

The Intensification of Drug Therapy for Diabetes and Its Complications: Evidence From 2 HMOs

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Objectives: To identify trends in the utilization of multidrug therapy for glycemic control, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), and lipid-modifying agents for persons with diabetes from 1997 to 2001. The trends in drug and total expenditures for diabetes patients also were examined.

Study Design: Cross-sectional analysis for each year from 1997 through 2001.

Patients and Methods: Subjects were identified from pharmacy and medical claims data by using Health Employer Data and Information Set diabetes indicator criteria, with the additional criterion that subjects must be receiving drug therapy for diabetes. All subjects were continuously enrolled within the commercial segment of 1 of 2 health maintenance organizations (HMOs) in different geographic areas. The proportion of patients in each year who used multiple antihyperglycemic agents was measured, as was the proportion of diabetes patients receiving ACEI/ARBs or lipid-modifying agents. Drug and total expenditures were estimated for the subjects in each HMO.

Results: Both HMOs experienced a substantial growth in the proportion of patients receiving multidrug therapy for glycemic control from 1997 to 2001. HMO 1 saw an increase from 27.1% to 43.4%; the increase in HMO 2 was from 27.3% to 39.6%. The use of ACEI/ARBs and lipid-modifying agents nearly doubled during this time period. Expenditures for drugs increased at a much greater rate than medical expenditures.

Conclusions: The intensity of drug therapy for persons with diabetes increased between 1997 and 2001. Consequently, drugs now represent a greater proportion of total expenditures for persons with diabetes.

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may be 4 times as high as those of the general population.³ Many of these costs are associated with the management of the complications of diabetes such as myocardial infarction, ischemic stroke, or end-stage renal disease.^{4,5}

However, the American Diabetes Association (ADA) estimates that the complications and costs of diabetes could be reduced dramatically if patients maintained adequate control of their diabetes. Results from the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study found that intensive glycemic control of persons with either type 1 or type 2 diabetes can reduce the rate of complications.^{6,7} When better glycemic control is achieved, the costs of diabetes decrease significantly.⁸⁻¹⁰

The intensification of drug therapy for patients with type 2 diabetes frequently involves the addition of a second or third pharmacologic agent.¹¹ There has been a substantial effort on the part of professional associations to advocate the increased control of type 2 diabetes through more intensive stepped therapy.¹² Additionally, numerous organizations have developed clinical guidelines for the treatment of diabetes mellitus based on the accumulated evidence.¹³

Many of these guidelines also address the need to aggressively treat the typical comorbidities of type 2 diabetes (eg, dyslipidemia, hypertension).^{12,14-16} The ADA also recommends that patients with diabetes and hypertension be treated with angiotensin-converting

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The Centers for Disease Control and Prevention has reported that the prevalence of diabetes rose dramatically during the 1990s.^{1,2} In 1990, approximately 4.9% of Americans had diagnosed diabetes, whereas an estimated 7.3% of Americans had diabetes in 2000. Nearly 800 000 new cases of diabetes are diagnosed each year; 90% to 95% of them are type 2 diabetes.

The long-term costs of uncontrolled diabetes are high. Persons with diabetes incur healthcare costs that

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enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) because of the ability of these drugs to delay the progression of nephropathy.¹⁶⁻¹⁷

A substantial body of evidence regarding the advantages of intensive therapy was generated in the mid-1990s. However, the extent to which this evidence has translated into changes in medical practice is unclear. Although trends regarding the use of individual drugs have been identified,¹⁸ the trends in use of multidrug therapy for hyperglycemia, as well as the trends in drug therapy for dyslipidemia and hypertension in persons with diabetes, have not been well established.

The objectives of this project were to:

1. Identify the trends in antihyperglycemic therapy for persons with diabetes and determine whether there has been a shift toward greater use of multidrug therapy for glycemic control.
2. Identify the trends in utilization for ACEIs/ARBs and lipid-modifying agents among persons with diabetes.
3. Identify the trends in drug and total expenditures for persons with diabetes in a managed care environment.

METHODS

Design

The trends in utilization of drug therapy for persons with diabetes were evaluated by comparing cross-sectional analyses for each year from 1997 through 2001, using pharmacy and medical claims data from 2 health maintenance organizations (HMOs). HMO 1 is located in a predominantly urban and suburban area of the Midwest and serves more than 200 000 members. HMO 2 is located within Appalachia and serves approximately 100 000 members in rural areas.

