



# Antihypertensives, Sympatholytics

## Therapeutic Class Review (TCR)

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## FDA-APPROVED INDICATIONS<sup>1</sup>

Drug	Manufacturer	Hypertension	Hypertensive Emergency	Hypertensive Urgency
clonidine immediate-release tablet (Catapres®)	generic	X		
clonidine transdermal (Catapres-TTS®)	generic	X		
clonidine /chlorthalidone (Clorpres®)	Bertek/Mylan	X		
guanfacine (Tenex®)	generic	X		
methyldopa	generic	X	X	X
methyldopa/hydrochlorothiazide	generic	X		
reserpine	generic	X		

**Other Indications:** Clonidine is available and approved in other dosage formulations for other indications including severe pain and attention deficit-hyperactivity disorder (ADHD). Guanfacine is also available and approved for the treatment of ADHD; dosage regimens and available tablet strengths differ for use in ADHD.

## OVERVIEW

Hypertension (HTN) affects over 30 percent of adult Americans and is an independent risk factor for the development of cardiovascular disease.<sup>2</sup> Hypertension can increase the risk of myocardial infarction (MI), stroke, heart failure (HF), and kidney disease. To reduce the risk of cardiovascular events, the current blood pressure goal is less than 140/90 mm Hg for most patients. **For patients with diabetes the current blood pressure goal is less than 140/80 mmHg** and for patients with chronic renal disease, with or without diabetes, goal for blood pressure therapy is less than 130/80 mm Hg.<sup>3,4</sup> Only about half of hypertensive patients have their disease under control.<sup>5</sup> Attainment of blood pressure goals results in a reduced risk of cardiovascular events.<sup>6</sup> There is inter-patient variability in response to various antihypertensive classes of medications. In the absence of compelling indications, reaching target blood pressure is central in determining cardiovascular benefit in patients with hypertension, not the specific agent used to reach target blood pressure.<sup>7,8,9</sup>

First-line therapy for HTN according to The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), published in 2003, is diuretics.<sup>10</sup> Angiotensin-converting enzyme (ACE) inhibitors may be used as first-line therapy for treatment of essential hypertension when a diuretic cannot be used or when a compelling indication is present. According to the JNC-7 guidelines, compelling indications for ACE inhibitors are: congestive heart failure (CHF), post-myocardial infarction (MI), high-risk coronary disease, diabetes mellitus, chronic kidney disease, and recurrent stroke prevention.<sup>11</sup> ACE inhibitors have been shown to reduce mortality in CHF, delay progression of diabetic nephropathy, and reduce risk of adverse cardiovascular outcomes in high-risk patients.<sup>12,13,14,15,16</sup> Additionally, the JNC-7 guidelines also state that more than two-thirds of hypertensive individuals cannot be controlled on one drug and will require two or more antihypertensives from different drug classes. In hypertensive patients with lower BP goals or with substantially elevated BP, three or more antihypertensive drugs may be necessary.<sup>17</sup>

Since the publication of JNC-7 guidelines for the treatment of hypertension, a meta-analysis aimed at evaluating the blood pressure lowering effects and incidences of heart attack, stroke and death in

patients taking hydrochlorothiazide (HCTZ) has been published.<sup>18</sup> Based on 14 studies including 1,234 patients taking HCTZ, blood pressure lowering with HCTZ was inferior to all other classes, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and calcium antagonists. Additionally, the meta-analysis concluded that there are no studies or evidence that HCTZ reduces myocardial infarction, stroke, or death.

This review focuses on the use of centrally-acting alpha2 adrenergic agonists and other sympatholytic agents used in the treatment of hypertension. Although there are newer antihypertensives like angiotensin-converting enzyme (ACE) inhibitors, the sympatholytics remain a viable treatment option for hypertension for patients refractory or sensitive to the newer agents.

