Combination Drugs: Innovation in Pharmacotherapy

Albert I. Wertheimer, PhD and Alan Morrison, PhD

Educational Objectives

- To describe the therapeutic benefit from combination therapy for various disease states
- To critique the rationale for formulary inclusion of selected combination drug therapies
- To identify advantages and barriers to utilizing combination drug therapy in clinical practice

Although most pharmaceutical innovation is incremental, small improvements in therapy often add up to substantial progress over time.[1] Incremental innovation in drug therapy can take various forms, including new agents, new indications for existing drugs, and new dosage forms with improved pharmacologic profiles.[1] Combination therapy with two or more agents having complementary mechanisms of action represents a type of incremental innovation that has extended the range of therapeutic options in the treatment of almost every human disease. Combination products—also known as fixed-dose combinations—are combinations of two or more active drugs produced in a single tablet (see Table 1). They provide the advantages of combination therapy while reducing the number of prescriptions and the attendant administrative costs. Unfortunately, the real contribution of combination products to therapeutics has been blurred by perceptions of inherent disadvantages and, as a result, these products are often perceived only as second-line therapy. In this article, we describe the advantages of combination products and discuss the evidence in support of their role in pharmacotherapy.

Rationale for Combination Therapy

All drugs have unwanted side effects in addition to the desired therapeutic effect. The idea of combining two or more drugs with complementary modes of action is to produce additivity of the desired therapeutic effect but not of the side effects. As an example, at least five classes of drugs are commonly used to treat hypertension: diuretics, beta-blockers, ACE-inhibitors, angiotensin receptor blockers, and calcium-channel blockers. The antihypertensive effects of an ACE-inhibitor and a calcium channel blocker, for instance, are additive, but these drug classes have different spectra of side effects, none of which are additive (although the spectrum can be broadened in a combination drug). Because the combination produces the same antihypertensive effect as higher doses of either constituent, the exposure to side effects is reduced and the therapeutic ratio is increased. The therapeutic ratio can be increased in certain instances by the phenomena of potentiation and cancellation. Potentiation is the synergistic effect on drug A by adding a dose of drug B without a therapeutic effect. An example is the combination of bisprolol[2] or enalapril[3] with a low dose of hydrochlorothiazide itself without antihypertensive effect. Cancellation is a phenomenon in which the adverse effects of one drug are nullified by the addition of a second (e.g., the hypokalemic effects of thiazide diuretics are counteracted by the slight hyperkalemic effect of an ACE-inhibitor).[4,5]

The conceptual basis for combination treatment of infectious disease is somewhat different from conditions such as hypertension, in which the drug target is human tissue. In infectious disease, the drug target is an evolutionarily unrelated microbe, and drug side effects are of less concern than the loss of efficacy caused by the emergence of drug-resistant strains. Consider a bacterium with a spontaneous rate of mutation to antibiotic resistance of 10^{-9}, i.e., one in 10^{9} bacteria (a titer that can be grown in a milliliter of culture) will grow in the presence of the antibiotic. Consider next a combination of two different antibiotics: the spontaneous rate of appearance of a strain resistant to both antibiotics is 10^{-18}, so that a million liters of culture would have to be grown to isolate a single resistant bacterium. With triple antibiotic therapy, the number of bacteria needed to generate a resistant cell is an astronomical 10^{27}. However, the spontaneous mutation rate is under genetic control, and in some microorganisms it is drastically increased as a survival strategy. Because viruses are far smaller than bacteria and can reach much higher titers, triple-combination therapy is required to prevent the appearance of drug-resistant strains of HIV.

Dr. Wertheimer is Professor of Pharmacy and Director of the Center for Pharmaceutical Health Services Research, and Dr. Morrison is Associate Director of the Center for Pharmaceutical Health Services Research, at Temple University School of Pharmacy in Philadelphia, Pennsylvania.

