Received: 12 February 2022 | Revised: 26 March 2022 | Accepted: 26 March 2022

DOI: 10.1111/jch.14482

META-ANALYSIS

WILEY

Controlled-release oral melatonin supplementation for hypertension and nocturnal hypertension: A systematic review and meta-analysis

Eric Kam-Pui Lee MSc[1] | Paul Poon MSc[1] | Chun-Pong Yu PhD[2] | Vivian Wing-Yan Lee PharmD[3] | Vincent Chi-Ho Chung PhD[1,4] | Samuel Yeung-Shan Wong MD[1]

[1]Jockey Club School of Public Health and Primary Care, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong

[2]Li Ping Medical Library, The Chinese University of Hong Kong, Hong Kong

[3]the Centre for Learning Enhancement and Research, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong

[4]School of Chinese Medicine, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong

Correspondence
Eric Kam-Pui Lee, MSc, 4/F, School of Public Health, Prince of Wales Hospital, Shatin, NT, HKSAR.
Email: lkp032@cuhk.edu.hk

Eric Kam-Pui Lee and Paul Poon contributed equally to the manuscript.

Abstract

Oral melatonin is a potential alternative treatment for hypertension and nocturnal hypertension. However, high-quality and relevant meta-analyses are lacking. This meta-analysis aimed to investigate whether oral melatonin supplementation reduces daytime/asleep blood pressure and cardiovascular risk, improves sleep quality, and is well-tolerated compared with placebo. Relevant articles were searched in multiple databases, including MEDLINE, EMBASE, CINAHL Complete, and the Cochrane Library, from their inception to June 2021. The included studies were randomized controlled trials recruiting patients with hypertension, using oral melatonin as the sole intervention, and investigating its effect on blood pressure. The mean out-of-office (including 24-h, daytime, and asleep) systolic and diastolic blood pressures, sleep quality, and side effects were compared between the melatonin and placebo arms using pairwise random-effect meta-analyses. A risk of bias assessment was performed using the Cochrane risk-of-bias tool. Four studies were included in the analysis and only one study was considered to have a low risk of bias. No study reported on cardiovascular risk or outcomes. Only controlled-release melatonin (not an immediate-release preparation) reduced asleep systolic blood pressure by 3.57 mm Hg (95% confidence interval: −7.88 to .73; $I^2 = 0\%$). It also reduced asleep and awake diastolic blood pressure, but these differences were not statistically significant. Melatonin improves sleep efficacy and total sleep time and is safe and well-tolerated. Due to the limited number of high-quality trials, the quality of evidence was low to very low. Therefore, adequately powered randomized controlled trials on melatonin are warranted.

KEYWORDS
ambulatory BP monitoring, cardiovascular disease, hypertension, melatonin

1 | INTRODUCTION

Hypertension (HT) is a major cause of cardiovascular deaths worldwide, but good blood pressure (BP) control is obtained in less than one-third of patients.[1,2] Although asleep BP and nocturnal BP dipping are the strongest independent predictors of cardiovascular outcomes, evidence-based treatment is lacking.[3–6] Nocturnal HT is increasingly observed clinically, due to the use of the recommended 24-h ambulatory BP monitoring (ABPM) in primary care and cardiology clinics.[7] Clearly, more treatment options, particularly evidence-based treatments for nocturnal HT, are needed.

Inexpensive, safe, and accessible oral melatonin supplementation is a potential candidate because it may reduce BP by (1) causing vasodilation via direct calcium channel blocking and enhancing nitric oxide and cyclic guanosine monophosphate production in the endothelium, (2) its anti-oxidant properties, (3) inhibiting the sympathetic nervous system and reducing the production of non-adrenaline, and (4) activating the parasympathetic nervous system.[8] Furthermore, melatonin may be a potential treatment for nocturnal HT and non-dipping because it is usually taken before bedtime, may enhance sleep duration and quality, and thereby reduce sleeping BP.[9] Low endogenous melatonin secretion during sleep is associated with nocturnal HT, BP non-dipping, and cardiovascular disease.[8] Moreover, melatonin has an excellent side effect profile and is well tolerated.[10–13]

Although several meta-analyses suggested that melatonin reduces BP, they included people with normotension and adolescents, did not distinguish between office and out-of-office BP readings, had highly heterogeneous results, and/or did not extract all important BP parameters, that is, daytime/asleep BP and BP dipping (Supplementary Introduction S1).[10–13] Therefore, the external validity of these results in patients with HT is limited. Furthermore, no meta-analysis has extracted or discussed important outcomes such as the corresponding reduction in cardiovascular risks or events. Consequently, there is a lack of direct evidence for melatonin use in the treatment of HT and/or nocturnal HT.