## PHARMACOLOGY<sup>19</sup>

Drug	Mechanism Of Action
<b>Centrally-Acting Alpha2 Agonists</b>	
clonidine guanfacine	Both clonidine and guanfacine stimulate central alpha2-adrenergic receptors, thereby inhibiting sympathetic nervous system outflow, reducing peripheral vascular resistance, and lowering blood pressure. Guanfacine is a selective agonist, exhibiting a greater affinity for alpha2-adrenergic receptors than for alpha1-adrenergic receptors. Additionally, clonidine is also a partial agonist at presynaptic alpha2-adrenergic receptors of peripheral nerves in vascular smooth muscle. However, this site of action contributes minimally to its antihypertensive effects.
<b>Dihydroxyphenylalanine (DOPA) Carboxylase Inhibitor</b>	
methyldopa	Methyldopa is decarboxylated to produce alpha-methylnorepinephrine after it crosses the blood-brain barrier (BBB). This metabolite stimulates central inhibitory alpha-adrenergic receptors, thereby reducing peripheral resistance and lowering blood pressure.
<b>Combination DOPA Carboxylase Inhibitor and Diuretic</b>	
methyldopa and hydrochlorothiazide	Thiazide diuretics lower blood pressure by increasing the excretion of sodium, whereas methyldopa lowers blood pressure by inhibiting alpha-adrenergic receptors and subsequently reducing peripheral resistance and blood pressure.
<b>Catecholamine Reuptake Inhibitor</b>	
reserpine	Reserpine depletes stores of serotonin and norepinephrine in the brain, adrenal medulla, and other tissues, and reduces the reuptake of catecholamines by adrenergic nerve terminals. The drug binds tightly to catecholamine storage vesicles in the adrenergic neuron, eventually destroying these vesicles so that the terminals cannot concentrate or store norepinephrine or dopamine. This process also occurs in vesicles that store serotonin (5-hydroxytryptamine).

## PHARMACOKINETICS<sup>20</sup>

Drug	Half-Life (Hr)	Active Metabolites	Excretion (%)
clonidine immediate-release tablet (Catapres)	--	--	Urine: 40 to 60
clonidine transdermal (Catapres-TTS)	5.7 to 19.7		
clonidine/chlorthalidone (Clorpres)	Refer to individual product information	Refer to individual product information	Refer to individual product information
guanfacine (Tenex)	10 to 30	--	--
methyldopa	2	--	Biphasic elimination
methyldopa/hydrochlorothiazide	Refer to individual product information	Refer to individual product information	Refer to individual product information
reserpine	weeks	Multiple metabolites	--

## CONTRAINDICATIONS/WARNINGS<sup>21</sup>

Abrupt discontinuation of clonidine, regardless of the route of administration, can precipitate a withdrawal syndrome consisting of rebound increases in both serum and urine catecholamines. If it is necessary to discontinue clonidine, doses should be slowly tapered over two to four days to avoid withdrawal symptoms. Patients who have received clonidine therapy for greater than four weeks may require slower dosage tapers (e.g., dosage reduction every three days).

Use caution when administering guanfacine to patients with a history of hypotension, atrioventricular (AV) block, bradycardia, severe coronary artery disease, acute myocardial infarction, cerebrovascular disease, severe hepatic disease (hepatic failure), or renal disease associated with renal impairment or renal failure. These patients may be at higher risk of adverse effects associated with dose-related hypotension.

Methyldopa is contraindicated for use with monoamine oxidase inhibitors (MAOIs). Administration of MAOIs with methyldopa has resulted in headaches, severe hypertension, and hallucinations. Linezolid is an antibiotic that is also a reversible, non-selective MAO inhibitor that should not be used with methyldopa.

Methyldopa/HCTZ is contraindicated in patients with active hepatic disease such as acute hepatitis and decompensated liver disease. Because of the risk of hemolytic anemia, patients receiving methyldopa/HCTZ should have a baseline hemoglobin, hematocrit, or red blood cell count assessed before and during therapy. Positive Coombs' tests occur in 10 to 20 percent of patients receiving methyldopa therapy within six to 12 months of therapy, with the lowest incidence occurring with a daily dosage of one gram or less.

