Research Overview

Development of a Melatonin-Based Formulation for the Treatment of Insomnia in the Elderly

Nava Zisapel*

Department of Neurobiochemistry, Tel-Aviv University and Neurim Pharmaceuticals Ltd., Tel-Aviv, Israel

ABSTRACT Melatonin, a hormone produced by the pineal gland at night, influences circadian rhythms, most notably the sleep–wake cycle. Much scientific evidence indicates that melatonin has sleep-enhancing properties. Sleep after melatonin administration is more similar to that recorded during normally occurring sleep than after administration of currently available hypnotic agents. Impairment in melatonin production may contribute to the well-known increased incidence of insomnia in the aged. In addition, some medications may impair sleep by inhibiting or distorting the melatonin rhythm. Insomnia associated with diminished nocturnal melatonin secretion may benefit from melatonin replacement therapy. Melatonin is rapidly eliminated from the body. Hence, to maintain effective serum concentrations of melatonin throughout the night, a prolonged-release (PR) formulation of melatonin (Circadin™) has been developed which provides a melatonin profile that simulates the normal nocturnal increase in melatonin concentrations. The sleep-inducing effects of PR-melatonin, at a dosage strength of 2 mg, have been demonstrated in exploratory studies in elderly insomnia patients and patients with depression or schizophrenia and sleep complaints. In the USA melatonin is available without any medical indication as a nutritional supplement. Animal toxicological studies and clinical experience has not revealed any consistent pattern of adverse events or laboratory test value alterations associated with the administration of the PR-melatonin. Clinical trials in a large population of elderly insomniacs have been set up to provide the regulatory bodies with the required evidence on the safety and efficacy of PR-melatonin. Drug Dev. Res. 50:226–234, 2000. © 2000 Wiley-Liss, Inc.

Key words: melatonin; insomnia; elderly; drug development

INTRODUCTION

Insomnia is the subjective complaint of insufficient or inadequate sleep and is characterized by difficulty in initiating and/or maintaining sleep (increased nocturnal awakenings and sleep fragmentation). Insomnia is one of the most common health complaints in the general population and may lead to serious health problems. The prevalence of insomnia has been estimated to be about one-third of the adult population [Ancoli-Israel, 1999]. The prevalence of insomnia increases steeply with age in the fifth decade of life [Sharma et al., 1989]. About half of the people in the age group 50–59, 60–69, and 70+ stated that they had insomnia, and in half of them the insomnia was severe [Roth et al., 1999]. In the largest study to date, the American National Institute on Aging multicenter study entitled “Established Populations for Epidemiological Studies of the Elderly” (EPESE) looked at the most common sleep complaints of over 9,000 participants over the age of 65; 25% of the participants had frequent difficulty initiating sleep and/or early morning arousal. When difficulty maintaining sleep was added, the prevalence of one or more these complaints was 42% [Daniel Foley, 1999]. Insomnia may lead to or exacerbate serious medical and psychiatric

Contract grant sponsor: Neurim Pharmaceuticals.

*Correspondence to: Nava Zisapel, PhD, Department of Neurobiochemistry, Tel-Aviv University, Tel-Aviv 69978, Israel. E-mail: navazis@post.tau.ac.il

© 2000 Wiley-Liss, Inc.
problems, as well as accidents and impaired occupational performance [Kryger et al., 1994] and decreased quality of life [Zammit et al., 1999].

This overview focuses on the current therapeutic approaches for insomnia, the medical need for novel therapeutic aids for chronic insomnia, particularly in elderly patients, and the rationale for developing melatonin-based formulations for this indication.

**IS THERE A MEDICAL NEED FOR NEW DRUGS TO TREAT INSOMNIA?**

While behavioral treatment programs for insomnia exist, pharmacological treatment is the most commonly used approach for the treatment of insomnia. The “ideal” hypnotic would allow sleep to occur, with normal sleep architecture, rather than produce a pharmacologically altered sleep pattern. It could be used chronically without causing dependence or rebound insomnia on discontinuation.

