Discontinuation Rates of Cholesterol-Lowering Medications: Implications for Primary Care

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Abstract

Objective: **To evaluate long-term continuation rates for cholesterol-lowering therapy (niacin, sequestrants, statins) in a multidisciplinary lipid clinic and to evaluate the effectiveness of 2 different dosing strategies designed to improve long-term continuation of therapy.**

Study Design: **An observational study was done at the Milwaukee Department of Veterans Affairs Medical Center Lipid Clinic, where healthcare personnel were trained to improve patient tolerance to cholesterol-lowering medications. Primary outcomes were recorded prospectively.**

Patients and Methods: **Patients were 970 consecutive veterans who began therapy with niacin, sequestrants, or statins between March 1988 and December 1995. In 1992, two different dosing strategies were initiated to reduce the discontinuation rates for niacin and sequestrants: (1) the niacin titration schedule was lengthened from 3 to 6 weeks and (2) the initial sequestrant dose was reduced from four to two scoops daily.**

Results: **Discontinuation rates for niacin and sequestrants were both very high. For niacin, 48% and 71% of all patients who began therapy discontinued the drug by 1 and 4 years, respectively. For sequestrants, drug discontinuation rates were 59% and 83% at 1 and 4 years, respectively. On the other hand, statin discontinuation rates at 1 and 4 years were only 10% and 28%, respectively. Neither the longer niacin titration schedule nor the lower sequestrant initiation dose reduced these high discontinuation rates.**

Conclusions: **Despite initiation of niacin and sequestrant therapy in the setting of a multidisciplinary lipid clinic, drug discontinuation rates were high and were similar to rates observed in primary care settings. Neither the specialized resources available in a lipid clinic nor protocols designed to improve tolerance to therapy reduced the high drug discontinuation rate. Unless more tolerable niacin and sequestrant formulations become available, reliance on statins as the preferred cholesterol-lowering agents will continue because they have fewer side effects and lower discontinuation rates.**

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Evidence from clinical studies has shown that treatment for hyperlipidemia decreases morbidity and mortality.[1,2] According to National Cholesterol Education Program guidelines, 7% of the US population will require lipid-modifying therapy to reduce elevated levels of low-density lipoprotein cholesterol (LDL-C).[3] Attaining goal LDL-C in patients with moderate to severe hypercholesterolemia may be difficult and frequently requires combination drug therapy,[4] which usually includes the addition of niacin, sequestrants, or both to 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins). The ability of these patients to

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tolerate therapy with niacin and sequestrants has been shown to be an important predictor of whether LDL-C goals are achieved.[5]

Long-term drug discontinuation rates for lipid-lowering agents appear to be unusually high. We initially reported drug discontinuation rates for niacin and sequestrants of 28% and 37%, respectively. These rates were achieved in a lipid clinic where patient care was focused on lipid disorder management with ample clinic personnel, including nurse-clinicians and clinical pharmacists, available for medication counseling to enhance continuation to therapy. However, this study included only a small number of patients, many of whom were followed for less than 1 year.[6] More recently, drug discontinuation rates of 50% or higher at 1 year were reported for cholesterol-lowering drugs in primary care settings.[7,8] Compared with lipid specialty clinics, primary care delivery systems may not have sufficient personnel to regularly reinforce continuation of cholesterol-lowering drugs. Reinforcement may be particularly important for patients taking niacin and sequestrants, because they may benefit from advice about how to overcome frequent noxious side effects. If drug discontinuation rates are substantially higher in primary care compared with lipid subspecialty clinics, appropriation of additional resources to improve long-term continuation rates in the primary care setting may be appropriate.

To our knowledge, different dosing schedules designed to reduce the discontinuation rate for niacin or sequestrants have not been formally evaluated. Initial adverse effects of niacin (eg, pruritus, flushing) are common but become less severe with time.[9] Therefore, efforts to reduce these side effects during the initial period of drug therapy might be helpful. In the case of sequestrants, lower doses may be almost as effective as full-dose therapy, with fewer side effects.[10] Therefore, a trial of lower doses of sequestrants to improve the drug discontinuation rate would appear reasonable.

