



## Nontraditional combination pharmacotherapy of hypertension

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■ Traditional drug combinations that have additive hypotensive effect include double therapy with a diuretic and any other antihypertensive agent and triple therapy with a diuretic, direct vasodilator, and either a beta blocker or reserpine. Due to the availability of new classes of antihypertensive agents, other combinations of drugs are now increasingly used. The effectiveness of combination therapy for hypertension has been investigated; the results of these studies are reviewed.

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**T**HE HYPERTENSIVE PATIENT whose blood pressure fails to fall to the target level with a single antihypertensive agent should have another agent substituted (sequential monotherapy) or should receive two or more agents in combination. Traditionally, the two most effective and commonly used drug combinations have been (1) double therapy with a diuretic and almost any other antihypertensive agent and (2) triple therapy with a diuretic, a direct vasodilator, and either a beta blocker or reserpine (sometimes referred to as "standard" triple therapy).<sup>1-4</sup> However, with the availability of new classes of antihypertensive agents, combinations other than these are now increasingly used.

### RATIONALE FOR MULTIPLE-AGENT REGIMENS

Antihypertensive agents are categorized by their actions as diuretics, beta blockers, vasodilators (direct vasodilators, alpha-1 blockers, calcium-channel block-

ers, and angiotensin-converting enzyme [ACE] inhibitors), central adrenergic inhibitors (methyldopa, clonidine, guanabenz, guanfacine), or peripheral adrenergic inhibitors (guanethidine, guanadrel, reserpine). It should not be assumed that combining two agents from different antihypertensive classes will have an additive hypotensive effect, since the response to combination therapy can be reduced by pharmacokinetic or pharmacodynamic interactions. Beta blockers and ACE inhibitors both decrease blood pressure in part via a decrease in angiotensin II; central adrenergic inhibitors and alpha-1 blockers both inhibit the sympathetic nervous system; and central adrenergic inhibitors and ACE inhibitors both affect the sympathetic nervous system (angiotensin II modulates sympathetic nervous system activity).

The effectiveness of combination therapy for hypertension has been investigated in numerous studies. These studies have been limited by factors such as exclusion of patients with complicating medical illnesses, small sample sizes, short "wash-out" and treatment periods, infrequent use of 24-hour blood pressure monitoring, dose ranges too narrow to determine whether a combination is synergistic or merely additive, and a paucity of data on the pharmacology, hemodynamics, and side effects of combination therapy.<sup>5,6</sup> While most of the initial studies were uncontrolled,

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**TABLE 1**  
DOUBLE THERAPY COMBINATIONS WITH NO OR MINIMAL ADDITIVE ANTIHYPERTENSIVE EFFECT

Reference	Initial agent, dose/day (mg)	Added agent, dose/day(mg)	No. of patients	Study conditions	Duration (weeks)	Supine BP with monotherapy (mm Hg)	Change in BP with second agent (mm Hg)
12	Clonidine, 0.3	Prazosin, 15	9	UN	4	142/92	+1/+1
9	Clonidine, 0.2-0.4	Propranolol, 160	12	UN	3	156/102	-5/-5
13	Enalapril, 20	Atenolol, 50	16	RAN, DB, CO	4	147/85	-3/-7*
14	Nicardipine, 60	Prazosin, 4	14	UN	1	147/100	+2/0

UN, uncontrolled; RAN, randomized; DB, double-blind; CO, crossover; BP, blood pressure

\*Significantly different than monotherapy

**TABLE 2**  
ADDITION OF A SECOND AGENT TO AN ACE INHIBITOR

Reference	ACE inhibitor, dose/day (mg)	Second agent, dose/day (mg)	No. of patients	Study conditions	Duration (weeks)	Supine BP on an ACE inhibitor (mm Hg)	Change in BP with second agent (mm Hg)
29	Enalapril or Captopril, stable dose	Doxazosin, 1-8	56	SB, UN	10	158/101	-15/-17*
30	Captopril, 50-150	Diltiazem (sustained release), 120-360	31	UN	8	146/97	-5/-7*
13	Enalapril, 20	Atenolol, 50	16	RAN, DB, CO	4	147/85	-3/-7*
31	Enalapril, 20	Hydrochlorothiazide, 50	485	RAN, DB, PAR	48	146/94	-18/-10*