Among the wide variety of available treatments of sleep disturbances, the benzodiazepines (BZD) are the most widely prescribed hypnotic drugs. In France, 50% of BZDs are prescribed by general practitioners, and 10% of the population are thought to consume BZDs regularly [Millet et al., 1998]. Similar proportions have been described in other European countries and the US [Ohayon and Caulet, 1995, 1996; Ohayon et al., 1998]. Although many kinds of sleep disturbances can be successfully treated with BZDs or the newer non-BZD hypnotics, none of them is an ideal hypnotic. BZD and non-BZD hypnotics induce similar changes in sleep EEG spectrum, including attenuation of low-frequency activity and enhancement of spindle frequency activity [Brunner et al., 1991; Trachsel et al., 1990]. The development of dependence, as well as the occurrence of abuse of BZDs, is also a matter of concern. Literature data indicate that administration of BZDs results in daytime residual disturbances, memory impairment, “hangover” effects [Millet et al., 1998; Shader and Greenblatt, 1993], and a higher risk for falls, mainly in the elderly population [Leipzig et al., 1999]. In fact, the BZDs have amnesic, performance-disruptive, and sedating effects. Some have argued that part of the amnesic and performance-disruptive effects of the BZDs are partly due to their sedative effects [Roth et al., 1990]. Long-lasting BZDs often produce daytime somnolence and performance deficits, whereas short-acting drugs have been associated with marked rebound insomnia and anterograde memory disturbances. Despite its unique neuropharmacological profile, the behavioral effects of the non-BZD hypnotic, zolpidem, are generally similar to those of BZDs [Rush, 1998]. Studies that compared the psychomotor, cognitive, and subjective effects in healthy volunteers between BZDs and newer non-BZD hypnotics showed that zolpidem produced even more impairment than triazolam on several measures of performance [Mintzer et al., 1997; Mintzer and Griffiths, 1999]. Thus, Roehrs et al. [1994] showed significant performance and memory disruption 90 min after administration and impaired recall the following morning (e.g., anterograde amnesia) with different doses of zolpidem and triazolam compared to placebo. There are increasing numbers of studies and case reports on abuse and dependence of zolpidem [Rush, 1998].

Older agents such as barbiturates, glutethimide, and meprobamate have high abuse potential and are dangerous in overdose. The most commonly used “hypnotic” is alcohol. However, alcohol has been linked with decreased sleep latency and sleep fragmentation and is not considered appropriate in the management of insomnia.

Therefore, there is a medical need for a safe and efficacious alternative treatment for chronic insomnia, particularly for older patients.

**MELATONIN AS A SLEEP REGULATOR IN HUMANS**

Melatonin (N-acetyl-5-methoxy-tryptamine) is a natural indolamine hormone produced by the pineal gland of the brain of humans and other mammals. Its biosynthesis is inhibited by lighting and stimulated by signals from the brain circadian clock (suprachiasmatic nucleus) during darkness. The serum concentrations of the hormone are high at night and low during daytime [Kauppila et al., 1987; Reiter, 1986; Wehr, 1991]. Melatonin is the signal of darkness in the organism and as such it is involved in the regulation of sleep in humans.

Soporific effects of melatonin (0.3–240 mg) were reported in humans following intravenous [Cramer et al., 1974], intranasal [Vollrath et al., 1981], and oral [Arendt et al., 1984; Dollins et al., 1994; Lieberman et al., 1984] administration of melatonin in the daytime (i.e., when it is not present in the blood). Unlike benzodiazepine hypnotics, melatonin-promoted sleep has normal or enhanced REM electroencephalographic patterns and normal sleep architecture [Cramer et al., 1974; Waldhauser et al., 1990; Zhdanova and Wurtman, 1997]. Apart from its soporific action effect, exogenous melatonin may affect sleep through its phase-resetting action on the biological clock. Melatonin administration advanced sleep in delayed–sleep phase syndrome patients and synchronized sleep to the day–night cycles in blind subjects [Arendt et al., 1984; Sack et al., 1991].

