NATIONAL LIPID ASSOCIATION

December 13, 2004

Cathy A. Groupe
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
5630 Fishers Lane, Room 1093
Rockville, MD 20857

RE: JOINT MEETING OF THE NON-PRESCRIPTION DRUGS ADVISORY COMMITTEE AND THE ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

Dear Ms. Groupe,

In accordance with the meeting notice for the January 13th and 14th, the National Lipid Association requests to provide oral and written testimony to the committee on January 13, 2004 concerning the question of OTC statin therapy.

The National Lipid Association has just completed a year long study of evidence relevant to the availability of over the counter statin therapies in the United States. This information is published in a monograph released in December 2004 entitled "***Should Consumers Be Given an OTC Statin Option to Help Reduce Their CHD Risk?*** **Exploring the Evidence**".

This document provides a review of the data, key survey findings of consumers, physicians and other allied health professionals, and formalizes public comment received by the NLA from other organizations with relevant input regarding the issue of statin therapies as an OTC. We would like to include a copy of this monograph for all committee members in advance of the meeting if possible.

Further, we would ask that James McKenney, Pharm.D, Chairman of our Consumer Affairs Committee be allowed not more than 10 minutes to address the key findings of the committee. We would also be pleased to provide copies of our surveys. Please provide us with the proper procedures for distribution. Dr. McKenney's direct contact information is:

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It is our desire to present information and data collected by our organization, but not to provide an opinion regarding the OTC question of statin therapy. If we are allowed this opportunity to present, please direct correspondence to either our headquarters office or to Dr. McKenney directly.

The NLA appreciates the opportunity to provide information and look forward to your response.

Sincerely,

Christopher R. Seymour
Executive Director

Cc: Dr. McKenney
NLA Board of Directors

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Should Consumers Be Given an OTC-Statin Option to Help Reduce Their CHD Risk?

Exploring the Evidence

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On behalf of the National Lipid Association (NLA), I wish to thank the Consumer Affairs Committee members for their hard work and recognize the organizations listed for their open and cooperative facilitation of advisory board meetings and symposium programs. I especially wish to thank the National Consumers League for allowing the NLA to present data from its consumer survey, and the cooperative efforts of the American Pharmacists Association.

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Consumer Affairs Committee

The members of the committee are as follows:

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American Pharmacists Association
http://www.aphanet.org

National Consumers League
http://natlconsumersleague.org

Preventive Cardiovascular Nurses Association
http://www.pcna.net

Sports, Cardiovascular and Wellness Nutritionists
http://www.scandpg.org

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The National Lipid Association would like to thank the following supporters who provided unrestricted educational grants in support of this project:

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*** Member of the Consumer Affairs Committee until August 2004**

Should Consumers Be Given an OTC-Statin Option to Help Reduce Their CHD Risk?

Exploring the Evidence

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Discussion of Unlabeled Uses of Commercial Products

The authors of this monograph will discuss the potential use of statin therapy in an over-the-counter (OTC) setting. Although unapproved for OTC use, two pharmacologic statins (lovastatin and pravastatin) have been considered for OTC distribution and therefore are discussed in this monograph.

Disclosure of Affiliations and Significant Relationships

The authors of this monograph disclose the following:

Eric P. Brass, MD, PhD

Dr. Brass has received honoraria related to formal advisory activities from Johnson & Johnson • Merck.

W. Virgil Brown, MD

Dr. Brown has received honoraria related to speakers' bureau activities from Merck & Co. and Merck/Schering-Plough. He has also received honoraria related to formal advisory activities from Merck & Co., Bristol-Myers Squibb, and Merck/Schering-Plough.

Jerome D. Cohen, MD

Dr. Cohen has received honoraria related to formal advisory activities from Johnson & Johnson • Merck, Pfizer Inc, and Wyeth. He has also received honoraria related to speakers' bureau activities from Abbott Laboratories, Bristol-Myers Squibb, Merck & Co., Pfizer Inc, and Wyeth.

Janet P. Engle, PharmD, FAPhA

Dr. Engle has disclosed that she has no significant relationships with the grantor or any other commercial company whose products and services are discussed in her article.

James M. McKenney, PharmD

Dr. McKenney has received honoraria related to speakers' bureau activities from AstraZeneca LP, Kos Pharmaceuticals, Merck & Co., and Pfizer Inc. He has also received grant support related to research activities from AstraZeneca LP, GlaxoSmithKline, Kos Pharmaceuticals, LipoScience, Merck & Co., Pfizer Inc, Schering-Plough, and Takeda. He has also been a consultant to AstraZeneca LP, Kos Pharmaceuticals, Merck & Co., Pfizer Inc, and Sankyo Pharma Inc.

INTRODUCTION

James M. McKenney, PharmD

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Approval of one or more of the HMG COA reductase inhibitors (statins) for sale over-the-counter (OTC) would mark a major turning point in OTC-based therapies. To date, most OTC medications have been used for short-term therapy and symptom relief. An OTC statin would be used for long-term therapy and prevention of atherosclerosis-related events in individuals without symptoms. Currently, there are no OTC medications available to the consumer for lipid management, although there are many nutritional supplements claiming cholesterol-lowering efficacy (eg, red yeast rice, niacin, flaxseed oil, garlic, fish oils, soy protein, fibers, gums, etc.). Unlike an OTC product, nutritional supplements do not have to demonstrate efficacy and safety to the Food and Drug Administration (FDA), nor are they required to adhere to "good manufacturing practices" to assure product quality. And so, approval of an OTC statin would mark a turning point in OTC-based therapies in that it would provide the consumer with the first FDA-approved product for cholesterol lowering.

Today, statins are available only by prescription to reduce a patient's coronary heart disease (CHD) risk. The decision to recommend a statin to a patient is made in a medical setting by a trained health professional with knowledge of the disease and its treatment. Guidelines have been developed by experts assembled by the National Institutes of Health (NIH) and leading health organizations to help health professionals make good, evidence-based decisions relative to lipid management and CHD risk-reduction. Those of us who work with patients every day know just how complex these decisions can be. They involve, among other things, an assessment of the patient's future risk of a coronary event, concurrent illnesses and therapies, and personal motivation and receptivity to treatment. When it comes to decisions to initiate lipid-altering drug therapy, we must consider contraindications and potentially interacting drugs, the dose most likely to achieve treatment goals, and how to minimize, monitor, and manage side effects.

No wonder, when faced with the prospect of an OTC-statin option, we ask: How could this ever work? How can the patient ever do what we do and do it as well as we do every day? The proposition immediately seems totally ridiculous.

And yet, we have to admit, we are not getting the job done. Everywhere we look, there is evidence that *millions* of people who have a substantial risk of a future coronary or cerebrovascular event are not being given the benefit of treatment. Less than half of those with a moderate to high CHD risk don't even know it. Less than half of those who know it are being treated. And less than half of those who are being treated are achieving treatment goals. This evidence forces us to look at the issue and search for new solutions.

One solution that is at least worth considering is broadly defined as the public health model (in contrast to the medical model), in which the consumer takes more responsibility for his or her own health care. The concept is that the consumer who has a moderate CHD risk (ie, a 5% to 15% 10-year risk) and who may not need the intensity of physician-directed lipid management, can combine lifestyle modification and a low-dose OTC statin to carry out an efficacious risk-reduction therapy. This OTC-based therapy could be guided by the patient's primary physician or by other health professionals (eg, the pharmacist), or the patient could choose to carry it out alone. If treatment goals are not achieved, consumers would be instructed (via package labeling) to move up to more aggressive therapy with their primary physician. There is evidence that many consumers are interested in and capable of being more involved in managing their personal health care. If this happens, more people could receive effective CHD risk-reduction therapy.

But is this a good idea? Will an OTC statin really increase the number of patients on effective CHD risk-reducing treatments and will the prevalence of CHD events decline? Can consumers initiate statin therapy effectively and safely, or will they get themselves in trouble or miss more effective treatment offered by a physician or other health professional? Can consumers avoid interacting drugs, monitor their cholesterol levels to assure adequate control, and identify and manage associated side effects? And how can the consumer be properly supported to carry out this treatment successfully? The only way to answer these and the myriad other questions about this issue is to examine the evidence. Answers should not be based on impression and opinion, but rather, evidence.

This is where the National Lipid Association (NLA) comes in. It has undertaken the task of identifying the critical evidence that relates to this topic and has archived what it has found in this monograph. By doing so, the NLA hopes to provide the basis for productive and informed discussions and debates between health professionals regarding the wisdom of having an OTC-statin option for consumers in the United States. The NLA has been careful to take no position on this subject and does not anticipate doing so in the future. It has tried to be dispassionate, unbiased, and totally balanced in its collection and presentation of the available data. The reader can be the judge of whether it has succeeded. And if it has succeeded, the evidence should take each of us to a final conclusion on the topic. Even though some questions inevitably will remain, most should be answered and lead us to a determination of whether this is a good idea.