This meta-analysis aimed to investigate the efficacy and safety of oral melatonin for treating HT. Our research question, using the participant, intervention, control, and outcome format, was as follows: "In patients with HT (receiving or not receiving anti-HT drug treatment), does oral melatonin supplementation reduce office and out-of-office BP (asleep [primary outcome]/24-h/daytime systolic BP [SBP] and diastolic BP [DBP]) when compared to placebo or no treatment?" Only randomized controlled trials (RCTs) were included to provide the highest possible level of evidence. Secondary outcomes included the degree of dipping and dipping status, sleep quality, and melatonin side effects. Whenever available, data concerning the reduction of cardiovascular risk or incidence of cardiovascular events were also collected. Previous meta-analyses suggested a differential BP reduction effect by different preparations of melatonin (controlled-release [CR] versus immediate-release [IR]); therefore, relevant subgroup analyses were conducted whenever feasible. The results will benefit the clinical treatment of HT or nocturnal HT, highlight research gaps, and guide future research.

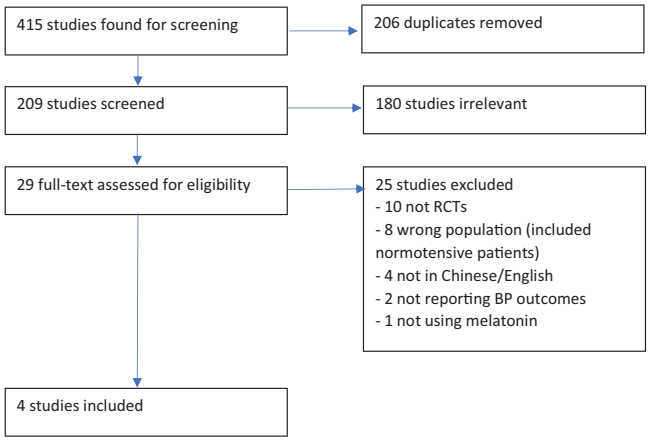

FIGURE 1 PRISMA flowchart

2 | METHOD

This systematic review and meta-analysis was pre-registered in PROSPERO (CRD42021276835) and is reported in accordance with the PRISMA guidelines (http://prisma-statement.org/).

We included RCTs that included patients with HT, used oral melatonin as the sole intervention, used a control arm receiving no treatment or placebo, and reported on BP outcomes. A comprehensive search was conducted in multiple databases, including Chinese databases. A grey literature search was conducted, including a search in ClinicalTrials.gov. Study inclusion and data extraction were conducted by two independent reviewers. Risk of bias was assessed by two independent reviewers using the Cochrane risk of bias tool.[13] The primary outcomes were the weighted mean differences in 24-h/awake/asleep SBP and DBP on ABPM between melatonin and the control arm. Results were meta-analyzed by a random effect model. Details of study eligibility, search strategy, data screening and data extraction, risk of bias assessment, and statistical analysis can be found in Supplementary Method S2.

3 | RESULTS

3.1 | Search results

Of 415 studies from the database search, four placebo-controlled, parallel ($n = 1$), or crossover RCTs ($n = 3$) (including a total of 137 participants) were included in the final analysis (Figure 1).[14–17] These RCTs had small sample sizes ($n = 16$–47) and were conducted in Israel, Italy, the Netherlands, and the USA. The intervention period range was 3–4 weeks (Table 1). Only one RCT had a low risk of bias because most RCTs did not clearly describe their randomization process (Figure 2).

The mean age and body mass index of included participants were 56.36 years and 28.01 kg/m^2, respectively. Approximately 55% and 5.65% of patients were men and had diabetes mellitus, respectively. Other clinical data, such as the presence of cardiovascular or psychiatric disease, were under-reported (Supplementary Results S4).