The purposes of this study were (1) to quantify long-term drug discontinuation rates for cholesterol-lowering drugs in a subspecialty lipid clinic; (2) to determine whether drug discontinuation rates for niacin and sequestrants stabilize after the first 6-12 months once patients became acclimated to common side effects; and (3) to determine whether specific dosing and scheduling strategies could improve the ability of patients to tolerate niacin and sequestrants. We evaluated 6-week vs 3-week niacin titration schedules and low (2 scoops daily) vs high (4 scoops daily) initiation doses of sequestrants.

··· METHODS ···

The study group included all patients attending the Milwaukee Department of Veterans Affairs Medical Center (VAMC-Milwaukee) Lipid Clinic since its inception in March 1988 through December 1995. Patients were included if hyperlipidemia was treated with 1 or more of the following medications: bile acid sequestrants, nicotinic acid, or statins. The statin used during this study was either pravastatin or lovastatin.

The operation of the VAMC-Milwaukee Lipid Clinic has been described previously.[5,6] This clinic accepts primary and secondary referrals; most patients had not received prior lipid-lowering therapy. Once enrolled, patients were monitored closely for response and tolerance to therapy and were seen at 2-month intervals until the LDL-C goals established by the National Cholesterol Education Program were achieved. Routine laboratory testing to monitor for drug toxicity was performed at each clinic visit and included liver function tests for the statins and liver function tests and glucose for niacin. Entered prospectively into a computerized database were patient-specific data including the lipid profile, compliance data, results of laboratory monitoring, and reasons why each regimen was discontinued. Indications for drug discontinuation were divided into several categories, including adverse symptoms attributable to the drug and laboratory abnormalities discovered during routine monitoring. These were recorded by the clinician at the time that the drug was discontinued. Laboratory abnormalities that resulted in drug discontinuation included liver function test results greater than three times the upper limit of normal for either niacin or statins and glucose elevations in a nondiabetic patient for niacin. Creatine kinase and uric acid levels were not monitored routinely with any drug.

The clinic operates with a multidisciplinary staff including a lipidologist (G.S.), clinical pharmacist (J.G.H.), nurse-clinicians, and dietitians. Medical residents and students frequently rotate through the clinic. All staff personnel were trained to provide drug education and counseling for patients prescribed lipid-lowering drug therapy. Reading material explaining the medication and the initiation protocol was provided to all patients. Potential adverse effects were discussed, and ways to alleviate them were suggested as described previously.[11] Patients were encouraged to call between visits if any problems with therapy were encountered. At each clinic

visit, tolerance to therapy was evaluated and counseling was provided, if necessary, to reinforce the importance of drug and diet adherence.

The clinic niacin titration schedule and bile acid sequestrant dose were modified in 1992. From March 1988 through May 1992, the niacin titration schedule was as follows: begin niacin therapy at 100 mg 3 times daily with meals (week 1), increase to 200 mg 3 times daily (week 2), increase again to 300 mg 3 times daily (week 3), and start 500 mg 3 times daily (week 4). This regimen is referred to as the short 3-week niacin titration schedule. To improve patient acceptance of niacin, a longer titration schedule was adopted in May 1992: begin niacin therapy at 100 mg daily for 3 days, then increase to 200 mg daily for 3 days, then increase further by 100-mg increments every 3 days. The daily niacin dosage was increased to 1500 mg at the beginning of the seventh week of therapy. This regimen is referred to as the long 6-week niacin titration schedule.

With both regimens, the patient was scheduled for a return visit at 2 months after niacin was initiated to evaluate tolerance and effectiveness of therapy at the 1500-mg daily dose. If bothersome side effects occurred, the medication sheet instructed patients to reduce the niacin dose to a more tolerable level and to attempt to increase the dose again after several days. If the side effects recurred when the dose was increased, the patient was instructed to continue the more tolerable dose until the next visit. Only patients newly started on niacin were included in the analysis. No exceptions were made to either titration schedule.

From March 1988 through November 1992, bile acid sequestrants (either colestipol or cholestyramine) were initiated at 1 scoop in the evening, and patients were instructed to increase the dose to 1 scoop twice daily after 1 week. The dose was increased to 2 scoops twice daily (4 scoops daily) at the beginning of the third week of therapy. Beginning in November 1992, the dose of sequestrants was reduced from 4 scoops to 2 scoops daily to improve patient tolerance. Patients were instructed to take 1 scoop in the evening for the first week of therapy and then increase the dose to 2 scoops in the evening by the beginning of the second week. In most patients, the dose was maintained at 2 scoops even when this lower dose was well tolerated and effective.