The chapters that follow review the key evidence the NLA has found that relates to the debate over the OTC-statin option. In Chapter 1, "The Current State of Cardiovascular Disease Risk-Reduction in the US," Virgil Brown, MD puts into perspective the enormity of the problem of CVD in the US, the risk factors of CVD, and treatments currently employed to reduce elevated LDL-C, and poses questions for the reader to consider about consumer behavior.

In Chapter 2, "Considerations for Approval of Prescription Drugs for Over-the-Counter Sale," Eric Brass, MD reviews the criteria for and regulatory process of transferring a drug from prescription-only status to the OTC category and focuses attention on the strengths and weaknesses inherent in label comprehension and consumer-use studies.

In Chapter 3, "A Survey of the Attitudes, Beliefs, and Perceptions of Consumers Regarding CHD and High Blood Cholesterol," the results of consumer survey research sponsored by the NLA and the National Consumers League are presented. Also, key questions raised by physicians, pharmacists, nurses, and nutritionists who attended one of the NLA key opinion-leader roundtables and larger town hall sessions are listed.

Jerome Cohen, MD is author of arguably one of the most important chapters, Chapter 4, "Overview of Consumer-Use Research," which reviews three consumer-use studies that shed light on and raise issues about human behavior in managing the use of an OTC statin in an OTC-like environment.

In the fifth and last chapter, "Value-Added Services Provided by Pharmacists in an Environment of Over-the-Counter Statins," Janet Engle, PharmD assesses the potential for a Pharmacy-Care OTC category and the expanded role pharmacists may play in collaborating with primary physicians to support consumer adherence.

This monograph is intended to spur healthy debate, the result of which should advance improved management of CHD risk in our country. The NLA will continue to work to increase our understanding of lipid management and human behavior through evidence-based research and ongoing dialogue. ■

CHAPTER 1: The Current State of Cardiovascular Disease Risk-Reduction in the US

W. Virgil Brown, MD

THE MAGNITUDE OF THE CARDIOVASCULAR DISEASE PROBLEM IN THE US

As we begin 2005, cardiovascular disease (CVD) continues to be the single largest killer of American men and women. CVD is responsible for more deaths annually than cancer, respiratory diseases, accidents, diabetes mellitus, and influenza and pneumonia combined.[1] For men, the death rate (adjusted for age) had shown a 20-year decline. Progress seems to have ended, however, and growth in cardiovascular death rates may be on the horizon. For women, there has been a lack of progress and new concerns that an increased CVD death rate may be impending due to the growing incidence of weight gain and obesity *(Figure 1)*.

Contrary to common belief, a diagnosis of cardiovascular disease does not discriminate significantly by gender. When one includes the most common diagnosis, high blood pressure, a large segment of both men and women in America are affected. In middle age (ages 44 to 54), CVD affects slightly more men than women (34% of men, 29% of women), but becomes equal in prevalence among older men and women (ages 65 to 74), and is dominant in women over age 75 (79%.) Similarly, while the risk of CVD increases with age, about one-third (32%) of CVD-related deaths occur in men and women under age 75.[1]

Of total deaths reported in the US in 2001, CVD was the cause of more than 38 percent – nearly 1.4 million people. Of these, 150,000 occurred in those under 65

Leading Causes of Death for US Men and Women, 2001

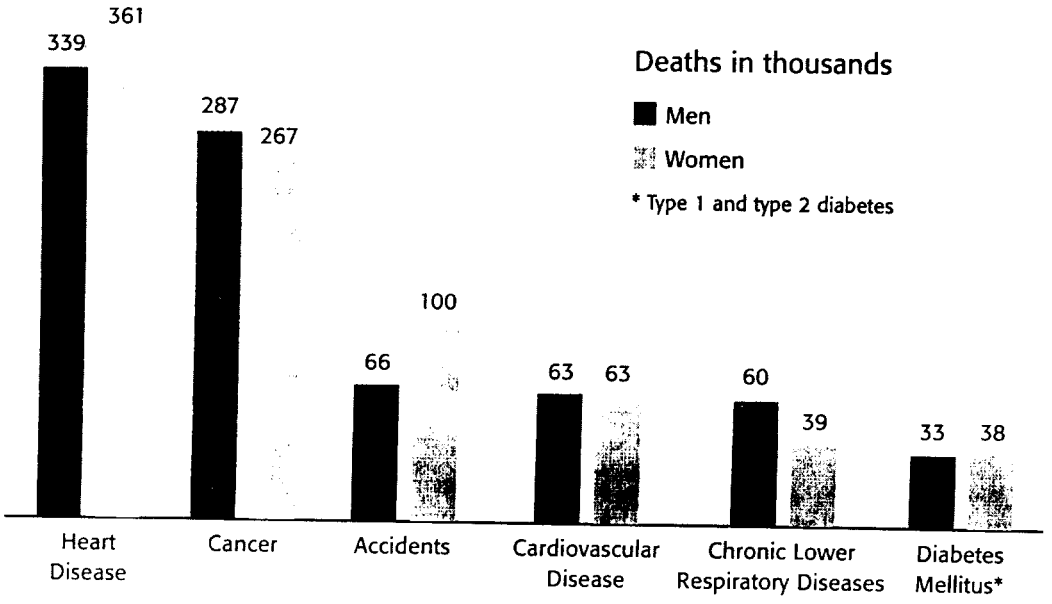

Figure 1

years of age. Disease in the coronary arteries leads to over 500,000 deaths per year, and over 13 million Americans are living with coronary heart disease (CHD). In people 40 years and older, the lifetime risk of developing CHD is almost 50 percent for men and 33 percent for women. The probability of developing and dying of CVD increases with age, and the aging population will provide a tremendous challenge to our efforts in achieving effective prevention. The US Administration on Aging estimates that, in 2000, 35 million Americans were over age 65, by 2020, that number will increase to 55 million and, by 2040, 80 million people in this country will have passed that age *(Figure 2)*.

Stroke and heart attack affect all races, causing more death and disability among Americans of African than of European ancestry. Hispanics, East Asians, and particularly those from South Asia (India, Pakistan, etc.) are suffering rapidly increasing rates of CVD.

The financial cost to individuals and society is also of great concern. The American Heart Association estimates that in 2004 the total cost of cardiovascular disease for medical expenses and lost productivity will be $368.4 billion *(Table 1)*.

Reducing the incidence of CVD not only lessens individual suffering but eases the considerable economic burden carried by society.

Key CVD Statistics

- CVD is the single largest killer of American men and women.
- The 20-year decline in CVD death is slowing and even may be growing.
- The prevalence of CVD increases with age (79% among women over age 75) and will reach enormous proportions when, by 2040, the number of Americans over 65 years will increase from 35 million to 80 million.
- Deaths for CVD number 1.4 million each year, of which, CHD deaths account for 500,000.
- The prevalence of CVD is disproportionate among African-Americans, Hispanic Americans and South Asian Americans.
- The direct and indirect cost of CVD in the US is $368.4 billion.

Figure 2

Direct and Indirect Health Care Costs of CVD in 2004

Direct costs of $226.7 billion	
• Hospital	$101.7
• Physicians/Other professionals	$33.4
• Nursing home	$38.1
• Home health care	$10.3
• Drugs/Med durables	$43.3
Indirect costs of $141.7 billion	
• Lost productivity/Morbidity	$33.6
• Lost productivity/Mortality	$108.1

Table 1

REDUCING THE RISK OF CORONARY HEART DISEASE (CHD)

Major risk factors for CHD are well documented but many provide opportunity for prevention. These include hypercholesterolemia, hypertension, smoking, atherogenic diet, excess weight/obesity, and sedentary lifestyle. Others such as insulin resistance, age, and genetic predisposition/family history can be recognized and used as guides in developing management strategies. Research confirms that elevated low-density lipoprotein cholesterol (LDL-C) is a chief cause of CHD,[2] and that lowering it is the primary avenue to preventing and reducing the risk for CHD.[3-4] The benefits are impressive: A reduction of 1% in LDL-C produces about a 1% reduction in "hard" CHD events (nonfatal MI and sudden cardiac death) with five years of treatment. A 10% decrease in LDL-C can result in more than a 30% reduction in the incidence of CHD over a lifetime.

Significant efforts to lower LDL-C, through education programs aimed at physicians and the general public, have had positive effects: Studies conducted by the National Health and Nutrition Examination Survey (NHANES) in 1976-1980 and 1999-2000, demonstrate an approximate drop of 10mg/dL in the average blood cholesterol level among Americans (ie, from 215 mg/dL to 203 mg/dL). However, the rate of decline appears to be slowing.[5] Furthermore, more than 50% of the patients who have been identified as having high LDL-C and have been placed on lipid-lowering drug treatments withdraw from therapy within one year. The growth in the prevalence of obesity and of type 2 diabetes suggests that the admonition to

keep calories in balance with our energy expenditure has not been heard and certainly not practiced by the public. These factors raise the risk of CVD and increase the number of people who should be considered for lipid-lowering therapy. The need for renewed activity to prevent, detect, and treat elevated levels of LDL-C to reduce CHD is evident.