SB, single-blind; UN, uncontrolled; RAN, randomized; DB, double-blind; CO, crossover; PAR, parallel; BP, blood pressure

\*Significantly different than with an ACE inhibitor alone

recent studies have used either a double-blind crossover or parallel group design.<sup>5</sup>

## DOUBLE THERAPY

### Beta blocker and central adrenergic inhibitor

**Beta blocker and clonidine.** The combination of a beta blocker and clonidine has been variously reported to be effective,<sup>7,8</sup> ineffective,<sup>9</sup> or even to elevate blood pressure.<sup>10,11</sup> Two small, prospective, randomized studies investigated this combination; one demonstrated an insignificant hypotensive response (Table 1),<sup>9</sup> and the other a slight but significant response.<sup>7</sup> A large retrospective study found this combination to be effective when compared with no antihypertensive therapy, but the combination was not compared with either agent alone.<sup>8</sup> There are anecdotal reports of adverse interactions between these agents: paradoxical hypertension upon the addition of clonidine to a nonselective beta blocker, or vice versa<sup>10,11</sup>; rebound hypertension on withdrawal of clonidine, especially in those also receiving a nonselective beta blocker<sup>15</sup>; and marked bradycardia due to additive chronotropic effects.<sup>16</sup> The poor hypotensive response to this combination may relate to a possible shared central site of antihypertensive action<sup>17</sup> or to an interaction between

their peripheral effects (alpha-2 agonist-mediated vasoconstriction and inhibition of beta-2-dependent vasodilation).<sup>18-20</sup>

**Other central adrenergic inhibitors.** Although combining a beta blocker with clonidine does not appear to be particularly effective, adding a beta blocker to methyldopa further reduced blood pressure in a double-blind crossover study,<sup>21</sup> as did using a beta blocker in conjunction with guanfacine in an uncontrolled post-marketing study.<sup>22</sup> There is one case report of paradoxical hypertension with the use of propranolol and methyldopa.<sup>23</sup>

### Beta blocker and vasodilator

While the various beta blockers are all equally effective as monotherapy for hypertension, it is not known whether each is equally effective in combination with the various vasodilators.<sup>24-26</sup> Beta blockers without prominent intrinsic sympathomimetic activity (ISA) decrease cardiac output, while those with prominent ISA decrease peripheral resistance.<sup>27</sup> Possibly, when a beta blocker with ISA is added to a vasodilator, the further vasodilation reduces blood pressure less than would the addition of a beta blocker that decreases cardiac output. For example, in hypertension in pregnancy, hydralazine reduced blood pressure in 55% of

TABLE 3  
ADDITION OF A SECOND AGENT TO A BETA BLOCKER

Reference	Second agent, dose/day (mg)	No. of patients	Study conditions	Duration (weeks)	Supine BP on a beta-blocker (mm Hg)	Change in BP with second agent (mm Hg)
32	Felodipine, 10-20	51	RAN, DB, PAR	4-8	172/114	-30/-24*†
	Hydrochlorothiazide, 25-50	47		4-8	170/112	-20/-16*
33	Felodipine, up to 40	50	RAN, DB, PAR	6	177/104	-33/-22*‡
	Prazosin, up to 8	50		6	176/103	-15/-13*
34	Hydralazine, up to 200	20	RAN, PAR	12	166/109	-17/-17*
	Prazosin, up to 8	19		12	172/108	-16/-15*
35	Bendrofluzide, 5-10	19	RAN, CO	4-8	191/117	-21/-12*
	Prazosin, 6-15	19		4-8	191/117	-25/-15*
36	Lisinopril, 10-20	297	RAN, DB, PAR, PC	8	160/102	/-3.2§

