

**During a hypertensive urgency do you have any insight into the use of clonidine for acute lowering of blood pressure in the outpatient setting? Is this in any guideline? Are there alternatives?**

Clonidine is a centrally-acting alpha-2 agonist approved by the Food and Drug Administration (FDA) for several uses.<sup>1-5</sup> The drug is available in multiple preparations: immediate-release (IR) and extended-release (ER) oral tablets, transdermal films, and epidural solution. The IR tablets and transdermal films are approved for management of hypertension, alone or in combination with other antihypertensive agents.<sup>2,3</sup> In contrast, the ER tablets are approved for treatment of attention deficit hyperactivity disorder,<sup>4</sup> and the epidural solution is approved for treatment of severe pain that is inadequately relieved by opioids, alone, in patients with cancer.<sup>5</sup>

Hypertension, defined as high blood pressure (BP), is the single most common risk factor for cardiovascular disease and is 1 of the most common reasons for ambulatory clinic visits by adults worldwide.<sup>6</sup> Patients with hypertension may be at risk for hypertensive crises, defined as large elevations in systolic BP (>180 mmHg) or diastolic BP (>120 mmHg) associated with impending or progressive organ damage.<sup>7-9</sup> Hypertensive crises include hypertensive emergencies or hypertensive urgencies; emergencies are associated with target organ damage while urgencies are not.<sup>7</sup>

*Guidelines*

There are several guidelines for the management of hypertension, listed in [Table 1](#).<sup>6,8,10-15</sup> Use of clonidine for treatment of hypertension is not discussed in most of these guidelines. The American Society of Hypertension (ASH) and International Society of Hypertension (ISH) state that clonidine is effective in some patients, but they do not provide further details or specific recommendations on its use.<sup>11</sup> The American College of Cardiology (ACC), American Heart Association (AHA), and Centers for Disease Control and Prevention (CDC) caution co-administration of clonidine (or verapamil or diltiazem) and a beta-blocker, stating that this combination can cause symptomatic bradycardia over time.<sup>10</sup> The International Society on Hypertension in Blacks (ISHIB) also recommends avoiding clonidine in combination with a beta-blocker, due to significant risk of bradycardia and orthostatic hypotension.<sup>13</sup> Clonidine use is not otherwise described in these guidelines. The European Society of Hypertension (ESH) and European Society of Cardiology (ESC) recommend avoiding sudden withdrawal of therapy in patients taking clonidine (or beta-blockers), but they do not provide further recommendations on use of clonidine.<sup>8</sup>

Among the guidelines listed in [Table 1](#), only 1 was found to address the management of hypertensive urgency.<sup>8</sup> The ESH/ESC state that hypertensive urgencies are often associated with treatment discontinuation or reduction, as well as with anxiety; therefore, they recommend treatment with reinstatement or intensification of drug therapy and treatment of anxiety.

Though not addressed in JNC 8, hypertensive urgency is discussed in JNC 7.<sup>9,14</sup> Immediate BP reduction (not necessarily to normal) is recommended in patients with hypertensive urgency to prevent or limit target organ damage.<sup>9</sup> JNC 7 states that some patients may benefit from treatment with an oral, short-acting agent, followed by several hours of observation. Suggested agents include captopril, labetalol, or clonidine. However, there are concerns for overly aggressive management in patients with uncomplicated hypertension. JNC 7 asserts that overly aggressive management in patients with uncomplicated hypertension may result in hypotension and other cumulative effects.

Table 1. Selected guidelines for the management of hypertension in adults and recommendations regarding clonidine and/or hypertensive urgency.<sup>6,8,10-15</sup>

Organization, year of publication	Recommendations on:	
	Use of clonidine	Treatment of hypertensive urgency
ACC/AHA Task Force, 2017	--	--
ACC/AHA/CDC, 2014	Dosing range, drug interactions	--
ASH/ISH, 2014	Dosing range, brief notes on effectiveness	--
CHEP, 2009	Non-therapeutic*	--
ESH/ESC, 2013	Brief notes on administration	Reinstitute or intensify drug therapy, treat anxiety
ISHIB, 2010	Drug interactions	--
JNC 8, 2013**	--	--
NICE, 2011	--	--