Although combination therapy is typically a matter of two (or more) different classes of drugs with a common therapeutic effect, there are many types of combinations. In the combination of amoxicillin and clavulanate (see Table 1), the latter compound acts by inhibiting bacterial degradation of amoxicillin, rather than having any direct therapeutic activity itself. This renders amoxicillin effective against strains that have become resistant through acquisition of a plasmid-borne gene encoding beta-lactamase. Similarly, in the combination of carbidopa and levodopa, carbidopa itself has no beneficial therapeutic effect, but it inhibits the systemic decarboxylation and inactivation of levodopa before it crosses the blood–brain barrier and is converted to dopamine, the active metabolite that relieves the symptoms of Parkinson's disease. The combinations of amoxicillin/clavulanate and carbidopa/levodopa are further examples of potentiation.

Some combinations are made from drugs in the same class. For example, the protease inhibitors ritonavir and saquinavir, or the nucleoside analogs zidovudine and lamivudine, are all anti-retroviral agents used to treat HIV infection (see Table 1). In these examples, the mechanism of the two combined drugs is the same, but there is little or no cross-reactivity, so that their inhibitory effects on HIV replication are additive, and HIV strains spontaneously resistant to one constituent drug are not cross-resistant to the second. Combination therapy can also be used to treat two different infectious diseases: a combination vaccine for hepatitis A and B is available (although both viruses cause hepatitis, they are unrelated species).

It is important to note that the distinction between a single drug with a single pharmacological activity and a combination drug with combined pharmacological activities is not absolute. Clozapine, for example, is a single drug with a relatively high affinity for multiple receptor sites, including a wide range of monaminergic, cholinergic, and histaminergic receptors.[6] A combination product with a pharmacological activity equivalent to that of clozapine could, in principle, be produced from several different drugs each specific to a single receptor class. Such a combination product exactly mimicking the pharmacological effects of clozapine would not, however, be approved by the FDA. The FDA requires that each constituent in a combination product contribute to the therapeutic effect, and it is not established that all the receptor-binding activities of clozapine contribute to its antipsychotic activity.

The Office of Health Policy and Clinical Outcomes, Thomas Jefferson University Hospital, is approved by the American Council on Pharmaceutical Education (ACPE) as a provider of continuing pharmaceutical education and complies with the Criteria for Quality for continuing pharmaceutical education programming. This program (079-999-02-13-H01) is acceptable for 1.0 hour of continuing education credit (0.1 CEUs) in states that recognize ACPE-approved providers. Statements of Credit indicating hours/CEUs will be mailed quarterly to participants who completed this activity and submitted a completed evaluation with payment.

Advantages of Combination Products

Combination products have the advantages of combination therapy as well as advantages related to reducing the number of pills to be taken. Reduced administration costs stem from simplified packaging, fewer prescriptions, and fewer dispensing fees and co-pays. It has been known for many years that there is an inverse relationship between patient adherence and the complexity of the drug regimen.[7] Reducing the number of pills diminishes the complexity of the regimen, so that improved patient adherence is expected with combination products. Combination products make particular sense in the treatment of infectious disease, where partial adherence can lead to the development of drug-resistant strains and a threat to public health. The likelihood of a strain acquiring resistance to a constituent of combination therapy is zero if adherence is either zero or 100%, and reaches a maximum at intermediate levels of adherence.[8] With combination products, patients take either all of the drugs or none of them, and the possibility of the serial development of strains resistant to each constituent drug taken individually is eliminated.

Combination products make particular sense in the treatment of infectious disease, where partial adherence can lead to the development of drug-resistant strains and a threat to public health.

