

Effect of melatonin on nocturnal blood pressure: meta-analysis of randomized controlled trials

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Background: Patients with nocturnal hypertension are at higher risk for cardiovascular complications such as myocardial infarction and cerebrovascular insult. Published studies inconsistently reported decreases in nocturnal blood pressure with melatonin.

Methods: A meta-analysis of the efficacy and safety of exogenous melatonin in ameliorating nocturnal blood pressure was performed using a random effects model of all studies fitting the inclusion criteria, with subgroup analysis of fast-release versus controlled-release preparations.

Results: Seven trials (three of controlled-release and four of fast-release melatonin) with 221 participants were included. Meta-analysis of all seven studies did not reveal significant effects of melatonin versus placebo on nocturnal blood pressure. However, subgroup analysis revealed that controlled-release melatonin significantly reduced nocturnal blood pressure whereas fast-release melatonin had no effect. Systolic blood pressure decreased significantly with controlled-release melatonin (-6.1 mmHg; 95% confidence interval [CI] -10.7 to -1.5 ; $P = 0.009$) but not fast-release melatonin (-0.3 mmHg; 95% CI -5.9 to 5.30 ; $P = 0.92$). Diastolic blood pressure also decreased significantly with controlled-release melatonin (-3.5 mmHg; 95% CI -6.1 to -0.9 ; $P = 0.009$) but not fast-release melatonin (-0.2 mmHg; 95% CI -3.8 to 3.3 ; $P = 0.89$). No safety concerns were raised.

Conclusion: Add-on controlled-release melatonin to antihypertensive therapy is effective and safe in ameliorating nocturnal hypertension, whereas fast-release melatonin is ineffective. It is necessary that larger trials of longer duration be conducted in order to determine the long-term beneficial effects of controlled-release melatonin in patients with nocturnal hypertension.

Keywords: melatonin, nocturnal blood pressure, meta-analysis

Introduction

The diurnal pattern of blood pressure is an important factor in determining cardiovascular complications in hypertensive patients. Impaired nocturnal blood pressure fall is associated with a high risk of developing target organ damage¹ and morbid cardiovascular events.² The mechanism responsible for the reduction in blood pressure during sleep and the pathophysiological explanations for the lack of this nocturnal fall remain unclear.

Melatonin is a hormone normally secreted from the pineal gland at night. It serves as the signal of darkness in the organism, and as such plays a pivotal role in the physiological regulation of circadian rhythms, including sleep.³ Evidence from the last ten years suggests that melatonin may influence the cardiovascular system in humans.⁴

Furthermore, exogenous melatonin has induced several hemodynamic effects in healthy men and women.⁵⁻⁷

Several studies have evaluated the effects of melatonin on nocturnal blood pressure.⁸⁻¹⁴ The results were not consistent, as in some studies melatonin reduced, and in some it did not, or even increased nocturnal blood pressure. Not all studies used the same melatonin formulation, ie, some used controlled-release formulations and others used fast-release formulations. We hypothesized that the inconsistent results in the various studies may be related to the formulation used. Therefore, we conducted a meta-analysis to assess the effect of melatonin on nocturnal blood pressure and further analyzed the data by type of melatonin formulation used.

Methods

Data sources

We searched the PubMed database for randomized, placebo-controlled studies which were published between January 1980 and December 2010, using melatonin in humans and in which the primary endpoint reported was blood pressure. For this search, we used the terms melatonin, blood pressure, and clinical trials. Pertinent articles cited as references in the identified trials and reviews were also culled. We included only studies that compared the effect of melatonin with placebo, reported nocturnal systolic and diastolic blood pressure as measured by 24-hour ambulatory blood pressure monitoring for blood pressure assessment, and were published in the English language. We excluded open-label studies and studies that were not randomized, controlled, or used melatonin agonists. Two reviewers assessed the methodological quality of these seven studies independently using the Jadad scale.¹⁵ Papers with a Jadad scale result of three or more were judged as suitable for this meta-analysis.