TABLE 1 Characteristics of included studies

Study	Country	RCT design	Inclusion criteria	Exclusion criteria	n	Melatonin dosage	Melatonin preparation	Method to define night-time on ABPM	Melatonin duration
Grossman 2006[16]	Israel	Parallel	nocturnal HT (mean night-time systolic BP > 125 mm Hg) on stable dose of anti-HT medications	unorganized lifestyle, such as shift workers	38	2 mg	controlled release	diary	4 weeks
Lusardi 2000[14]	Italy	Crossover	mild to moderate HT, taking nifedipine GITS, well-controlled clinic BP	Secondary hypertension, patients with end organ damage	47	5 mg	immediate release	fixed period	4 weeks
Scheer 2004[15]	The Nether-lands	Crossover	male, mild-moderate uncomplicated, essential HT		16	2.5 mg	controlled release	actigraphy and sleep diary	3 week
Rahbari-Oskoui 2019[17]	USA	Crossover	African American ages 18–64 years, essential HT and nocturnal HT (SBP≥115 mmHg)	Secondary causes of hypertension, ≥2 anti-HT medications, Severe uncontrolled HT (SBP > 170 or DBP > 110), History of CVS disease, DM, Liver disease, Pregnancy, Breastfeeding, Usage of NSAIDs, Usage of corticosteroids, Usage of COX-II inhibitors, Usage of warfarin, History of sleep apnea requiring CPAP, Active malignancies, caffeinated beverage consumption > 3 cups of coffee per day, current use of melatonin	36	24 mg	controlled release	diary	4 weeks

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CPAP, continuous positive airway pressure; CVS, cardiovascular; DM, diabetes mellitus; HT, hypertension; NSAIDs, non-steroidal anti-inflammatory drugs; USA, United States of America.

3.2 | The effect of melatonin on BP

CR melatonin was used in three RCTs and reduced asleep SBP by −4.67 mm Hg (95% confidence interval (CI): −8.79 to −.55, $I^2 = 0\%$). CR melatonin also reduced asleep DBP by −2.39 mm Hg (95% CI: −5.01 to .23, $I^2 = 0\%$), daytime SBP by −3.57 mm Hg (95% CI: −7.88 to .73, $I^2 = 0\%$), and daytime DBP by −1.06 mm Hg (95% CI: −4.3 to 2.18, $I^2 = 0\%$); however, these were not statistically significant. Although a wide range of doses of melatonin (2–24 mg) was used, BP reduction by different doses of melatonin was similar (Figure 3). Conversely, Lusardi and coworkers investigated the effect of IR melatonin, which increased asleep and daytime SBP/DBP (Figure 3). Furthermore, the effect of melatonin on 24-h BP was under-reported; only Lusardi and coworkers reported that IR melatonin increased 24-h SBP by 6.5 mm Hg (95% CI: 2.3–10.7 mm Hg, $p < .001$) and 24-h DBP by 4.9 mm Hg (95% CI: 1.2–8.4 mm Hg, $p < .001$).[14] Similarly, no RCT reported on the effect of melatonin on office BP. The effect of CR melatonin on the proportion of nocturnal non-dippers was only investigated by Rahbari-Oskoui, and no significant difference was observed between the two arms (27/36 melatonin vs. 24/36 placebo).[17] CR and IR melatonin reduced the asleep heart rate by 2.99 bpm (95% CI: 1.87–4.10, $I^2 = 0\%$), and daytime heart rate by 2.46 bpm (95% CI: −.38 to 5.30, $I^2 = 0\%$; Supplementary Results S5). No RCT investigated the effect of melatonin on cardiovascular risk or outcomes.

3.3 | Safety and side effects of melatonin

Melatonin increased the risk of daytime drowsiness, although not statistically significantly (odds ratio: 2.32, 95% CI: .43–12.59, $I^2 = 78.3\%$; Supplementary Results S6). Other side effects were only discussed in one RCT; they included fatigue (41.7% melatonin vs. 30.6% placebo), early morning awakening (38.9% melatonin vs. 25% placebo), and weakness (21.3% melatonin vs. 6.4% placebo).[14,17] All RCTs reported that side effects were mild and drop-out due to side effects were rare.[14,16,17]

3.4 | Effect of melatonin on sleep

Melatonin improved sleep efficacy by 2.72% (95% CI: −.97 to 6.41, $I^2 = 0\%$) and total sleep time by 10.97 min (95% CI: −14.06 to 35.99; $I^2 = 1.4\%$), although these were not statistically significant (Supplementary Results S7).