For both dosing regimens, patients were scheduled for a return visit at 2 months to evaluate tolerance and effectiveness of therapy. Like patients taking niacin, patients taking sequestrants received

Table 1. Pretreatment Characteristics of the VAMC-Milwaukee Lipid Clinic Patients Before Treatment With Sequestrants or Niacin

	Sequestrants		Niacin	
Characteristic	**2 scoops (n = 106)**	**4 scoops (n = 229)**	**3 wk (n = 392)**	**6 wk (n = 172)**
Males (%)	93	93	98	96
Mean age (y)	65 ± 12	65 ± 12	65 ± 11*	60 ± 11
Race (% white)	84	85	89	92
Alcoholic drinks per week (mean ± SD)	3.4 ± 5.9	5.0 ± 11.2	4.1 ± 8.8	3.8 ± 8.3
Non-lipid lowering medications prescribed (mean ± SD)	3.4 ± 0.2	3.3 ± 0.2	3.4 ± 0.1	3.5 ± 0.2
Medical illnesses (mean ± SD)	5.7 ± 0.3	5.5 ± 0.2	5.4 ± 0.1	5.3 ± 0.2
Hypertension (%)	60	62	59*	49
Diabetes (%)	17	15	11*	3
Current smoker (%)	17	21	23	27
Coronary artery disease (%)	53	47	46	53
Body mass index (mean ± SD)	28.6 ± 4.4	28.5 ± 4.8	28.4 ± 4.3	28.6 ± 4.2

VAMC-Milwaukee = Milwaukee Veterans Affairs Medical Center.
*$P < 0.05$ compared with the 6-week niacin titration schedule.

instructions on what to do if bothersome side effects occurred (see above). Only patients newly started on sequestrants were included in the analysis. The sequestrant initiation schedule and dose were modified in fewer than 5% of patients because of patient or provider preference.

The statin protocol consisted of starting at the usual recommended dose. Adverse events and laboratory abnormalities were monitored. If goal LDL-C was not attained, the dose of statin was doubled.

Differences in baseline characteristics between treatment groups were determined by the unpaired *t* test for continuous variables and by the chi-square test for dichotomous variables (Table 1). The time to drug discontinuance was determined by using survival analysis, and differences between cohorts (short and long niacin titration schedules, high- and low-dose sequestrants) were analyzed for significance by the Lee-Desu statistic.[12] This approach adjusts for the different follow-up periods among patients receiving lipid-lowering therapy.

Table 2. Pretreatment Characteristics of the VAMC-Milwaukee Lipid Clinic Patients Prescribed Niacin, Sequestrants, or Statins (n = 970)

Characteristic	Value
Males (%)	97
Mean age (y)	64 ± 11
Race (% white)	89
Hypertension (%)	59
Diabetes (%)	22
Current smoker (%)	24
Coronary artery disease (%)	46
Body mass index (mean ± SD)	29.1 ± 4.9
Non-lipid lowering medications prescribed (mean ± SD)	3.7 ± 2.4
Medical illnesses (mean ± SD)	5.8 ± 3.0
Alcoholic drinks per week (mean ± SD)	4.05 ± 9.34
Pretreatment blood lipids	
Cholesterol (mg/dL)	274 ± 61
Triglycerides (mg/dL)	320 ± 215
HDL (mg/dL)	40 ± 11
LDL-C (mg/dL)	163 ± 40

HDL = high-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; VAMC-Milwaukee = Milwaukee Veterans Affairs Medical Center.

Two Cox regression analyses were performed to evaluate baseline differences between cohorts, 1 for niacin and 1 for sequestrants. Variables considered in the model for niacin included assignment to the short or long niacin titration schedule, age, alcohol use expressed as the number of drinks weekly, and the presence of hypertension, coronary heart disease, and diabetes. The same variables were utilized in the model constructed for sequestrants, except assignment to high- or low-dose sequestrant therapy was substituted for assignment to a niacin titration schedule.