The mechanisms underlying melatonin’s hypnotic effect are not entirely clear. It has been suggested that melatonin exerts its hypnotic effect through thermoregulatory mechanisms. By lowering core body temperature, melatonin might reduce arousal and increase sleep propensity. An increase in sleep propensity and shortened latency has been demonstrated in low physiological doses (0.1, 0.3 mg), both in the daytime [Dollins et al., 1994] or
in the evening [Zhdanova et al., 1995], but were not effective in sustaining sleep. Physiologic, sleep-promoting doses of melatonin do not have any effect on body temperature [Zhdanova et al., 1995], and temperature-lowering seems to occur later than sleep induction due to the increase in melatonin [Shochat et al., 1997]. The sleep effects of melatonin and its analogs are not mediated by interactions with BZD or cannabinoid receptors [Nave et al., 1996].

Alternatively, melatonin might modify brain levels of monoamine neurotransmitters, thereby initiating a cascade of events culminating in the activation of sleep mechanisms. Owing to its lipid solubility, melatonin might acutely modulate the activity of many brain structures that are directly involved in sleep initiation and maintenance. An acute suppression of suprachiasmatic-nucleus (SCN) activity by melatonin might also contribute to the sleep-promoting effect of the hormone. This effect is strongly related to melatonin’s ability to alter the phase of the circadian rhythm and thereby to affect the sleep–wake cycle.

A possible mechanism of action for melatonin can be provided by a recent study showing that melatonin exerts opposite effects on GABA-a receptors in specific brain areas potentiating the GABA-a receptors in the SCN via Mel1a receptors, while inhibiting it in the hippocampus via Mel1b receptors. The GABA-a effects of melatonin at the SCN may explain some of its sleep-promoting effects, whereas the anti-GABAergic effect explains why melatonin is devoid of memory impairment activity [Wan et al., 1999].

**MELATONIN PRODUCTION IN INSOMNIA PATIENTS**

A large body of evidence indicates that nocturnal melatonin concentrations in serum and biological fluids markedly decrease with advancing age [Iguchi et al., 1982; Kennaway et al., 1999; Pierpaoli and Maestroni, 1987; Sharma et al., 1989; van Coevorden et al., 1991; Waldhauser et al., 1988]. In older subjects, melatonin pulse starts later, and ends sooner, its peak being lower and delayed [Iguchi et al., 1982; Nair et al., 1986; Sharma et al., 1989]. The primary age-related disturbances in the sleep–wake cycle are associated with changes in melatonin output [Czeisler et al., 1992; Pollack et al., 1992].

It should be noted that 70% of the circulating melatonin is bound to plasma albumin [Miles, 1989] and perhaps, hemoglobin [Gilad and Zisapel, 1995]. The amount of free melatonin averages 23% of the total plasma melatonin [Kennaway and Voultsios, 1998] and this proportion may change with age and posture [Deacon and Arendt, 1994]. These confounding factors may bias estimates of the daily melatonin output obtained by assessment of free melatonin in plasma (or saliva). Melatonin is rapidly metabolized by the liver and over 85% is eliminated in the urine as 6-sulfatoxy-melatonin (6-SMT). Notably, some medications, particularly those that inhibit cytochrome P-450, may slow down melatonin metabolism and consequently increase its blood levels [Hartter et al., 2000]. The amount of metabolite excreted in urine may be a useful measure of the total amount of melatonin produced [Bojkowski et al., 1987].

We have previously found that 6-SMT excretion in healthy elderly subjects was lower than in young adults, but not significantly so [Haimov et al., 1995], suggesting that a decrease in melatonin output may be related to some age-related pathologies rather than to normal aging. A recent publication has also debated the age-related decrease in melatonin output by measuring plasma melatonin levels in healthy subjects [Duffy et al., 1999].