Reserpine is contraindicated in patients receiving electroconvulsive therapy (ECT) because depletion of catecholamines can increase the risk of convulsions. It is recommended that following reserpine therapy, at least one week should elapse before electroconvulsive therapy is initiated. Reserpine is also contraindicated in patients with active peptic ulcer disease or ulcerative colitis as reserpine can exacerbate these conditions.

Reserpine should not be used in patients with a seizure disorder and is contraindicated in patients with a history of major depression, especially those who have suicidal ideation.

Reserpine can cause decreased mental function, and patients should be warned of the hazards of operating heavy machinery or driving an automobile while receiving reserpine.

Depression can be aggravated by reserpine therapy. Also, reserpine should be used with caution in patients with Parkinson's disease.

Reserpine should not be used in patients with a history of rauwolfia alkaloid hypersensitivity.

Reserpine should be used with caution in patients with cardiac disease such as cardiac arrhythmias or pheochromocytoma.

## **DRUG INTERACTIONS<sup>22</sup>**

Concurrent use of clonidine with tricyclic antidepressants (TCAs) should be avoided when possible, due to multiple interactions. Clonidine can produce bradycardia and should be used cautiously in patients who are receiving other drugs that lower the heart rate, such as beta-blockers. It also may have additive hypotensive effects (which may be advantageous) with other drugs like diuretics. Clonidine can produce bradycardia and should be used cautiously in patients who are receiving other drugs that lower the heart rate, such as amiodarone and cardiac glycosides.

Guanfacine interacts with MAO inhibitors, sympathomimetics, trazodone, and tricyclic antidepressants. Increased dosages of guanfacine may be required in patients who are receiving tricyclic antidepressants concurrently. In addition, concurrent tricyclic antidepressants may enhance the potential for rebound hypertension following guanfacine discontinuation. If guanfacine is withdrawn in the presence of tricyclic antidepressants, guanfacine should be tapered gradually and the patient should be monitored for potential hypertension.

Sympathomimetics, such as cocaine, dobutamine, dopamine, norepinephrine, epinephrine, phenylephrine, phenylpropanolamine, and ephedrine, can antagonize the antihypertensive effects of methyldopa when administered concomitantly. Additionally, iron salts have been reported to dramatically reduce the oral absorption of methyldopa. Methyldopa can cause psychosis if administered concomitantly with levodopa and additive hypotensive effects also may occur. Patients receiving lithium and methyldopa concomitantly can develop lithium toxicity. Ironically, lithium levels may appear to be in the therapeutic range in the presence of signs of lithium toxicity. Therefore, plasma lithium concentrations are not an accurate indicator of lithium toxicity in patients receiving concurrent methyldopa therapy.

Administration of reserpine to patients receiving MAOI therapy can cause hypertension and increased excitation. Additionally, other major interactions with reserpine include concomitant administration with levodopa, procarbazine, sympathomimetics, tricyclic antidepressants, linezolid, and furazolidone.

## ADVERSE EFFECTS<sup>23</sup>

Drug	Nausea and/or vomiting	Diarrhea	Sexual Dysfunction	Depression or Other CNS effects	Fatigue	Dizziness
clonidine immediate-release tablets	X	X	X	X	X	X
clonidine transdermal (Catapres-TTS)	X	X	X	X	X	X
guanfacine	X	X	X	X	X	X
methyldopa	X	X	X	X	X	nr
reserpine	X	X	X	X	X	X

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Orthostatic hypotension can occur with methyldopa administration. Sinus bradycardia, worsening angina, and myocarditis have been reported, as well as congestive heart failure and carotid sinus hypersensitivity. Sodium and fluid retention can occur, producing edema, and can often be alleviated with concomitant thiazide diuretic therapy.

Patients receiving methyldopa can develop a positive Coombs' test. This is usually not clinically important, but hemolysis with anemia has occurred on rare occasions, causing death in two patients. If hemolysis is present, methyldopa therapy should be discontinued. Methyldopa has also been associated with thrombocytopenia.