TREATING ELEVATED LDL-C

Therapeutic lifestyle changes (TLC) are the foundation to lowering LDL-C. A healthy diet (ie, restricted intake of saturated and trans fats and cholesterol-rich foods), regular physical activity, healthy weight maintenance, cessation of smoking, and controlling diabetes all can have very significant effects on the incidence of heart attack and stroke as underscored by the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP). The NCEP ATP III recommends that therapeutic lifestyle changes be initiated when LDL-C is greater than 100mg/dL.

When TLC are insufficient to reach LDL-C goals, drug therapy is advised. Treatment guidelines to aid the health care provider were established in 1987 by NCEP ATP I, and revised and updated in 1993 and again in 2001. In July 2004, the NCEP published a statement based on a review of recent studies and provided additional interpretation and guidance in the use of the 2001 ATP III guidelines.[6] The National Heart, Lung and Blood Institute, the American College of Cardiology Foundation, and the American Heart Association have endorsed this statement. In sum, the guidelines called for the following *(Table 2)*:

- For high-risk patients (those with CHD, a CHD risk-equivalent condition, or two or more risk factors, and an estimated 10-year risk for a coronary event of greater than 20%), LDL-C should be <100mg/dL and consideration may be given to lowering LDL-C to an optional goal of <70mg/dL in patients with very-high risk.

- For moderately high-risk patients (two or more risk factors and a 10-year risk of 10% to 20%), LDL-C should be <130mg/dL, and consideration may be given to lowering it to an optional goal of< 100 mg/dL.

Treatment for lesser risk patients remained unchanged as follows:

- For moderate-risk patients (two or more risk factors and a 10-year risk of <10 percent), LDL-C should be <130/mg/dL.

- For low-risk patients (0-1 risk factor), LDL-C should be <160mg/dL.

These guidelines define the goal for LDL-C and represent the upper limits of acceptable values, not necessarily the targets of treatment. The values should remain less than those suggested for each risk group.

Prescription drugs are available (ie, HMG CoA reductase inhibitors [statins], bile acid sequestrants, nicotinic acid, cholesterol absorption inhibitors, and fibric acids) for managing elevated lipoprotein concentrations. The statin group of drugs has been the subject of the largest studies

LDL-C Treatment Goals (ATP III) [6]

Risk Category	LDL-C Goal	Consider Drug Therapy
High risk CHD or CHD risk equivalent	<100mg/dL (optional goal <70mg/dL)	LDL-C ≥100mg/dL (<100mg/dL: consider drug options)
Moderately high risk ≥2 risk factors (10-year CHD risk 10% to 20%)	<130mg/dL (optional goal <100mg/dL)	LDL-C >130mg/dL (100-129mg/dL: consider drug options)
Moderate risk ≥2 risk factors (10-year CHD risk < 10%)	<130mg/dL	LDL-C >160mg/dL
Low risk 0 to 1 risk factor	<160mg/dL	LDL-C >190mg/dL (160-189mg/dL: drug optional)

Table 2

Major Endpoint Lipid Trials

Trial	Drug	↓ LDL-C	LDL-C ▲ (mg/dL)	Placebo *CHD Rate	**CHD Risk-Reduction
Patients with Multiple CHD Risk Factors					
WOSCOPS[7]	Pravastatin	-26%	192-142	14.9%	-31%
TexCAPS/AFCAPS[8]	Lovastatin	-25%	150-115	3.0%	-40%
ASCOT[10]	Atorvastatin	-31%	132-85	4.7%	***-50%
Patients with CHD and CHD Risk Equivalent					
4S[3]	Simvastatin	-35%	188-117	21.8%	-34%
LIPID[4]	Pravastatin	-25%	150-112	15.9%	-24%
CARE[11]	Pravastatin	-32%	139-98	13.2%	-24%
HPS[9]	Simvastatin	-32%	131-89	11.8%	-24%
PROSPER[12]	Pravastatin	-34%	147-97	19.1%	-30%

*5 years; **Nonfatal MI or CHD death; ***Extrapolated

Table 3

with the greatest periods of observation, many five years or longer in duration. As a result, we have documented evidence of safety and efficacy in the reduction of LDL-C and of non-HDL-C. Most importantly, the incidence of various vascular-disease-related events such as stroke and myocardial infarction (MI), as well as cardiovascular death, has been reduced from 20% to 40% or more. These drugs are now considered first-line therapy in the effort to achieve the various targets set for LDL-C. Curiously, during the last 20 years we have seen a developing market of relatively untested, non-prescription, nutritional supplement preparations with putative cholesterol-lowering effects. These now include various niacin preparations, vegetable fiber and plant sterols and stanols, garlic preparations, and even crude fungal products that apparently contain varying amounts of statins.

EVIDENCE OF STATIN EFFECTIVENESS

In the past decade, several large, randomized, long-term, and controlled clinical trials, for both primary and secondary prevention were completed among a variety of patient groups. They demonstrate that statins are effective in reducing cardiovascular events and mortality by lowering LDL-C *(Table 3)*.

Primary Prevention (Moderate-Risk Patients)

Over 40,000 patients have been included in long-term placebo-controlled studies (three to six years) demonstrating that statin therapy reduces the first myocardial infarction, coronary death, stroke, and other major vascular endpoints. These include:

- The West of Scotland Coronary Prevention Study (WOSCOPS) examined men, ages 45 to 64, with elevated cholesterol levels and no history of MI. Among patients treated with pravastatin 40mg/day, there was a decrease of 20% in total cholesterol, a 26% reduction in LDL-C, and a 31% decrease in MI.[7]

- The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) evaluated men and women with low HDL-C but normal or mildly elevated total and LDL cholesterol and no cardiovascular disease. Patients treated with lovastatin had a 25% reduction in LDL-C and a 37% decrease in the incidence of first-time acute major coronary events (defined as MI, unstable angina, or sudden death).[8]

- The MRC/BHF Heart Protection Study (HPS) is the largest trial to date of a cholesterol-lowering drug used to treat people at high risk for atherosclerosis. The study followed 20,536 men

and women, aged 40 to 80 years, with coronary disease, other occlusive arterial disease, or diabetes. Among patients treated with simvastatin 40 mg/day, there was a 12% decrease in total mortality, an 18% reduction in coronary mortality, and the rates of MI and stroke were reduced by 24% irrespective of cholesterol level. [9]

• The Anglo-Scandinavian Cardiac Outcomes Trial - Lipid-Lowering Arm (ASCOT-LLA) studied patients with hypertension and at least three other risk factors. Among patients treated with atorvastatin 10mg/day, there was a 36% reduction in non-fatal MI and fatal CHD and a 27% reduction in the incidence of non-fatal and fatal stroke. [10]

Secondary Prevention (High-Risk Patients)

Similar studies of patients with known heart disease or a CHD-risk equivalent have also shown impressive benefit in reducing similar endpoints when placebo treatment was compared to a variety of statin preparations. For example:

• The Scandinavian Simvastatin Survival Study (4S) examined patients with cardiovascular disease and elevated cholesterol levels. Patients treated with 20 mg to 40mg simvastatin experienced a 25% reduction in total cholesterol, a 35% reduction in LDL-C, a 42% reduction in relative risk of coronary mortality, and a 30% reduction in relative risk of death from any cause. [3]

• The Cholesterol and Recurrent Events (CARE) Study followed patients with a history of myocardial infarction but "average" levels of cholesterol (mean LDL-C of 139 mg/dL). Among men and women treated with 40mg pravastatin daily, LDL-C was reduced by 32% and recurrent MI and coronary death were reduced by 24%. [11]

• The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study followed patients with CHD to determine the effects of 40mg pravastatin daily on reducing mortality. Among pravastatin-treated patients, there was a 24% reduced risk of death from CHD and a 22% reduced risk of overall mortality. [4]

• Heart Protection Study (HPS) studied people at high risk for CVD in the United Kingdom. Daily dose of 40mg simvastatin resulted in a reduction by 27% in nonfatal MI and coronary death. [9]

• The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) followed older men and women with a history of vascular disease or high-risk factors for vascular disease. Those treated with 40 mg pravastatin daily experienced a 19% reduction in coronary events, a 24% reduction in coronary mortality, and a 15% relative risk-reduction in the end points of death or suspected death from CHD, nonfatal MI, or fatal or nonfatal stroke. [12]

EVIDENCE OF STATIN SAFETY

The overall safety of statins, as a class, has been well studied in such trials as those described above and statins are considered to be extremely safe and well tolerated in the vast majority of patients.