--=absence of recommendations, ACC=American College of Cardiology, AHA=American Heart Association, ASH=American Society of Hypertension, CDC=Centers for Disease Control and Prevention, CHEP=Canadian Hypertension Education Program, ESC=European Society of Cardiology, ESH=European Society of Hypertension, ISH=International Society of Hypertension, ISHIB=International Society on Hypertension in Blacks, JNC=Joint National Committee, NICE=National Institute of Health and Care Excellence

\*use of clonidine suppression test recommended as an option for screening and diagnosis of pheochromocytoma

\*\*JNC 7 addresses management of hypertensive urgency but is not included in the table due to availability of a more recent report<sup>9</sup>

#### *Management of hypertensive urgency – use of clonidine*

From a search of the literature, few studies were identified evaluating management of hypertensive urgency. Few studies were found that evaluate use of clonidine for management of hypertensive urgency. Some clinical trials were identified, but they involved a small number of patients (e.g., 13 to 51 patients), were not specific to hypertensive urgency, and were published many years ago (1988-1990).<sup>16-18</sup> Thus, they were excluded from this review. More recently, several case reports were published. Those identified described hypertensive urgency resulting from concurrent use of clonidine and mirtazapine,<sup>19,20</sup> adverse outcomes associated with clonidine (namely dizziness and lack of effectiveness in reducing BP),<sup>21</sup> and lack of effect attributed to an interaction with yohimbine.<sup>22</sup> In 3 reports, patients were admitted to an emergency department (ED) or hospitalized and administered intravenous labetalol or nitroprusside,<sup>19,20,22</sup> while 1 report described outpatient management through addition of felodipine to the patient's antihypertensive regimen.<sup>21</sup>

In addition to these case reports, a prospective observational cohort was identified in which Chim et al sought to evaluate a protocol and algorithm for management of hypertensive urgency developed by clinical pharmacists at the Institute for Family Health (IFH – consisting of 19 federally qualified health centers in New York).<sup>23</sup> As part of the protocol, clinicians were advised to assess patients presenting with hypertensive urgency for risk factors that may have contributed to the BP elevation. A repeat BP measurement was recommended after at least 5 minutes; if still elevated, clinicians were advised to start or change an antihypertensive, enforce adherence to medications and low-sodium diet, and/or discontinue any offending drug(s). Clinicians were advised to also follow-up with patients within 2 days to determine if patients had new or continuing signs or symptoms of hypertensive urgency, and/or if they were adherent with their medication regimen, and to schedule visits within 1-2 weeks of the initial visit.

Chim et al expressly advised against administering clonidine in the office for acute management of hypertensive urgency.<sup>23</sup> Their rationale was multi-fold: they had found a lack of data demonstrating the need for treatment of asymptomatic BP elevations, and noted that non-pharmacologic management (e.g., transferring patients to quiet rooms for rest and observation) has been associated with sufficient BP

lowering in up to one-third of patients. The investigators also stated that hypertensive urgency may not arise suddenly but occur over an extended period of days to weeks, suggesting that effective BP reduction should be achieved through optimization of current antihypertensive regimens or initiation of long-term pharmacotherapy, as opposed to short-acting antihypertensives. The primary objective of their study was to achieve decreased rates of ordering clonidine for the immediate treatment of hypertensive urgency in the outpatient setting. The secondary objective was to determine if reduced use of clonidine was associated with a decline in poor outcomes, such as ED referrals, clonidine-associated adverse events, and severe hypotension.

Prior to implementation of the protocol, there were 625 hypertensive urgency visits; 106 patients received clonidine in the office for reduction of BP (17.4%).<sup>23</sup> Post-implementation, there were 702 visits; 73 patients received clonidine in the office (10.6%,  $p=0.001$ ) Reviewing characteristics of the patients who received clonidine in the office, pre- or post-intervention, several similarities were identified. Patients were typically middle-aged (mean 53 to 54 years), presenting with stage 2 hypertension, and taking more than 1 antihypertensive for pre-existing hypertension. Approximately 60 to 70% of patients were on 2 or more antihypertensive agents, some of which already included clonidine. Comparing groups, significantly more patients in the post-intervention group had neuropsychiatric and musculoskeletal disorders, illicit drug use, and home clonidine use.