··· RESULTS ···

Cumulative Discontinuation Rates

A total of 970 patients were included in this study. Patients receiving cholesterol-lowering drug therapy in the lipid clinic were primarily elderly white men; a high proportion had coronary heart disease and hypertension and were overweight (Table 2). The number of patients prescribed niacin, sequestrants, and statins were 564 (58%), 363 (37%), and 648 (67%), respectively (patients receiving combination therapy were counted more than once).

The cumulative discontinuation rates for niacin at 1 and 4 years were 48% and 71%, respectively. Discontinuation rates for sequestrants were higher: 59% and 83% at 1 and 4 years. Statins had the lowest 1- and 4-year discontinuation rates: 10% and 28%. The primary reason for discontinuing niacin and sequestrants was adverse effects. At 1 year, the discontinuation rates for niacin and sequestrants due to symptomatic adverse effects or laboratory abnormalities were 42% and 41%, respectively (Figure 1). For statins, adverse effects requiring drug discontinuation were unusual, occurring in only 4% of patients started on this therapy at 1 year. Adverse effects were the predominant reason for discontinuing therapy with either niacin or sequestrants at 1 year. The proportion of the discontinuation rate attributable to adverse effects was 88% and 69% for niacin and sequestrants, respectively. On the other hand, only 39% of patients who discontinued therapy with a statin did so because of adverse effects.

Low-Dose Sequestrants vs High-Dose Sequestrants

Of the patients taking sequestrants, 29% (n = 106) received low-dose therapy (2 scoops per day) and 63% (n = 229) received high-dose therapy (4 scoops per day); 28 patients received other seques-

trant regimens and were excluded from the analysis. Characteristics including age, incidence of concomitant diseases, and medications did not differ significantly between patients taking low- and high-dose sequestrants (Table 1). Drug discontinuation rates were similar for both sequestrant dosages. The cumulative discontinuation rate at 1 year for 2-scoop compared with 4-scoop sequestrant regimens was 64% vs 60% (Figure 2). This difference was not statistically significant ($P < 0.05$).

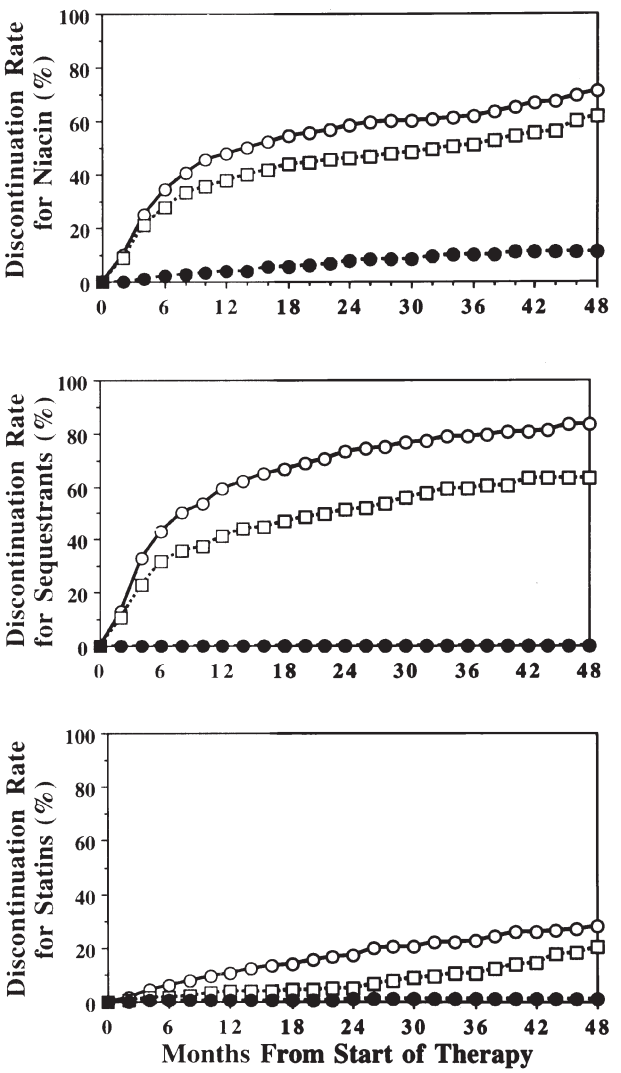
Short and Long Nicotinic Acid Titration Regimen