Data extraction

We extracted from each paper the patient characteristics, the melatonin formulation and dose, duration of treatment, baseline blood pressure, and nocturnal blood pressure values after treatment. We also extracted from the studies the number of patients in the melatonin and in the placebo groups. For the crossover studies, we counted the patients twice, once in the active group and once in the placebo group. The meta-analysis was calculated with reported endpoints for melatonin and placebo treatments for both the crossover and parallel studies.

Data analysis

Because all of the studies compared melatonin with placebo, we considered our study as a direct head-to-head

comparison of two treatments (placebo versus melatonin). The meta-analysis was performed using the software program MIX 2 (Meta-analysis with Interactive eXplanations, version 2). The descriptive method was used, and the input was the results of the blood pressure parameters as described previously. All of these measures could therefore be defined as continuous (noted by mmHg), by utilizing the random effects method. The alpha level was set at 0.05 for each outcome.

We assessed per parameter the overall mean difference, the 95% confidence interval (CI) and the z score. The cross-over and parallel studies were done simultaneously. The results were also assessed according to the melatonin formulation, irrespective of age. We have presented the results in standard forest plots containing mean differences, 95% CI, weight of each study, and pooled analysis.

Results

Study characteristics

Altogether 63 articles on melatonin and blood pressure were found. Twenty-five trials did not use exogenous melatonin and 20 trials using exogenous melatonin did not test nocturnal blood pressure and were therefore excluded. The full texts of all articles thought to be potentially relevant were retrieved ($n = 12$) and read by two reviewers (EG and ML). After careful evaluation, only seven studies met the inclusion criteria and qualified to be included in the meta-analysis (Figure 1). The mean quality score was 3.8 out of 5 (range 3-5) based on the Jadad scale. Of the seven placebo-controlled studies, six studies involved 200 adults and one study involved 21 adolescents. Of the subjects included in the analysis, 60 had coronary artery disease, 11 had type 1 diabetes, 51 were normotensive, and 99 had hypertension (Table 1). One study reported the results separately for the normotensive and diabetic patients, and therefore was included as two separate studies in the meta-analysis.⁸

In three studies, patients received either melatonin or placebo in parallel, and in the other three adult studies and the adolescent study treatments were given in a crossover design. In the three parallel-group studies, the treatment duration ranged from 28 to 90 days. In two of the three crossover studies in adults, the participants received the trial medication during two consecutive periods of three weeks each that were not separated by a washout period. In the other adult crossover study, the trial medications were given for two subsequent periods of four weeks each, separated by a four-week washout period. In the adolescent crossover trial, the participants received the trial medications for two consecutive periods of one week, separated by a one-week