The most serious adverse events documented with statin use is muscle toxicity including myopathy (defined as muscle pain or weakness + creatine phosphokinase (CPK) >10 times the ULN) and rhabdomyolysis (myopathy with kidney impairment); this occurs at a rate of one to 10 in 10,000 (0.01% to 0.1%) for myopathy to two to 50 in 100,000 (0.002% to 0.05%) for rhabdomyloysis. These problems are reversible with dose reduction or withdrawal of the statin. Fatal rhabdomyolysis has been detected in less than one in 1 million people and rarely with currently marketed statins. There are no well-documented cases of liver failure from statin therapy. Nevertheless, statins have been associated with rare cases of hepatocellular toxicity and jaundice. [13]

Contraindications for statins include hypersensitivity, active liver disease or unexplained persistent elevations in serum transaminases, and pregnancy and lactation. In addition, there is a potential for interaction between statins, particularly those metabolized by P450 3A4 enzymes, with other drugs which inhibit or utilize this same metabolic pathway, including macrolide antibiotics, various azole anti-fungal agents, protease inhibitors, fibrates, cyclosporins, and other agents.

In AFCAPS/TexCAPS[8], a primary prevention trial in which lovastatin 20mg to 40mg daily (one of the statins being proposed at a 20mg dose for OTC status) was compared with a placebo in 6,600 relatively healthy individuals, rhabdomyolysis actually occurred in two placebo patients and one lovastatin patient. Other serious and drug-related adverse events – including myopathy and discontinuation rates secondary to muscle pain or weakness – were equivalent to placebo.

AFCAPS/TexCAPS

Liver and Muscle Findings

	Lovastatin (n=3,304)	Placebo (n=3,301)
LFT >3 xs ULN on consecutive visits	18 (0.6%)	11 (0.3%)
Liver failure	0	0
Any muscle sx	2,053 (62%)	1,971 (60%)
Statin DCed due to myalgia	11 (0.3%)	9 (0.3%)
CPK >10 xs ULN	21 (0.6%)	21 (0.6%)
Myositis (CPK↑ + Sx)	0	0
Rhabdomyolysis	1 (0.03%)	2 (0.06%)

Table 4

Rates of liver enzyme elevation greater than three times the upper limit of normal were not significantly different between the lovastatin and placebo groups. Other laboratory abnormalities, such as increased creatine phosphokinase, occurred equally in the placebo and lovastatin-treated group *(Table 4)*.[8]

Evaluation of pravastatin 40mg daily (another statin being proposed at a 20mg dose for OTC status) in approximately 10,000 individuals, who participated in the LIPID[4], CARE[11], and WOSCOPS[7] studies, revealed no cases of rhabdomyolysis and rare cases of increases in CPK greater than 10 times the ULN (without myalgias) (0.2% to 0.6%) with five years of treatment.

Many lipid specialists consider statins to be as effective and as safe as an adult aspirin. Both products have the potential for reducing cardiovascular events by 15% to 30%. Aspirin increases the risk of major bleeding complications by 69%.[14] The estimated rates of major gastrointestinal bleeding episodes are approximately two to four per 1,000 middle-aged persons and four to 12 per 1,000 older persons given aspirin for five years. For 1,000 patients with a 10% risk for CHD events over 10 years, aspirin would cause zero to two hemorrhagic strokes and two to four major gastrointestinal bleeding events over that five-year time period.[15] The rate of serious muscle and liver toxicity is no greater and probably lower with statin therapy.

THE CHALLENGE

There is general agreement that, when it comes to LDL-C, lower is better, and that statins are a safe and effective means to decrease LDL-C levels when TLC alone are inadequate. Furthermore, the longer the treatment is sustained, the greater the long-term benefit relative to those untreated with similar risk factors. The conundrum is that in the US, there is a sizable treatment gap between individuals who have a moderate to high risk of CVD and need LDL-C lowering therapy, and those receiving effective treatment.[16-18] Furthermore, many who have been assessed and were put on a statin treatment are no longer taking it.

How should we address this problem? We can try to provide more and better dietary and exercise advice and medical treatment, including more screening, aggressive treatment, and monitoring. We can mount more medical education programs and try to increase public education. Of course, we can advocate better drugs. But in many respects, this is simply more of the same. All of these approaches have been and are being tried and yet we are losing ground in our effort to reduce this number-one killer of Americans.

Another option that we can consider is giving consumers more responsibility for health care by encouraging moderate-risk consumers (ie, 5% to 15% 10-year risk) to utilize lifestyle change with a low dose of an OTC statin to help reduce their LDL-C. Currently, through the medical model and prescription lipid-lowering lifestyle and drug therapy, we are attempting to reduce the burden of CHD in our country by focusing on the 40 million Americans at highest risk. The proposal for an OTC-statin option views CHD risk-reduction through the eyes of a public health model and focuses on moderate-risk patients (eg, 5% to 15% 10-year risk) and reducing their risk of CHD through self-directed lifestyle and low-dose OTC therapies *(Figure 3)*. Will this work? Will consumers appropriately choose and carry out this therapy and can they implement it safely and effectively? The idea is at least worth considering. Given the critical challenge that CVD poses to the health of the American public, we should at least consider the benefits and drawbacks of an OTC-statin option.

For this to be effective, education programs targeted to health care professionals and the general public would be critical.

8

Two Views of the Utility of an OTC Statin

The bell curve demonstrates that the current US medical model focuses prescription statin use on patients with a 10% or greater risk of CHD in the next 10 years. An OTC-statin option would seek to reduce CHD risk through a public health model by encouraging self-care with lifestyle modification and low-dose OTC-statin therapy by patients with a moderate 10-year CHD risk (eg, 5% to 15%).

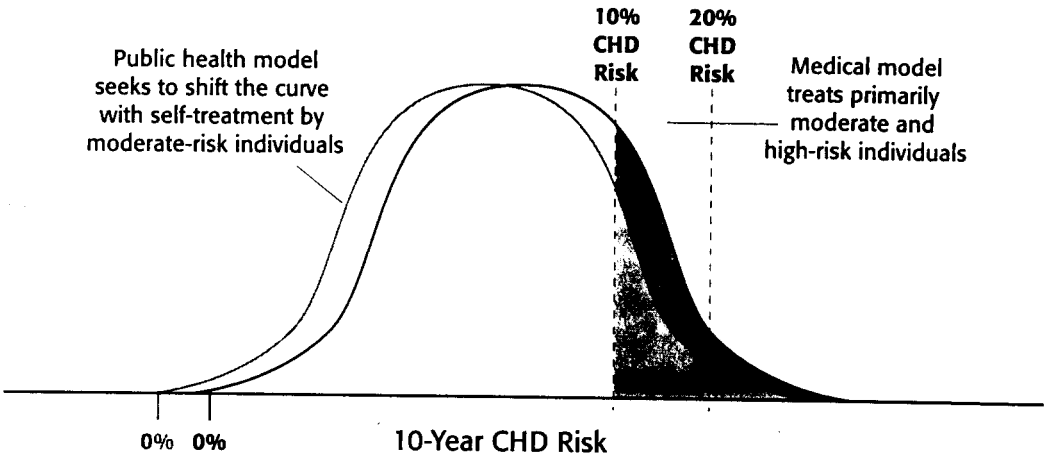

Figure 3

SUMMARY

Arteriosclerotic vascular disease remains our most common serious illness and is showing signs of resisting the current attacks on causative risk factors. LDL-C reduction has proven to be an effective strategy if successfully applied. A very large database has been accumulated regarding the use of statins under a physician's guidance providing reassurance regarding safety and effectiveness. There are also data on models of the OTC provision of these drugs that need careful review. These data and the vision and concern of medical experts need to be brought together in an active discussion of the potential benefits and possible pitfalls of adding this new approach to available treatments. ■

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CHAPTER 2: Considerations for Approval of Prescription Drugs for Over-the-Counter Sale

Eric P. Brass, MD, PhD

11

In the United States, some drugs require a prescription for purchase while others can be readily obtained by the public in a variety of venues without prescription. This wide availability without prescription is termed over-the-counter (OTC). This chapter will briefly review the reasons some drugs are available only by prescription, the health care issues that differentiate drug use in an OTC setting from prescription-based therapy, and the data on which the Food and Drug Administration (FDA) assesses whether OTC availability of a drug is appropriate.

Why are Some Drugs Available Only by Prescription?

The FDA's regulation of drugs is based on enabling legislation passed by Congress *(Figure 1)*. The Food and Cosmetic Act of 1938, which established the requirements for new drugs to be safe, and the 1951 Durham-Humphrey Amendment, which specified differences between prescription and OTC drugs, are of particular importance. Collectively, the legislation provides the FDA the authority to regulate OTC drugs to ensure that they are safe and effective as labeled. Further, these laws specify that a drug should be limited to prescription availability if it is habit-forming, requires professional supervision for use, or was approved through a New Drug Application (NDA) that specifies the requirement for professional supervision. The latter is important as it also provides the major route for switching a prescription drug to OTC status through the filing by the manufacturer of a new NDA requesting OTC availability and the associated change in product labeling.

An NDA to make a drug available OTC is reviewed by the FDA with a focus on the safety and efficacy of the drug if used without professional supervision. The issues related to use without professional supervision can be broadly considered as related to the consumer's ability to recognize and self-diagnose the condition for which the drug is intended, the ability of the OTC drug label to communicate all of the information that the consumer requires to use the drug safely and effectively, and the ability of the consumer to use this information to make appropriate use/don't use decisions and self-manage the condition if OTC drug therapy is used. These points are discussed in more detail below.

