health issue.[6] The major risk factors for chronic insomnia include increasing age, female sex, the presence of psychiatric illness, medical comorbidities, impaired social relationships, lower socioeconomic status, separation from a spouse or partner, and unemployment.[7]

Diagnostic Considerations

It is easiest to separate insomnia into either acute (i.e., less than 30 days), or chronic (i.e., greater than or equal to 30 days) for diagnostic purposes.[8-10] The majority of insomnia cases are associated with other medical conditions, giving rise to a more appropriate diagnosis of "comorbid insomnia" (**Table 1,** p.111). In a mere 15-20% of cases, insomnia is unrelated to medical conditions, denoting "primary insomnia."[11] The work-up of chronic insomnia should include: (1) a thor-

ough medical history (involves a medication inventory and sometimes an interview with a patient's spouse, partner, or caregiver); (2) physical examination, which should involve a neurologic and mini-mental status exam; (3) sleep diary, which should span 2-weeks and also cover daytime symptoms and frequency of napping if present; and (4) specialized tests if necessary, such as polysomnography/PSG (multiple sleep latency testing), actigraphy (an activity monitor or motion detector to evaluate sleep patterns), and/or neuroimaging (to look for structural lesions).[12]

Sleep Hygiene

Improving sleep habits should be the foundation of a program designed to correct insomnia, especially if it has lasted longer than 30 days. Improving sleep hygiene is uncomplicated, but it does require a consistent commitment from your patients. To achieve better sleep hygiene a patient must be willing to:

1. Fix a bedtime and an awakening time;
2. Avoid daytime napping;
3. Avoid alcohol and caffeine 4-6 hours prior to bedtime;
4. Avoid heavy, spicy, or sugary foods 4-6 hours prior to bedtime; and
5. Exercise regularly, but not immediately prior to bedtime.

In addition, the bedding and room temperature should be comfortable, the room should be well ventilated, all distracting noises need to be blocked-out (if possible), and the bed should only be reserved for sleeping and sexual activity. Prior to bed, a light snack might help, such as warm milk (assuming no dairy allergy and/or sensitivity) and a banana. It might be a good idea for patients to do some type of relaxation technique to facilitate sleep to reduce muscle tension and anxiety. Some patients should be encouraged to create a pre-sleep ritual, such as taking a warm bath or even reading for a few minutes prior to sleep. Once ready for sleep, it is important to tell patients that they should start sleeping in their most comfortable (i.e., favorite) position.[13]

Orthomolecular Therapeutics

I have been experimenting clinically with a variety of orthomolecular substances for over 15 years. While I have not found one substance by itself to be enough to facilitate adequate and restful sleep, I have found a specific combination of three orthomolecules to be particularly effective for many cases of acute or chronic insomnia. I call this the "SRR" approach to insomnia since this specific combination of orthomolecules promotes sedation, relaxation, and regulation. To encourage sedation I use gamma-aminobutyric acid (GABA), to encourage relaxation I use niacin (nicotinic acid), and to encourage regulation I use prolonged-release melatonin. I have included a brief description of each of these orthomolecules below, with the appropriate prescribing information that clinicians ought to review prior to prescribing them.

GABA for Sedation

GABA functions as an inhibitory neurotransmitter in the central nervous system. The mechanism of GABA's neuroinhibition is mediated through an increase in the permeability of post-synaptic membranes to chloride ions, leading to hyperpolarization.[14] There continues to be uncertainty if GABA can traverse the blood-brain barrier when administered orally. GABA might act on central nervous system without crossing the blood-brain barrier.[15] There are two forms of GABA available: crystalline GABA and PharmaGABA® (produced by a fermentation process that utilizes Lactobacillus hilgardii).[16] Both forms have the same molecular structure and mechanism of action, and therefore it is unscientific to contend that one form somehow traverses the blood-brain barrier while another form does not.[15] PharmaGABA® has been shown to favorably moderate various biochemical markers of stress.[16] In a study (n=13) that evaluated the therapeutic effects of PharmaGABA®, 60 minutes after ingesting 100 mg the electroencephalographic readings showed statistically significant increases in alpha waves ($p<0.05$) and decreases in beta waves compared to results obtained when the same