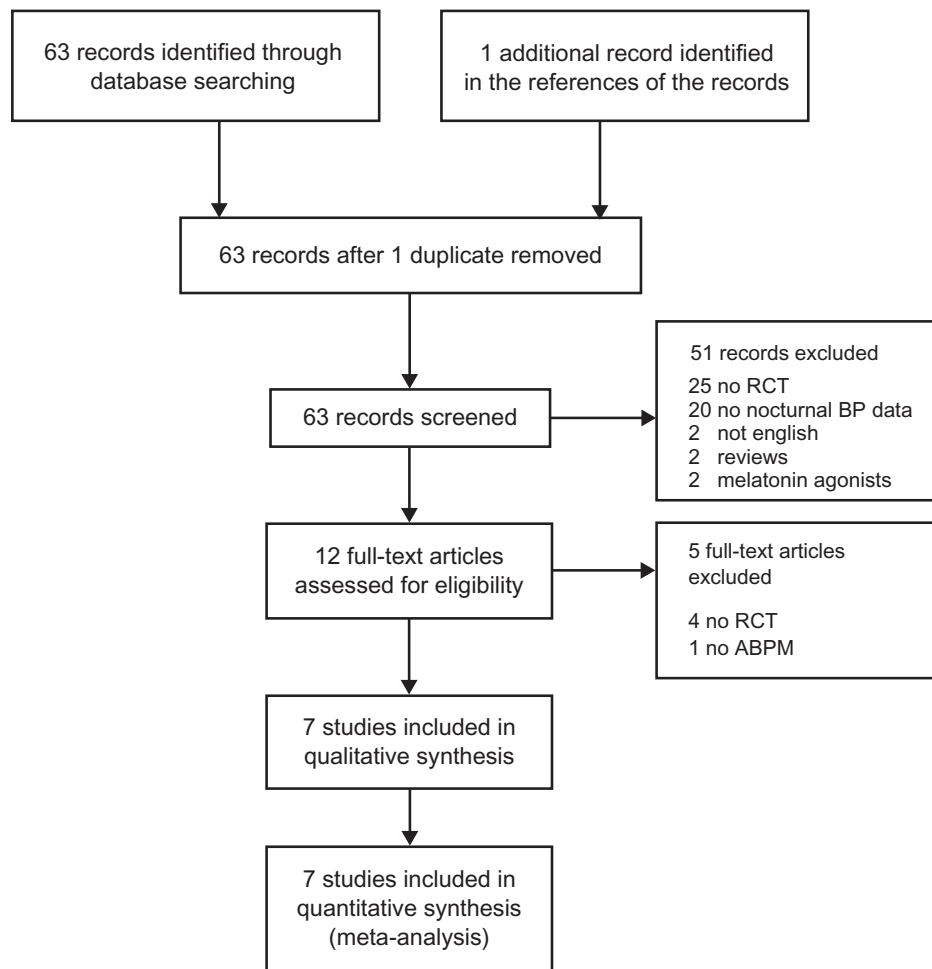


Figure 1 Flowchart of the study selection process.

washout period. Altogether the analysis included 344 data points recorded from 221 subjects.

Dosage and formulations

In four studies that included 149 subjects, fast-release melatonin at a dosage of 5 mg was used, and in three studies that included 72 subjects, controlled-release melatonin at a dosage of 2–3 mg was used. In this meta-analysis, the dosage was not taken into account.

Systolic blood pressure

Meta-analysis based on all seven studies showed that melatonin treatment decreased nocturnal systolic blood pressure slightly and insignificantly compared with placebo. The net effect of melatonin over placebo on nocturnal systolic blood pressure was -2.3 mmHg (95% CI -6.94 to 2.45 ; $P = 0.35$, Table 2). Analysis of the data according to the formulation shows that controlled-release melatonin significantly reduced while fast-release melatonin had no effect

on nocturnal systolic blood pressure (Figure 2, Table 2). Thus, systolic blood pressure decreased by 6.1 mmHg (95% CI -10.69 to -1.50 ; $P = 0.009$) with controlled-release melatonin whereas it decreased by only 0.27 mmHg (95% CI -5.88 to 5.33 ; $P = 0.92$) with fast-release melatonin (Figure 2, Table 2).

Diastolic blood pressure

Meta-analysis based on all seven studies showed that melatonin treatment decreased nocturnal diastolic blood pressure slightly and nonsignificantly. The net effect of melatonin over placebo on nocturnal diastolic blood pressure was -1.4 mmHg (95% CI -4.01 to 1.29 ; $P = 0.31$, Table 3). Analysis of the data according to the formulation used showed that controlled-release melatonin significantly reduced while fast-release melatonin had no effect on nocturnal diastolic blood pressure; diastolic blood pressure decreased by 3.51 mmHg (95% CI -6.14 to -0.86 ; $P = 0.009$) with controlled-release melatonin, whereas it decreased by

Table 1 Details of the studies included in the meta-analysis

Study	No. subjects/ disease	Gender (M/F)	Age (years) (mean ± SD)	Melatonin treatment dose/ formulation	Duration (days)	Initial BP (mmHg)	The effect of melatonin on nocturnal systolic/ diastolic BP (mmHg), change from baseline
Parallel group studies							
Lusardi et al ¹²	21 Norm.	7/14	25 ± 2	5 mg /FR	28	NA	-4/-1
Lusardi et al ¹⁰	50 EHT	28/22	54 ± 4	5 mg/FR	28	136/72	-7*/-3*
Grossman et al ¹¹	38 EHT	22/16	63 ± 11	2 mg/CR	28	Plc: 137/72 Mel: 136/72	-6*/-3*
Crossover studies							
Cavallo et al ⁸	21 Norm (10) Diabet. (11)	14/7	16 ± 2	5 mg/FR	7	NA	-1/-1 (Diabet) -0.5/-2 (Norm)
Cagnacci et al ¹⁴	18 EHT + Norm.	0/18	53 ± 1	3 mg/CR	21	NA	-4*/-4*
Scheer et al ⁹	16 EHT	16/0	55 ± 8	2.5 mg/CR	21	NA	-6*/-4*
Rechchinski et al ¹³	60 CAD	44/16	57 ± 7	5 mg/FR	90	Plc: 118/66 Mel: 117/65	-4*/-2