Methyldopa-induced fever can occur within three weeks of initiating therapy. This may be associated with eosinophilia and/or elevated hepatic enzymes. Hepatocellular injury, cirrhosis, hepatitis, and cholestasis have been reported. If methyldopa is the source of these abnormalities, temperature and liver function will usually return to baseline a few months after discontinuance of the drug.

Adverse dermatological effects of methyldopa therapy include rash, urticaria, and hyperkeratosis. Photosensitivity has been observed, but appears to be rare.

For the combination products, clonidine/chlorthalidone and methyldopa/HCTZ, please refer to the individual prescribing information for specific adverse effects associated with each component ingredient.

## SPECIAL POPULATIONS<sup>24</sup>

### Pediatrics

Safe and effective use of immediate-release oral clonidine and transdermal clonidine has not been established in patients less than 18 years of age. The National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents does not recommend the use of clonidine immediate-release for the management of hypertension in children under 12 years of age.

Safe and effective use of guanfacine in patients less than 18 years of age for the treatment of hypertension has not been established. Furthermore, hallucinations have been reported in post marketing studies of pediatric patients receiving Tenex (guanfacine) for treatment of attention-deficit hyperactivity disorder.<sup>25</sup>

There are no well-controlled clinical trials of methyldopa in children. Information from the drug manufacturer in regard to dosing methyldopa in pediatric patients is supported by published data in the medical literature regarding the treatment of hypertension in children

## **Pregnancy**

Methyldopa oral dosage forms and guanfacine are classified as Pregnancy Category B.

Hydrochlorothiazide/methyldopa is classified as Pregnancy Category C.

Although the manufacturer of reserpine has it classified as Pregnancy Category C, reserpine more closely corresponds to Pregnancy Category D because it has demonstrated adverse fetal effects in animal reproduction studies. All clonidine-containing drugs in this review are classified as Pregnancy Category C.

## **Renal Impairment**

Dosage of all forms of clonidine should be reduced in patients with impaired renal function according to the degree of impairment, and patients should be carefully monitored for bradycardia, sedation, and hypotension.

Dosing of methyldopa must be individualized based on a patient's renal function. If creatinine clearance (CrCl) is between 10 and 30 mL/min, then the dosage interval should be eight to 12 hours. If the CrCl is less than 10 mL/min, then the dosage interval should be every 12 to 24 hours.

Methyldopa/HCTZ should be used cautiously in patients with renal disease such as severe renal impairment or renal failure; in addition, HCTZ is contraindicated in patients with anuria.

Avoid using reserpine in patients who have advanced renal disease, renal failure, or severe renal impairment (CrCl < 10 mL/min) due its potential for long-lasting antihypertensive effects and the potential adverse effects of hypotension on the kidney.

## **Hepatic Impairment**

Although no quantitative recommendations are available, it appears that dosage reductions may be considered in patients with severe hepatic impairment due to substantial metabolism of clonidine.

Methyldopa is contraindicated in patients with active hepatic disease, such as acute hepatitis and decompensated cirrhosis.

Dosage reduction may be warranted for patients with hepatic impairment because reserpine is extensively metabolized in the liver. Initiate dosage cautiously; adjust dosage based on clinical response.