Attitudes Toward Combination Products

The medical establishment has in the past been indisposed to the use of combination products. This historical resistance is in part a reflection of the checkered history of fixed-dose combination drugs. In the post-World War II era, many drugs with dubious viability were made marketable by combining them with drugs of known effectiveness.[9] In the resulting backlash, a generation of medical students was taught that fixed-dose combinations were an anathema. The American Medical Association opposed fixed-dose combinations because they denied physicians the discretion to decide both the components and the ratios in which they were used.[10,11]

These objections would seem to hold little merit today, when many different combination products have been approved by the FDA. Combination products are typically available in a variety of dose ratios that cover the therapeutically relevant range of possibilities and allow for control of the dose ratios in which combinations are prescribed. The use of antibiotic or antiviral drug combinations has received acceptance, particularly since it was seen that this was the only way to control HIV/AIDS. Elsewhere, however, a dogmatic bias

Table I **Some New and Old Combination Products in Different Disease Classes**

Component Drugs	Drug classes	Therapeutic Action
Cardiovascular Disease		
Aspirin/dipyridamole	Cyclo-oxygenase inhibitor/cyclic-AMP—cyclic-GMP phosphodiesterase inhibitor	Platelet inhibition by two separate drug classes allows better anticoagulation for secondary prevention of stroke
Atorvastatin/amlodipine*	HMG-CoA reductase inhibitor (statin)/calcium-channel blocker	Combination cholesterol-lowering drug and antihypertensive agent treats two different major risk factors for coronary heart disease
Captopril/hydrochlorothiazide	ACE-inhibitor/thiazide diuretic	Combination of two antihypertensive drug classes and is FDA-approved as initial therapy for hypertension
Respiratory Disease		
Fluticasone/salmeterol	Corticosteroid/long-acting beta-adrenergic-receptor agonist	Combination anti-inflammatory agent and bronchodilator addresses two physiological components of persistent asthma
Ipratropium bromide/albuterol	Anticholinergic agent/beta-adrenergic-receptor agonist	Inhaled aerosol of two different bronchodilators for chronic obstructive pulmonary disease
Montelukast/loratadine*	Leukotriene receptor antagonist/antihistamine	Combination of an anti-inflammatory/bronchodilator and an anti-allergen to treat different components of chronic asthma
Infectious Disease		
Amoxicillin/clavulanate	Penicillin derivative/beta-lactamase inhibitor	Clavulanate increases the effectiveness of amoxicillin against resistant strains that carry the beta-lactamase gene
Ritonavir/lopinavir	Protease inhibitors	Use of two different anti-retroviral agents for treatment of HIV infection delays the appearance of resistant HIV strains
Zidovudine/lamivudine	Pyrimidine nucleoside analogs	Combination of reverse transcriptase inhibitors has synergistic anti-retroviral activity and delays the appearance of resistant HIV strains
Miscellaneous		
Dorzolamide/timolol maleate	Carbonic anhydrase inhibitor/beta-adrenergic receptor blocker	Topical combination decreases intraocular pressure (by reducing aqueous humor secretion) more than either component alone
Fluoxetine/olanzapine*	Selective serotonin reuptake inhibitor/multi-receptor antagonist	Combination anti-depressant and anti-psychotic for treatment of depression with psychotic features
Hydrocodone/ibuprofen	Opiate agonist/non-steroidal anti-inflammatory agent	Combination narcotic and anti-inflammatory effective against chronic pain

*Combination product in development

against the use of combination products seems to have persisted, based apparently on the principles of drug therapy (i.e., accepted conventions of drug treatment intended to minimize exposure to adverse effects). These principles state that drug treatment should begin with monotherapy, followed by dose titration if the initial dose is insufficient. Only if this process fails is combination therapy considered as a potential alternative to repetition of the process of monotherapy titration with a different drug.

Because of these principles, combination products have been allowed only a secondary role in the treatment guidelines promulgated by some institutions and professional bodies. For example, the JNC VI guidelines for the treatment of hypertension, published in 1997, recommend monotherapy with either a diuretic or a beta-blocker as initial treatment, and upward titration of the dose if the initial dose is inadequate.[12] If this procedure fails, the guidelines recommend either switching to monotherapy with an agent of a different class or the addition of a second-line drug from another class (i.e., combination therapy). The 1999 guidelines from the World Health Organization–International Society of Hypertension are similar,[13] but do not stipulate initial therapy with a diuretic or beta-blocker, the use of which is viewed by some as dated practice.[14] The JNC VI recommendations for either a diuretic or a beta-blocker as first-line therapy were based on the results of long-term trials in which morbidity and mortality were reduced.[15,16] It is, then, ironic that many of these trials in fact tested drug algorithms that began with combination therapy. In the Medical Research Council (MRC), Swedish Trial in Old Patients with Hypertension (STOP-Hypertension), and European Working Party on High Blood Presssure in the Elderly (EWPHE) trials, the first-line therapy was not diuretic monotherapy but a fixed-dose com-