Note: * $P < 0.05$ vs baseline.

Abbreviations: Norm, normotensive; EHT, essential hypertension; Diabet, Diabetes type I; CAD, coronary artery disease; Plc, placebo; Mel, melatonin; FR, fast release; CR, controlled release; NA, not applicable; BP, blood pressure.

only 0.24 mmHg (95% CI -3.76 to 3.28; $P = 0.89$) with fast-release melatonin (Figure 2, Table 3).

Safety

No serious adverse events were reported in the seven studies included in the meta-analysis. Adverse events, including headache, drowsiness, weakness, and nightmares, were reported in three studies.^{8,10,12} No significant side effects were noted in the other four studies. Based on available studies and clinical use, melatonin is generally regarded as safe.¹⁶ Available trials report that overall adverse effects are not significantly more common with melatonin than placebo. The safety of melatonin in hypertensive patients is good, and implies that add-on melatonin therapy does not present significant risks of detrimental drug interactions with the main major

drugs used to treat hypertension. It is necessary that trials of longer duration be conducted in order to determine the long-term safety of melatonin in patients with nocturnal hypertension.

Discussion

The results of this meta-analysis when including all double-blind, placebo-controlled ambulatory blood pressure monitoring trials do not provide evidence that exogenous melatonin significantly reduces nocturnal blood pressure. However, the originally planned subgroup analyses intended to evaluate the impact of the melatonin formulation used (fast-release or controlled-release) on the outcome revealed that administration of controlled-release melatonin preparations consistently and significantly reduced nocturnal blood

Table 2 Effect of FR and CR-melatonin on systolic nocturnal blood pressure

	Study	N	md	ci-	ci+	z	P	w
FR melatonin	Lusardi ¹²	42	-4.10	-9.48	1.284	-1.493	0.136	14.34%
	Lusardi ¹⁰	94	6.70	3.66	9.739	4.321	0.000	16.45%
	Cavallo ⁸ (Diabetics)	22	-1.40	-9.80	7.004	-0.326	0.744	11.28%
	Cavallo ⁸ (Controls)	20	-0.80	-8.69	7.093	-0.199	0.843	11.78%
	Rechchinski ¹³	60	-4.10	-12.49	4.290	-0.958	0.338	11.30%
	Total FR melatonin	238	-0.27	-5.879	5.337	-0.095	0.925	
CR melatonin	Scheer ⁹	32	-5.60	-14.07	2.870	-1.296	0.195	11.22%
	Cagnacci ¹⁴	36	-3.70	-12.43	5.032	-0.830	0.406	10.97%
	Grossman ¹¹	38	-8.00	-15.02	-0.976	-2.232	0.026	12.66%
	Total CR melatonin	106	-6.10	-10.698	-1.505	-2.602	0.009	
All studies	Total	344	-2.25	-6.94	2.45	-0.938	0.348	

Notes: The following parameters are reported: Number of data points (N); Mean BP difference between melatonin and placebo treatments (md); Lower-bound confidence interval (ci-); Upper-bound confidence interval (ci+); Z-value (Z); P-value (P); Weight (W) given to each study is calculated by the inverse sum of the within study and between study variance estimates.

Abbreviations: FR, fast release; CR, controlled release.