3.5 | Sensitivity analysis

Sensitivity analyses found similar results (Supplementary Results S8–S9).

3.6 | GRADE quality of evidence rating

The overall certainty of the current evidence was ranked low for all BP outcomes because (1) there was an inadequate number of studies to assess publication bias, and (2) most RCTs had an unclear risk of bias and/or imprecision in some outcomes that is, the 95% CI of CR

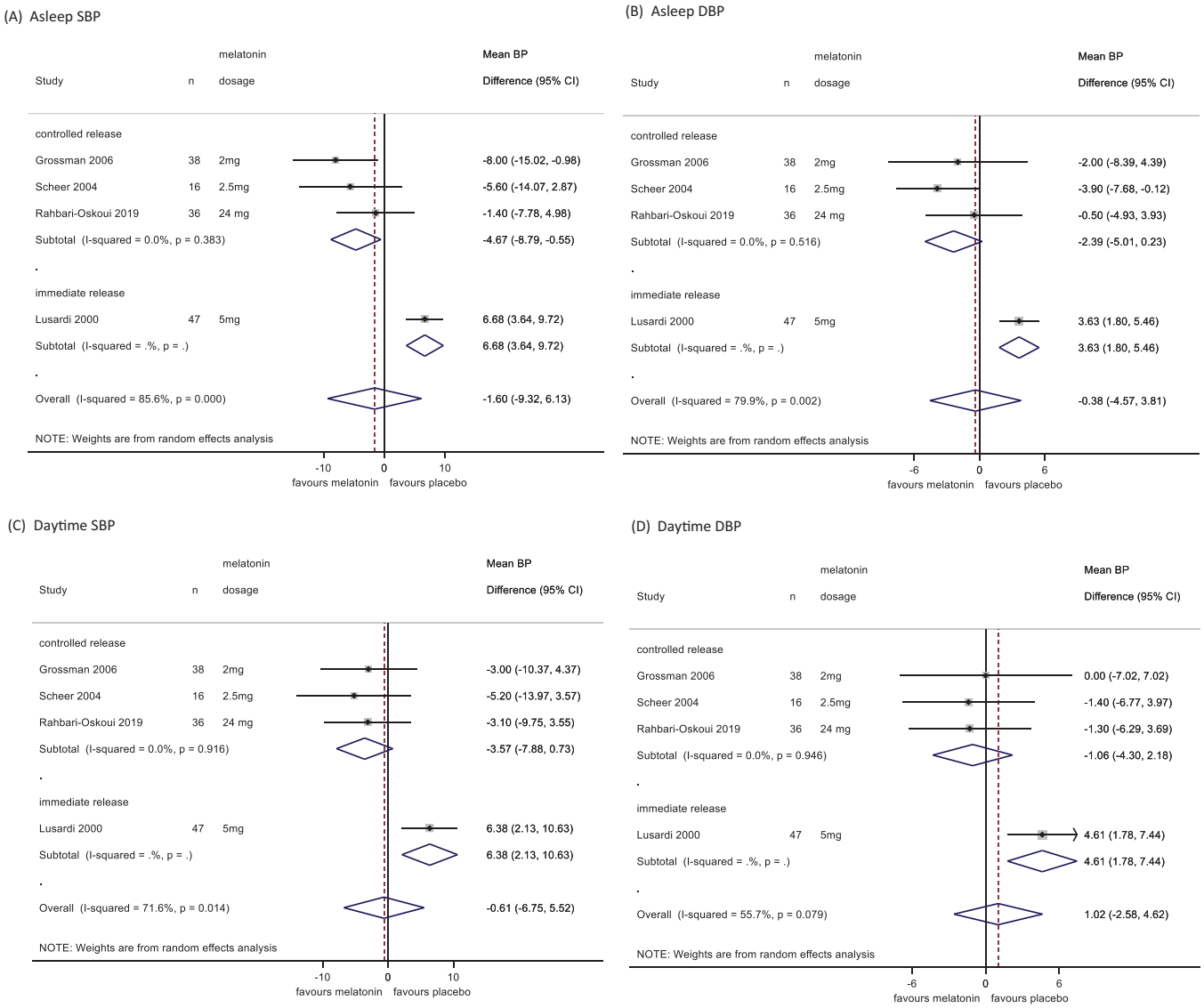

FIGURE 3 Meta-analyses of effect of melatonin on daytime/asleep BP

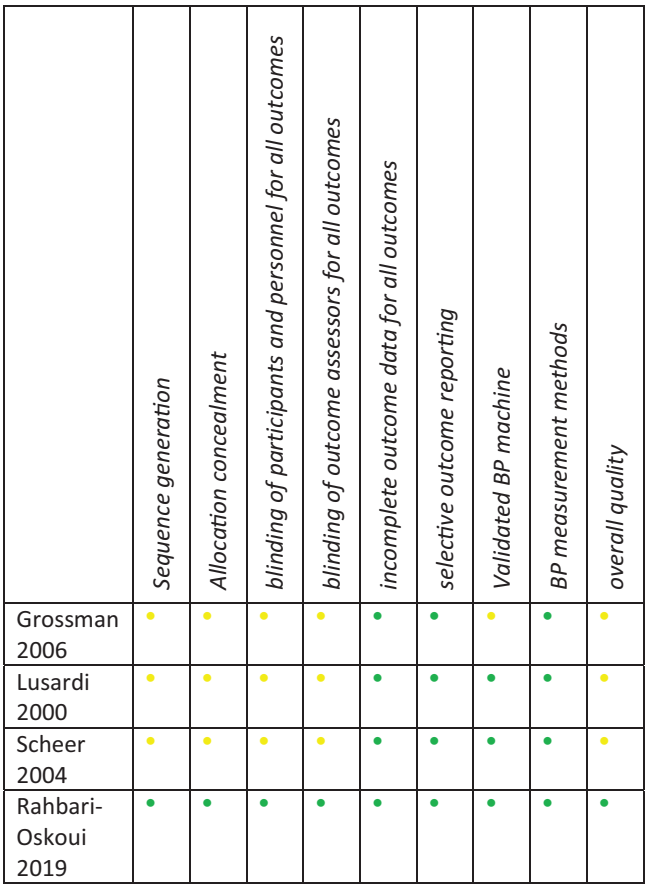

FIGURE 2 Risk of bias assessment of included studies

melatonin on asleep SBP was −8.79 to .55 mm Hg. Furthermore, the evidence on sleep quality and safety were ranked very low due to the very limited number of RCTs ($n = 2$) and imprecise outcomes.

4 | DISCUSSION

4.1 | Comparison with existing literature

In accordance with previous meta-analyses, we suggested that administration of a CR melatonin supplement may reduce asleep BP by approximately 5/2 mm Hg.[10–13] Furthermore, similar to previous meta-analyses, we reported a difference in the BP reduction effect of CR melatonin and IR melatonin.[12,13] However, our results also suggested that CR melatonin may reduce daytime BP by −3.6/1 mm Hg (despite not reaching statistical significance). The current absence of statistical significance of daytime BP results may be attributed to the limited numbers of trials and patients. Although melatonin improves sleep and thereby reduces asleep BP, it can reduce BP by other mechanisms, for example, enhancing parasympathetic nervous system functioning, and may thereby also reduce daytime BP.[8]

Our results were also in agreement with previous evidence reporting that melatonin may improve sleep duration/quality. Melatonin is an emerging treatment for sleep disorders because of its ability to improve total sleep time, sleep efficiency, and onset latency.[18] Furthermore, melatonin was also shown to be safe and well-tolerated in an RCT, confirming good safety and tolerability for a minimum of 6 months in patients with HT.[19]