Table 2 **Price Ratios of Selected Combination Products and the Separate Constituents***

Class	Combination	Dose (mg)	Price Ratio†
Antidiabetics			
	Glyburide/metformin	1.25 – 500	0.99
		2.5 – 500	0.98
		5 – 500	1.23
Antihyptertensives			
	Triamterene/HCTZ	37.5 – 25	0.31
	Enalapril/HCTZ	10 – 25	1.54
	Captopril/HCTZ	25 – 25	1.24
		50 – 25	1.35
	Lisinopril/HCTZ	20 – 25	1.40
	Benazepril/HCTZ	20 – 25	0.88
	Losartan/HCTZ	100 – 25	0.79
	Benazepril/amlodipine	5 – 10	0.53
Antiretrovirals			
	Zidovudine/lamivudine	300 – 150	1.01
Hormone Replacement			
	Premarin/medroxyprogesterone	0.625 – 2.5	1.24
		0.625 – 5	1.15
NSAIDs			
	Diclofenac/misoprostol	50 – 200	0.79
		75 – 200	0.69

*Retail list prices for brand-name drugs. Source: www.Rxlist.com, July/August 2001. † Price of combination product/Price of the same dosages of the separate constituents. HCTZ = hydrochlorothiazide; NSAIDs = non-steroidal anti-inflammatory drugs.

bination of a thiazide and a potassium-sparing diuretic.[17-19] A substantial proportion of the patients in these trials eventually received diuretic/beta-blocker or other combination therapy, reflecting the fact that monotherapy fails to control hypertension in about half of patients.[20-22]

The Role of Combination Products

It might be instructive to contrast the principles of drug therapy with empirical evidence from clinical trials, taking as examples the treatment of asthma and hypertension. Several classes of drugs are used in the long-term control of chronic asthma—principally inhaled corticosteroids (as anti-inflammatory agents), but also long-acting beta-agonists (as bronchodilators), theophylline, and the newer leukotriene modifiers. The alternatives of increasing the dose of monotherapy or combination therapy (the addition of a different class of drug) in patients failing the previous dose of monotherapy have been tested directly in several randomized, double-blinded clinical trials.

In one trial, patients who still had symptoms following treatment with a low-dose inhaled corticosteroid (beclomethasone) were randomly assigned either to a higher dose of the inhaled corticosteroid or to combination therapy with a long-acting beta-agonist (salmeterol).[23] Control of asthma symptoms was better with the combination therapy, while there was no difference in adverse effects between the two treatments. In two similar trials, combination therapy with fluticasone and salmeterol (see Table 1) was superior to an increased dose of fluticasone in patients still symptomatic after treatment with a lower dose of the corticosteroid.[24,25] In another trial, a combination of a low-dose inhaled corticosteroid (budesonide) and doses of theophylline below the recommended therapeutic range produced control of asthma similar to that with high-dose budesonide but without affecting serum cortisol.[26]

Finally, the idea, embedded in national guidelines,[27] that initial therapy should be monotherapy rather than combination therapy was also tested in a randomized, double-blinded trial. Initial therapy with a combination of fluticasone and salmeterol was tested against both monotherapies.[28] Initiation with the combination therapy provided greater improvements in lung function and symptom control than either monotherapy with no differences in any safety measure.