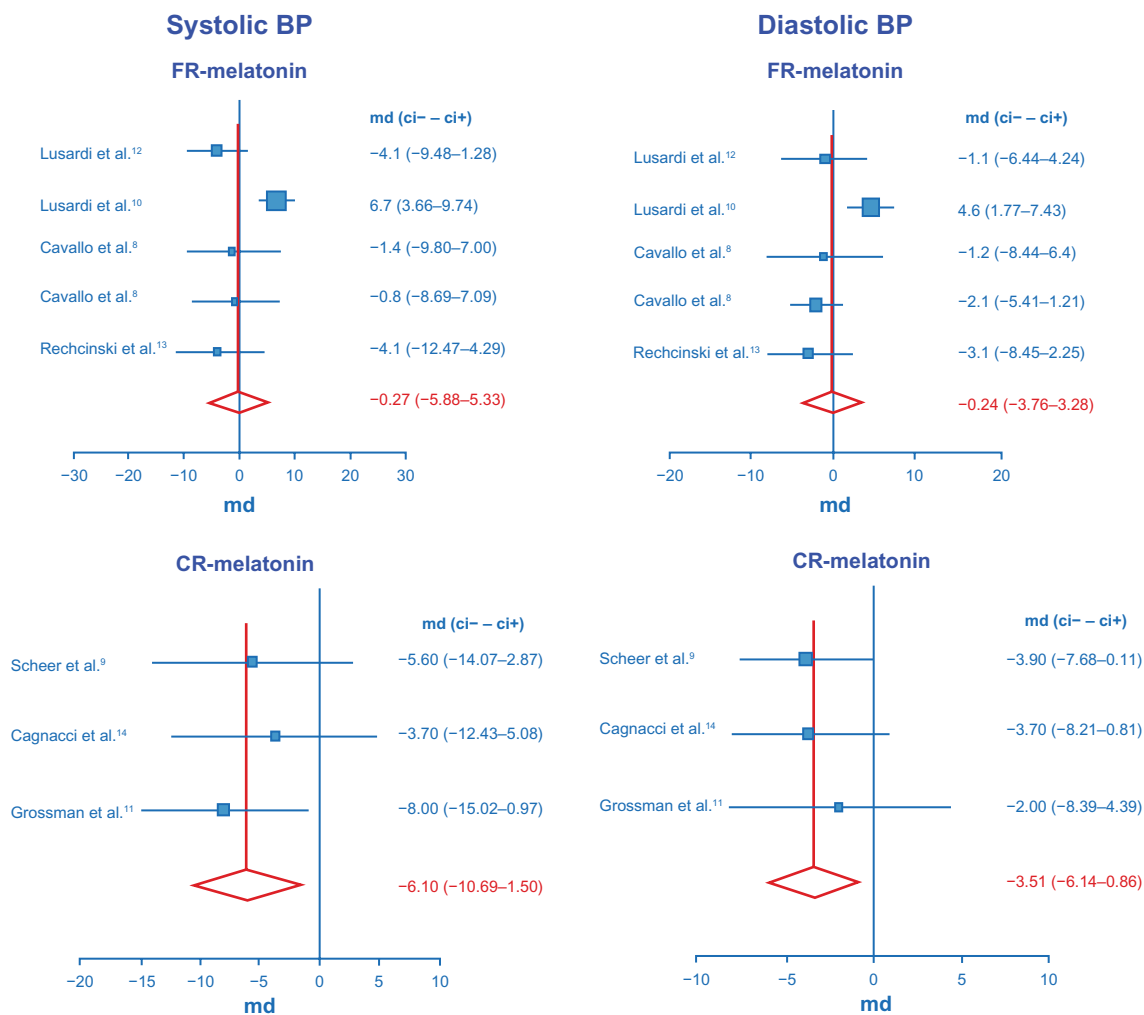


Figure 2 Effect of FR and CR-melatonin on nocturnal systolic/diastolic BP. Effect of FR and CR-melatonin on systolic blood pressure (left panel) and diastolic blood pressure (right panel). The following parameters are reported: Mean difference (md); Confidence interval (CI).

pressure as compared with placebo treatment. The decrease in nocturnal blood pressure with controlled-release melatonin versus baseline was also evident in each and every study separately. The use of melatonin was safe with respect to adverse events experienced, as was observed in other studies that used melatonin.¹⁶