Abnormal melatonin rhythms have been observed in patients with primary insomnia (ages 25–65 years) compared to age- and gender-matched controls [MacFarlane et al., 1984]. We have shown that urinary excretion of 6-SMT was significantly lower and its peak delayed in healthy elderly insomniacs, but not in age-matched controls that did not complain of insomnia [Haimov et al., 1994]. Similarly, in elderly females who complained of poor sleep 6-SMT levels were found to be significantly lower compared to good sleepers [Hajak et al., 1996]. Furthermore, nocturnal plasma melatonin levels in young and middle-aged patients suffering from primary insomnia were significantly lower than those of healthy controls [Rodenbeck et al., 1997, 1998]. In age-related sleep maintenance insomnia it was found that a high proportion (50%) of patients had very low plasma melatonin levels. In this population, total sleep time and sleep efficiency correlated with the timing of the offset of the endogenous melatonin rhythm [Hughes et al., 1998]. A recent study reported on significant decrease in urinary 6-SMT with age in sleep-maintenance insomnia patients, but contrary to others [Duffy et al., 1999; Haimov et al., 1994] found a comparable decrease in 6-SMT levels in the age-matched control group [Lushington et al., 1998].

Geriatric patients complaining of insomnia or depression frequently present disturbed 6-SMT excretion rhythms, with those with more deviant acrophases displaying more disturbed sleep [Kripke et al., 1998]. Another study [Youngstedt et al., 1998] failed to show correlation between measure and amplitude of 6-SMT rhythms and sleep in a mixed population of volunteers (60–79 years of age) who complained of insomnia or depression. Nevertheless, significant correlation was found in this group between mean 6-SMT during the sleep period and total sleep time and wake after sleep onset [Youngstedt et al., 1998].

Sleep abnormalities in chronic heart patients are accompanied by impairment in the nocturnal release of endogenous melatonin [Malik et al., 1997].
sive patients treated with β-blockers (i.e., atenolol, propranolol, or metoprolol) for 4 weeks, melatonin levels decreased. Sleep disturbance records revealed a significant relationship between the fall in melatonin and the percentage of disturbed nights [Brismar et al., 1988]. Clonidine and nonsteroidal antiinflammatory drugs occasionally cause insomnia, consistent with their effects on melatonin [Lewy et al., 1986].

Several clinical syndromes are associated with melatonin abnormalities. These include primary degeneration of the autonomic nervous system and diabetic neuropathy [Arendt, 1995], some types of neoplasms [Bartsch et al., 1983, 1992; Khoory and Stemme, 1988; Stemme et al., 1986; Tamarkin et al., 1981; Touitou et al., 1985], Alzheimer disease [Uchida et al., 1996], coronary heart disease [Brugger et al., 1995; Nagtegaal et al., 1995], and schizophrenic patients [Monteleone et al., 1997]. Some drugs, such as β-blockers, clonidine, naloxone, and the NSAID ibuprofen, abolish the nocturnal production of melatonin and may impair normal sleep [Arendt et al., 1985; Demitrack et al., 1990; Espositi et al., 1988; Grasby et al., 1988; Lewy et al., 1986; Surrall et al., 1987]. BDZs, which are the most commonly used drugs for the treatment of insomnia in the elderly, may paradoxically suppress the nocturnal rise in plasma melatonin and shift its day–night rhythmicity in humans and rats [Acuna Castroviejo et al., 1986; McIntyre et al., 1988; Monteleone et al., 1989; Wakabayashi et al., 1991]. Therefore, impairment in melatonin production as a result of aging, diseases, or drugs may contribute to the increased incidence of insomnia, particularly in the aged.