In hypertension, randomized clinical trial data supports a role, for some combination antihypertensives, that is distinct from that recommended in national guidelines. First, some combinations are superior to either of their component monotherapies as initial treatment. The beta-blocker/diuretic combination bisoprolol/hydrochlorothiazide has a better therapeutic ratio than that of either constituent monotherapy.[2] Similarly, ACE-inhibitor/calcium-channel blocker combinations as a class have a better therapeutic ratio than their constituent monotherapies.[29-32] Second, a combination product ACE-inhibitor-diuretic (lisinopril-hydrochlorothiazide) was tested against ACE-inhibitor (lisinopril) dose titration in patients failing the initial ACE-inhibitor dose.[33] Blood pressure control was similar in the two patient groups, but there were significantly fewer adverse events among patients receiving the combination product.

Not all combinations have unequivocally better therapeutic ratios than their constituent monotherapies. For example, ACE-inhibitor/hydrochlorothiazide combinations as a class are more effective than their constituent monotherapies but also cause more adverse effects (captopril-hydrochlorothiazide is an exception, with a considerably better therapeutic ratio than either constituent monotherapy).[34] Many drug combinations, however, do have better therapeutic ratios than their constituent monotherapies and, as clinical trial data have shown, have a role as initial therapy and, in particular, in place of monotherapy dose escalation. The principles of drug thera-

py are a prudent guide to treatment in the absence of empirical evidence, but should be superseded by such evidence when it exists—this is a tenet of evidence-based medicine.

Combination Products as Incremental Innovation

The predominant mechanism of product development within most high-technology industries is a process of repeated incremental improvement punctuated by infrequent radical change—the pharmaceutical industry is no exception to this. Radical change is exemplified by the discovery and marketing of the first agents within a drug class (e.g., beta-blockers). Incremental innovations are follow-on modifications in molecular structure or dosage formulation having a similar, but not identical, pharmacological action (e.g., beta-1 selective beta-blockers versus nonselective beta-blockers). The history of pharmacology is typified by incremental improvements in the safety, efficacy, selectivity, and utility of drugs within a given class. The statins provide an example: the newer statins are considerably more potent than the earlier ones in reducing serum LDL-C (low-density lipoprotein cholesterol) and are an effective treatment for patients with severe hypercholesterolemia. The earlier, less potent statins might nevertheless be adequate for individuals with mildly elevated serum cholesterol and who at low risk of developing coronary heart disease. The statins vary in price and in their effects on high-density lipoprotein cholesterol (HDL-C) and serum triglycerides. Thus, the availability of a range of statins enables physicians to treat each patient with precision and at the lowest cost. New combinations of existing drugs taken from one or more classes are another form of incremental innovation. Combination products have increased efficacy; they broaden the array of therapeutic options; and they enable doctors to customize treatment to the patient's specific needs. For example, combination drugs are necessary to treat a substantial proportion of patients with moderate or severe hypertension, whereas monotherapy is adequate for many mildly hypertensive individuals.

Incremental innovation does not inevitably inflate the costs of pharmaceuticals, because the new drugs must compete with their predecessors for market share. Analysis of drug pricing indicates that most new drugs are launched at discounts relative to existing drugs in the same class.[35] Thus, the more recently introduced statins are more cost-effective than earlier ones for secondary prevention in elderly patients[36,37] (though not for lower-risk patients).[37] The prices of combination products are generally comparable to those of monotherapies. In Table 2, the prices of several combination products are compared to those of the individual constituents purchased separately. In half of the cases, the combination is less expensive than the separate constituents and in half of the cases, it is more expensive (i.e., the median price ratio for the listed products is 1). The benazepril/amlodipine combination product is about half the price of the separate constituents. It is estimated that a potential cost savings of $1,080 per patient per year if a benazepril/amlodipine combination product were substituted for combined therapy with calcium channel blockers and ACE-inhibitors prescribed separately.[39] The constituents of many combination products, however, are not marketed separately and/or are not available at the dosages present in the combination product.