No adverse events associated with clonidine were documented in either of the groups.<sup>23</sup> Among the pre-intervention group, 7 patients (6.8%) were referred to the ED; in comparison, 9 patients in the post-intervention group (12.5%) were referred to the ED ( $p=0.198$ ). Four of the 7 patients in the first cohort and 3 of the 9 patients in the second cohort chose to go to the ED. None of the patients was hospitalized. No follow-up documentation was found regarding post-hypertensive urgency visits.

Chim et al concluded that their protocol was associated with a significant reduction in number of in-office orders for clonidine.<sup>23</sup> They noted, however, that several factors needed adjustment for implementation of their protocol. Importantly, this study was limited to reviewing patients for whom clonidine was ordered and did not include a review of alternative management options of hypertensive urgency.

#### *Optimal management of hypertensive urgency*

Based on the available data, it is unclear whether there is an oral antihypertensive of choice for management of hypertensive urgency. Several review articles indicate that current recommendations regarding management of hypertensive crises are based on expert opinions and retrospective studies.<sup>24-27</sup>

There are conflicting recommendations regarding optimal management of hypertensive urgency. For example, Padilla Ramos and Varon recommend use of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker to reduce BP over 24-48 hours.<sup>28</sup> Ipek et al state that the choice of therapy should be based on the underlying cause of the hypertensive urgency, patient demographics, and comorbidities.<sup>24</sup> Ipek et al caution against use of high loading doses of oral antihypertensives, as this may cause hypotension after discharge and increase risk of hypotension-related complications as well as medication non-adherence. Kessler and Joudeh state that treatment intended to rapidly lower BP is considered unnecessary in asymptomatic patients, and the authors state that this practice may be harmful – for example, with overly rapid reduction of BP, there may be hypoperfusion leading to ischemia or infarction).<sup>25</sup> Recommended treatment involves initiation of a maintenance dose of an oral medication before discharge with consideration for a short follow-up period or hospitalization, depending on the patient's risk factors. Fast-acting agents should be reserved for true hypertensive emergencies. Hebert and

Vidt state that management of severe hypertension should include brief observation (hours), initiation or resumption of oral antihypertensive medication, and scheduling of follow-up care within 72 hours.<sup>26</sup> Citing expert opinion, they state that judicious acute treatment with an oral agent known to have a rapid onset of action could be recommended. Oral medications that they consider potentially appropriate include clonidine, labetalol, or captopril. Regarding clonidine, Hebert and Vidt note the rebound hypertension may occur shortly after discharge to home. To avoid this occurrence, they recommend either continuing the dose as an outpatient or beginning a long-acting drug in the office (e.g., amlodipine, metoprolol [ER]). Hebert and Vidt also note that for patients with hypertensive urgency attributable to non-adherence, resumption of prior medications may suffice, and for patients previously untreated for hypertension, initiation of a long-acting agent is appropriate.

Despite differences in treatment recommendations, most of the reviewed sources stress the importance of evaluating a patient's medical history and conducting a physical exam in the initial assessment of a patient with hypertensive urgency.<sup>24-26,28</sup> The evaluation should include observation of signs and symptoms of secondary causes of hypertension or presence of target organ damage. Secondary causes may include medications, illicit drugs, drug or substance withdrawal, and comorbid conditions. However, hypertensive urgency commonly occurs due to medication non-adherence or interruption of antihypertensive therapy.<sup>24,25,28</sup>

### Conclusion

In summary, there are several guidelines for the management of hypertension, but only 2 were identified with recommendations on management of hypertensive urgency.<sup>8,9</sup> Use of clonidine is not well-described in the guidelines with most providing dosing information and drug interactions.<sup>8-13</sup> Few studies were found evaluating management of hypertensive urgency, and few studies were identified evaluating clonidine use for this condition. There appears to be a lack of consensus on optimal treatment of hypertensive urgency, with some sources recommending initiation of short-acting antihypertensives to reduce BP over a short period (24 to 72 hours),<sup>26-28</sup> and others suggesting that treatment be chosen with consideration for the patient's presentation, medical history, and the underlying cause(s) of hypertensive urgency.<sup>24,25</sup> Thus, the available evidence precludes a definitive recommendation for management of hypertensive urgency.