The mean reduction in nocturnal blood pressure was of a magnitude that is considered to be clinically relevant. Thus, with controlled-release melatonin, systolic blood pressure was reduced by 6 mmHg and diastolic blood pressure by 3 mmHg. The various studies were remarkably consistent in the nature and extent of the effects of bedtime controlled-release melatonin on blood pressure, and most of the benefit was observed in the late night-early morning hours, when blood pressure elevation is on the rise. Importantly, the fast-release melatonin doses (5 mg) exceeded those of the controlled-release preparations (2–3 mg), and their inability to decrease nocturnal blood pressure is therefore not related to a lower dose.

Endogenous melatonin secretion starts soon after the onset of darkness, peaks in the middle of the night, and gradually declines thereafter towards the morning.³ Diminished melatonin production at night with normal day production is consistently reported in severely hypertensive patients and in hypertensive patients with nondipping blood pressure patterns.^{17–19} Melatonin deficiency has also been found in patients with coronary heart disease.^{20,21}

Melatonin is rapidly metabolized, with an elimination half-life of 40–50 minutes.^{22,23} Following oral administration of exogenous fast-release melatonin, peak plasma levels are reached 20–30 minutes after ingestion, which are then maintained for 90 minutes and rapidly decline afterwards.²⁴ Fast-release melatonin formulations are thus unable to provide melatonin for the second half of the night. Controlled-release formulations circumvent the fast clearance of the hormone and provide melatonin profiles in the blood that more closely match the normal physiological release. Therefore, in order

Table 3 Effects of FR and CR-melatonin on diastolic nocturnal blood pressure

	Study	N	md	ci-	ci+	z	P	w
FR melatonin	Lusardi ¹²	42	-1.10	-6.44	4.240	-0.404	0.686	11.26%
	Lusardi ¹⁰	94	4.60	1.77	7.430	3.186	0.001	16.77%
	Cavallo ⁸ (Diabetics)	22	-1.20	-8.45	6.048	-0.325	0.746	8.13%
	Cavallo ⁸ (Controls)	20	-2.10	-5.41	1.211	-1.243	0.214	15.67%
	Rechcinski ¹³	60	-3.10	-8.46	2.256	-1.134	0.257	11.23%
	Total FR melatonin	238	-0.24	-3.766	3.281	-0.135	0.893	
CR melatonin	Scheer ⁹	32	-3.90	-7.68	-0.118	-2.021	0.043	14.58%
	Cagnacci ¹⁴	36	-3.70	-8.21	0.810	-1.608	0.108	12.96%
	Grossman ¹¹	38	-2.00	-8.39	4.391	-0.613	0.540	9.40%
	Total CR melatonin	106	-3.51	-6.147	-0.868	-2.605	0.009	
All studies	Total	344	-1.36	-4.01	1.29	-1.008	0.313	

Notes: The following parameters are reported: Number of data points (N); Mean BP difference between melatonin and placebo treatments (md); Lower-bound confidence interval (ci-); Upper-bound confidence interval (ci+); Z-value (Z); P-value (P); Weight (W) given to each study is calculated by the inverse sum of the within study and between study variance estimates.

Abbreviations: FR, fast release; CR, controlled release.

for exogenous melatonin to be present during the late part of the night, it has to be administered via a controlled-release preparation, or at very high doses.

Melatonin may lower blood pressure via several mechanisms. Vascular melatoninergic receptors have been demonstrated and shown to be functionally linked with vasoconstrictor or vasodilatory effects of melatonin.⁵ Other neurohormonal properties of melatonin, such as sympathetic inhibition, could also contribute to its cardioprotective effects.²⁵ Impaired nocturnal sympathetic suppression with sustained adrenergic activity during sleep was reported in patients with nocturnal hypertension (nondippers).^{26,27} Administration of melatonin may therefore contribute to the nocturnal suppression of the sympathetic nervous system. The reduction of the activity of the oxidative enzyme, myeloperoxidase, by melatonin may also contribute to the vasoprotective and blood pressure-lowering effects of melatonin.²⁸ Melatonin may also dilate peripheral arteries directly,⁵⁻⁷ thereby reducing peripheral resistance and leading to a nocturnal blood pressure fall. Moreover, melatonin has been shown to stimulate the release of tissue factor pathway inhibitor from the vascular endothelium, which may suppress thrombosis and arterial restenosis.²⁹