Conclusion

Combination products represent incremental rather than radical change, both of which are important for progress in pharmaceutical technology. This is true for medical technology in general and for most other high-technology products as well.[1] Combination products have a place in medicine based on their improved clinical effectiveness, enhanced patient adherence, and reduced administrative costs. Policies or business strategies, such as restrictive formularies, that result in reduction in the availability of incremental pharmaceutical innovations, in general, and combination products, in particular, can have negative implications for health care cost containment and can ultimately be self-defeating. ■

References

1. Wertheimer AI, Levy R, O'Connor TW. Too many drugs? The clinical and economic value of incremental innovations. In: *Investing in Health: The Social and Economic Benefits of Health Care Innovation*. 2001; 14:77-117.
2. Frishman WH, Burris JF, Mroczek WJ et al. First-line therapy option with low-dose bisoprolol fumarate and low-dose hydrochlorothiazide in patients with stage I and stage II systemic hypertension. *J Clin Pharmacol* 1995; 35(2):182-188.
3. Guul SJ, Os I, Jounela AJ. The efficacy and tolerability of enalapril in a formulation with a very low dose of hydrochlorothiazide in hypertensive patients resistant to enalapril monotherapy. *Am J Hypertens* 1995; 8(7):727-731.
4. Chalmers J. Efficacy and acceptability of the fixed low-dose perindopril-indapamide combination as first-line therapy in hypertension. *Eur Heart J Supplements*. 1999; 1(Suppl L):L20-L25.
5. Chrysant SG, Fagan T, Glazer R, Kriegman A. Effects of benazepril and hydrochlorothiazide, given alone and in low- and high-dose combinations, on blood pressure in patients with hypertension. *Arch Fam Med*. 1996; 5(1):17-24; discussion 25.
6. Blin O. A comparative review of new antipsychotics. *Can J Psychiatry*. 1999; 44(3):235-244.
7. Haynes RB. A critical review of the "determinants" of patient compliance with therapeutic regimens. In: Sackett DL, Haynes RB, Editors. *Compliance with therapeutic regimens*. Baltimore: Johns Hopkins University Press, 1976: 26-39.
8. Friedland GH, Williams A. Attaining higher goals in HIV treatment: the central importance of adherence. *AIDS* 1999 Sept; 13 Suppl 1:S61-S72.
9. Herxheimer H. The danger of fixed drug combinations. *Int J Clin Pharmacol Biopharm*. 1975; 12(1-2):70-73.
10. Fixed combinations of antimicrobial agents. *N Engl J Med*. 1969; 280(21):1149-1154.
11. Fixed-dose combinations of drugs. *JAMA*. 1970; 213(7):1172-1175.
12. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med*. 1997; 157:2413-2445.
13. 1999 World Health Organization—International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Sub-Committee. *Blood Press* Suppl 1999; 1:9-43.
14. Sica DA. Old antihypertensive agents-diuretics and beta-blockers: do we know how and in whom they lower blood pressure? *Curr Hypertens Rep*. 1999; 1(4):296-304.