RAN, randomized; DB, double-blind; PAR, parallel; CO, crossover; PC, placebo-controlled; BP, blood pressure

\*Significantly different than with a beta blocker alone

†Significantly different than beta blocker/diuretic

‡Significantly different than beta blocker/prazosin

§Significantly different than beta blocker/placebo

patients, but hydralazine combined with pindolol (prominent ISA activity) was effective in only 59%.<sup>28</sup>

**Beta blocker and ACE inhibitor.** Although initial uncontrolled studies suggested these two classes of drugs in combination have no additive hypotensive effect (Tables 1-3),<sup>37,39</sup> several double-blind, randomized, crossover trials have in fact found a small additive effect.<sup>13,40-42</sup> In a multicenter trial adding 5 mg of lisinopril to the regimen of patients who remained hypertensive on atenolol monotherapy, the combination did not further reduce blood pressure. Adding 10 or 20 mg of lisinopril reduced blood pressure by only 3/3 mm Hg and 7/5 mm Hg, respectively (Table 3).<sup>39</sup> Combining a beta blocker and an ACE inhibitor has been reported to be less effective than combining a diuretic and an ACE inhibitor.<sup>13,38</sup> The blunting by a beta blocker of the increase in plasma renin activity induced by an ACE inhibitor may contribute to the hypotensive response to the combination.<sup>40,41</sup> Variations in response may relate to differences in renin status and age.<sup>40,41</sup>

**Beta blocker and calcium-channel blocker.** Most of the studies with this very effective combination have used a dihydropyridine calcium-channel blocker (eg, nifedipine, nicardipine, isradipine, felodipine, nitrendipine),<sup>32,33,42-47</sup> while several have used either diltiazem (Table 4)<sup>47</sup> or verapamil.<sup>51</sup> Multiple double-blind, randomized, controlled studies have found that combining a beta blocker and a dihydropyridine calcium-channel blocker reduces blood pressure more than either agent alone,<sup>42-45</sup> or than a beta blocker with either hydralazine,<sup>45</sup> a diuretic,<sup>32,46</sup> or prazosin<sup>33</sup> (Tables 3 and 4). This combination may even be as effective as triple

therapy with a beta blocker, hydralazine, and a diuretic.<sup>45</sup> This combination also has an additive effect in the treatment of angina.<sup>52,53</sup>

The efficacy of combining a beta blocker with a calcium-channel blocker is due to their complementary antihypertensive mechanisms and to their pharmacokinetic interactions. Dihydropyridine calcium-channel blockers increase cardiac output, heart rate, and plasma renin activity, while they decrease peripheral resistance; beta blockers have the opposite effects. Pharmacokinetic effects that influence the hypotensive response in combinations of a beta blocker and a calcium-channel blocker include an increase in peak plasma concentrations of propranolol with verapamil, and enhanced bioavailability of propranolol by nifedipine and of metoprolol by verapamil.<sup>54-56</sup>

Adverse cardiovascular reactions to the combination of a beta blocker and a calcium-channel blocker<sup>52,53,56</sup> have been reported primarily in patients with angina, not hypertension alone. Precipitation of congestive heart failure has rarely been reported with combination therapy using a beta blocker and a dihydropyridine calcium-channel blocker or diltiazem, but it has commonly been reported with the combination of a beta blocker and verapamil. Risk factors for congestive heart failure with this therapy include left ventricular systolic dysfunction, use of either agent in high doses or intravenously, and concurrent use of other agents that decrease inotropy. Symptomatic conduction system abnormalities have not been reported with the combination of a beta blocker and a dihydropyridine calcium-channel blocker but have been reported with the combination of a beta blocker

