Bedtime Blood Pressure Chronotherapy Significantly Improves Hypertension Management

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KEYWORDS

• Hypertension chronotherapy • Asleep blood pressure • Cardiovascular risk • Ambulatory blood pressure monitoring • Hygia project • Diabetes • Chronic kidney disease • Resistant hypertension

KEY POINTS

- Consistent evidence of numerous studies substantiates the asleep blood pressure (BP) mean derived from ambulatory BP monitoring (ABPM) is both an independent and a stronger predictor of cardiovascular disease (CVD) risk than are daytime clinic BP measurements or the ABPM-determined awake or 24-hour BP means.
- Cost-effective adequate control of sleep-time BP is of marked clinical relevance.
- Ingestion time, according to circadian rhythms, of hypertension medications of 6 different classes and their combinations significantly improves BP control, particularly sleep-time BP, and reduces adverse effects.
- Recent findings authenticate therapeutic reduction of the sleep-time BP by a bedtime hypertension treatment strategy entailing the entire daily dose of $\geq$1 hypertension medications significantly reduces not only CVD risk but also progression toward new-onset type 2 diabetes and renal disease.

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INTRODUCTION

Blood pressure (BP) exhibits a mostly predictable 24-hour pattern as the culmination of the interrelationship of many 24-hour cyclic biological, behavioral, and environmental determinants: (1) endogenous circadian (~24-hour) variation in neuroendocrine, endothelial, vasoactive peptide and opioid, and hemodynamic parameters (eg, plasma noradrenaline and adrenaline [autonomic nervous system, ANS], atrial natriuretic and calcitonin gene-related peptides, and renin, angiotensin, and aldosterone [renin-angiotensin-aldosterone system, RAAS]); (2) rest-activity–associated changes in behavior such as activity routine and level, fluid and stimulant (eg, caffeine) consumption, meal timings and content, emotional and mental stress, and posture; (3) day-night divergence in ambient light intensity and spectrum, temperature, humidity, and noise.[1–4] The normally lower BP during nighttime sleep relative to daytime wakefulness thus represents the simultaneous influence of several predicable-in-time behavioral and environmental cycles combined with circadian rhythm stage-dependent alterations, most prominently the decline of sympathetic and increase of vagal tone, elevation of atrial natriuretic and calcitonin gene-related vasoactive peptides, and depression of the RAAS during the first half of the rest span followed by progressive activation during the second half of rest until peaking in the morning.[2,4–7]

Only ambulatory BP monitoring (ABPM) properly describes and quantifies the BP 24-hour variation. The findings of multiple ABPM studies consistently document strong association between the abnormal physiologic feature of blunted sleep-time relative BP decline (non-dipper/riser BP patterning) and the increased incidence of fatal and nonfatal cardiovascular disease (CVD) events, not only in hypertensive[8–13] but also in normotensive individuals.[14] Furthermore, various independent prospective studies demonstrate CVD events are better predicted by the ABPM-derived asleep than either the awake or 24-hour BP means or conventional daytime office BP measurements (OBPM).[10–13,15–20] Accordingly, there is great clinical interest of how to best tailor treatment to achieve the novel therapeutic goals of normalizing asleep BP and sleep-time relative BP decline (percent decrease in mean BP during nighttime sleep relative to the mean BP during awake-time activity) to the usual dipper pattern, which as a consequence protects against CVD and other events.[12,13,21] Thus, the purpose of this review is to present the latest findings pertaining to bedtime hypertension chronotherapy: the judicious scheduling of *conventional* BP-lowering medications in accord with circadian rhythm determinants, as a simple and cost-effective means to both regularize these abnormal characteristics of the 24-hour BP pattern and reduce CVD, stroke, renal, metabolic, and other risks.

INGESTION-TIME DIFFERENCES IN PHARMACODYNAMICS OF HYPERTENSION MEDICATIONS

The pharmacokinetics (PK) of hypertension medications are significantly influenced by the well-documented circadian rhythms in gastric pH, transport, and emptying; gastrointestinal motility; biliary function; glomerular filtration; hepatic enzyme activity; and organ (duodenum, liver, and kidney) blood flow.[22–24] Statistically and clinically significant ingestion time (more specifically, circadian stage) differences in the pharmacodynamics (PD) of hypertension medications,[25–31] that is, therapeutic modulation of the features of the 24-hour BP pattern and risk to adverse effects, can result not only from circadian rhythm dependencies of their PK but also from their circulating active free fraction plus receptor number/conformation and second messengers/signaling pathways of drug-targeted sites, for example, blood vessel, heart, and kidney tissue, and ANS and RAAS.[25,26,32] However, ingestion-time differences in the therapeutic and adverse effects of BP-reducing medications need not be solely dependent upon PK because the timing of peak and trough drug blood concentrations relative to the staging of the many underlying circadian rhythms that give rise to the unique 24-hour BP pattern may be more important.[3,4]

Two common mistakes made in the design and conduct of chronopharmacology–, ingestion-time differences of the PK and PD of medications due to biological rhythm influences, and chronotherapy trials of BP-lowering agents are (1) failure to require as a key inclusion criterion only subjects who have a life routine of diurnal activity alternating with nighttime sleep as confirmed by diary entries, and (2) selection of treatment times according to clock hour rather than meaningful biological markers of circadian stage, for example, upon morning awakening and at bedtime for participants adhering to a consistent diurnal wake and nocturnal sleep routine. Such an approach takes into account individual differences in exact activity onset (awakening from repose) and activity offset (bedtime), as consistently done in the authors' prospective trials.[28] Another frequent error is reliance solely upon daytime OBPM. Qualification of subjects for medication trials when relying