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Compliance in the Real World

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ABSTRACT

Until 1994, rates of noncompliance for lipid-lowering therapies were largely drawn from clinical trials and showed favorable risks for drug discontinuation, ranging from 4–15% for 1-year risk to 11–30% for 5-year risk. Although cross-study comparisons are difficult to make because of variations in study design and measures collected, when evaluating compliance to antihyperlipidemic drugs in primary care settings, results in general show substantially higher rates of discontinuation than those reported from randomized clinical trials. Recent studies from the United States, Australia, and Canada support the conclusion that adherence to lipid-lowering drugs is very poor in primary care settings.

Compliance with prescribed drug therapy is an issue of widespread concern. Do patients adhere to suggested treatment regimens? Lack of compliance with drug therapy encompasses the improper use of a prescription to complete discontinuation of the drug. Estimates of compliance with lipid-lowering therapy have largely been drawn from randomized clinical trials, which have reported the 1-year risk of discontinuation to be between 4% and 15% [1–4]. Of the longer trials, the 5-year risk was reported to be between 11% and 30% [1–4]. These rates suggest that a large proportion of patients are able to stay compliant with therapy for extended periods of time. However, clinical trials usually evaluate patient compliance within the confines of a monitored study. What happens in the real world? Prior to 1994, little information existed about compliance with lipid-lowering therapy in primary care settings. Published reports of compliance [5,6] did not accurately account for variable times of patient follow-up, and so did not reflect the actual risk of noncompliance. As a result, the reported rates of discontinuation could not be validly compared to rates acquired in clinical trials. It was of interest, then, to investigate, over a specific time frame, the compliance with lipid-lowering therapy of patients from primary care settings and compare these results to those found in clinical trials. Portions of this review have been reported in an article that appeared in the *New England Journal of Medicine* [7].

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A Study of Noncompliance in Primary Healthcare Settings

With the aim of determining antihyperlipidemic drug discontinuation rates in primary care settings, and to compare these rates to those in randomized clinical trials, two health maintenance organizations (HMOs) were studied using a retrospective cohort design [7]. The Fallon Community Health Plan and the Harvard Community Health Plan provided demographic, enrollment, and health services data for patients with a documented lipid disorder who began drug therapy from 1988 to 1990. The patient population was 52% female, with a mean age of 57 years (range 12–88 years). Approximately 53% of patients had a diagnosis of hypertension and 12% had a diagnosis of diabetes in the automated health plan records.

Identification of drug discontinuations was performed using computerized databases and chart review. Comparisons were limited to niacin, lovastatin, gemfibrozil, and the bile acid sequestrants, cholestyramine and colestipol. The study population consisted of 2369 new users of lipid-lowering drugs during the study period, accounting for 3223 prescribed courses of drug therapy. The bile acid sequestrants were the most commonly dispensed agents (41.4%), followed by niacin (22.6%), lovastatin (16.7%) and gemfibrozil (14.1%).

There were 1047 discontinuations, accounting for 32% of the prescribed courses of therapy. Of all discontinuations, the majority resulted from switching to a new agent (56%), but 30% of patients received no other drug therapy during the study period. Eleven percent had their treatment supplemented with additional agents and 3% con-

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tinued on a single agent of an initial combination therapy. Using survival analysis techniques, the 1-year risk of discontinuation for all the drug therapies combined was 38%. Table 1 lists the 1-year risk of discontinuation for the four most commonly prescribed individual classes of agents. The lowest discontinuation rate measured was for lovastatin at 15%, followed by gemfibrozil at 37%, bile acid sequestrants at 41%, and niacin at 46%. On the whole, adverse events accounted for approximately 60% of discontinuations, and drug ineffectiveness accounted for 30%.

Comparison to Randomized Clinical Trials

Randomized clinical trials of at least 6 months' duration and published from 1975 to 1993 were identified from searching the medical literature. Of the 17 long-term clinical trials that met study criteria, duration of follow-up ranged from 6 months to over 7 years (see [7] for individual study citations). Comparing summary estimations of the 1-year risk of discontinuation, bile acid sequestrants, niacin, and gemfibrozil all demonstrated risks substantially lower than those reported in the HMOs (Table 1). Bile acid sequestrants showed a 1-year risk of discontinuation of 31% in clinical trials compared to 41% in the HMOs; gemfibrozil showed a risk of 15% in clinical trials compared to the 37% found in HMOs; and niacin showed a discontinuation risk of 4% in clinical trials compared to 46% in HMOs. Clinical trials providing longer periods of study showed a widened gap between the risks from HMOs and clinical trials. Unlike the other antihyperlipidemic agents, lovastatin was demonstrated to have similar rates of noncompliance in the clinical trials and HMOs (16% vs. 15%).