**TABLE 4**  
ADDITION OF A SECOND AGENT TO A CALCIUM-CHANNEL BLOCKER

Reference	Calcium-channel blocker, dose/day (mg)	Second agent, dose/day (mg)	No. of patients	Study conditions	Duration (weeks)	Supine BP on a calcium-channel blocker (mm Hg)	Change in BP with second agent (mm Hg)
48	Nifedipine, 15-40	Doxazosin, 1-8	52	UN	10	158/104	-16/524*
14	Nicardipine, 60	Prazosin, 4	14	UN	1	147/100	+2/0
14	Nicardipine, 60	Clonidine, 0.3	14	UN	1	153/101	-17/-9*
30	Diltiazem (sustained release), 120-360	Captopril, 50-150	29	RAN, DB	8	146/95	-7/-4*
47	Diltiazem (sustained release), 240	Atenolol, 50	15	RAN, DB, CO, PC	4	172/92	-8/-4*
49	Diltiazem (sustained release), 0-360	Hydrochlorothiazide, 0-100	297	FAC, PC	4	152/99	-8/-3*
50	Diltiazem, 120	Nifedipine, 40	11	DB, RAN, PC	1	134/x	-17/x*

UN, uncontrolled; RAN, randomized; DB, double-blind; CO, crossover; PC, placebo-controlled; FAC, factorial; BP, blood pressure

\*Significantly different than with a calcium channel blocker alone

and diltiazem (sinus bradycardia or arrest) or verapamil (sinus bradycardia, atrioventricular block, junctional rhythms).

Noncardiovascular side effects of the combination of a beta blocker and a calcium-channel blocker are usually not limiting. Combining a beta blocker with diltiazem has the fewest noncardiovascular side effects (at least in the treatment of angina).<sup>52,53,57</sup> The combination of a beta blocker and a dihydropyridine calcium-channel blocker may be better tolerated than dihydropyridine alone, due to inhibition of the latter's vasodilatory side effects (eg, flushing, headache).<sup>42,43</sup>

**Beta blocker and alpha-1 blocker.** Combining a beta blocker with prazosin was as effective as combining a beta blocker with hydralazine<sup>34,58</sup> or a diuretic,<sup>35</sup> but was less effective than combining a beta blocker with felodipine<sup>33</sup> (Table 3). Beta blockade may augment the first-dose hypotensive response to prazosin.<sup>59</sup> The ability of alpha-1 blockers to reduce lipids has also been seen when used with a beta blocker: adding terazosin to atenolol reduced low-density lipoprotein and very-low-density lipoprotein cholesterol by 5.7% when compared with atenolol with placebo.<sup>60</sup>

### Central adrenergic inhibitor and vasodilator

**Alpha-1 blocker.** The combination of a central adrenergic inhibitor and an alpha-1 blocker has been demonstrated to be ineffective in animal studies and short-term controlled human studies (Table 1).<sup>9,12,61-63</sup> Studies suggesting the contrary have all been uncontrolled, and in many cases subjects were also receiving other antihypertensive agents.<sup>22,64-66</sup> The poor hypotensive response to this combination may relate to a failure of alpha-1 blockade to further inhibit the

adrenergic nervous system if sympathetic outflow is already reduced by a central alpha-2 agonist, and vice versa.<sup>67</sup>

**Calcium-channel blocker.** No controlled studies of dual therapy with a central adrenergic inhibitor and a calcium-channel blocker have been performed in humans. In uncontrolled studies, adding methyldopa, clonidine, or guanfacine to a calcium-channel blocker further reduced blood pressure (Table 4).<sup>14,22,68-70</sup> On the other hand, a calcium-channel blocker inhibited the hypotensive response to guanabenz in the conscious spontaneously hypertensive rat<sup>71</sup> and to guanabenz or clonidine in the anesthetized rat or cat.<sup>72</sup> Such inhibition could be explained if the hypotensive action of central adrenergic inhibitors (at least in these animals) were mediated through an increase in intracellular calcium. Such an increase mediates their peripheral vasoconstrictive effect.