**MELATONIN THERAPY FOR INSOMNIA**

A number of studies have documented improvement of sleep in insomnia patients by pharmacological doses of melatonin. In young, healthy volunteers exposed to artificial insomnia, melatonin (80 mg), given at bedtime, decreased the polysomnography-assessed sleep latency and the number of awakenings during the total sleep period, and increased sleep efficiency over placebo [Lieberman et al., 1984]. In chronic insomniacs melatonin at similar doses (75 mg/Os) given at 10 PM daily for 14 consecutive days significantly increased subjective assessment of total sleep time and daytime alertness as compared to placebo [MacFarlane et al., 1991]. In elderly insomniacs, administration of melatonin (50 mg) improved sleep efficiency and decreased wake-time after sleep onset; the effect was significant after 16 days but not 2 days treatment [Singer et al., 1995]. Administration of melatonin (5 mg/Os) at bedtime (e.g., when the endogenous production is halted) decreased sleep latency in insomniacs [Lushington et al., 1997]. However, the first attempts to study the efficacy of low doses of melatonin (acute administration; 1 and 5 mg regular release at night) failed to show significant effects on the polysomnography-recorded sleep in insomnia patients [James et al., 1990].

Only later studies demonstrated the efficacy of melatonin (0.3–5 mg/Os) at night for insomnia [Malik et al., 1997]. The majority of these studies were performed with elderly insomniacs [Hughes et al., 1998; Wurtman and Zhdanova, 1995], or patients with low melatonin production (i.e., a pinealectomized patient, a child with germ cell tumor involving the pineal gland and marked suppression of melatonin secretion, patients treated with atenolol, and chronic heart patients) [Etzioni et al., 1996; Malik et al., 1997; Petterborg et al., 1991; van den Heuvel et al., 1997; van den Heuvel and Dawson, 1997].

In elderly subjects complaining of sleep onset insomnia, sleep-maintenance insomnia, and early morning awakening, it was found that a physiological dose of melatonin (0.3 mg/Os for 3 days) significantly reduced actigraph estimated sleep latency, nighttime movements, and the number of awakenings [Wurtman and Zhdanova, 1995]. More recently, the sleep-promoting effects of melatonin replacement therapy were assessed in a group of patients with age-related sleep maintenance insomnia. Melatonin (0.5 mg) was administered as immediate-release (evening or mid-night administration) or prolonged-release forms (evening administration). All treatments shortened sleep latency but were not effective in sustaining sleep [Hughes et al., 1998].

Therefore, melatonin replacement therapy appears to provide a new therapeutic approach for insomnia in older patients and patients with decreased melatonin production due to disease or the use of certain drugs.

**PROLONGED-RELEASE MELATONIN FORMULATION PROPERTIES AND DOSE JUSTIFICATION**

Melatonin is short-lived in humans and its half-life in serum is only 40–50 min. Peak serum concentrations are reached within 20 min of oral administration of melatonin and then decay rapidly. Because of its fast clearance, regular melatonin formulations can produce physiological levels for only 2–4 h. Hence, in order to maintain effective serum concentrations of melatonin throughout the night high doses or repeated administration of low doses are required. To address the therapeutic situation, Neurim Pharmaceuticals developed a prolonged-release (PR) formulation of melatonin (Circadin™) which circumvents the fast clearance of the hormone and provides a melatonin profile in the blood more closely matched to the normal physiological release. The sleep-inducing effects of melatonin have been reported in scientific trials to require doses in the range of 0.3–5 mg, regardless of formulation, protocol, or subject inclusion criteria (Fig. 1). Hence, the PM formulation has been developed at dosage strength of 2 mg.
EFFICACY OF PR-MELATONIN IN INSOMNIA

Two early exploratory studies were performed with the aim of providing experience with the trial methodology and study design, with the use of the wrist actigraph as a method of measurement, and as preliminary safety data. These studies were based on insomnia in the elderly (55–93 years) and the use of melatonin administration to improve sleep quality. One study investigated the effects of melatonin replacement therapy on melatonin-deficient elderly insomniacs [Haimov et al., 1995]. The study comprised a run-in, no treatment period, and four experimental periods. During the second, third, and fourth periods, subjects were administered tablets for 7 consecutive days, 2 h before the desired bedtime. The tablets were 2 mg PM-melatonin, 2 mg immediate release formulation, and placebo. A concluded fifth part to the study consisted of a 2-month period of daily administration of 1 mg PM-melatonin, 2 h before desired bedtime. Sleep–wake patterns were monitored by wrist actigraphy. Analysis of the results revealed that a 1-week treatment with 2 mg PM-melatonin was effective for sleep maintenance, which deteriorated after cessation of treatment. The regular release formulation improved sleep initiation but not maintenance. There was no indication of decreased efficacy during the 2-month extension period.