**DOSAGES<sup>26</sup>**

Drug	Initial Dose	Maintenance and Maximum Daily Dose	Special Instructions	Availability
clonidine immediate-release (Catapres)	0.1 mg twice daily (morning and bedtime)	0.2 mg to 0.6 mg daily in divided doses; Maximum daily dose is 2.4 mg	Elderly patients may benefit from a lower starting dose. Dosage adjustments may be needed based on degree of renal impairment, and patients should be carefully monitored.	0.1 mg , 0.2 mg, and 0.3 mg immediate-release tablets
clonidine transdermal (Catapres-TTS)	Apply one 0.1 mg/24 hr transdermal patch every seven days to a hairless area of intact skin on the upper outer arm or chest	If the desired blood pressure reduction does not occur within the first two weeks, an additional TTS-1 patch may be applied or a larger system may be used. More than two of the TTS-3 transdermal patches have not been associated with increased efficacy.	Dosage adjustments may be needed based on degree of renal impairment, and patients should be carefully monitored.	0.1 mg/24 hr transdermal 0.2 mg/24 hr transdermal 0.3 mg/24 hr transdermal
clonidine /chlorthalidone (Clorpres)	1 or 2 tablets two to four times daily	Maximum recommended daily dose of 2.4 mg of clonidine; titrate dose in increments of 0.1 mg to 0.2 mg of clonidine daily until the desired response is achieved.	The dosage is determined by individual titration of the separate components.	0.1 mg/15 mg tablet 0.2 mg/15 mg tablet 0.3 mg/15 mg tablet
guanfacine (Tenex)	1 mg once daily at bedtime	Maximum dose is 3 mg to 4 mg daily. Increase dose after first three to four weeks to 2 mg once daily then further increases up to 3 mg once daily if needed.	Greater sensitivity in elderly patients to the antihypertensive and sedative effects may occur.	1 mg and 2 mg tablet

**Dosages (continued)**

Drug	Initial Dose	Maintenance and Maximum Daily Dose	Special Instructions	Availability
methyldopa	Adults: 250 mg two to three times daily Pediatrics: 10 mg per kg per day in two to four divided doses Neonates: 5 mg to 10 mg per kg daily in divided doses every six to eight hours	500 mg to 2000 mg daily in two to four divided doses. Maximum adult dose is 3,000 mg daily. Maximum geriatric dose is 1,000 mg daily. Maximum pediatric daily dose is 65 mg per kg per day or 3,000 mg daily, or whichever is less	--	125 mg, 250 mg, and 500 mg tablets
methyldopa/HCTZ	One 250 mg/15 mg tablet two or three times daily or one 250 mg/25 mg tablet twice daily or one 500 mg/30 mg or 500 mg/50 mg tablet once daily	Maximum recommended dose of methyldopa component is 750 mg daily and of HCTZ component is 50 mg daily	Elderly patients may require lower doses.	250 mg/15 mg tablet 250 mg/25 mg tablet 500 mg/30 mg tablet 500 mg/50 mg tablet
reserpine	0.05 mg to 0.1 mg once daily	0.1 mg to 0.25 mg once daily as maintenance dose Maximum adult daily dose is 0.5 mg and maximum geriatric daily dose is 0.25 mg	Use of the lowest possible dose is recommended to minimize side effects. Dose reduction may be necessary for patients with hepatic impairment. This drug should not be used in patients with creatinine clearance (CrCl) of less than 10 mL/min.	0.1 mg and 0.25 mg tablets

Dosage changes may need to be made for each agent based on the other concomitant medications that the patient is currently receiving, decreased renal and/or hepatic function, and tolerability of the agent. Please consult package inserts for additional information.

**CLINICAL TRIALS****Search Strategy**

Due to the multiple indications for use of the antihypertensive medications, many of the comparative clinical trials currently available do not specifically focus on treatment of primary hypertension. However, the studies identified in this review, attempt to isolate those comparative studies that facilitate identification of the clinically proven sympatholytic therapies in the treatment of hypertension that optimize the quality of life for the patient. When comparative trial information was unavailable, well-designed placebo-controlled studies have been included.

Articles were identified through searches performed on PubMed and review of information sent by the manufacturers. The search strategy included the use of all drugs in this class and the keywords “hypertension.” Randomized, controlled, comparative trials of FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no comparative clinical trials evaluating the sympatholytic antihypertensives. Good quality, double-blind, comparative trials have not been performed with these agents in the management of hypertension.