**ACE inhibitor.** No studies have examined the use of a central adrenergic inhibitor with an ACE inhibitor in the chronic therapy of hypertension. In single-dose studies in man, the addition of clonidine to captopril further reduced blood pressure.<sup>73</sup> Captopril also reversed the rebound hypertension that developed with discontinuation of clonidine.<sup>74</sup> The response to this combination may be affected by angiotensin II's enhancement of the sympathetic nervous system at both central and peripheral sites.<sup>75</sup>

### Two vasodilators

**Calcium-channel blocker and ACE inhibitor.** This combination, also effective when used in triple therapy with a diuretic,<sup>76</sup> significantly reduces blood pressure compared with either agent alone<sup>30,77-81</sup> and may be

TABLE 5  
ADDITION OF A THIRD AGENT TO A BETA BLOCKER AND A DIURETIC

Reference	Added agent, dose/day (mg)	No. of patients	Study conditions	Duration (weeks)	Supine BP on beta blocker-diuretic (mm Hg)	Change in BP with third agent (mm Hg)
97	Hydralazine, 50-200	28	RAN, PAR, PC	12	155/107	-22/-15*
	Prazosin, 1-20	29		12	169/103	-37/-19*
	Minoxidil, 5-20	10		12	159/98	-22/-14*
	Methyldopa, 25-2000	18		12	159/103	-36/-16*
	Placebo	26		12	158/102	-10/-6
98	Nifedipine (sustained release), 40-80	19	RAN, DB, CO	9	146/96	-27/-16†‡
	Hydralazine, 50-200	19		9	146/96	-17/-15†
99	Prazosin, 8-16	23	RAN, OB, CO	8	178/114	-25/-15†
	Hydralazine, 100-200	23		8	178/114	-24/-16†
100	Nifedipine (sustained release), 20-40	19	RAN, SR, CO	8	164/109	-27/-19†
	Captopril, 50-100	19		8	165/108	-23/-20†

RAN, randomized; PAR, parallel; PC, placebo-controlled; DB, double-blind; CO, crossover; OB, observer-blind; SR, slow-release; BP, blood pressure

\*Significantly different than beta blocker/diuretic/placebo

†Significantly different than beta blocker/diuretic

‡Significantly different than beta blocker/diuretic/hydralazine

even more effective than the combination of a beta blocker, hydralazine, and a diuretic.<sup>80</sup> These trials include a double-blind, randomized, crossover trial with nifedipine and enalapril<sup>79</sup> and a large, randomized, parallel study with diltiazem and captopril (Tables 2 and 4).<sup>30</sup> Either verapamil, isradipine, or nitrendipine was as effective with captopril as was a diuretic,<sup>80,81</sup> with a direct correlation ( $r=0.88$ ) between the hypotensive response to a calcium-channel blocker used with either captopril or a diuretic.<sup>80</sup>

Combining a calcium-channel blocker and an ACE inhibitor also has an additive effect in reducing diabetic proteinuria.<sup>82</sup> An ACE inhibitor may prevent the reflex tachycardia<sup>77,78,83,84</sup> and ankle edema that can accompany dihydropyridine use.<sup>77,78</sup>

**Calcium-channel blocker and alpha-1 blocker.** Prazosin further reduced blood pressure when added to verapamil in a randomized, single-blind, parallel study,<sup>85</sup> as did doxazosin when added to nifedipine in an uncontrolled study (Table 4).<sup>46</sup> Prazosin may potentiate nifedipine's tendency to cause first-dose hypotension.<sup>86,87</sup> Potentiation of the first-dose response to an alpha-1 blocker by a calcium-channel blocker has not been examined, but it should be anticipated. The hypotensive response to verapamil and prazosin may relate to verapamil increasing prazosin's bioavailability and peak plasma concentration.<sup>85</sup>

The hypotensive response to the combination of a calcium-channel blocker and an alpha-1 blocker may depend on which calcium-channel blocker is used.<sup>14,88,89</sup> In uncontrolled studies, adding prazosin to nicardipine did not further decrease blood pressure

(Table 1).<sup>14</sup> Pedrinelli et al found that nicardipine, but not verapamil, inhibited the forearm vascular response to exogenous norepinephrine in humans, suggesting that alpha-1 antagonism contributed to the hypotensive response to nicardipine.<sup>89</sup> If alpha-1 blockade is a significant component of a calcium-channel blocker's hypotensive action, that agent would not be very effective in combination with an alpha-1 blocker.

