

# Combination Medications in Diabetes Care: An Opportunity That Merits More Attention

Steven B. Leichter, MD, FACP, FACE, and Stephanie Thomas, CRC

During the past few years, new pills have been marketed that are combinations of two separate medications. At present, these products apply to three specific treatment areas related to diabetes: diabetes itself, lipidemia, and hypertension (Table 1). Until recently, the only combination pills on the market for these disease states were combinations of diuretics and one other blood pressure medication. In the past few years, a number of newer combination diabetes and lipid medications have been released, starting with metformin-glyburide, metformin-glipizide, metformin-rosiglitazone, and lovastatin-niacin. More combinations are planned.

In all cases, these combination medications are mixtures of two existing drugs that have already been marketed. In all cases thus far, providers have had extensive opportunities to gain experience with both of the combined drugs as single agents, as well as moderate experience in combining them to treat more resistant cases. Clearly, a primary motive for developing and marketing the combination tablet has been economic—an effort by the manufacturer either to extend the patent life and profitability of the key agent in the combination because patent protection was about to expire or to create a new market for an agent that would perform better than the single-agent competition.

Although the economic motives for the introduction of combination products seem understandable, the benefits of these combination agents for patients and providers have not been explored in detail. One possibility, that these drugs

improve patient adherence to treatment by eliminating one pill in the polypharmacy many patients face,<sup>1</sup> has recently been challenged.<sup>2</sup> A new study in the journal *Diabetes Care* suggests that, in contrast to other patient populations,<sup>3</sup> diabetic patients do not have a reduction in adherence to their medical regimen when multiple medications are prescribed. If true, this eliminates one possible benefit of combination medications. If there is no benefit to patient adherence, then the only other advantage that might occur is economic. In some cases, the economic benefit is exclusively for manufacturers, in that the new combination opens a new market or preserves patent protection. In other cases, the benefit is also to consumers, who sometimes get one pre-

scription that is cheaper than the sum of the costs for its component parts and may avoid an additional copayment under some insurance plans.

## Combination Drugs and Patient Adherence

Diabetes, hypertension, and hyperlipidemia are all interesting models for the evaluation of combination medications. Patients with these conditions often take multiple medications.<sup>1</sup> Some studies have suggested that patients fail to adhere to the medical regimen because of the number of medicines required.<sup>4</sup> The more medications prescribed, the less patients adhere to the full treatment regimen. Multiple medications also entail high daily costs for prescriptions. One study suggests that the average

**Table 1. Newer Combination Products for the Treatment of Diabetes, Lipidemia, and Hypertension\***

Product Brand Name	Components	Marketing Company**
Lotrel	Benazepril Amlodipine	Novartis
Tarka	Trandopril Verapamil	Abbott Laboratories
Avandamet	Rosiglitazone Metformin	GlaxoSmithKline
Glucovance	Metformin Glyburide	Bristol-Myers Squibb
Metaglip	Metformin Glipizide	Bristol-Myers Squibb
Advicor	Lovastatin Niacin	Kos Pharmaceuticals

\*Established combinations of diuretics and anti-hypertensive agents were excluded from this analysis.

\*\*In some cases, the marketing company and the manufacturer are not the same.

retail cost of oral medications for all conditions related to diabetes may exceed \$170 per month.<sup>1</sup> If combination medications moderate the cost of therapy, that would be a significant advantage.

### **Adherence to oral medication regimens in diabetic patients**

Studies involving patients with hypertension have suggested that patient adherence to treatment schedules with medications was often lower than health providers appreciate.<sup>5,6</sup> In one large study of more than 16,000 hypertensive patients in Italy, 64.9% were nonadherent to their drug treatment regimens over a 1-year period.<sup>7</sup>

Similar issues have been cited in diabetic patients using oral hypoglycemic agents.<sup>8</sup> Rates of adherence to oral hypoglycemic regimens in one study of a population of diabetic patients with prescription insurance ranged from 31 to 60%. One implication of this study was that financial issues were not the primary cause for poor adherence. A British study of statin use in diabetic patients demonstrated a clinically significant rate of nonadherence to the treatment regimen with simvastatin.<sup>9</sup> This experience has been duplicated in a general population of patients with lipidemia in Italy.<sup>10</sup>

These and other studies suggest that patients with chronic disorders, such as hypertension, lipidemia, and diabetes, often fail to adhere to their treatment regimens. The literature in hypertension also suggests that the number of medications prescribed for a patient is inversely correlated with adherence to the treatment regimen.<sup>11</sup> The possible reduction in adherence with multiple medications has been cited as an important issue in the treatment of patients with diabetic nephropathy and hypertension.<sup>12</sup>

The question of whether the prescription of multiple medications reduces patient adherence to treatment in chronic disease has become especially important in diabetes care. This is

because of the well-recognized trend to use more than one medication in a comprehensive approach to treatment.<sup>13</sup> One recent study in diabetic patients claimed that treatment regimens with multiple medications did not reduce the adherence of diabetic patients.<sup>2</sup> However, its findings were based on subjective reporting by diabetic patients during telephone interviews. These findings were unique; they contrasted not only with many previous studies as cited above, but also with an earlier study about the same question in diabetes management based on actual pill counts, arguably a stronger methodology.<sup>14</sup>