From the Patient's Perspective, How Does OTC Drug Use Differ from Prescription-Based Access?

For many consumers, having a drug available OTC removes substantive barriers to accessing safe and effective drugs, and thus may yield public health benefits. The switch of a drug from prescription to OTC status fundamentally changes the health care dynamic, removing the health care professional from the center of the decision and management process and

OTC Drugs

Legislative Foundation

- FDA's authority to regulate OTC drugs to ensure safety and efficacy is based on Congressional legislation
- 1951 Durham-Humphrey Amendment to Food, Drug and Cosmetic Act
  - Habit-forming drugs are available only by prescription
  - If a drug can be used safely only under the supervision of a licensed practitioner, then it must be by prescription only
  - If an approved New Drug Application (NDA) specifies professional supervision, then it must be by prescription only

Status may be subsequently changed to OTC from prescription based on new NDA establishing safety and efficacy if used OTC.

Figure 1

OTC Appropriateness

What is being asked of the consumer?

- Consumer must be able to recognize a symptom, condition or disease for which OTC therapy may be appropriate
- Product label allows consumer to recognize whether drug's indication and consumer's condition match
- Label information prevents consumer use if symptom has alternative etiology or severity of condition requires professional input to avoid adverse outcome

Figure 2

placing the consumer in this role. This implicitly places enormous responsibility on the consumer and forces a series of decisions onto the consumer that are integral to self-care *(Figure 2)*.

At the outset, consumers must recognize that they have a symptom or condition for which OTC therapy may be appropriate. Next, guided by their own knowledge and OTC drug labels, consumers identify a specific OTC drug for their condition. However, guided by the label information, consumers may also need to avoid using an OTC drug if their symptoms could reflect a more serious medical condition (eg, they are experiencing myocardial infarction rather than heartburn) or if the symptoms are sufficiently severe to require more intensive evaluation and treatment. In these situations, timely professional care may be required to avoid adverse outcomes. Additionally, consumers may need to avoid a specific OTC therapy if their use of other medications or their medical history would result in an increased risk if the OTC drug is used *(Figure 3)*.

Once consumers decide to use the OTC drug, they must use the right dose, at the right dosing interval, for the duration of therapy based on the label directions. They must be able to self-manage the therapy once initiated, including recognition of symptoms that may represent adverse drug effects or worsening of the underlying condition, and self-triage appropriately. Optimally, consumers will use the OTC drug as an adjunct to their integrated health care, and not as a substitute for otherwise indicated medical care.

Most importantly, these various responsibilities must be met by the typical American consumer who experiences the condition and may seek treatment using OTC drugs. This places significant limitations on expectations as to what can be achieved through label materials due to heterogeneity in the American consumer population.

On a practical basis, these considerations have resulted in most OTC drugs being indicated for self-limited, symptomatic conditions. Further, drugs are often approved for OTC status on the basis of their ease of use, absence of need for dose adjustments (except for children), low risk of clinically significant drug interactions, and safety profiles that are well understood and acceptable for wide exposure.

How Does the FDA Assess Whether OTC Availability of a Specific Drug is Appropriate?

The above considerations define the basis for FDA decision making for a prescription-to-OTC switch. In most cases, the request for a change in status will be made to the FDA by the drug's manufacturer in the form of an NDA. The NDA will incorporate, and the FDA will review, a broad spectrum of data germane to the decision. This will include efficacy and safety data from the original prescription NDA; experience with the drug since its prescription approval, including post-marketing surveillance and published research;

OTC Appropriateness

What is being asked of the consumer?

- Must not use drug if contraindications exist
- Use the product at proper dose, at proper intervals, for proper duration of treatment
- Use OTC drug in context of other appropriate health care measures for underlying indication
- Self-monitor therapy for efficacy and adverse events, and manage course appropriately
- All of above must be accomplished by typical American consumer based on guidance from label and not with requirement for professional supervision

Figure 3

supplemental efficacy data from the manufacturer if the OTC indication or dose differ from the prescription label; and new clinical research specifically designed to address the OTC appropriateness of the drug. These latter OTC-specific trials will most commonly include label comprehension studies and actual-use studies. The unique role of these OTC clinical trials will be discussed in more detail below.

LABEL COMPREHENSION STUDIES

As made clear above, the OTC drug label is the primary tool used by the consumer in guiding the intended use of the OTC drug in self-management. Thus, the label must effectively communicate a number of key messages to maximize the probability that the consumer will use the drug as intended. These key messages will include information relevant to the drug's indication, proper use, risk factors that should result in a consumer not using the product, and guidance for the consumer to address self-management decisions if the drug is used. Some of these messages are similar for most OTC drugs (eg, avoiding use without consulting a physician if pregnant), while others are specific to the intended indication and/or drug.

An additional challenge to label design is ensuring effective communication to the diverse American population. Consumers with poor reading skills, decreased visual acuity, varied ethnic backgrounds, and different life experiences must all be able to extract the content of the key messages in order to use the drug as intended.

Label comprehension studies are designed to test the hypothesis that the designed label effectively communicates the key messages relevant to the candidate OTC drug's use. Study subjects are recruited and provided the proposed OTC label. They are then asked to respond to a series of questions in either multiple choice or fill-in-the-blank format. These questions are designed to be directly relevant to prospectively defined key label messages. Label comprehension studies are implemented in a manner designed to attract a diverse study population, increasing the ability to generalize the results. Thus, the data output from label comprehension studies will be the percentage of study participants who understood each of the key messages as defined in the trial. Label development may be iterative, with messages failing on initial evaluation redesigned and retested.

While addressing critical questions relevant to OTC drug use, label comprehension studies have clear limitations. The design of label comprehension studies almost invariably incorporates significant cueing to the participants of the label messages of interest. For example, participants may be allowed to restudy the label after reading a study question, searching explicitly for the requested information. This may not reflect qualitatively or quantitatively the attention paid to labels in the real-world consumer setting. Label comprehension studies may not be able to include representative participants from all consumer groups of interest, particularly those that might be at increased risk from using the drug due to comorbid conditions or potential drug interactions. Overall, there are only limited data that allow any validation of the label comprehension study as a tool for understanding real-world consumer use of OTC labels.

OTC-Centric Clinical Research: Actual-Use Studies

Examples of consumer behaviors of interest:

- How often do consumers without the indication use the drug?
- How often do consumers who would benefit from more intensive therapy use the drug (diversion from optimal therapy)?
- How often do patients at increased risk of adverse effects from the drug buy and use the drug?
- How frequently are appropriate self-triage decisions made during and after the directed therapy?

Figure 4

ACTUAL-USE STUDIES

Actual-use studies build upon the label comprehension studies to test hypotheses based on the ability of the label to guide consumer behaviors and decision making. Actual-use studies are clinical trials conducted in a simulated OTC setting. Investigators may use simulated storefronts in shopping malls and other techniques to allow consumers to evaluate a potential OTC drug and make a decision about purchasing the drug. Study participants will then be followed to assess their use of the drug and health-care decision making after purchase. Importantly, there should be as little interference as possible by the investigators in the study participants' decision making. Thus, the design of these trials is challenging due to the potentially competing

needs of testing the study hypotheses and conducting the study in an ethical and rigorous manner. Importantly, unlike conventional phase 3 clinical trials, the study results are not centered on the efficacy of the OTC drug but rather on the frequency with which specific behaviors are followed by the participants.

The specific behaviors to be quantified in an actual-use study depend on the drug and indication being studied *(Figure 4)*. An example of a behavior that might be of particular interest is the frequency with which participants without the intended indication purchase and use the drug. To the degree that this occurs, consumers will be exposed to the risks of the drug without potential benefit, and may delay treatment for their actual condition. Similarly, some consumers might benefit from more intensive therapy than that offered by the OTC drug, and the frequency with which these consumers use the OTC drug may be of importance. This diversion from optimal therapy due to OTC drug availability might result in adverse health outcomes in extreme cases. Consumers at increased risk of adverse events from the use of the OTC drug should be included in the study cohort (with safeguards against adverse outcomes) to define the ability of the label to prevent their purchase and use of the drug. This might include consumers with comorbid conditions such as liver disease or those using drugs that could result in drug-drug interactions with the OTC drug. Decisions made during the course of treatment with the study OTC drug are also important when issues such as self-triage for further medical evaluation are expected or required.

In order for an actual-use study to meet its objectives, it is critical that the key behaviors of interest be defined prior to the design of the study *(Figure 5)*. These behaviors can be defined as those that represent potential decisions by consumers that could modify their health outcome in the context of the OTC drug's availability. Once these behaviors are identified, the actual-use study must incorporate an adequate sample size, including subgroups for whom specific behaviors are of unique importance, to allow meaningful point-estimates for the frequency at which these behaviors will occur (eg, how often will a patient with renal disease decide to take the medication?).