## META-ANALYSES

In 2009, a meta-analysis was conducted to quantify the effect of methyldopa compared to placebo in randomized controlled trials (RCTs) on all cause mortality, cardiovascular mortality, serious adverse events, myocardial infarctions, strokes, withdrawals due to adverse effects and blood pressure in patients with primary hypertension.<sup>27</sup> A search of the following databases was conducted: Cochrane Central Register of Controlled Trials (1960-June 2009), MEDLINE (2005-June 2009), and EMBASE (2007-June 2009). Randomized controlled trials of patients with primary hypertension were selected for inclusion. Twelve trials (n=595) met the inclusion criteria for this review. None of these studies evaluated the effects of methyldopa compared to placebo on mortality and morbidity outcomes. Data for withdrawals due to adverse effects were not reported in a way that permitted meaningful meta-analysis. Data from six of the twelve trials (N=231) were combined to evaluate the blood pressure lowering effects of methyldopa compared to placebo. This meta-analysis showed that methyldopa at doses ranging from 500 to 2,250 mg daily lowers systolic and diastolic blood pressure by a mean of 13 mmHg (95 percent CI 6 to 20) / 8 (95 percent CI 4 to 13). Overall, the risk of bias was considered moderate. The authors concluded that methyldopa lowers blood pressure to varying degrees compared to placebo for patients with primary hypertension. Its effect on clinical outcomes, however, remains uncertain.

Another meta-analysis was conducted in 2009 to investigate the dose-related effect of reserpine on blood pressure, heart rate and withdrawals due to adverse events.<sup>28</sup> The databases CENTRAL, EMBASE, and MEDLINE were searched. Included studies were randomized controlled trials comparing reserpine monotherapy to placebo or no treatment in patients with primary hypertension. Four RCTs (n=237) were found that met the inclusion criteria. The overall pooled effect demonstrates a statistically significant systolic blood pressure (SBP) reduction in patients taking reserpine compared to placebo (-7.92, 95 percent CI -14.05, -1.78). Due to significant heterogeneity across trials, a significant effect in diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) could not be found. The SBP effects were achieved with 0.5 mg/day or greater. However, the dose-response pattern could not be determined because of the small number of trials. None of the included trials reported

withdrawals due to adverse effects. The authors concluded that reserpine is effective in reducing SBP roughly to the same degree as other first-line antihypertensive drugs. However, they could not make definite conclusions regarding the dose-response pattern because of the small number of included trials. The authors stated that more RCTs are needed to assess the effects of reserpine on blood pressure and to determine the dose-related safety profile before its role in the treatment of primary hypertension can be established.

## SUMMARY

Many antihypertensive agents exist today for the treatment of primary hypertension (systolic blood pressure of 140 mmHg or greater and/or diastolic blood pressure of 90 mmHg or greater). Hypertension is associated with an increased risk of stroke, myocardial infarction and congestive heart failure. The oral, centrally-acting, alpha2-adrenergic receptor agonists currently in use include clonidine and guanfacine. Clonidine (Catapres) is available in both a transdermal formulation and an oral formulation for the treatment of hypertension. Clonidine and chlorthalidone (Clorpres) are also generically available in a combination tablet formulation. Guanfacine (Tenex) is used alone or in combination with other drugs for the treatment of hypertension. While it is similar to clonidine, guanfacine is more selective for alpha2-adrenergic receptors, longer acting, dosed once daily, and has less frequency and severity of rebound hypertension following abrupt discontinuation. Methyldopa is a centrally-acting antihypertensive agent, which was commonly used in the past for blood pressure control but whose use has largely been replaced by other antihypertensive drug classes with more favorable adverse effect profiles. However, methyldopa is still used in developing countries due to its low cost and in the treatment of chronic hypertension in pregnant women. Hydrochlorothiazide and methyldopa are used together in an oral preparation for the treatment of hypertension. The effects are additive for blood pressure reduction with the combination of hydrochlorothiazide and methyldopa. The combination product may be used once the dose has been successfully titrated and the optimal dose corresponds to a ratio contained in the combination formulation. The use, however, of this combination product should be minimal due to dosing constraints from each individual component found in the combination product. The HCTZ component negates the use of this combination product in pregnant women. Reserpine has been used as a second-line therapy. Recently, the use of reserpine as an antihypertensive agent has diminished due its adverse CNS effects. Newer agents have shown to be much better tolerated.

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