Subjects

For each study year, subjects were initially identified by using the criteria for the Health Employer Data and Information Set (HEDIS) diabetes indicators. An additional criterion was that subjects were required to have at least 1 prescription claim for a diabetes medication during the selected year. All of the subjects were members of the commercial segment of each HMO and had similar pharmacy benefits. Subjects were excluded from each year's analyses if they were not enrolled throughout the year.

Variable Definitions

Medication-class variables were created to track the proportion of persons who used a particular class of diabetes medications during each year. The variable for

each class of drugs was coded as 1 (yes) if the member received any drug in that class at any point in the year. Variables were created for secretagogues (sulphonylureas, meglitinides, and phenylalanine derivatives), biguanides (metformin), thiazolidinediones (TZDs), insulin, and α -glucosidase inhibitors (acarbose). Glucovance (a combination product of sulphonylurea and metformin) was counted within both constituent classes. The multidrug variable was considered positive if the member received drugs from 2 or more classes of antihyperglycemic agents in the same year or had received a combination medication. Total expenditures reflected the HMO's payment for all pharmaceutical and medical claims. Drug expenditures represented the HMO's payment for all pharmaceutical claims. The diabetes drug expenditures represented spending on antihyperglycemic medications (not including glucose strips or monitors). All of these expenditures were from the HMO's perspective and therefore did not include copayments or deductibles.

Analyses

Cross-sectional descriptive statistics were calculated for each of the 5 years (1997-2001). All analyses were conducted with SPSS, version 11.0 (SPSS Inc, Chicago, Ill).

RESULTS

Subjects

Both HMOs experienced growth in the number of members with diabetes during the study period. In HMO 1, the number of members with diabetes increased from 1042 to 2548 between 1997 and 2001; for HMO 2, the corresponding increase was from 920 to 1207 members. The distribution of the commercial HMO samples by sex and age remained relatively stable over the 5-year period. Detailed information is provided in **Tables 1 and 2**.

Diabetes Drug Utilization

The use of multidrug therapy increased in both HMOs over the 5-year period. The percentage of patients with diabetes receiving multidrug therapy in HMO 1 grew from 27.1% to 43.4% between 1997 and 2001; HMO 2 saw an increase from 27.3% to 39.6%.

The pattern of medication use by drug class also shifted during the 5-year period. The percentage of persons using insulin declined in both HMOs as the proportion of persons using multiple oral therapies increased. The use of secretagogues declined slightly, while use of biguanides (eg, metformin) increased substantially in both HMOs. The use of TZDs more than

Table 1. Trends in Utilization and Expenditures for Patients With Diabetes in HMO 1 (1997-2001)*

Patient Characteristics, Type of Drug Therapy, and Expenditures	1997 (n = 1042)	1998 (n = 1303)	1999 (n = 1805)	2000 (n = 2197)	2001 (n = 2548)
Age, mean (SD), y	47 (15)	47 (14)	47 (14)	47 (13)	48 (13)
Male, %	49.8	51.1	50.7	50.0	50.4
Drug class, %					
Secretagogue	51.0	51.0	50.9	49.7	48.8
Biguanide	27.7	32.1	40.7	48.8	56.5
TZD	10.9	14.2	14.0	20.8	25.8
α -Glucosidase inhibitor	1.5	1.2	1.1	1.0	0.9
Insulin	41.2	37.5	35.3	32.8	29.5
Multiple diabetes drugs, %	27.1	29.5	33.9	39.9	43.4
Antilipemic drugs, %	24.9	32.3	33.6	37.5	41.9
ACEIs/ARBs, %	28.5	35.0	37.8	43.2	49.8
Total expenditures (medical + drug), \$					
Median	2895	3111	3598	4117	4481
Mean (SD)	4995 (6247)	5125 (6960)	5617 (7392)	6142 (7570)	6980 (8355)
Drug expenditures, \$					
Median	1128	1299	1571	2072	2386
Mean (SD)	1524 (1262)	1605 (1328)	1897 (1702)	2384 (1927)	2761 (1845)
Diabetes drug expenditures, \$					
Median	399	458	552	753	882
Mean (SD)	539 (441)	597 (524)	781 (625)	905 (729)	1006 (687)

*ACEIs/ARBs indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; TZD, thiazolidinedione.

doubled in HMO 1. However, TZD use in HMO 2 followed a different pattern: it increased modestly during 1997-1999, but dropped after the removal of troglitazone (Rezulin) from the market in March 2000. Please refer to Tables 1 and 2 for further details.