OTC-Centric Clinical Research: Actual-Use Studies

- Requires understanding the key behaviors of interest prior to designing trial
- Design must ensure adequate sample size, including subgroups for whom behaviors will be relevant, to allow meaningful conclusions
- Study must minimize bias, yet be conducted in ethical and rigorous manner

Figure 5

INTEGRATION OF THE OTC CLINICAL RESEARCH

As with label comprehension studies, there are limited data attempting to validate the results of actual-use studies as predictors of consumer behaviors once a drug is actually made available OTC. Several studies suggest that consumers frequently use OTC drugs in ways other than those specified on the drug label.

Ultimately, the decision of whether a specific drug should be available OTC is a risk-to-benefit analysis based on the impact on individual consumers who use the drug and the overall public health. If conducted properly, the OTC clinical development program should allow this to be an informed, scientific-based evaluation. If the various behaviors pertinent to OTC drug use that can affect health outcomes are defined, the quantitative impact of each different behavior understood, and the frequency of each behavior delineated in actual-use studies, a truly informed decision can be made. While this ideal construct may never be achieved, the degree to which it is approximated ensures a well-founded public health decision-making process.

CONCLUSION

The improved access to important medications inherent in switching a drug from prescription to OTC status has great potential for improving the health of Americans. However, this potential can only be achieved, and unacceptable risks avoided, if decisions on OTC drug availability are based on data and an understanding of the dynamics of consumer decision making with respect to OTC drugs. Ongoing developments in clinical research methodologies and educational efforts directed at the public promise to allow continued evolution of the OTC marketplace. ■

CHAPTER 3: A Survey of the Attitudes, Beliefs, and Perceptions of Consumers Regarding CHD and High Blood Cholesterol

James M. McKenney, PharmD

QUESTIONS, QUESTIONS, QUESTIONS

During 2004, the National Lipid Association (NLA) convened advisory boards of key opinion leaders among cardiologists and lipid specialists, preventive-care nurses, nutritionists, and pharmacists to ask their opinions about an OTC-statin option. While the proposal was favored by the majority of these individuals, they identified a number of questions they felt should be addressed in whole or part before an OTC statin was approved. Some of these questions are listed below:

Will patients at high risk for cardiovascular disease (CVD) under-treat with an OTC statin and not consult a physician or other health care professional?

Will patients at minimal risk for CVD over-treat with an OTC statin, thereby exposing themselves to potential risk for drug interactions and/or adverse effects?

Will patients find a way to obtain cholesterol tests, understand the results, correctly interpret their meaning, and take appropriate next steps (eg, consult their physician)?

Will patients regard an OTC statin as a "magic bullet," using it to compensate for unhealthy lifestyle behaviors or replace prescriptive therapy?

Will patients remain compliant with treatment over a lifetime?

Will patients be able to avoid potential drug interactions and contraindications to therapy?

Can patients safely take these products, recognizing important symptoms of side effects and seek appropriate steps to resolve them?

Will a coronary heart disease (CHD) risk-reduction benefit be derived in our society?

Will an OTC statin close the gap between those who need CHD risk-reducing therapy and those receiving it?

As you read the remainder of this chapter, and especially as you review the next chapter on consumer-use study results, look for answers to these and other questions you may have.

WHAT DO CONSUMERS THINK?

One way to determine how consumers may behave if presented with the opportunity to pursue CHD risk-reduction with an OTC statin is to ask them. While obviously not as definitive a measure of consumer behavior as actually observing it, carefully constructed surveys of representative populations can give a good view of consumers' beliefs, attitudes, and perceptions about cholesterol and heart disease, which ultimately form the basis for subsequent behavior.

Methods

In January 2004, the NLA commissioned Applied Research Consulting, NY, a market research company which specializes in consumer polling, to assist in constructing and carrying out a survey of consumers representative of the US population to address the following objectives: (1) characterize consumers' perceptions regarding the significance of high cholesterol and CHD, (2) identify the barriers consumers face in preventing CHD and managing their cholesterol, and (3) characterize the degree to which consumers appear willing to take an active role in their own CHD prevention and cholesterol management, including the use of an OTC statin. A panel of six physicians and other health professionals were assembled to assist in crafting the key questions. Survey questions followed a consistent pattern and had sufficient redundancy to test for internal validity. Consumers were asked to indicate the degree to which they agreed with a series of statements using a 10-point scale; responses of eight to 10 were quantified and reported as being in strong agreement with the statement.

Subsequently, and independently, the National Consumers League (NCL) commissioned Harris Interactive, NY, a market research firm, to help design and execute a survey of consumers to address attitudes, beliefs, and perceptions about OTC statins and other approaches to the self-care of CHD risk. The survey followed a consistent pattern and presented respondents with questions followed by categorical responses, which allowed consumers to give their answers indicating viewpoints from most to least favorable.

Both surveys were conducted via the Internet. The study population for the NLA survey was sampled from a panel of 200,000 consumers and, for the NCL survey, from a panel of several million people. The NLA survey sampled 600 consumers, 200 of whom were currently receiving treatment for lipids and the remaining 400 of whom were not. Of the 400 untreated consumers, 325 were estimated to have a moderate CHD risk profile (10% to 20% 10-year CHD risk, based on the presence of major CHD risk factors). The NCL sampled 730 consumers, all of whom were untreated and had an estimated moderate CHD risk profile. The sampled populations in both surveys were similar in terms of age (> 30 years of age), gender (about 50% women), ethnicity (82% Caucasian), education level (about 95% were at least high school graduates), and household income (median household income was $50,000 to $75,000). The methodology and results of the NLA survey are described in detail in two published articles.[1,2]

Consumer Survey Results

Place of Self-Care

The majority (89%) of consumers believed strongly that it is important that they participate actively in their own health care and 81% are willing to do so. In fact, only 1% of consumers indicated that they were unable or unwilling to participate in their own health management. Further, 52% indicated that they were making many more decisions about their health today than they were five years ago.

Awareness of High Cholesterol

Over half of consumer respondents (60%) believed strongly that a high cholesterol level is a serious health threat and 83% wanted to learn more about its dangers. Nearly 80% of respondents selected: *concerned*, *very concerned*, or *extremely concerned* about their cholesterol level. Most consumers (81%) believed strongly that reducing their cholesterol level would help prevent heart attacks and strokes.

When it came to having their cholesterol level tested, 82% strongly agreed that people should have their cholesterol level tested regularly, and a comparable number (73%) said that they personally have had their cholesterol level tested within the past year. However, just one-third of these consumers (31%) could state their total cholesterol level and even fewer (20%) could state their LDL-C level.

There appears to be a significant divergence in behaviors between those who are currently treated with lipid therapy vs. those who are not. For example, of currently treated consumers 81% regularly visit a physician compared to 44% of those untreated. Of currently treated consumers, 86% regularly get their cholesterol tested compared to 33% of untreated consumers.

Methods of Managing Elevated Cholesterol Levels

Most consumers (82%) believed strongly that high cholesterol could be effectively lowered without medication by eating right and exercising. In fact, over half of consumers (58%) said they personally use exercise and diet to try to control their cholesterol. Consumers in both the NLA and NCL surveys indicated that they were already doing things regularly to reduce their risk of heart disease, such as taking nutritional supplements, exercising, following a low-fat diet and trying to lose weight *(Table 1)*. In fact, 49% of consumers indicated strongly that they preferred OTC products and nutritional supplements to prescription medication to lower their cholesterol level.

Steps Consumers Said That They Were Currently Pursuing to Reduce Cholesterol and CHD Risk

	NLA Survey (n=600)	NCL Survey (n=730)
Taking Nutritional Supplements	31%	18%
Exercising	29%	30%
Following a Low-Fat Diet	33%	38%
Trying to Lose Weight	43%	31%

Table 1

The NLA survey showed that consumers who are receiving lipid-lowering treatment are more likely to be taking steps on their own to reduce their CHD risk, than are consumers who are not receiving lipid-lowering therapy *(Table 2)*. This may indicate that the treated population is more "activated" and more prone to pursue risk-reduction on their own, or has been positively influenced by its interaction with the health system. It is likely that both explanations are operative.

Barriers to Treatment

There appears to be a disconnect between physicians and consumers as to the barriers the consumer faces in carrying out effective lipid-lowering drug treatment. The most commonly given reasons by physicians for patients not taking cholesterol treatments include the cost of therapy, side effects, and poor compliance. The consumer appears to have a different perspective. Less than one-third (31%) said they worry about side effects of lipid-lowering medications. Fewer than one in 10 (6%) said they often forget to take their medication. And only 34% said prescription drugs are too expensive. In contrast, reasons given by consumers for not taking lipid-lowering drugs were that they were trying to control their cholesterol level with diet and exercise (57%) and that their physician had not recommended drug therapy (52%). One-third of consumers (34%) felt there was not enough time during physician visits to talk about high cholesterol and a similar number (36%) wished for more convenient ways to obtain information about high cholesterol. This suggests that more communication between physicians and consumers may be needed.