4.2 | Implications for research and practice

For clinicians, CR melatonin may be prescribed to patients with nocturnal HT, particularly for patients who have poor sleep quality. On the contrary, IR melatonin has either no effect or adversely affects the BP, as observed in previous meta-analyses and the current meta-analysis, respectively.[12,13] IR melatonin has a short half-life of around 45 min and therefore cannot provide sustained BP reduction.[20] Furthermore, the optimal dosage and timing of CR melatonin require further investigation. Although all included RCTs administrated melatonin in the evening or bedtime, the optimal timing was not known.[14–17] Similarly, although a CR melatonin dosage of 2–10 mg was commonly used in RCTs, supraphysiological serum level is expected at a dosage of >0.5 mg.[21] Clinically, lower doses are preferred because of reduced side effects.[21] Our results also demonstrated similar BP reduction regardless of the dosage of CR melatonin. While the exact reasons cannot be delineated from our results, melatonin has both vasoconstriction and vasodilatation properties (via MT1 and MT2 receptors), and it was suggested that melatonin may paradoxically cause vasoconstriction at high doses by the differential activation of MT1 versus MT2 receptors.[17,22] Similarly, a lack of dose-response relationship was observed between melatonin and other parameters. For instance, a higher dose of melatonin was less effective to improve sleep than its lower dose (i.e., 0.5 mg).[21] Even though a combination of treatments is often required to achieve optimal BP, the interaction between melatonin and anti-hypertensive medications was understudied.[5] While Lusardi and coworkers (who conducted the only RCT that showed an elevated BP after IR melatonin) explained their BP results by the use of nifedipine (a calcium-channel blocker) in all their participants, similar observations were not discussed in the other included studies.[14] It was unclear whether BP elevation after melatonin was due to the melatonin preparation (CR vs. IR), the use of calcium-channel blockers, or other patient/trial factors. Repeated monitoring of asleep BP used to be difficult in routine clinical practice because it was only detectable by 24-h ABPM, which may be poorly tolerated by some patients.[23] The recent development of home BP monitors measuring asleep BP may enhance patient compliance and allow for repeated asleep BP monitoring.[6] Although melatonin may also reduce daytime BP, adequately powered RCTs are warranted to confirm these findings. Furthermore, it is unclear whether melatonin harms patients with normal asleep BP when it produces excessive nocturnal BP reduction, associated with increased cardiovascular risk in some populations.[24] Moreover, it remains unclear whether the long-term use of melatonin reduces cardiovascular events. However, long-term use of CR melatonin may

reduce cardiovascular risk and events because it also reduces hyperglycemia and hyperlipidemia, which are important comorbidities and cardiovascular risk factors in patients with HT.[25,26]

For researchers, an adequately powered RCT is urgently needed to confirm the effect of melatonin on both daytime and asleep BP. Second, the characteristics of responders to melatonin remain unknown. In particular, inter-individual differences in endogenous melatonin (> 10× difference) have been well described.[27] Although nocturnal HT and non-dipping were associated with lower endogenous melatonin levels, it remains unclear whether melatonin supplementation was more effective in patients with lower melatonin levels because all existing RCTs did not control their results for endogenous melatonin levels.[14–17] Similarly, melatonin may be particularly effective in patients with certain characteristics, for example, insomnia or psychiatric disease, but none of our included studies reported on the proportion of patients with psychiatric illness. Third, although cardiovascular outcomes (e.g., stroke/heart disease) and long-term safety were included in our original registered protocol in PROSPERO, none of the included studies reported these. An improvement in cardiovascular outcomes and confirmation of long-term safety are essential for melatonin to be a standard treatment for HT or nocturnal HT. While hard cardiovascular outcomes (e.g., stroke and death) take years to develop and may not be feasible for many RCTs, surrogate cardiovascular outcomes, for example, carotid-femoral pulse wave velocity, accurately predict cardiovascular events and death and may be considered.[28] Moreover, the BP reduction mechanisms of melatonin remain unclear in humans, although numerous mechanistic studies in animals have been published.[29,30] Furthermore, the existing studies were conducted in Western populations, and external validity for other ethnicities are not known. Finally, most included RCTs ($n = 3$) used a cross-over design, but order effects (i.e., participants receiving melatonin after a course of placebo showing a greater reduction in BP) were observed in one RCT.[17]

4.3 | Strengths and limitations

The current meta-analysis was the first to include only patients with HT, thoroughly investigating all clinically relevant parameters (e.g., daytime/asleep BP and heart rate) and providing the most advanced evidence regarding the use of melatonin to treat HT or nocturnal HT. Our extensive search included Chinese databases. Owing to our strict criteria, almost all our results were homogeneous. The current meta-analysis was pre-registered and conducted according to the PRISMA guidelines. Therefore, the results provide important guidance for clinicians and researchers.