The 3-week niacin titration schedule was prescribed to 70% (n = 392) of the patients, and the 6- week titration schedule was prescribed to 30% (n = 172). Titration was to the same daily dose in both groups of patients. Patients on the 3-week titration schedule were older and had a higher incidence of non-insulin dependent diabetes compared with those on the 6-week schedule. The slower titration was not associated with a significantly lower discontinuation rate (51% vs 47% at 1 year, $P < 0.05$; Figure 3). The niacin titration schedule was not associated with the niacin discontinuation rate after adjustment for age and the presence of diabetes with Cox regression analysis.

··· DISCUSSION ···

Despite the need to maintain therapy with cholesterol-lowering drugs for long periods, few studies assessing long-term cumulative discontinuation rates of cholesterol-lowering medications have been published. Our results suggest that drug discontinuation rates are high for niacin and sequestrants, even when therapy with these agents is initiated in specialized settings that use substantial resources to improve continuation of and tolerance to therapy. Second, we found that drug discontinuation rates continued to increase even after 1 year of treatment, suggesting that tolerance may not improve with time for many patients taking these drugs. Finally, efforts to improve the acceptability of these agents, including the use of low-dose sequestrants and a slow niacin initiation protocol, were unsuccessful. Very high drug discontinuation rates have been observed for niacin

Figure 1. Drug Discontinuation Rates for Niacin, Sequestrants, and Statins due to All Reasons (Open Circles), Symptomatic Adverse Effects (Open Squares), and Abnormal Laboratory Test Results (Closed Circles).



Number of patients entering each 6-month interval:
Niacin: 564 (0 mo); 331 (6 mo); 233 (12 mo); 180 (18 mo); 146 (24 mo); 121 (30 mo); 95 (36 mo); 63 (42 mo); 44 (48 mo).
Sequestrants: 363 (0 mo); 180 (6 mo); 121 (12 mo); 95 (18 mo); 65 (24 mo); 48 (30 mo); 40 (36 mo); 24 (42 mo); 14 (48 mo).
Statins: 648 (0 mo); 510 (6 mo); 411 (12 mo); 345 (18 mo); 280 (24 mo); 219 (30 mo); 164 (36 mo); 116 (42 mo); 70 (48 mo).

and bile acid sequestrants in primary care settings.[7,8] Andrade et al reported 1-year discontinuation rates of 41% and 46% for sequestrants and niacin, respectively, in health maintenance organizations providing primary care.[8]

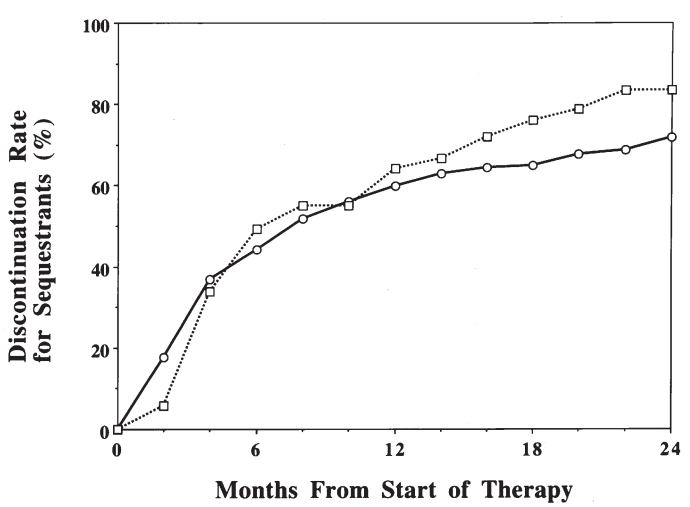
In contrast to most primary care settings, the VAMC-Milwaukee Lipid Clinic utilized specialized resources, including clinical pharmacists and nurse specialists, to evaluate patients receiving lipid-lowering therapy and to encourage them to continue. Poor tolerance to cholesterol-lowering therapy despite these resources suggests that these additional clinic personnel, although trained to counsel patients about cholesterol-lowering drug therapy, may not enhance long-term acceptability of these agents. Supporting this concept is a recent study in which patients with hypercholesterolemia were randomized to receive treatment in either a lipid or a primary care clinic. The lipid clinic utilized a trained nurse-clinician to implement therapy according to protocol. Despite the focused approach to therapy and the use of physician extenders trained to maintain continuation of lipid-lowering drug therapy, there was no improvement in long-term tolerance to therapy among patients assigned to the lipid clinic compared with those assigned to the primary care clinic.[13] In another study, patients who received regular telephone calls to assess and provide counseling for adverse effects after starting sequestrants or niacin had no better drug maintenance rates than did patients randomized not to receive telephone contact.[11] An observational study showing poor long-term tolerance to niacin in another established lipid clinic also was recently reported.[14] These findings indicate that clinics in primary care settings will be unlikely to improve long-term continued use of either niacin or sequestrants by devoting additional attention or resources to this problem.