A blunted nocturnal decrease in blood pressure is independently associated with increased aortic stiffness in patients with nocturnal hypertension. Carotid-femoral pulse wave velocity, a direct measure of aortic stiffness, has become increasingly important for total cardiovascular risk estimation.^{30,31} Even in dippers, absolute night-time blood pressure is associated more closely with pulse wave velocity than is daytime blood pressure.³² In a recent study, increased levels of melatonin during the night were found to cause a decrease in velocity of the aortic pulse wave, along

with blood pressure.³³ Moreover, melatonin administration, compared with placebo, has been found to decrease pulse wave velocity and systolic blood pressure in the supine position in healthy young men.³⁴ Administration of controlled-release melatonin may thus replenish the cycle of an important cue of blood pressure control in patients with nocturnal hypertension.

A controlled-release melatonin formulation (Circadin[®]) has recently been approved in the European Union and other countries for the treatment of insomnia in patients aged 55 years and older. However, it should be noted that the improvement in nocturnal hypertension appears to be related to the mechanism of action of controlled-release melatonin and not to the hypnotic action per se. Thus, benzodiazepine and benzodiazepine-like hypnotics that treat insomnia effectively do not improve hypertension. In fact, zolpidem, which is the most widely prescribed hypnotic drug, does not lower and may even increase nocturnal blood pressure.^{35,36} Furthermore, the effect of zolpidem on blood pressure is seen in the early morning hours, at the time when blood pressure elevation has been implicated as a risk for cardiovascular events.³⁷

The clinical relevance of a decrease of 6 mmHg in systolic and 3 mmHg in diastolic blood pressure in reducing the risk of cardiovascular complications in patients with hypertension can be evaluated in view of recent studies looking at the Spanish Society of Hypertension Ambulatory Blood Pressure Monitoring Registry.^{38,39} The prevalence of nondipping/nocturnal hypertension among untreated hypertensive patients in Spain was found to be 41%. In patients treated with antihypertensive drugs, 53% had nondipping/nocturnal hypertension despite pharmacotherapy,³⁸ indicating that antihypertensive

treatment, while having a general blood pressure-lowering effect, does not restore proper circadian rhythms in blood pressure. The cardiovascular risk adjustment per 5 mmHg reduction in nocturnal systolic blood pressure of patients aged 55 years and above (adjusted by age and gender) has been shown to be 0.92 (95% CI 0.88–0.96) and per 5 mmHg reduction in nocturnal diastolic blood pressure it is 0.82 (95% CI 0.77–0.88).³⁹ A decrease of 5 mmHg in mean asleep systolic blood pressure or 2.1 mmHg in diastolic blood pressure saved 1585 events per 100,000 patient years.³⁹

The results of this study suggest that addition of controlled-release melatonin at night to stable antihypertensive treatment may improve nocturnal blood pressure control. Thus, because of its effects on nocturnal blood pressure, add-on controlled-release melatonin treatment is expected to reduce the cardiovascular risk in high-risk patients with nocturnal hypertension.⁴⁰ Because the reviewed studies were relatively small size and short-term, additional large studies employing long-term administration of controlled-release melatonin are needed to substantiate the benefits of this add-on treatment in reducing risk of complications in patients with hypertension.

Disclosure

EG has received research grants from Neurim Pharmaceuticals Ltd for an investigator-initiated study of controlled-release melatonin (Circadin®) for nocturnal hypertension and declares no conflicts of interest. ML is an employee of Neurim Pharmaceuticals Ltd, the manufacturers of Circadin®. NZ is the founder and chief scientific officer of Neurim Pharmaceuticals. All authors (except NZ) declare that they have no spouses, partners, or children having relationships with commercial entities who might have an interest in the submitted work.

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