poll of 3,465 Californians aged 18 years or older with chronic illness, conducted in November and December 2002, found that nearly one half (46%) reported doing nothing when faced with an increase in drug cost sharing.³⁵ (The specific survey question stated that the survey respondent had prescription drug coverage and the amount paid to fill a prescription increased in the past year.) More than one third of respondents (36%) reported that they asked their physician or pharmacist for a generic prescription drug, 21% asked the physician to prescribe a less-expensive alternative drug, 16% did not get the prescription filled, and 18% used mail-order service to fill the prescription.

In a previous issue of the *Journal*, Cox and Henderson found that Medicare+Choice members with an annual drug benefit maximum relied in part on prescription drug samples to mitigate the financial burden of prescription drug needs.³⁶ This practice is likely to be self-defeating in reducing the financial burden since (a) higher-cost drugs are more heavily sampled and (b) the availability of drug samples may affect physician prescribing practices by reducing the immediate pressure to find lower-cost therapeutic alternatives.³⁷ We await the results of research in which investigators ask the important questions regarding the nature and usefulness of interactions with physicians in offering recommendations for generic drugs and other lower-cost therapeutic alternatives to help reduce out-of-pocket expenditures for the elderly.

■ Hypertension, Prescription Drug Copayments, and Drug Therapy Adherence

In this issue of the *Journal*, Wogen, Kreilick, Livornese, Yokoyama, and Frech found that drug therapy adherence differs by type of drug.³⁸ In this study, a higher rate of adherence to therapy was found for valsartan compared with lisinopril or amlodipine. Several factors can affect adherence to drug therapy aside from the safety and effectiveness of the drug. A factor not addressed in the extant study, but a curious one is the relationship of member cost share to drug therapy adherence. Some drug industry analysts attributed the small increase in U.S. sales of the block-buster drug atorvastatin (Lipitor, for hypercholesterolemia) in 2003 Q1 and declines in sales of category leaders sertraline (Zoloft, for depression), and amlodipine (Norvasc, for blood pressure) during this period to rising copayments in drug benefit plans.³⁹ One wonders how formulary status and copay design (e.g., relative copayments) might have influenced the results observed by Wogen, Kreilick, Livornese, Yokoyama, and Frech, particularly since one of their study drugs was amlodipine. Neither formulary status nor copay design was reported, and one of the study medications, lisinopril, became available in generic form during the study period, but not until the 35th month of the 36-month study period. It is reasonable to speculate that adherence with generic lisinopril, with its lower copayment, would have been more resilient over time compared with brand drugs amlodipine and valsartan, both with

higher (brand drug) copayments.

There are also data to suggest that pharmacy provider type, mail-service versus community pharmacy, another feature of drug benefit design, may influence drug therapy adherence.⁴⁰ This variable, certainly relevant in the database employed by Wogen, Kreilick, Livornese, Yokoyama, and Frech (a pharmacy benefit manager database with a high penetration of mail-service prescriptions), was not measured in the current study. Future studies of drug therapy adherence derived from drug claims data might also include a measure of the average member cost share per day of therapy, in dollar amount and percentage, for the target drugs in the study. This variable has become increasingly important with the proliferation of multi-tier copay drug plans and sometimes widely disparate copayments for generic versus preferred brand versus nonformulary drugs. Managed care pharmacists also need to know if and how mail-service pharmacy is a factor in drug therapy adherence, through the simple convenience of a 90-day supply or home delivery versus store purchase or a lower cost-share requirement.⁴¹

There are also the important subjects of midpoint and end-point clinical outcomes, none of which were measured in the current study. A study of blood pressure control in a New York health maintenance organization (HMO) in 1998 found that only 35% of patients reached target blood pressure (<140 mm Hg systolic and 90 mm diastolic for the general population and <130/85 mm Hg in diabetics and patients with renal insufficiency).⁴² An equally important finding in this “real-world” study was that only 68% of patients were treated with drugs recommended in the HMO’s treatment guidelines based upon the Joint National Committee (JNC) recommendations. Others have found that members of HMOs and preferred provider organizations were more likely to use angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs) for essential hypertension compared to fee-for-service health insurance and out-of-pocket purchasers who were more likely to use diuretics and beta-blockers, the latter consistent with JNC guidelines.⁴³ A survey of 316 primary care physicians responding to a 26-item questionnaire in the year 2000 found that 41% reported little or no knowledge of JNC guidelines, at that time in its sixth iteration.⁴⁴ This lack of familiarity was also evidenced in the use of ACEIs as the most common first-line drug of choice for hypertension, contrary to both JNC guidelines dating back to version III (1984) that advocated the use of diuretics and beta-blockers as first-line therapy.⁴⁵