These findings were substantiated by a further study in 12 elderly subjects who had received various medications for chronic illnesses and were complaining of insomnia [Garfinkel et al., 1995]. In all 12 subjects, the peak excretion of the main melatonin metabolite (6-SMT) during the night was lower than normal when compared with noninsomniac elderly people. The subjects were treated for 3 weeks with one PM-melatonin (2 mg) tablet per night and for 3 weeks with a placebo. Sleep efficiency was found to be significantly greater after melatonin than after placebo, and wake time after sleep onset was significantly shorter. Safety monitoring of these trials found two adverse effects reported. Both were cases of pruritus, once during melatonin, and once during placebo treatment.

PR-MELATONIN USE WITH BENZODIAZEPINES

Melatonin augments the sleep-inducing effects of BZDs when given concomitantly [Ferini-Strambi et al., 1993]. Investigational studies carried out in Israel demonstrated that the use of PM-melatonin (2 mg) tablets reduces BZD side effects and dependency.

In a single-center, randomized double-blind, crossover study, the efficacy of PM-melatonin (2 mg) once daily in elderly insomniacs was compared with those treated with BZDs. Twenty-one patients (13 men and 8 women) were treated for over 6 months with at least one benzodiazepine tablet per day for sleep. Patients with liver or renal problems (serum creatinine ≥1.5 mg/dL) were excluded. Sleep efficacy was objectively monitored by wrist actigraphy. Statistically significant and clinically important improvements in sleep quality parameters over placebo were estimated for sleep efficiency (+10.26%), sleep latency (–17.5 min), wake time after sleep onset (–37.2 min), total sleep time (+33 min), and number of awakenings (–4.76). The overall safety and tolerability results were identical in both crossover periods. No unexpected adverse events were reported. The number of adverse events reported was low for both arms of the treatment, primarily being headache [Garfinkel et al., 1997].

The efficacy and general safety of PM-melatonin (2 mg) tablets administered once daily were compared to placebo in adult insomniacs discontinuing chronic use of BZDs. Thirty-four patients were enrolled and 30 patients completed the study. BZD and melatonin consumption, as well as sleep quality scores, were assessed following 6-month administration of PM-melatonin (2 mg). Patients were between 40–90 years of age complaining of poor sleep quality despite chronic use (daily, over 6 months) of at least one BZD tablet for sleep. Patients were ran-
cilitate discontinuation [Garfinkel et al., 1999]. The results indicated that melatonin may effectively fa-
cebo-treated groups discontinued BZD use (the melatonin-treated and only 4 out of 16 in the pla-
BDZ-treated insomniacs with Circadin™, 14 out of 18 in the melatonin-treated and only 4 out of 16 in the placebo-treated groups discontinued BZD use (P = 0.002). The results indicated that melatonin may effectively fa-
cilitate discontinuation [Garfinkel et al., 1999].

From analysis of both trials, PM-melatonin has been demonstrated to be safe, even when taken concomitantly with BZDs or during BDZ withdrawal.

PR-MELATONIN USE IN PSYCHIATRIC PATIENTS

The effects of slow-release melatonin on sleep during the initial 4 weeks of treatment with fluoxetine were investigated in 19 patients with major depressive disor-
der. Ten patients were treated with fluoxetine plus PM-
melatonin (5 mg) and nine were given fluoxetine plus placebo in a double-blind protocol for 4 weeks. Responses were assessed by using rating scales for depression and sleep. The 10 patients given PM-melatonin reported signifi-
cantly better scores on the Pittsburgh Sleep Quality Index than the nine patients given placebo. PM-melato-
nin had no effect on the rate of improvement in symp-
toms of major depressive disorder [Dolberg et al., 1998].

