



Editorial

What is the Best Antihypertensive Treatment for OSA?



Obstructive sleep apnea (OSA), a common condition characterized by intrathoracic pressure reduction, sleep fragmentation and intermittent hypoxia due to repetitive upper airway obstructions during sleep, is a recognized cause of Hypertension (HTN).¹ In clinical practice, however, it is difficult to prove causality, but the management of patients with co-morbid OSA and HTN may require an integrative approach. While the main treatments for OSA are well established regardless of presence of HTN (and may have a positive impact on blood pressure, BP, especially in those with resistant HTN),² important questions related to the anti-hypertensive treatment deserve reflections: (1) Does OSA influence BP response to anti-hypertensive therapy?; (2) What is the best antihypertensive treatment in the OSA scenario? The first question was previously approached by our group in 2018.³ In an observational Cohort of 94 patients with HTN (55% of them with OSA) under a standard 30-day regimen of hydrochlorothiazide 25 mg plus enalapril (20 mg BID) or losartan (50 mg BID), we evaluated the BP response up to 18 months of follow-up (no specific OSA treatment occurred during the investigation). Medical appointments were conducted regularly to perform medical adjustments in the antihypertensive medication regimens if necessary (in a blinded fashion). Compared with baseline, we did not observe significant differences between groups in 24-h BP, daytime systolic and diastolic BPs, or nighttime systolic BP at 6 and 18 months. The BP control rate at 24 h (<130/80 mmHg) was

similar between the groups. Consistently, there were no differences in the number and class of antihypertensive medications prescribed during follow-up.³ Because patients in the aforementioned study used a combination of drugs, we speculated that multiple antihypertensive drugs acting in several pathways related to hypervolemia, the renin-angiotensin-aldosterone system, endothelial function, and sympathetic activation, among others, to mitigate the potential cardiovascular effects of OSA.³

The second question has a simple, but at the same time a challenge response: lessons learned from multiple studies revealed that continuous positive airway pressure (CPAP) *per se* is certainly not the best anti-hypertensive treatment. Overall, the modest BP lowering effects² and the worst performance as compared to single drug therapy make this question apparently easy to address.⁴ However, in a recent retrospective analysis using insurance-based data, Revol and colleagues⁵ noted a significant reduction in the median cost of antihypertensive therapy and the use of two drug classes (calcium channels blockers, CCB and renin-angiotensin-system-acting agents) and a significant decrease in drug use for the same classes only in the OSA group. Despite the lack of data on OSA severity, BP values, and adherence to OSA therapy, these results suggest a specific effect related to OSA therapy, but the study design only generated hypothesis for future well-controlled prospective investigations.

Table 1
Summary on the studies that explored the effects of anti-hypertensive classes for patients with OSA.

Author year	Study design	N	Compared drug classes	Follow-up	Concomitant OSA treatment?	Main results
Mayer, 1990 (6)	Randomized	12	Metoprolol (100 mg) or cilazapril (2.5 mg)	8 days	No	Both caused a significant decrease in nocturnal BP and OSA severity.
Kraczi, 2000 (7)	Randomized	40	Several classes once per day: Atenolol (50 mg); Amlodipine (5 mg); Enalapril (20 mg); Hydrochlorothiazide (25 mg); Losartan (50 mg)	6 weeks	No	The drugs had similar effects on daytime BP, although atenolol played a more efficient role in reducing mean nocturnal diastolic and systolic BP.
Heitmann, 2010 (8)	Randomized	31	Nebivolol (5 mg) or valsartan (80 mg)	2 weeks	No	The two drugs effectively reduced systolic and diastolic BP, but nebivolol had a more significant impact on heart rate reduction when compared to valsartan
Gaddam, 2010 (9)	Prospective open label	12	Spironolactone (25–50 mg)	8 weeks	Yes	A significant reduction in the severity of OSA was observed in parallel to BP reduction.
Kasiakogias, 2015 (10)	Prospective open label	41	Valsartan (160 mg) and a fixed combination of Amlodipina (5 mg) and Valsartan (160 mg)	16 weeks	Yes	The evening dosing induced the greatest BP decrease.