Comparison of CHD Risk-Reducing Approaches Being Pursued by Consumers Currently Receiving Lipid Treatment vs. Those Who Are Currently Untreated

	Treated (n=200)	Untreated (n=400)
Taking Nutritional Supplements	39%	29%
Smoking Cessation	70%	53%
Taking ASA	52%	25%
Following a Low-Fat Diet	41%	28%
Trying to Lose Weight	48%	38%

Table 2

Consumer Interest in Learning More About an OTC Statin and in Purchasing It If Approved

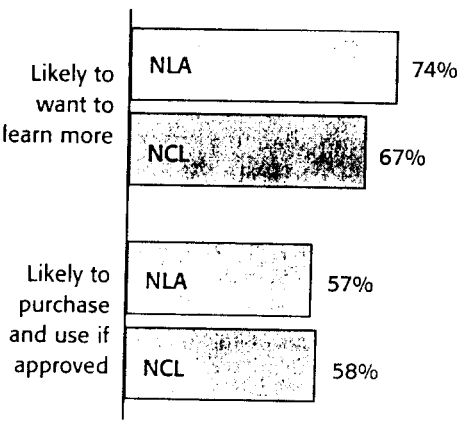

Figure 1

Interest in an OTC Statin

Consumers indicated a high level of interest in an OTC statin; 67% to 74% wanted to learn more about it. Interestingly, 80% of untreated consumers voiced interest compared to 62% of treated consumers. The majority, 57% to 58%, indicated that they would be highly likely to purchase and use an OTC statin if approved *(Figure 1)*.

The consumer who is most interested in an OTC statin appears to be different from the consumer who is not as interested. While the two groups are demographically similar in terms of age, income, and ethnicity, they appear to be attitudinally different. Those who are most interested in the OTC statin are also more concerned and more interested in learning more about cholesterol and more open to OTC medications in general. They are also more likely to be trying to stop smoking (64%), exercising (72%), following a low-fat diet (80%), and trying to lose weight (82%) regularly or occasionally.

The consumer in general appears to have a positive view of OTC-statin therapy. Fifty-one percent of consumers think the OTC statin would be one of the following:

The Consumer's Answer to the Question: Which Product Would You Be More Likely to Consider Taking, Recommending, Learning More About, and Discussing With Your Doctor?[3]

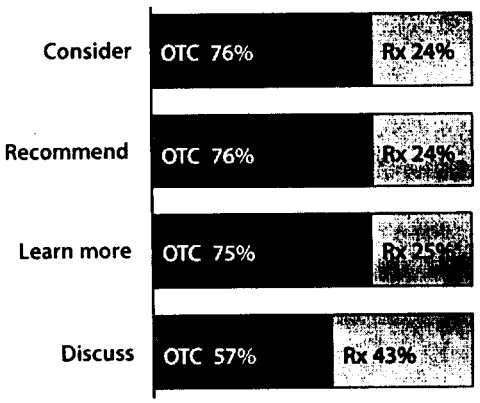

Figure 2

effective, very effective, or extremely effective in lowering cholesterol levels. Only 7% said they thought it would be ineffective. Two in three consumers (71%) expressed at least some concern about potential side effects associated with an OTC statin; 29% indicated that they would have no concerns about side effects. Compared with a prescription product, the consumer was more likely to consider taking an OTC statin and recommending it to a family member or friend *(Figure 2)*.

One of the most frequently asked questions by physicians and others when addressing the OTC statin question is whether the patient will maintain contact with their physician. The NLA survey indicates that consumers will keep in close touch with their physician. A large majority of consumers (85%) said they were very likely to consult with their physician or other health care professional before or just after purchasing an OTC statin, while a similar number (82%) would continue to consult with their physician after buying an OTC statin.

SUMMARY

The major conclusions from these surveys are:

- Consumers are concerned about cholesterol and heart disease.
- Consumers are already taking steps to lower their cholesterol levels and reduce their risk of coronary events.
- Consumers need support in their self-care efforts, particularly when it comes to cholesterol testing and counseling.
- Consumers are favorable toward OTC statins.
- Consumers are likely to stay in touch with their primary physicians both before and after they initiate OTC-statin therapy. ■

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CHAPTER 4: Overview of Consumer-Use Research

Jerome D. Cohen, MD

Cardiovascular disease (CVD) continues to be the leading cause of death in men and women in the US.[1] When therapeutic lifestyle changes are insufficient to decrease the risk of CVD by lowering LDL-C to goals established by the National Cholesterol Education Program (NCEP), HMG CoA reductase inhibitors (statins) are often prescribed. With the exception of cerivastatin, which was removed from the market, these drugs have been proven safe and effective in lowering LDL-C and the risk of cardiovascular disease.[2-4] In light of the significant gap between the number of people with high LDL-C who are at intermediate risk for CVD and the number of people receiving treatment with Rx statins,[5] a low-dose OTC statin is one possible option for reaching that portion of the population which is currently untreated.

The current discussion of an OTC option for statins in the US is preceded by two significant events. In May 2001, members of the Adult Treatment Panel of NCEP (ATP III) found the prospect of statins becoming OTC sufficiently noteworthy to mention it in their final report, "Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults."[6]

Some cholesterol-lowering agents are currently available without prescription, such as nicotinic acid, and manufacturers of several classes of LDL-lowering drugs (eg, statins, bile acid sequestrants) have previously applied to the FDA to allow these agents to become OTC medications. ATP III [May 2001] acknowledges the possibility in its report and advises that if an OTC cholesterol-lowering drug becomes available, patients should continue to consult physicians about whether to initiate drug treatment.[6]

More recently, the Medicines and Healthcare Products Regulatory Agency of the United Kingdom reclassified simvastatin 10mg as an OTC product available to the public from pharmacists without need of a prescription.[7] This precedent-setting action, approved in July 2004, is now operational and provides an additional treatment option for people at moderate risk for heart disease who may otherwise go untreated.

In light of growing interest in low-dose statin therapy as an OTC option in the US, this paper reviews the design and results of three consumer-use studies to address the following questions:

Will people self-select appropriately to use an OTC statin?

Can consumers self-manage their cholesterol over time?

Will consumers involve health care professionals in self-management?

Will lifestyle behaviors change and, if so, change favorably?

Will users of an OTC statin achieve beneficial lipid-lowering?

Although obviously an important issue, safety questions are best addressed through randomized clinical trials, and consumer-use studies offer only limited data for review in this regard. The three consumer-use studies that are examined in this chapter are:

- Pravachol [pravastatin] Experience Documented in a Consumer Trial (PREDICT), presented at the July 2000 meeting of the Food and Drug Administration's Nonprescription Drugs and Endocrinologic and Metabolic Advisory Committees.[8]
- OTC Pravachol [pravastatin] Trials in an Observed Naturalistic Setting (OPTIONS), also presented at the same July 2000 FDA meeting.[8]
- Consumer Use Study of OTC Mevacor [lovastatin] (CUSTOM), recently published in the Journal of American Cardiology.[9,10]

PREDICT

PREDICT was a consumer-behavior study conducted in 1999 to determine whether participants would visit a physician within two months of using OTC pravastatin 10mg as advised, whether there would be the predicted LDL-C reduction, and whether the drug would be used safely in accordance with package labeling. In 20 diverse communities, 11,065 participants responded to print and broadcast recruitment advertising. Much of the advertising was placed in African-American and Hispanic communities. The recruiting sites were visited by a total of 3,888 individuals, 80% of whom responded to the advertising and 20% of whom were "walk-ins."

Of the 3,872 who volunteered for the study, about half – 1,924 people – were randomized to an OTC arm, where pravastatin 10mg was available for purchase at any time. The remaining 1,948 were randomized to a prescription arm in which participants had to procure a prescription at the discretion of their personal physician. Participants in both groups also could elect to receive educational newsletters. Follow-up was planned for six months, but the study was extended to one year to evaluate longer-term LDL-C reduction.

Among all participants, 85% said they had a doctor, 83% said they visited their doctor yearly, 25% had seen a physician specifically for cholesterol, and 24% said they had a history of elevated cholesterol for a minimum of five years. Seventy-two percent had prescription coverage. Regarding cholesterol management, 81% said they were following the AHA diet (MEDFICTS), 18% were taking non-prescription therapy, and 9% were taking a prescription medicine.