Examination of the relative value of ACEIs, CCBs and angiotensin receptor blockers (ARBs) in the treatment of hypertension must include the context of the results of the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT), released in December 2002. The ALLHAT study results suggest that most of the more than 40 million Americans with hypertension⁴⁶ could be treated more effectively, more safely, and more cheaply with low-cost diuretics such as chlorthalidone and hydrochlorothiazide at a

fraction of the cost of ACEIs such as ramipril or quinapril and CCBs such as amlodipine, felodipine and long-acting nifedipine and diltiazem.⁴⁷ The 8-year ALLHAT study, conducted in a real-world environment with a mean follow-up of 4.9 years, produced unequivocal evidence that amlodipine and lisinopril were associated with the same incidence of the primary outcome of combined fatal coronary heart disease or nonfatal myocardial infarction as a diuretic (chlorthalidone); all-cause mortality was also the same among the 3 treatment groups.⁴⁸ However, the diuretic (chlorthalidone) was superior to CCB (amlodipine) in the 6-year rate of heart failure (HF), 7.7% versus 10.2%, relative risk (RR) 1.38, and chlorthalidone was superior to lisinopril in the 6-year rates of combined cardiovascular disease, 30.9% versus 33.3%, RR 1.10, stroke (5.6% versus 6.3%, RR 1.15) and HF (8.7% versus 7.7%, RR 1.19). Robert Anderson, one of the ALLHAT investigators, had additional observations regarding the ALLHAT study findings in a previous issue of the *Journal*.⁴⁹

The study by Wogen, Kreilick, Livornese, Yokoyama, and Frech contains some interesting data in the area of combination drug therapy. More than one third (36.7%) of the patients started on valsartan were already taking a diuretic or diuretic combination. More than 40% of the patients started on amlodipine (45.2%) or lisinopril (42.4%) were taking a diuretic or diuretic combination; 31% to 33% were taking an antilipid drug. Amlodipine and lisinopril patients appeared to be more likely to be on concomitant therapy with nitrates, digitalis, or nitrates. Concurrent use of beta-blockers was more common among first-therapy amlodipine patients (28.0%) compared with lisinopril (23.8%) and valsartan (21.4%). Interesting subanalyses would have determined how many first-therapy patients with amlodipine, lisinopril, or valsartan were also taking both diuretics and beta-blockers or were diabetic patients, as determined by proxy of drug therapy for diabetes.

Managed care pharmacists might also note that Wogen, Kreilick, Livornese, Yokoyama, and Frech found that the study drugs were used as first-line, monotherapy in 30.5% of the cohort of patients, utilization that is contrary to JNC VII guidelines and the evidence produced in the ALLHAT study. Valsartan was most likely to be used as monotherapy (35.5%), followed by lisinopril (32.5%) and amlodipine (27.4%, $P<0.001$). Also noteworthy in this study is that the valsartan patients were more likely to have a lower Chronic Disease Score (CDS), further distancing these results from current evidence-based treatment guidelines.

Conclusions derived from this current study should be framed in the context of the very large case numbers that tend to make small variation in every value of every independent variable statistically significant. For example, the 3 groups, taking valsartan, amlodipine, or lisinopril, are not homogenous in patient characteristics such as age and gender (Table 1, $P<0.0001$).⁵⁰ A mean age of 62.4 years for the 29,669 valsartan patients is practically no different than the 62.1 mean age for

the 40,128 lisinopril patients or 63.9 mean age for the 73,148 amlodipine patients. Similarly, the 3 groups are statistically different in mean CDS, with valsartan associated with the lowest CDS. However, while statistically different ($P<0.0001$), a CDS of 9.62 for valsartan does not seem to be clinically or practically different from the mean 10.15 CDS for lisinopril or 10.34 for amlodipine. The need to evaluate practical significance against statistical significance flows through to the study dependent variables. All measures for drug therapy compliance and adherence were statistically significant ($P<0.0001$), favoring valsartan, but 88.5% mean compliance for valsartan seems clinically and practically no different than the mean 86.7% compliance with amlodipine or 86.3% for lisinopril.

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