Because the side effects of niacin and sequestrants are thought to diminish with time as the patient becomes accustomed to therapy,[9] the progressive deterioration in drug discontinuation curves after 1 year was surprising. Approximately 44% of patients taking niacin and 59% of patients taking sequestrants through the first year discontinued therapy during the next 3 years, usually because of adverse effects. Recurrence of severe flushing or pruritus with niacin or constipation with sequestrants was observed in some patients even after years of therapy. Attempts to restart therapy often were unsuccessful. These data suggest that patients taking niacin and sequestrants should be carefully evaluated for adverse effects at each visit, even if they have tolerated therapy well in the past.

Our efforts to improve tolerability to niacin and sequestrants were unsuccessful. Low-dose sequestrant regimens have been shown to be effective in reducing LDL-C,[10,15] and it was reasonable to expect that continued use of and tolerability to sequestrants would improve with lower doses and once-daily dosing. However, patients taking 2 scoops once daily and patients taking 2 scoops twice daily had similar drug discontinuation rates. There are several possible explanations for this finding. First, the adverse effects of sequestrants may not be fully dose dependent, as suggested by a higher adverse effect rate at lower doses observed in a small dose-response study with colestipol.[10] Second, patients receiving two scoops once daily may not have expected significant benefit from treatment and therefore may have been less likely to tolerate milder adverse effects. Third, our patients were older and more ill than patients usually included in sequestrant dose toxicity studies, rendering them more susceptible to adverse effects even at lower doses.

The use of the 6-week niacin titration schedule also did not reduce the drug discontinuation rate. The incidence of flushing and other niacin-related adverse effects was not

Figure 2. Drug Discontinuation Rates for Sequestrants (for All Reasons) at Two Doses: Four Scoops (Open Circles) and Two Scoops (Open Squares).



affected by the titration schedule. The slower titration regimen had no effect on drug discontinuation rates even within the first 6 months of niacin therapy. Patients on either the 3- or 6-week titration schedule had similar baseline characteristics, although those prescribed the 3-week schedule were somewhat older and had a higher prevalence of diabetes. These small differences were unlikely to significantly affect the overall drug discontinuation rate.

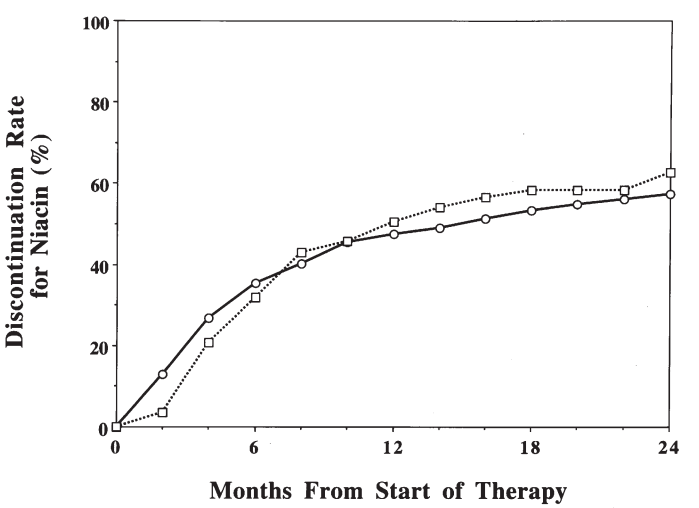
Our study was conducted in a VA lipid clinic, where the preponderance of patients were elderly men with multiple medical problems. We are not aware of data suggesting that women or younger or healthier individuals would have better drug discontinuation rates than our population. In fact, patients at lower risk for coronary artery disease may be less motivated to take cholesterol-lowering agents. Therefore, the poor long-term acceptance of niacin and sequestrants found in our study is likely to be present in other populations. Andrade et al reported similar drug discontinuation rates in men and women in a primary care setting.[8] Because the drug protocols evaluated were sequential, a time-dependent variable (to address changes with time of subjective factors such as provider and/or patient motivation to continue the niacin or sequestrant) could not be evaluated in the statistical model. Because our lipid program strongly emphasized use of both sequestrants and niacin as important cost-effective alternatives to the statins throughout the study period, we do not believe that motivational factors changed appreciably during the study period. However, these subjective factors were not formally assessed in this study.