Utilization of Lipid-Modifying Drugs and ACEIs/ARBs

In both HMOs, use of lipid-modifying drugs and ACEIs/ARBs nearly doubled over the 5-year period. Notably, use of ACEI/ARB drugs was much greater in HMO 1: approximately half of the diabetes patients received these drugs in 2001. Only 36.9% of diabetes patients in HMO 2 received ACEI/ARBs. About 40% of diabetes patients in both HMOs received lipid-modifying agents in 2001.

Trends in Drug Utilization and Expenditures

Expenditures for diabetes drugs and all drugs increased substantially for persons with diabetes over the 5-year period. Spending on pharmaceuticals

increased at a much greater rate than medical spending for these diabetes populations (**Figures 1 and 2**). For HMO 1 in 1997, the proportion of total (median) spending due to drugs was 38.9%. This increased to 53.2% in 2001. HMO 2 also saw an increase from 32.6% to 39.4% for the proportion of total expenditures due to drugs. Notably, the majority of drug expenditures for persons with diabetes were for drugs other than antihyperglycemics.

DISCUSSION

The diffusion of any new knowledge or technology takes time.¹⁹ The translation of new evidence into written standards for medical practice and the subsequent adoption of these standards in general practice may take several years.²⁰ Evidence from the Diabetes Control and Complications Trial and United Kingdom Prospective Diabetes Study in the mid-1990s did not translate into immediate, widespread changes in the care of persons with diabetes. Rather, the data from

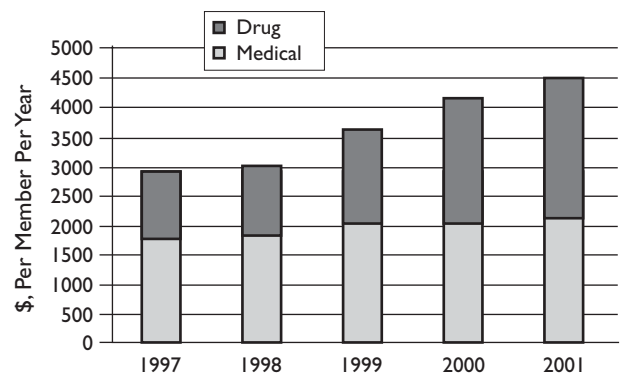
Table 2. Trends in Utilization and Expenditures for Patients With Diabetes in HMO 2 (1997-2001)*

Patient Characteristics, Type of Drug Therapy, and Expenditures	1997 (n = 920)	1998 (n = 1179)	1999 (n = 1098)	2000 (n = 1115)	2001 (n = 1207)
Age, mean (SD), y	57 (12)	56 (12)	55 (12)	54 (12)	54 (11)
Male, %	50.7	51.5	50.9	51.2	50.7
Drug class, %					
Secretagogue	58.9	59.7	55.5	57.9	58.5
Biguanide	31.7	34.1	41.6	56.5	57.1
TZD	8.6	12.7	13.6	7.8	8.7
α -Glucosidase inhibitor	1.7	2.1	2.1	2.0	1.3
Insulin	33.0	30.6	31.6	26.5	24.8
Multiple diabetes drugs, %	27.3	32.1	35.5	36.0	39.6
Antilipemic drugs, %	22.5	25.5	31.1	34.5	39.5
ACEIs/ARBs, %	20.2	31.9	34.2	35.5	36.9
Total expenditures (medical + drug), \$					
Median	3023	3105	3362	3727	4405
Mean (SD)	5373 (7060)	5399 (7942)	6059 (10098)	6389 (9136)	7959 (12,587)
Drug expenditures, \$					
Median	987	1204	1452	1497	1734
Mean (SD)	1246 (950)	1577 (1405)	1767 (1254)	1811 (1432)	2052 (1452)
Diabetes drug expenditures, \$					
Median	267	345	398	377	444
Mean (SD)	348 (258)	489 (401)	566 (467)	498 (370)	571 (434)

*ACEIs/ARBs indicates angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; TZD, thiazolidinedione.