Recent Reports of Compliance

Two primary care studies in the United States that included discontinuation (but not specific risks because they did not incorporate variations of patient follow-up time) reported frequencies of discontinuation ranging from 4% with lovastatin to 65% with bile acid sequestrants [8], and 52% with lovastatin to 73% with niacin [9]. In a recent Australian study [10], the overall 1-year risk of discontinuation was 60% and the specific risk for gemfibrozil was 78%, both of which were much higher than that reported in the study by Andrade et al. [7] (see Table 1). The main reason for discontinuation in the Australian study was that the patients were unconvinced that there was a need for treatment, whereas in the primary care study using HMOs, discontinuation was mainly due to adverse drug effects. In the Australian study [10], Simons et al. also reported a 1-year risk of discontinuation for two other agents, pravastatin and simvastatin, of 56% and 57%, respectively. A primary care study in Saskatchewan [11], using the Saskatchewan Drug Prescription Plan, reported the percentage of patients who stopped taking the drug after one prescription. The lowest estimate was for simvastatin, for which 24% of patients never renewed their prescriptions, followed closely by pravastatin, lovastatin, gemfibrozil, and cholestyramine at 25%, 26%, 35%, and 53%, respectively. Niacin, at 69% of patients discontinuing use after one prescription, was the highest.

On the other hand, recent large-scale randomized clinical trials have still reported favorable rates of discontinuation. One-year risks of 16% and 5-year risks of 2–30% have been published [12–14]. This is likely due to the selection criteria used and, more importantly, to these patients being followed up and observed much more closely than the average patient in a primary care setting. Little information exists for compliance to diet therapy. In the Cholesterol Reduction Intervention Study [15], diet therapy also had poor compliance. At the start of the study, 50% of patients receiving step-care therapy, beginning with either niacin or bile acid sequestrants, were not compliant with their diet therapy and 40% of lovastatin users were not compliant.

Table 1 One-year risk of antihyperlipidemic drug discontinuation

Drug	Primary care*‡	Clinical trials†‡
Lovastatin	15% (11–19)	16% (15–17)
Gemfibrozil	37% (31–43)	15% (13–16)
Bile acid sequestrants	41% (38–44)	31% (30–33)
Niacin	46% (42–51)	4% (3–5)

*Data from two health maintenance organizations [7].
†See [7] for study citations.
‡Values in parentheses are 95% confidence intervals, as percentages.

Conclusions

The general conclusion of the compliance studies is that adherence to lipid-lowering drugs is very poor in primary care settings. The importance to policy-makers assessing cost-effectiveness is that the reports found in randomized clinical trials do not accurately reflect the compliance with lipid-lowering therapy in the real world. Cautious inter-

pretation is necessary because discontinuation rates may not accurately reflect the success rate that lipid-lowering therapeutic agents have in primary care settings. Biases were likely present in the prescribing patterns of the agents at these two managed care plans, which make direct head-to-head comparisons of the agents inappropriate, based on these data alone.

Editor's Addendum

A recent article [16] was published after the ISPOR Lipid Conference and therefore was not discussed in the conference presentation. It describes a cross-national study that examined the persistence of use of lipid-lowering agents in elderly patients who received Medicaid, state pharmacy assistance programs, or Quebec's provincial medical care program between the period of 1990 to 1991. The study showed high rates of discontinuation of about 40% in 1 year and 48% in 5 years. In contrast to Andrade's findings on compliance in managed care populations [7], statins were the most frequently prescribed agent (39.4%) in this low-income or indigent elderly population. Persistency rates for statins were significantly higher than that of other agents. Patients with comorbid conditions such as hypertension, diabetes, or coronary artery disease had significantly higher rates of compliance. This study supports the need to consider compliance in the real world in cost-effectiveness analyses of lipid-lowering agents. In addition, variation in rates of compliance, dependent upon the choice of agent prescribed, comorbidity, and socioeconomic status of the patient population, should be considered.

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