Table 1. Common Causes of Insomnia*

Causes of Acute Insomnia	Causes of Chronic Insomnia
* Situation stress, such as occupational, interpersonal, financial, academic, or medical problems * Environmental stressors, such as noise pollution * Death or illness of a loved one	* Medical disorders (e.g., cancer, chronic pain, congestive heart failure, and gastroesophageal reflux disease) * Medications (e.g., antidepressants, bronchodilators, and central nervous system stimulants) * Primary sleep disorder (e.g., restless leg syndrome, and sleep apnea) * Psychiatric illness (e.g., anxiety disorders, bipolar disorder, and schizophrenia) * Sleep-wake schedule disorder (e.g., jet lag and shift work) * Substance abuse (e.g., alcohol, caffeine, drug withdrawal, and central nervous system stimulants)

*Adapted from: Ramakrishnan K, Scheid DC: Treatment options for insomnia. Am Fam Physician, 2007;76:518.

subjects were administered L-theanine and water.[17] The study results showed that PharmaGABA® possess both relaxation and anti-anxiety effects.

Dosage: I only use the PharmaGABA® form for insomnia. The crystalline form usually comes in much higher doses per pill, such as 500 mg or 600 mg, and these doses seem unnecessary and even unhelpful for patients struggling with insomnia. I have no idea why, but I have simply found through empirical observation that 100-200 mg of PharmaGABA® (in combination with niacin and melatonin) produces very good sedating effects when administered at bedtime.

Side Effects: I have not observed any side effects from PharmaGABA®. This preparation has been tested in rats that were administered doses of 5000 mg/kg.[16] There were no deaths and the LD50 was determined to be > 5000 mg/kg.

Niacin for Relaxation

I have published a number of reports discussing the therapeutic uses of niacin and its diverse mechanisms of action.[18-21] Niacin is extremely helpful for insomnia because it augments the sedating properties of PharmaGABA® and it ameliorates muscular tension. Many decades ago Dr. Abram Hoffer reported on the sedating properties of niacin based on the vitamin's ability to augment the effects of neuroleptics, anticonvulsants, and barbiturates.[22]

The other property that seems therapeutic is the cutaneous flushing that typically happens within about 15-20 minutes following the oral ingestion of niacin. The time to flush can be delayed, for instance, depending on how much food is in one's stomach, or can be quickened if the patient had fasted for some reason. The cutaneous flushing leads to vasodilatation and reddening of the skin. The cutaneous flushing usually begins on the forehead and face and then travels to the bellybutton or toes, usually concentrating on the chest, arms, and knees.[22] The cutaneous flushing leads to a profound relaxation of hypertonic skeletal muscles, which helps to facilitate restful sleep.

Dosage: Doses as low as 50 mg produce either no cutaneous flushing or a very minimal effect, whereas 250 mg or more produces a more moderate-to-marked cutaneous flush.[22] For patients that are unusually nervous about niacin, consider starting with 100 mg pills and slowly working up to 500 mg. The majority of patients, however, can be given instructions to begin with 250 mg and can increase to 500 mg in a couple of days.

Side Effects: Except for the discomfort of the cutaneous flushing, most patients tolerate these doses of niacin very well and some even look forward to the cutaneous flushing. There is always the rare possibility that niacin could cause headaches, faintness from lowering blood pressure, and/or insomnia. It is important to inform your patients that these rare side effects could happen, even though niacin generally helps with insomnia when combined with PharmaGABA® and melatonin.

Melatonin for Regulation

Melatonin is included here since it is a heavily used over-the-counter hormone, and the best studied natural intervention for insomnia. It is an excellent regulator as it is secreted by the pineal gland and establishes the circadian rhythm.[23] It is effective when there are circadian rhythm disruptions, as in jet lag and shift work.[12] It is also effective for primary insomnia, even when unrelated to jet lag or shift work. Even though melatonin levels decline with age, and even though some young individuals have low melatonin levels, low production of the hormone does not predict a therapeutic response.[24] Melatonin (as prolonged release melatonin/PRM) will reduce sleep latency in elderly patients even if their endogenous production of the hormone is normal.[24] PRM can also be used for six months, is generally well tolerated, and is not associated with any rebound or withdrawal symptoms upon discontinuation among patients 18-80 years of age.[25] Even among patients between the ages of 20 and 80 that took PRM continuously for 12 months, discontinuation of the hormone after 12 months was not associated with adverse events, withdrawal symptoms, or even suppression of endogenous melatonin secretion.[26] In a review that systematically evaluated the benefits of melatonin, the authors concluded that PRM (2 mg once daily) has no safety concerns if patients are concurrently taking antihypertensive, antidiabetic, lipid-lowering or anti-inflammatory drugs.[27] While this review specifically addressed the usefulness of prolonged-release melatonin for patients 55 years of age and older, I have found this preparation useful for the treatment of insomnia among adults of all ages.