**Alpha-1 blocker and ACE inhibitor.** In an uncontrolled study adding doxazosin to an ACE inhibitor further decreased blood pressure (Table 2).<sup>29</sup> A higher likelihood of first-dose hypotension with an alpha-1 blocker has been reported in patients already receiving an ACE inhibitor.<sup>90</sup> The response to this combination may be influenced by angiotensin II modulation of the functional activity of alpha-1 adrenoreceptors.<sup>91</sup>

**Two calcium-channel blockers.** Several small series of patients with angina who received the combination of a dihydropyridine calcium-channel blocker and either verapamil or diltiazem found an additive hypotensive and antianginal effect. The additive hypotensive response is consistent with the quite different chemical structures and binding sites of these agents (Table 4).<sup>50,92,93</sup> Diltiazem increases nifedipine blood levels.<sup>50,92</sup> Side effects of a dihydropyridine and either diltiazem or verapamil may be more common than with either agent alone.<sup>92</sup>

#### Peripheral adrenergic inhibitor with a beta blocker or central adrenergic inhibitor

Reserpine, guanethidine, and guanadrel are rarely used due to a high incidence of side effects, especially

**TABLE 6**  
EFFICACY OF COMBINATION ANTIHYPERTENSIVE  
DRUG THERAPY

Additive hypotensive effect clearly documented
Diuretic + any other antihypertensive agent
Diuretic + direct vasodilator + beta blocker or reserpine
Beta blocker + alpha-1 blocker
Beta blocker + calcium-channel blocker
Calcium-channel blocker + ACE inhibitor
Additive hypotensive effect shown in preliminary studies
Central adrenergic inhibitor + ACE inhibitor
Central adrenergic inhibitor + calcium-channel blocker
Alpha-1 blocker + ACE inhibitor
Alpha-1 blocker + calcium-channel blocker
Disputed additive hypotensive response
Alpha-1 blocker + central adrenergic inhibitor
Beta blocker + central adrenergic inhibitor
Beta blocker + ACE inhibitor

orthostasis. Guanethidine exerted an additive hypotensive effect in a small controlled study with a beta blocker<sup>94</sup> and an uncontrolled study with methyl-dopa.<sup>95</sup> These combinations were also effective with a diuretic, as was the combination of guanadrel, propranolol, and a diuretic.<sup>96</sup>

#### TRIPLE THERAPY

##### Vasodilator, beta blocker, and diuretic

In uncontrolled studies the combination of an ACE inhibitor, a beta blocker, and a diuretic has been effective, probably more so than the combination of hydralazine, a beta blocker, and a diuretic (Table 5).<sup>38,100,101</sup> In the largest study, giving captopril to 201 patients with diastolic blood pressures greater than 95 mm Hg who were already taking a beta blocker and a diuretic reduced the blood pressure below 95 mm Hg in 59% (captopril 25 mg bid) and 56% (captopril 50 mg bid) of subjects.<sup>101</sup> However, most of the hypotensive response to this combination appears to be due to the ACE inhibitor and diuretic, there being little or no further hypotensive response with the addition of a beta blocker to these two agents.<sup>36,38</sup>

When added to a beta blocker and a diuretic, a dihydropyridine calcium-channel blocker reduced blood pressure further than hydralazine (Table 5)<sup>98,100,102,103</sup> and as much as minoxidil.<sup>104</sup>

The hypotensive response to 1 mg of prazosin was equal to that of 12.5 to 20 mg of hydralazine when combined with a beta blocker and a diuretic (Table 5).<sup>99,102</sup> Increasing prazosin dosage above 8 mg/day did not further reduce blood pressure.