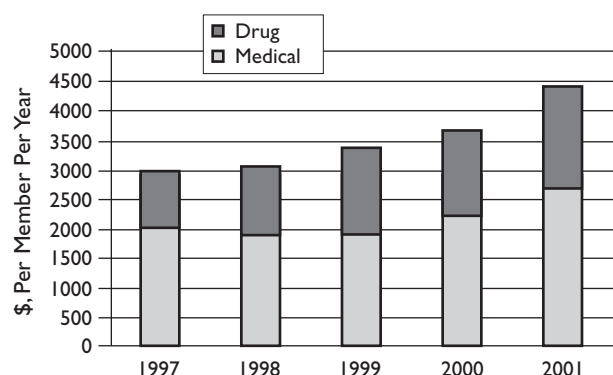
these 2 HMOs show that the change toward more intensive treatment of diabetes occurred gradually from 1997 to 2001. Given the limitations of the administrative data, it is difficult to determine whether these HMOs have maximized the use of intensive therapy or whether the trend toward increased utilization of drug therapy will continue.

The trends were fairly consistent across both HMOs, which indicates that this trend toward greater intensity of drug therapy was not unique to any particular payer or geographic location. Wennberg and colleagues have observed that the utilization of healthcare services may vary significantly across geographic regions of the country.²¹⁻²³ In this study, the HMOs represented different geographic regions (a midwestern HMO in an urban/suburban area vs an Appalachia-based HMO with primarily rural members). Although there were substantially more diabetes patients using TZD drugs in the midwestern HMO (HMO 1), there were only slight differences in utiliza-

Figure 1. HMO 1: Trends in Median Expenditures (per Member per Year)

tion across most classes of diabetes drugs. Additionally, the general trend toward increased use of newer pharmaceuticals and increased use of multidrug therapy was consistent across HMOs.

Figure 2. HMO 2: Trends in Median Expenditures (per Member per Year)



Another trend that appeared was the increased use of lipid-modifying agents and ACEIs/ARBs in both HMOs. Thus, it appears that greater attention is being given to the management of dyslipidemia, hypertension, and nephropathy in diabetes patients. However, differences still existed between the 2 HMOs in the use of ACEIs/ARBs. A substantially higher proportion of patients received these drugs in HMO 1 than in HMO 2 (49.8% vs 36.9% in 2001). Although no clinical data were available to compare the 2 populations, it is unlikely that these prescribing variations can be explained solely by differences in severity of illness.

Expenditures on diabetes medications and all drugs increased substantially across the HMOs and continue to represent a larger percentage of total expenditures for persons with diabetes. The increased use of multiple drugs for glycemic control, coupled with the increased use of lipid-modifying drugs and ACEIs/ARBs, may have produced much of this increase. These findings are consistent with a study by Dubois et al that showed although expenditures for diabetes drugs increased by more than 90% between 1994 and 1997, approximately 73% of this increase was due to volume factors.²⁴ However, the shift from low-cost sulfonylureas to more expensive drugs such as TZDs also contributed to the increased expenditures in these 2 HMOs. It is likely that lower use of multidrug therapy for glycemic control, lower use of TZD drugs, and lower use of lipid-modifying drugs and ACEIs/ARBs in HMO 2 led to its lower proportion of total expenditures due to drugs (39.4% in HMO 2 vs 53.2% in HMO 1).

Although both HMOs saw a dramatic increase in drug expenditures, this investment in drug therapy may be worthwhile if it leads to better glycemic control and fewer diabetes-related complications. Herman and Eastman estimated that intensive drug

therapy for both type 1 and type 2 diabetes will be cost effective in the long run because of reductions in complications and hospitalizations.²⁵ However, it is only recently that the relationship between intensive drug therapy, glycemic control, and total costs of care has been rigorously examined. Two recent studies demonstrated the economic benefit of improved glycemic control,^{9,10} whereas the Sterno-2 study demonstrated that stepwise intensification of therapy targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria reduced the risk of cardiovascular and microvascular events by about 50% in persons with type 2 diabetes.²⁶

For this study, the impact of drug therapy intensity on outcomes could not be determined due to the limitations of administrative data from the HMOs. However, both HMOs experienced only a small increase in median medical spending during 1997-2001, and neither saw an increase in hospitalization rates for members with diabetes during this period (unpublished data from both HMOs). This pattern of increased drug expenditures coupled with little or no increase in medical spending is consistent with other recent findings.^{27,28}

It appears that the efforts of professional associations and managed care organizations to encourage the aggressive treatment of diabetes are translating into actual increases in the intensity of therapy. Within this study, it was not possible to determine whether the increases in multidrug therapy were actually going to patients who had the greatest need for more intensive therapy. Nonetheless, the increase in drug regimen intensity may have long-term benefits for patients and third-party payers. For example, the trend toward greater use of multiple oral agents in lieu of insulin may permit patients to maintain adequate control while avoiding injections that many perceive as inconvenient or painful. More aggressive treatment also should lead to better glycemic control, fewer hospitalizations, and lower long-run costs of care.