Melatonin can also be useful in facilitating benzodiazepine discontinuation in approximately one-third of older adults (55 years of age and older) with insomnia.[28] For perimenopausal patients taking mirtazapine for insomnia, PRM can be used as a replacement sleep aid while also circumventing the mirtazepine-induced weight gain.[29] Melatonin is not associated with impairment of psychomotor functions, memory recall, or driving skills.[30] In addition, individuals on PRM will not experience impaired postural instability (i.e., body sway) should they wake up several hours after taking the hormone.[31]

Dosage: Based on numerous clinical studies, the ideal dose is 2 mg about one hour prior to sleep, while the ideal preparation of melatonin is the PRM formulation. Sometimes, increasing the PRM to 3 mg achieve better results. Some individuals have a very good initial response followed by a loss of response several weeks later. In such individuals, it is possible that they have developed tolerance due to slow liver metabolism of exogenous melatonin.[32] To help these patients regain an effective sleep pattern, it is wise to stop melatonin for about three weeks, and then resume it at a much lower dose. The therapeutic effects of melatonin (in combination with PharmaGABA® and niacin) might be enhanced by adding magnesium (at least 225 mg) and zinc (at least 11 mg) at bedtime.[33]

Side Effects: The most common are vivid dreams and morning grogginess. The vivid dreams are not a concern unless the dreams tend to be disturbing or frightening. The

morning grogginess typically goes away in less than 20 minutes upon waking.

Caution: Some labels recommend against taking melatonin concurrently with sedative or hypnotic medications. Some labels also warn against the use of melatonin among individuals having autoimmune diseases. I have safely used melatonin to augment the effects of sedative (for example, lorazepam) or hypnotic medications. I have also given melatonin to patients with autoimmune diseases when indicated. There does not appear to be any absolute contraindications when combining melatonin with PharmaGABA® and niacin, or with the aforementioned classes of medications, or among individuals with autoimmune diseases.

Clinical Considerations

1. In addition to the orthomolecules described above, patients should be encouraged to learn mind-body techniques (e.g., yoga, relaxation, and cognitive behavioral therapy) since they are effective interventions for insomnia.[34]

2. Treatment-resistant depression might be due, in part, to an underlying sleep disorder. Depressed patients that are not getting better should be referred to a sleep specialist for a complete evaluation.

3. For restless leg syndrome, only a few micronutrients have been shown to moderate symptoms. These include iron supplementation (i.e., among patients with low-normal ferritin levels),[35] magnesium[36] and folic acid.[36]

4. For sleep apnea, micronutrient supplementation will do very little to resolve the underlying sleep problem. When patients self-identify as having sleep apnea, it is important to encourage them to use their continuous positive airway pressure (C-PAP) device, as it is the first-line treatment for such patients. When they refuse to use the device because they find it inconvenient or a nuisance and request alternative (i.e., nutritional) treatments, it will not be possible to facilitate effective sleep unless they agree to regularly use it.

5. All patients with insomnia should be encouraged to regularly exercise no matter what limitations they have. Long-term moderate aerobic exercise (six months or more) can significantly improve sleep quality, moods, and quality of life.[37]

Conclusions

Insomnia is a common problem seen in clinical practice, and can sometimes be very difficult to treat. Patients have to be motivated and willing to improve their sleep hygiene and change certain lifestyles and behaviours if they want to fully benefit from the orthomolecules prescribed. It might be necessary to refer patients for specialized testing if they are not improving after a sufficient empirical trial of GABA, niacin, and PRM. Even though there are no formal clinical trials that have evaluated these specific orthomolecules in combination, I have found them to be routinely effective for both acute and chronic insomnia.

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Competing Interests

The author declares that he has no competing interests.

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