However, some limitations of this study should be discussed. Despite an explicit search in the Chinese database, only Western studies were found. The literature published in other languages could not be included because the reviewers could only read Chinese and English. However, since the abstracts of most trials were published in English, it is unlikely that a significant amount of literature was excluded. The current level of evidence was limited by the number, sample size, and quality of the existing RCTs. In fact, the limited number of RCTs prevented pre-planned analyses, as described in our protocol in PROSPERO. This included assessment of publication bias, meta-regression (to identify responders' characteristics and/or to investigate any heterogeneity), comparison of the drop-out rate between two arms (most studies were cross-over studies). Finally, data from crossover RCTs were statistically pooled together using the same method as in parallel RCTs. Although this was one of the methods discussed by the Cochrane handbook (chapter 23.2.6), this would underestimate the treatment effects from the crossover RCTs and produce more conservative effect sizes.[31] However, this has strengthened our conclusion that oral melatonin can reduce BP and improve sleep. Although another option was to extract data only from the first phase of the cross-over RCTs (before the cross-over), this was impossible because the relevant data was not reported by any of the included studies.[14,15,17]

4.4 | Summary

Although the hypotensive effects of oral melatonin have been long discussed, only four RCTs have investigated melatonin supplementation as a treatment in patients with HT, and most ($n = 3$) RCTs had an unclear risk of bias. CR melatonin is a potentially useful treatment for hypertension or nocturnal hypertension, but its effect size is imprecise owing to the limited number of included trials. Due to poor BP control worldwide, high-quality and adequately powered RCTs on melatonin are necessary to address the limitations of the current body of evidence.

ACKNOWLEDGEMENTS

This study was entirely self-funded.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ORCID

Eric Kam-Pui Lee MSc https://orcid.org/0000-0001-8267-9384

REFERENCES

1. Forouzanfar MH, Liu P, Roth GA, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. *JAMA*. 2017;317(2):165-182.
2. Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation*. 2016;134(6):441-450.
3. Yang W-Y, Melgarejo JD, Thijs L, et al. Association of office and ambulatory blood pressure with mortality and cardiovascular outcomes. *JAMA*. 2019;322(5):409-420.
4. Gavriilaki M, Anyfanti P, Nikolaidou B, et al. Nighttime dipping status and risk of cardiovascular events in patients with untreated hypertension: a systematic review and meta-analysis. *J Clin Hypertens*. 2020;22(11):1951-1959.
5. Unger T, Borghi C, Charchar F, et al. International society of hypertension global hypertension practice guidelines. *Hypertension*. 2020;75(6):1334-1357.
6. Kario K, Kanegae H, Tomitani N, et al. Nighttime blood pressure measured by home blood pressure monitoring as an independent predic-