The complex history relies on the comparison of anti-hypertensive classes. Based on the aforementioned pathways, in theory some of them may have advantages over others. Previous studies have analyzed the effects of beta-blockers, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACE), CCB and spironolactone are summarized on the following Table 1. Overall, the reported studies comprised small sample of patients followed by a short-term period.^{6–10} In addition, some of the studies did not have an active comparator or focused on the timing of anti-hypertensive intake. In two randomized studies,^{7,8} beta-blockers had some secondary advantages over the other classes but the aforementioned limitations preclude any definitive conclusions. Based on the available evidence, distinct Cardiology Societies did not determine any preference anti-hypertensive treatment with co-morbid OSA is present in patients with OSA.^{11,12}

In conclusion, the best available evidence so far did not support any specific preference for the pharmacological anti-hypertensive treatment. Important to highlight that the evidence is limited, underscoring the need of well-designed, multicenter studies with large samples and long follow-up periods to expand our knowledge in the field. As suggested by a previous randomized study,⁴ combining treatment strategies seems to be the best option for improving sleep-related symptoms in parallel to decrease BP. Despite the significant controversies in the hypertension field related to the timing of anti-hypertensive intake,^{13,14} OSA patients might have more BP benefits using evening than morning dose, but definitive conclusions is lacking.

Conflict of interests

The authors state that they have no conflict of interests.

References

1. Barroso WKS, Rodrigues CIS, Bortolotto LA, Mota-Gomes MA, Brandão AA, Feitosa ADM, et al. Brazilian guidelines of hypertension – 2020. *Arq Bras Cardiol.* 2021;116:516–658.
2. Fatureto-Borges F, Lorenzi-Filho G, Drager LF. Effectiveness of continuous positive airway pressure in lowering blood pressure in patients with obstructive sleep apnea: a critical review of the literature. *Integr Blood Press Control.* 2016;9:43–7.
3. Fatureto-Borges F, Jenner R, Costa-Hong V, Lopes HF, Teixeira SH, Marum E, et al. Does obstructive sleep apnea influence blood pressure and arterial stiffness in response to antihypertensive treatment? *Hypertension.* 2018;72:399–407.
4. Pépin JL, Tamisier R, Barone-Rochette G, Launois SH, Lévy P, Baguet JP. Comparison of continuous positive airway pressure and valsartan in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med.* 2010;182:954–60.
5. Revol B, Castelli C, Ben Messaoud R, Coffy A, Bailly S, Jullian-Desayes I, et al. Deprescribing antihypertensive drugs after starting OSA primary therapy? *Sleep.* 2022;45:zsac060.
6. Mayer J, Weichler U, Herres-Mayer B, Schneider H, Marx U, Peter JH. Influence of metoprolol and cilazapril on blood pressure and on sleep apnea activity. *J Cardiovasc Pharmacol.* 1990;16:952–61.
7. Kraiczi H, Hedner J, Peker Y, Grote L. Comparison of atenolol, amlodipine, enalapril, hydrochlorothiazide, and losartan for antihypertensive treatment in patients with obstructive sleep apnea. *Am J Respir Crit Care Med.* 2000;161:1423–8.
8. Heitmann J, Greulich T, Reinke C, Koehler U, Vogelmeier C, Becker HF, et al. Comparison of the effects of nebivolol and valsartan on BP reduction and sleep apnoea activity in patients with essential hypertension and OSA. *Curr Med Res Opin.* 2010;26:1925–32.
9. Gaddam K, Pimenta E, Thomas SJ, Cofield SS, Oparil S, Harding SM, et al. Spironolactone reduces severity of obstructive sleep apnoea in patients with resistant hypertension: a preliminary report. *J Hum Hypertens.* 2010;24:532–7.
10. Kasiakogias A, Tsioufis C, Thomopoulos C, Andrikou I, Aragiannis D, Dimitriadis K, et al. Evening versus morning dosing of antihypertensive drugs in hypertensive patients with sleep apnoea: a cross-over study. *J Hypertens.* 2015;33:393–400.
11. Drager LF, Lorenzi-Filho G, Cintra FD, Pedrosa RP, Bittencourt LRA, Poyares D, et al. 1º Posicionamento brasileiro sobre o impacto dos distúrbios de sono nas doenças cardiovasculares da sociedade brasileira de cardiologia. *Arq Bras Cardiol.* 2018;111:290–340.
12. Yeghiazarians Y, Jneid H, Tietjens JR, Redline S, Brown DL, El-Sherif N, et al. Obstructive sleep apnea and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation.* 2021;144:e56–67.
13. Hermida RC, Crespo JJ, Domínguez-Sardiña M, Otero A, Moyá A, Ríos MT, et al. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. *Eur Heart J.* 2020;41:4565–76.
14. Mackenzie IS, Rogers A, Poulter NR, Williams B, Brown MJ, Webb DJ, et al. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial. *Lancet.* 2022;400(10361):1417–25.

José Gilvam A. Lima-Junior^a, Ana Vitoria Vitoreti Martins^a,
Luciano F. Drager^{a,b,*}

^a Unidade de Hipertensao, Instituto do Coracao (InCor), Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil

^b Unidade de Hipertensao, Disciplina de Nefrologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil

Corresponding author.

E-mail address: luciano.drager@incor.usp.br (L.F. Drager).