Because this was an observational study, drug selection bias may have affected our results. For example, lipid clinic clinicians likely avoided niacin and sequestrants in patients with clinical characteristics suggesting poor tolerance, such as multiple concomitant medical conditions or medications. This bias suggests that drug discontinuation rates could be even higher in other settings, particularly if other clinicians did not use similar criteria. However, we believe that drug selection bias was unlikely to have an important effect on our comparison of niacin and sequestrant dosing studies for several reasons. First, only a few patient characteristics have been associated with tolerance to therapy in previous studies.[6] Second, the drug protocols evaluated (high- and low-dose sequestrants, short and long niacin titration schedules) were modified only minimally based on patient clinical characteristics. Third, multivariate analyses performed to adjust for baseline differences between groups did not alter the findings.

Our results have important implications for cholesterol-lowering therapy. First, because of the poor long-term patient acceptance of current niacin or sequestrant preparations, alternatives to their use are necessary. Although initially considered to be appropriate first-line agents for hypercholesterolemia, niacin and sequestrants now are usually considered as adjuncts to initial therapy with a statin.[15] Statins are well tolerated, and long-term drug discontinuation rates remain low in motivated patients, even after 4 years of therapy.[8] If LDL-C goals are not achieved and niacin or sequestrants are prescribed, patients should receive basic information about indications, adverse effects and their treatment, and drug titration schedules.

Despite the application of these conventional strategies, long-term continuation of therapy will likely remain poor even when therapy is implemented by highly trained, dedicated clinic personnel. Therefore, formal trials evaluating alternative approaches to improve long-term continuation rates for niacin and sequestrants are urgently needed. In addition, alternative niacin and sequestrant preparations that may have better long-term discontinuation rates should be evaluated. Although several

Figure 3. Drug Discontinuation Rates for Niacin (for All Reasons) With Two Titration Schedules: 3 Weeks (Open Circles) and 6 Weeks (Open Squares).



slow-release preparations of niacin have been associated with a high rate of adverse effects, reduced efficacy, or both,[14-16] newer preparations may have efficacy similar to that of immediate-release niacin and fewer adverse effects.[17] Newer sequestrant formulations that have a different taste, consistency, and form also may improve drug discontinuation rates.[18,19] Finally, the perceived cost-effectiveness of using agents with low acquisition costs may not be justified if the discontinuation rates are substantially higher than those for the statins.[4] This may be particularly true if the high rate of drug discontinuation leaves many patients without treatment because of poor follow-up with their providers. The direct and indirect costs of vascular disease that are potentially avoidable through cholesterol reduction are quite high. This information should be considered when choosing an initial agent for the management of hypercholesterolemia. However, statins as monotherapy will not achieve LDL-C goals in many patients, particularly those with coronary heart disease and moderate to severe hypercholesterolemia.[4,5] In these patients, the ability to maintain niacin and sequestrant therapy is an important predictor of achieving LDL-C goals.[5] Therefore, research to improve patient acceptance of sequestrants and niacin remains a high priority.

··· CONCLUSION ···

Our findings suggest that long-term tolerability of current preparations of sequestrants and niacin is unlikely to be substantially improved by using either specialized clinic personnel or alterations in dosing schedule. Unless more tolerable niacin and sequestrant formulations become available, reliance on statins as the preferred cholesterol-lowering agents will continue because they have fewer side effects and lower discontinuation rates.

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