### **Effects of combination medications on adherence**

Surprisingly few studies are available on the effects on adherence of combination medications versus individual medication treatment regimens. One study demonstrated that fixed combinations of angiotensin-converting enzyme (ACE) inhibitors and hydrochlorothiazide raised adherence rates in hypertensive patients by ~20%.<sup>15</sup> Another study in a long-term care setting noted no change in blood pressure control when hypertensive patients were switched from individual mixtures of calcium channel-blockers and ACE inhibitors to a fixed mixture of amlodipine and benazepril.<sup>16</sup> However, problems with patient adherence declined because of a surprising 81% reduction in reported side effects. Thus, a reduction in the number of pills taken daily may improve adherence for a reason that has not been considered previously: that the reduced number of pills resulting from the use of combination medications may reduce the number of side effects patients might be expected to experience.

There are no studies on the effects of combination medications on patient adherence in the treatment of diabetes or hyperlipidemia. Nevertheless, the existing literature suggests that the reduction in the daily number of medications for patients may improve compliance in the treatment of all of these conditions.

### **Cost Advantages of Combination Medications**

Any analysis of cost savings resulting from any alteration of an existing drug therapy is a complex task. There are differences between the potential advantages of medication substitutions for health plans versus individual consumers in any given geographical area. Health plans may receive substantial cost savings on medications that are not offered to consumers at the same discount. Also, consumers with prescription insurance coverage consider issues of copayment for drugs—a concern not shared by health plans.

One concern that has never been analyzed is the effect of a change in formulary by a health plan with a significant influence on consumer behavior in a given community. Such a change might increase overall provider prescribing for a drug, which may be more cost-effective for the health plan, but more expensive for individual consumers.

Thus, discussions about possible economic benefits of any medication should focus on whether the assessment relates to consumers, health plans, or the community as a whole. This analysis specifically pertains to the costs of medications to consumers.

Many combination medications compete with treatment regimens that would include generic drugs. In diabetes, health plans often prefer the first use of lower-cost sulfonylureas and exclude combination medications.<sup>17</sup> There is a prevalent perception that generic drugs reduce the costs of treatment more than combination medications do. Therefore, any comparison of the costs with combination agents versus mixtures of individual agents should include comparisons with generic drugs, where appropriate. Because diabetic patients often take anti-hypertensive medications or medications for hyperlipidemia, combination agents for the treatment of these conditions are included in the analysis.

Cost analyses were made by the retail price of 30 doses of each drug,

either the combination product or each individual agent. Prices were assessed at four pharmacies in Columbus, Ga.—two nationwide chain pharmacies and two locally owned pharmacies. In addition, two online pharmacy services were surveyed.

The results show that most combination agents cost the same or less than the retail purchase of their component drugs individually (Table 2). This is true whether the brand name product or its generic equivalent is studied. In some cases, the combination medication is considerably less expensive than the sum of the individual components.

The only exception found in our analysis was the combination of lovastatin and slow-release niacin. In this instance, assessment of costs was more complex because the combination product may be compared with generic lovastatin and generic niacin, or with generic lovastatin and the sustained-release niacin marketed by the manufacturer of the combination product (Kos Pharmaceuticals). The survey revealed that the purchase of generic lovastatin and generic niacin was considerably less expensive than the purchase of the combination product. However, the combination product was less expensive than individual purchase of generic lovastatin and the proprietary, sustained-release

niacin made by the manufacturer of the combination product.

Combination medications often offer cost savings to patients with prescription insurance, as well. Here the advantage relates to the reduction in copayments for prescriptions because combination medications eliminate one copayment. At best, the combination product may cost the same in copayments as either of the two individual drugs alone. If the insurance plan places combination medications on a higher copayment “tier” (i.e., charges a higher copayment for combination medications), then the copayment cost of the combination product may equal that of the two individual products.

**Clinical Application of Combination Products**

Combination medications may offer substantially more benefits to many diabetic patients than the literature currently suggests. As we previously described, many diabetic patients take multiple medications, most often for hypertension and lipidemia in addition to diabetes. This polypharmacy situation raises issues regarding cost and adherence to the treatment plan. Despite a recent article suggesting that polypharmacy does not adversely affect adherence among diabetic patients,<sup>3</sup> the weight of

evidence suggests that diabetic patients, like hypertensive or lipidemic patients, are adversely affected by the need to take multiple medications. Combination products may simplify the treatment regimen.

The degree to which combination products simplify the regimen may be substantial. For example, in diabetes treatment, a patient who requires metformin, rosiglitazone, and a sulfonylurea might take a total of eight pills per day if maximum doses of each medication are prescribed. In contrast, the total number of pills taken per day could be halved if both the metformin-rosiglitazone and the metformin-glyburide combinations were given to the same patient. In this instance, half the metformin dose would be in the rosiglitazone combination, and half in the sulfonylurea combination.