15. Psaty BM, Smith NL, Siscovick DS et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA*. 1997; 277(9):739-745.
16. Lever AF, Ramsay LE. Treatment of hypertension in the elderly. *J Hypertens*. 1995; 13:571-579.
17. Medical Research Council trial of treatment of hypertension in older adults: Principal results. MRC Working Party. *BMJ* 1992; 304(6824):405-412.
18. Ekbom T, Dahlof B, Hansson L, Lindholm LH, Schersten B, Wester PO. Antihypertensive efficacy and side effects of three beta-blockers and a diuretic in elderly hypertensives: A report from the STOP-Hypertension study. *J Hypertens*. 1992; 10(12):1525-1530.
19. Fletcher A, Amery A, Birkenhager W et al. Risks and benefits in the trial of the European Working Party on High Blood Pressure in the Elderly. *J Hypertens*. 1991; 9(3):225-230.
20. Mancia G, Grassi G. Rationale for the use of a fixed combination in the treatment of hypertension. *Eur Heart J Supplements*. 1999; 1(Suppl L):L14-L19.
21. Materson BJ, Reda DJ, Cushman WC et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *N Engl J Med*. 1993; 328(13):914-921.
22. Koshy S, Bakris GL. Therapeutic approaches to achieve desired blood pressure goals: focus on calcium channel blockers. *Cardiovasc Drugs Ther*. 2000; 14(3):295-301.
23. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. *Lancet*. 1994; 344(8917):219-224.
24. van Noord JA, Schreurs AJ, Mol SJ, Mulder PG. Addition of salmeterol versus doubling the dose of fluticasone propionate in patients with mild to moderate asthma. *Thorax*. 1999; 54(3):207-212.
25. Condemi JJ, Goldstein S, Kalberg C, Yancey S, Emmett A, Rickard K. The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma. Salmeterol Study Group. *Ann Allergy Asthma Immunol*. 1999; 82(4):383-389.
26. Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. *N Engl J Med*. 1997; 337(20):1412-1418.
27. Guidelines for the Diagnosis and Management of Asthma. Expert Panel Report 2. National Institutes of Health. National Heart, Lung, and Blood Institute, 1997.
28. Pearlman DS, Stricker W, Weinstein S et al. Inhaled salmeterol and fluticasone: a study comparing monotherapy and combination therapy in asthma. *Ann Allergy Asthma Immunol*, 1999; 82(3):257-265.
29. Frishman WH, RAM CV, McMahon FG et al. Comparison of amlodipine and benazepril monotherapy to amlodipine plus benazepril in patients with systemic hypertension: a randomized, double-blind, placebo-controlled, parallel-group study. The Benazepril/Amlodipine Study Group. *J Clin Pharmacol*. 1995; 35(11):1060-1066.
30. Kuschnir E, Acuna E, Sevilla D et al. Treatment of patients with essential hypertension: amlodipine 5 mg/benazepril 20 mg compared with amlodipine 5 mg, benazepril 20 mg, and placebo. *Clin Ther*. 1996; 18(6):1213-1224.
31. Cushman WC, Cohen JD, Jones RP, Marbury TC, Rhoades RB, Smith LK. Comparison of the fixed combination of enalapril/diltiazem ER and their monotherapies in stage 1 to 3 essential hypertension. *Am J Hypertens*. 1998; 11(1 Pt 1):23-30.
32. Messerli F, Frishman WH, Elliott WJ. Effects of verapamil and trandolapril in the treatment of hypertension. Trandolapril Study Group. *Am J Hypertens*. 1998; 11(3 Pt 1):322-327.
33. Pathe M. Lisinopril-hydrochlorothiazide combination vs lisinopril for the treatment of hypertension. *J Hum Hypertens*. 1991; 5 Suppl 2:53-54.
34. Kayanakis JG, Baulac L. Comparative study of once-daily administration of captopril 50 mg, hydrochlorothiazide 25 mg and their combination in mild to moderate hypertension. *Br J Clin Pharmacol*. 1987; 23 Suppl 1:89S-92S.
35. DiMasi JA. Price Trends for Prescription Pharmaceuticals: 1995-1999. Washington, DC: Background report prepared for the U.S. Department of Health and Human Services' Conference on Pharmaceutical Pricing Practices, Utilization and Costs.: Background report prepared for the U.S. Department of Health and Human Services' Conference on Pharmaceutical Pricing Practices, Utilization and Costs., 2000.
36. Elliott WJ, Weir DR. Comparative cost-effectiveness of HMG-CoA reductase inhibitors in secondary prevention of acute myocardial infarction. *Am J Health Syst Pharm* 1999; 56(17):1726-32.
37. Elliott WJ, Weir DR. Cost of cerivastatin in cost-effectiveness study. *Am J Health Syst Pharm* 2000; 57(18):1713.
38. Hilleman DE, Phillips JO, Mohiuddin SM, Ryschon KL, Pedersen CA. A population-based treat-to-target pharmacoeconomic analysis of HMG-CoA reductase inhibitors in hypercholesterolemia. *Clin Ther* 1999; 21(3):536-562.
39. Kountz DS. Cost containment for treating hypertension in African Americans: Impact of a combined ACE-inhibitor/calcium channel blocker. *J Natl Med Assoc* 1997; 89(7):457-460.