CONCLUSION

The proportion of persons with diabetes who received multidrug therapy increased substantially during 1997-2001. The general trend was toward increased use of newer oral medications and combinations of oral products. Utilization of lipid-modifying agents and ACEIs/ARBs by persons with diabetes nearly doubled in this time frame. Consequently, expenditures for drug therapy increased at a much higher rate than total spending for HMO patients with diabetes.

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REFERENCES

1. Mokdad AH, Bowman BA, Ford ES, et al. The continuing epidemics of obesity and diabetes in the United States. *JAMA*. 2001; 286:1195-1200.
2. Mokdad AH, Ford ES, Bowman BA, et al. Diabetes trends in the U.S.: 1990-1998. *Diabetes Care*. 2000;23:1278-1283.
3. American Diabetes Association. Economic consequences of diabetes mellitus in the U.S. in 1997. *Diabetes Care*. 1998;21:296-309.
4. American Diabetes Association. Position Statement: Diabetic Nephropathy. *Diabetes Care*. 1997;20:S24-S27.
5. O'Brien JA, Shomphe LA, Kavanagh PL, et al. Direct medical costs of complications resulting from type 2 diabetes in the U.S. *Diabetes Care*. 1998;21:1122-1128.
6. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.
7. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-853.
8. Gilmer TP, Manning WG, O'Connor PJ, Rush WA. The cost to health plans of poor glycemic control. *Diabetes Care*. 1997;20: 1847-1853.
9. Menzin J, Langley-Hawthorne C, Friedman M, et al. Potential short-term economic benefits of improved glycemic control. *Diabetes Care*. 2001;24:51-55.
10. Wagner EH, Sandhu N, Newton KM, et al. Effect of improved glycemic control of health care costs and utilization. *JAMA*. 2001; 285:182-189.
11. Mathews DR, Cull CA, Stratton IM, et al. UKPDS 26: sulphonylurea failure and non-insulin dependent diabetic patients over six years. *Diabet Med*. 1998;15:297-303.
12. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care*. 2003;26:S33-S50.
13. National Guideline Clearinghouse. Diabetes mellitus guidelines. Available at: <http://www.guidelines.gov>. Accessed November 12, 2003.
14. American Association of Clinical Endocrinologists. Medical guidelines for the management of diabetes mellitus. Available at: www.aace.com/clin/guidelines/diabetes_2002.pdf. Accessed November 12, 2003.
15. American Diabetes Association. Management of dyslipidemia in adults with diabetes. *Diabetes Care*. 2003;26:S83-S86.
16. American Diabetes Association. Treatment of hypertension in adults with diabetes. *Diabetes Care*. 2003;26:S80-S82.
17. American Diabetes Association. Diabetic nephropathy. *Diabetes Care*. 2003;26:S80-S82.
18. Express Scripts. 2002 Drug Trend Report. Available at: <http://www.expressscripts.com>. Accessed November 12, 2003.
19. Rogers EM. *Diffusion of Innovations*. New York, NY: The Free Press; 1995.
20. Sackett DL, Straus SE, Richardson WS, et al. *Evidence-Based Medicine*. New York, NY: Churchill Livingstone; 2000.
21. Wennberg JE. Understanding geographic variation in health care delivery. *N Engl J Med*. 1999;340:52-53.
22. O'Connor GT, Quinton HB, Traven ND, et al. Geographic variation in the treatment of acute myocardial infarction: the cooperative cardiovascular project. *JAMA*. 1999;281:627-633.
23. Fisher ES, Wennberg JE, Stukel TA, Sharp SM. Hospital readmission rates for cohorts of Medicare beneficiaries in Boston and New Haven. *N Engl J Med*. 1994;331:989-995.
24. Dubois RW, Chawla AJ, Neslusan CA, et al. Explaining drug spending trends: does perception match reality? *Health Aff*. 2000;19(2):231-239.
25. Herman WH, Eastman RC. The effects of treatment on the direct costs of diabetes. *Diabetes Care*. 1998;21:C19-C24.
26. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383-393.
27. Tufts Center for the Study of Drug Development. *Outlook 2001*. Boston, Mass: Tufts University; 2001.
28. Kleinke JD. The price of progress: prescription drugs in the health care market. *Health Aff*. 2001;20(5):43-60.