In an open-label trial, nine outpatients who had failed to respond to two or more 8-week trials of antide-
npressant medication received PM-melatonin (5 mg) per day for the first 2 weeks and 10 mg per day for the final 2 weeks, in addition to their antidepressant medication. Structured Clinical Interview for DSM-IV, Axis 1 Disorders, Hamilton Rating Scale for Depression (HRSD), Beck Depression Inventory, Response Style Question-
naire, sleep, and fatigue measures were recorded. One patient was excluded after 1 week because of the develop-
ment of a mixed affective state. In the remaining eight patients there was a 20% mean decrease in HRSD scores after 4 weeks of treatment, with no individual achieving an improvement of 50% or more. There was a 36% de-
crease on the three-item HRSD related to insomnia, with four of eight patients showing at least a 50% improve-
ment on this measure.

The greatest decrease in insomnia occurred during the last 2 weeks of the study, following the increase in dosage to 10 mg per day of PM-melatonin. Patients also reported significantly lower levels of fatigue posttreatment. Thus, PM-melatonin may be a useful adjunct for sleep, but does not substantially augment existing anti-
depressant therapies in some patients with treatment-
resistant depression [Dalton et al., 2000].

Plasma melatonin concentrations are significantly lower in chronic schizophrenic patients than in healthy controls [Robinson et al., 1991; Monteleone et al., 1992]. It was therefore investigated whether melatonin replace-
tment therapy would be effective in improving sleep in patients with chronic schizophrenia who complained of disturbed sleep. In a double-blind placebo-controlled crossover study, 21 patients were given PM-melatonin (2 mg) or placebo for 3 weeks, with 1 week washout be-
tween treatment periods. Sleep quality was objectively monitored by wrist actigraphy. Melatonin significantly improved sleep efficiency in these patients; patients with more disturbed sleep at baseline had a higher benefit from the treatment [Shamir, 2000b].

In an additional study, 14 patients with chronic schizophrenia were given PM-melatonin (2 mg) or placebo for 3 weeks in a randomized, double-blind, cross-
over method, with 1 week washout between treatment periods. Polysomnography was performed on the last two consecutive nights of each treatment period. A signifi-
cant first-night effect was observed with melatonin, but not with placebo: REM latency was shorter, sleep efficiency higher, percent Stage I sleep decreased, and per-
cent REM sleep increased on the second compared to the first night of sleep laboratory assessment. These re-
sults show that melatonin treatment exaggerated the first-
night effect in patients with chronic schizophrenia. This increase may imply that melatonin improves the ability of these patients to mobilize alertness in unfamiliar sur-
roundings [Shamir, 2000a].

PRECLINICAL AND CLINICAL DEVELOPMENT

In response to the clinical need for a safe and effi-
cacious alternative treatment for insomnia, Neurim Phar-
maceuticals began preclinical toxicology and clinical program with the PM formulation of melatonin. This pro-
gram systematically and rigorously addressed the toxi-
cology, safety, and efficacy issues of melatonin therapy for insomnia. The studies were designed to provide regu-
ulatory authorities with sufficient information to demon-
strate the efficacy of the product at the recommended doses, timing, and duration of melatonin use. In addition, the safety of the product has been established, es-
pecially in older persons who, in addition to poor sleep quality, quite often have additional health problems which require drug treatment.

REFERENCES

Acuna Castroviejo D, Rosenstein R, Romeo HE, Cardinale DP. 1996. Changes in gamma-aminobutiric acid high affinity binding to cere-
bral cortex membranes after pinealectomy or melatonin adminis-

Ancoli-Israel TRaS. 1999. Daytime consequences and correlates of insomnia in the United States: results of the 1991 National Sleep Founda-


PROLONGED RELEASE MELATONIN FOR INSOMNIA