### References

1. Clonidine. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc. [updated 11/8/17; accessed 11/15/17]. [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/6643](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6643).
2. Catapres® [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2016.
3. Catapres-TTS® [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2016.
4. Kapvay® [package insert]. St. Michael, Barbados: Concordia Pharmaceuticals Inc.; 2016.
5. Duraclon® [package insert]. Rockford, IL: Mylan Institutional LLC; 2016.
6. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. *J Am Coll Cardiol*. 2017; epub ahead of print. doi: 10.1016/j.jacc.2017.11.006.
7. Papadopoulos DP, Sanidas EA, Viniou NA, et al. Cardiovascular hypertensive emergencies. *Curr Hypertens Rep*. 2015;17(2):5.

8. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31(7):1281-1357.
9. National Heart, Lung, and Blood Institute. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. August 2004. <https://www.nhlbi.nih.gov/files/docs/guidelines/jnc7full.pdf>. Accessed November 15, 2017.
10. Go AS, Bauman MA, Coleman King SM, et al. An effective approach to high blood pressure control: a science advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. *Hypertension*. 2014;63(4):878-885.
11. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens (Greenwich)*. 2014;16(1):14-26.
12. Padwal RS, Hemmelgarn BR, Khan NA, et al. The 2009 Canadian Hypertension Education Program recommendations for the management of hypertension: Part 1 – blood pressure measurement, diagnosis, and assessment of risk. *Can J Cardiol*. 2009;25(5):279-286.
13. Flack JM, Sica DA, Bakris G, et al. Management of high blood pressure in Blacks: an update of the International Society on Hypertension in Blacks consensus statement. *Hypertension*. 2010;56(5):780-800.
14. Armstrong C; Joint National Committee. JNC8 guidelines for the management of hypertension in adults. *Am Fam Physician*. 2014;90(7):503-504.
15. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. August 2011. <https://www.nice.org.uk/guidance/cg127/resources/hypertension-in-adults-diagnosis-and-management-pdf-35109454941637>. Accessed November 15, 2017.
16. Greene CS, Gretler DD, Cervenka K, McCoy CE, Brown FD, Murphy MB. Cerebral blood flow during the acute therapy of severe hypertension with oral clonidine. *Am J Emerg Med*. 1990;8(4):293-296.
17. Jaker M, Atkin S, Soto M, Schmid G, Brosch F. Oral nifedipine vs. oral clonidine in the treatment of urgent hypertension. *Arch Intern Med*. 1989;149(2):260-265.
18. Houston MC. The comparative effects of clonidine hydrochloride and nifedipine in the treatment of hypertensive crises. *Am Heart J*. 1988;115(1 Pt 1):152-159.
19. Troncoso AL, Gill T. Hypertensive urgency with clonidine and mirtazapine. *Psychosomatics*. 2004;45(5):449-450.
20. Abo-Zena RA, Bobek MB, Dweik RA. Hypertensive urgency induced by an interaction of mirtazapine and clonidine. *Pharmacotherapy*. 2000;20(4):476-478.
21. Handler J. Hypertensive urgency. *J Clin Hypertens (Greenwich)*. 2006;8(1):61-64.
22. Malaty J, Malaty IA. Hypertensive urgency: an important etiology of rebound hypertension. *BMJ Case Rep*. 2014;2014.
23. Chim C, Dimitropoulos E, Ginzburg R. Implementing a policy and protocol on managing patients with hypertensive urgencies. *Ann Pharmacother*. 2016;50(7):548-554.
24. Ipek E, Oktay AA, Krim SR. Hypertensive crisis: an update on clinical approach and management. *Curr Opin Cardiol*. 2017;32(4):397-406.
25. Kessler CS, Joudeh Y. Evaluation and treatment of severe asymptomatic hypertension. *Am Fam Physician*. 2010;81(4):470-476.
26. Hebert CJ, Vidt DG. Hypertensive crises. *Prim Care*. 2008;35(3):475-487.
27. Cherney D, Straus S. Management of patients with hypertensive urgencies and emergencies: a systematic review of the literature. *J Gen Intern Med*. 2002;17(12):937-945.
28. Padilla Ramos A, Varon J. Current and newer agents for hypertensive emergencies. *Curr Hypertens Rep*. 2014;16(7):450.