Adding a nitroglycerin patch to a beta blocker and a diuretic in a double-blind, randomized, crossover trial

significantly decreased systolic blood pressure, especially in patients with the highest systolic pressures.<sup>105</sup>

##### Central adrenergic inhibitor, beta blocker, diuretic

In two double-blind, crossover studies, combining methyldopa (750 mg/day) with atenolol (150 mg/day) and a diuretic reduced blood pressure significantly more than combinations of either methyldopa or atenolol with a diuretic.<sup>106,107</sup>

##### Relative effectiveness

Several studies have investigated which agent is the most effective in combination with a beta blocker and a diuretic.<sup>97,100,103,104,108,109</sup> In the largest study, McAreavey et al compared the hypotensive response to placebo, methyldopa, hydralazine, minoxidil, prazosin, or labetalol (substituted for prazosin and a beta blocker) when these were added to a beta blocker and a diuretic (Table 5).<sup>97</sup> Each produced a significant further reduction in blood pressure, but only 9% to 25% of patients reached a level of 140/95 mm Hg. Similar incomplete responses have been noted by others.<sup>97,99,102,110</sup> In uncontrolled studies, supine diastolic blood pressure of 95 mm Hg was attained in 70% of 201 patients on adding captopril,<sup>101</sup> and in 81% of 19 patients on adding sustained-release nifedipine.<sup>100</sup>

Side effects of adding a third agent to a beta blocker and a diuretic were best documented by McAreavey et al.<sup>97</sup> The agents investigated can be ranked in order of decreasing patient acceptability: placebo, hydralazine, prazosin, methyldopa, minoxidil, and labetalol (however, up to 3.2 g/day of labetalol was used).

##### Central adrenergic inhibitor, vasodilator, diuretic

Central adrenergic inhibitors can mitigate the reflex tachycardia and loss of blood pressure control that occurs with the combination of a direct vasodilator and a diuretic.<sup>111-113</sup> In 18 patients taking hydralazine and a diuretic who were studied in a randomized, parallel fashion, clonidine was as effective as propranolol in reducing blood pressure and preventing reflex tachycardia.<sup>113</sup>

The combination of methyldopa, enalapril, and a diuretic was as effective as that of a beta blocker, hydralazine, and a diuretic in a randomized, double-blind, parallel group, multicenter study of 120 patients. Only 3.4% of patients withdrew from the methyldopa regimen vs 10% from the other regimen. With methyldopa there was also a lower incidence of hypokalemia (enalapril blunts the kaliuretic effect of diuretics).<sup>114</sup>

## QUADRUPLE THERAPY

In uncontrolled studies of quadruple therapy, adding clonidine,<sup>115</sup> methyldopa,<sup>116</sup> guanethidine,<sup>116</sup> prazosin,<sup>115-117</sup> captopril,<sup>118</sup> or nitrendipine<sup>119</sup> to the combination of a direct vasodilator, beta blocker, and diuretic further decreases blood pressure.

## SIDE EFFECTS OF NONTRADITIONAL ANTIHYPERTENSIVE PHARMACOTHERAPY

Side effects due to combination therapy have been poorly characterized. Most of the studies on combination drug therapy have been performed with small groups of patients, and most side effects occur in a minority of patients. For these reasons, statistically significant differences in the incidence of side effects between monotherapy and combination therapy have rarely been shown. Side effects have been investigated primarily by eliciting patient complaints at office visits, as opposed to the more sensitive method of a patient questionnaire.<sup>2</sup>

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## CONCLUSION

On reviewing the data on the use of two antihypertensive agents from different classes in combination (but not including a diuretic), most such combinations have an additive hypotensive response (Table 6). None have been shown to decrease mortality like some of the more traditional combinations. Many of these non-traditional combinations have been studied only preliminarily. Side effects of most of these combinations have been poorly characterized.

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