tor of cardiovascular events in general practice: the J-HOP nocturnal blood pressure study. *Hypertension*. 2019;73(6):1240-1248.
7. Bo Y, Kwok K-O, Chung VC-H, et al. Short-term reproducibility of ambulatory blood pressure measurements: a systematic review and meta-analysis of 35 observational studies. *J Hypertens*. 2020;38(11):2095.
8. Baker J, Kimpinski K. Role of melatonin in blood pressure regulation: An adjunct anti-hypertensive agent. *Clin Exp Pharmacol Physiol*. 2018; 45(8): 755-766.
9. Fatemeh G, Sajjad M, Niloufar R, Neda S, Leila S, Khadijeh M. Effect of melatonin supplementation on sleep quality: a systematic review and meta-analysis of randomized controlled trials. *J Neurol*. 2022;269(1):205-216.
10. Hadi A, Ghaedi E, Moradi S, Pourmasoumi M, Ghavami A, Kafeshani M. Effects of melatonin supplementation on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *Horm Metab Res*. 2019;51(03):157-164.
11. Akbari M, Ostadmohammadi V, Mirhosseini N, et al. The effects of melatonin supplementation on blood pressure in patients with metabolic disorders: a systematic review and meta-analysis of randomized controlled trials. *J Hum Hypertens*. 2019;33(3):202-209.
12. Grossman E, Laudon M, Zisapel N. Effect of melatonin on nocturnal blood pressure: meta-analysis of randomized controlled trials. *Vasc Health Risk Manag*. 2011;7:577.
13. De Vecchis R, Paccone A, Di Maio M. Property of melatonin of acting as an antihypertensive agent to antagonize nocturnal high blood pressure: a meta-analysis. *Inte J Stati Med Res*. 2019;8:67-71.
14. Lusardi P, Piazza E, Fogari R. Cardiovascular effects of melatonin in hypertensive patients well controlled by nifedipine: a 24-hour study. *Br J Clin Pharmacol*. 2000;49(5):423-427.
15. Scheer FA, Van Montfrans GA, van Someren EJ, Mairuhu G, Buijs RM. Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. *Hypertension*. 2004;43(2):192-197.
16. Grossman E, Laudon M, Yalcin R, et al. Melatonin reduces night blood pressure in patients with nocturnal hypertension. *Am J Med*. 2006;119(10):898-902.
17. Rahbari-Oskoui F, Abramson J, Bruckman A, et al. Nighttime administration of high-dose, sustained-release melatonin does not decrease nocturnal blood pressure in African-American patients: results from a preliminary randomized, crossover trial. *Complement Ther Med*. 2019;43:157-164.
18. Li T, Jiang S, Han M, et al. Exogenous melatonin as a treatment for secondary sleep disorders: a systematic review and meta-analysis. *Front Neuroendocrinol*. 2019;52:22-28.
19. Lemoine P, Wade AG, Katz A, Nir T, Zisapel N. Efficacy and safety of prolonged-release melatonin for insomnia in middle-aged and elderly patients with hypertension: a combined analysis of controlled clinical trials. *Integr Blood Pressure Control*. 2012;5:9.
20. Harpsøe NG, Andersen LPH, Gögenur I, Rosenberg J. Clinical pharmacokinetics of melatonin: a systematic review. *Eur J Clin Pharmacol*. 2015;71(8):901-909.
21. Vural E, Van Munster BC, De Rooij SE. Optimal dosages for melatonin supplementation therapy in older adults: a systematic review of current literature. *Drugs Aging*. 2014;31(6):441-451.
22. Doolen S, Krause DN, Dubocovich ML, Duckles SP. Melatonin mediates two distinct responses in vascular smooth muscle. *Eur J Pharmacol*. 1998;345(1):67-69.
23. Wood S, Greenfield SM, Haque MS, et al. Influence of ethnicity on acceptability of method of blood pressure monitoring: a cross-sectional study in primary care. *Br J Gen Pract*. 2016;66(649):e577-e586.
24. Cuspidi C, Tadic M, Sala C, Gherbesi E, Grassi G, Mancia G. Extreme dipping: is the cardiovascular risk increased? An unsolved issue. *J Hypertens*. 2019;37(10):1917-1926.
25. Doosti-Irani A, Ostadmohammadi V, Mirhosseini N, et al. The effects of melatonin supplementation on glycemic control: a systematic review and meta-analysis of randomized controlled trials. *Horm Metab Res*. 2018;50(11):783-790.
26. Loloei S, Sepidarkish M, Heydarian A, et al. The effect of melatonin supplementation on lipid profile and anthropometric indices: a systematic review and meta-analysis of clinical trials. *Diabetes Metab Syndr*. 2019;13(3):1901-1910.
27. Burgess HJ, Fogg LF. Individual differences in the amount and timing of salivary melatonin secretion. *PLoS One* 2008;3(8):e3055.
28. Ohkuma T, Ninomiya T, Tomiyama H, et al. Brachial-ankle pulse wave velocity and the risk prediction of cardiovascular disease: an individual participant data meta-analysis. *Hypertension*. 2017;69(6):1045-1052.
29. Pechanova O, Paulis L, Simko F. Peripheral and central effects of melatonin on blood pressure regulation. *Int J Mol Sci*. 2014;15(10):17920-17937.
30. Huang L, Zhang C, Hou Y, et al. Blood pressure reducing effects of piromelatine and melatonin in spontaneously hypertensive rats. *Eur Rev Med Pharmacol Sci*. 2013;17(18):2449-2456.
31. Deeks JJ, Higgins JP, Altman DG. Analysing data and undertaking meta-analyses. In *Cochrane Handbook for Systematic Reviews of Interventions* (eds J.P. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M.J. Page and V.A. Welch). 2019: 241–284. https://doi.org/10.1002/9781119536604.ch10

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Lee EK-P, Poon P, Yu C-P, Lee VW-Y, Chung VC-Ho, Wong SY-S. Controlled-release oral melatonin supplementation for hypertension and nocturnal hypertension: a systematic review and meta-analysis. *J Clin Hypertens*. 2022;24:529–535. https://doi.org/10.1111/jch.14482