Cost savings complement the simplification of the treatment regimen. By our cost surveys, the use of the two combination pills, metformin-glyburide and metformin-rosiglitazone, would save more than \$50 per month compared with taking the same doses of medications purchased individually.

**References**

<sup>1</sup>Leichter SB, Faulkner S, Camp J: On the cost of being a diabetic patient: variables for physician prescribing behavior. *Clin Diabetes* 18:42–44, 2000

<sup>2</sup>Grant RW, Devita NG, Singer DE, Meigs JB: Polypharmacy and medication adherence in patients with type 2 diabetes. *Diabetes Care* 26:1408–1412, 2003

<sup>3</sup>Logham-Adham M: Medication noncompliance in patients with chronic disease: issues in dialysis and renal transplantation. *Am J Man Care* 9:155–171, 2003

<sup>4</sup>Kroenke K, Pinholt EM: Reducing polypharmacy in the elderly: a controlled trial of physician feedback. *J Am Geriatr Soc* 39:103–105, 1991

<sup>5</sup>Conlin PR, Williams GH: Use of calcium channel blockers in hypertension. *Adv Intern Med* 43:533–562, 1988

<sup>6</sup>Patel RP, Taylor SD: Factors affecting medication adherence in hypertensive patients. *Ann Pharmacother* 36:40–45, 2002

<sup>7</sup>Degli Esposito L, Degli Esposito E, Valpiani G, Di Martino M, Saragoni S, Buda S, Baio G, Capone A, Sturani A: A retrospective, population-based analysis of persistence with anti-hypertensive drug therapy in primary care practice in Italy. *Clin Ther* 8:1347–1357, 2002

**Table 2. Cost of Combination Medications Versus Individual Constituents\***

Product Brand Name	Cost/30 Doses (\$)	Constituents	Cost/30 Doses (\$)**
Lotrel 5/20	73.99	Benazepril, 20 mg Amlodipine, 5 mg	91.95
Tarka 240/4	63.18	Trandopril, 4 mg Verapamil, 240 mg	80.95
Avandamet 500/2	57.63	Rosiglitazone, 500 mg Metformin, 2 mg	89.95
Glucovance 500/5	35.03	Metformin, 500 mg Glyburide, 5 mg	49.92
Metaglip 500/5	36.39	Metformin, 500 mg Glipizide, 5 mg	36.45

\*Based on a survey of four local pharmacies in Columbus, Ga.—two chain pharmacies and two locally owned pharmacies—and two online pharmacies.

\*\*Represents the sum of the cost of 30 doses of each of the two component medications.

<sup>8</sup>Bocuzzi SJ, Wogen J, Fox J, Sung JCY, Shah AB, Kim J: Utilization of oral hypoglycemic agents in a drug-insured U.S. Population. *Diabetes Care* 24:1441–1445, 2001

<sup>9</sup>Armitage CR, Parish S, Sleight P, Peto R: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomized placebo-controlled study. *Lancet* 361:2000–2001, 2003

<sup>10</sup>Larsen J, Vaccheri A, Andersen M, Montanaro N, Bergman U: Lack of adherence to lipid lowering drug treatment. *Brit J Pharmacol* 49:463–471, 2000

<sup>11</sup>Sica DA: Rationale for fixed dose combinations in the treatment of hypertension: the cycle repeats. *Drug Ther* 62:443–462, 2002

<sup>12</sup>Bakris GL: The role of combination anti-hypertensive therapy and the progression of renal

disease hypertension: looking toward the next millennium. *Am J Hypertens* 11:158S–162S, 1998

<sup>13</sup>Blonde L: Management of type 2 diabetes: update on new pharmacological options. *Manag Care* 9 (Suppl. 8):11–17, 2000

<sup>14</sup>Paes AH, Bakker A, Soe-Agnie CJ: The impact of dose frequency on patient compliance. *Diabetes Care* 20:1512–1517, 1997

<sup>15</sup>Dezii CM: A retrospective study of persistence with single pill combination therapy versus concurrent two-pill therapy in patients with hypertension. *Manag Care* 9 (Suppl. 9):2–6, 2000

<sup>16</sup>Sapienze S, Sacco P, Floyd K, DiCesare J, Doan QD: Results of a pilot pharmacotherapy quality improvement program using fixed-dose, combination amlodipine/benazapril anti-hypertensive therapy in a long-term care setting. *Clin Ther* 25:1872–1887, 2003

<sup>17</sup>Ramsdell J, Braunstein S, Stephens J, Bell C, Botteman M, Devine S: Economic model of first-line drug strategies to achieve recommended glycaemic control in newly diagnosed type 2 diabetes mellitus. *Pharmacoeconomics* 21:819–837, 2003

---

*Steven B. Leichter, MD, FACP, FACE, is co-director, and Stephanie Thomas, CRC, is a licensed practical nurse and clinical research coordinator at the Columbus Research Foundation in Columbus, Ga. Dr. Leichter is also a professor of medicine at Mercer University School of Medicine in Macon, Ga.*