Of the participants randomized to the OTC arm, 96% were free of CHD, 98% were free of diabetes mellitus, 87% said their total cholesterol exceeded 200mg/dL, and 74% understood their LDL-C was above the desired level. Of the 1,204 volunteers who declined to purchase the OTC product, almost half (47%) wanted to consult a physician, while 18% recognized a label warning that applied to them. The remainder of the participants (N=720) purchased the drug. Among this latter group, 77% met the primary objective of consulting a physician within two months of initial use, 5% consulted their physician after the two-month time frame, and 10% purchased the product but did not consult their physician *(Figure 1)*. The remaining

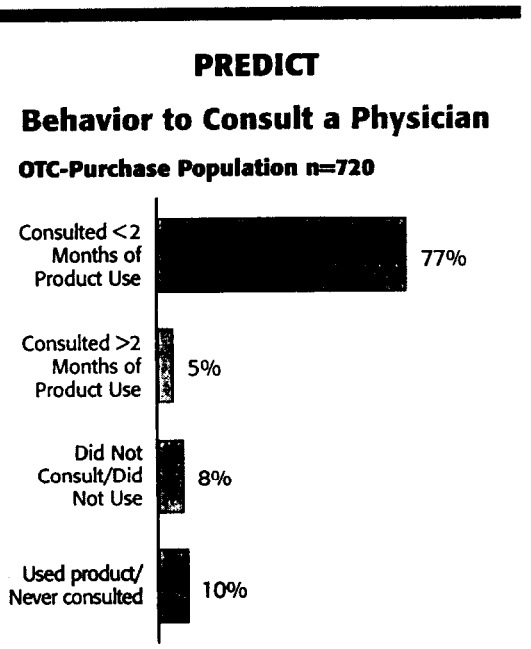

Figure 1

8% did not consult their physician and did not take the medication. Between the OTC arm and Rx control group, there was little difference in physician involvement: 85% of the OTC participants and 83% of the Rx participants consulted their physicians.

Among OTC participants, 83% met their NCEP-defined LDL-C goal. The observed LDL-C reduction was 17%, similar to what would be predicted from prior placebo-controlled randomized trials.

With regard to therapeutic lifestyle changes and specifically in dietary habits, 75% of the OTC group and 69% of the Rx-assigned group reported no change, while 11% of both groups reported improvement in dietary practices. Although the safety data are limited, there were no deaths, and 19 serious adverse events (AEs) reported were thought to be unrelated to pravastatin. The incidence of AEs was comparable in both the OTC and prescription groups.

OPTIONS

OPTIONS, also conducted in 1999, was a three-month observational study to assess the behavior of HMO members who chose to purchase pravastatin 10mg OTC at 20 participating pharmacies (14 HMO staff model and six Independent Practice Association retail pharmacies). Limiting participants to HMO

members permitted access to patient charts for verification of data in a real-world setting. As with PREDICT, the primary endpoints were consultation with a physician within two months of using pravastatin 10mg, appropriate self-selection, and safety.

Participants were solicited through flyers sent to 161,322 HMO members, radio and newspaper advertising, and floor displays in participating pharmacies. Of the 2,207 people who came to the pharmacies in response to the mailings, a total of 782 people enrolled. Participants were predominantly middle-aged and older (93% between ages 35 and 74) and slightly more female than male (54% and 46%, respectively). Sixty-eight percent of participants were Caucasian, 21% African-American, and 5% Hispanic. Health care characteristics were similar to those of PREDICT. Among the 782 enrollees, 96% visited their doctor annually, 31% specific to cholesterol; 70% had discussed cholesterol with a physician within the last six months; 23% said they had a history of elevated cholesterol for at least five years; 26% were using non-prescription treatment; and 16% were taking a prescription medicine.

At study-site pharmacies, participants completed a questionnaire, which included a survey of inclusion/exclusion criteria. Apart from the label instructions, they received no other advice to visit their primary care provider. Once enrolled, a participant had no further contact with study staff until the end of the 12-week assessment period.

Of the 782 enrollees, 404 – slightly more than half – purchased the drug. Among the 404 purchasers, 95% were free of CHD, and 90% were non-diabetic. Of volunteers who had lab values in their HMO chart, 89% had total cholesterol of >200mg/dL, and 79% had LDL-C >130/mg/dL. Consistent with the PREDICT results, those who chose not to participate in OPTIONS gave two reasons: 47% wanted to consult a doctor, and 20% recognized label warnings.

Among the 404 who purchased pravastatin, 44% consulted a physician within two months, and 5% consulted outside that time frame. Thirty-two percent did not consult a physician but properly self-selected (ie, no CHD or liver disease; not pregnant and not treated with a prescription product). Twelve percent neither consulted nor took the statin. Seven percent did not consult their physician or appropriately self-select in accordance with the label criteria *(Figure 2)*.

Of the 157 participants who did not consult with a physician, 82% were not at high risk, 75% had discussed cholesterol with their physician within the prior six months, and 90% had total cholesterol of >200mg/dL.

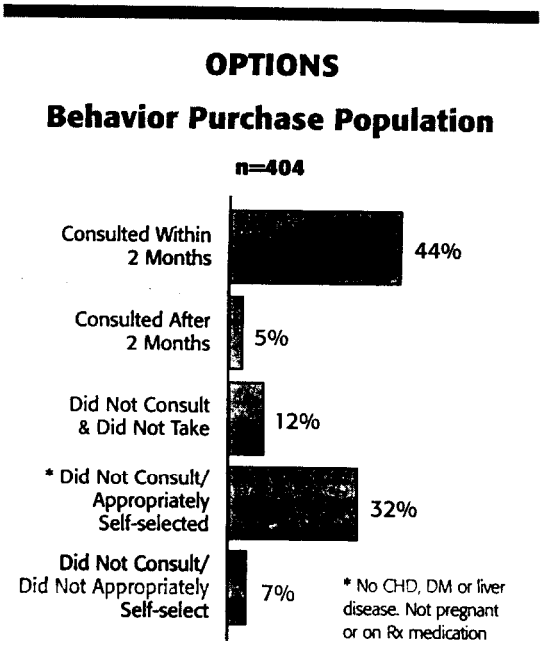

Figure 2

Although the numbers are small, no safety issues emerged. There were no deaths, no serious AEs related to pravastatin, and no transminase abnormalities.

CUSTOM

CUSTOM was an open-label, multicenter, "all-comers" study conducted in 2002-2003 to assess consumer behavior in selecting OTC lovastatin 20mg in a retail-like setting and over a period of 26 weeks using an OTC management system. Details of the study have been previously published.[9-10] Participants interested in managing their cholesterol were recruited and directed to one of 14 naturalistic retail storefronts where Mevacor OTC Self-Management System materials were available. Nurse investigators acting as pharmacists were on site to answer questions but were instructed to offer no unsolicited advice that would aid the self-selection decision.

The package label provided information needed for the consumer to decide whether to purchase lovastatin OTC (ie, purpose of the drug, eg, "to help lower LDL-C which may prevent a first heart attack"); warnings/contraindications (eg, liver disease, pregnant/breast feeding, allergic to lovastatin,

experienced muscle pain from taking a statin); suitability (eg, men age ≥45, women age ≥55; LDL-C 130-170mg/dL; plus at least one additional risk factor), and directions for use (ie, one tablet daily, cholesterol to be tested at six weeks, talk to your doctor if there is a change in health). The label was intended to allow consumers without CHD to determine if they were at intermediate risk of a CHD event and to self-select appropriately, as defined by ATP III (ie, 10-year risk <20%).

At the conclusion of the 26-week study, participants were asked to complete a questionnaire about their health behavior and the American Heart Association MEDFICTS dietary assessment.

Among 11,252 individual inquiries to the study, 3,316 interested parties presented at retail sites to evaluate OTC lovastatin. Of those evaluators, 1,205 bought an initial carton ("purchasers"), and 2,111 elected not to purchase. Among non-purchasers, 21% said they needed more information, and 79% said they were not interested. Of that latter group, 98% did not meet label criteria (eg, too young, lacking CHD risk factors, did not know cholesterol levels). Almost half of the non-purchasers (46%) said they intended to speak to a physician.

Of the 1,205 individuals who made an initial purchase, 1,061 took a minimum of one dose ("users"). The median age of users was 56 years, 60% were men, and the mean LDL-C was 157 mg/dL. Eighty-two percent were Caucasian, 9% were African-American and 5% were Hispanic. Thirteen percent were identified as low literacy. Among the 1,061 users, 56% visited a doctor two or more times annually, 80% had tried to lower their cholesterol levels with diet or exercise, and 74% had spoken to a doctor about cholesterol. Self-selection behavior was available for analysis from all 1,061 users, with the exception of two users who violated the protocol and 15 who were missing an eligibility assessment.

CUSTOM showed that consumers were able to self-select appropriately based on label safety criteria. Of individuals who had potential safety concerns at the time of self-selection (ie, pregnant, having liver disease, potential drug interactions, or on prescription therapy), the large majority chose not to use lovastatin or consulted prior to use with a physician *(Table 1)*.[9]

Among participants at higher risk (ie, those with a history of diabetes, CHD or stroke), 570 were evaluators and 167 were users. Of the 167 higher risk users, almost three-fourths (74%) spoke with their physicians.

CUSTOM

Potential Safety Concerns at the Time of Self-Selection[9]

	Evaluators with Specified Potential Safety Concern	Users with Specified Potential Safety Concern
Potential drug interactions	160	11
Reported current liver disease	80	3
Pregnant/Breast feeding	12	0
Previous drug allergy to lovastatin	13	0
Use of a prescription cholesterol-lowering medication	609	9
Total	764*	23**

** 23% of evaluators ** 2% of users*

Table 1

Continued involvement with physicians was substantial among the 2,111 non-users and 1,061 users. Forty-six percent of non-users said they intended to speak to their doctor, while 57% of users consulted their health care professional.

The majority of users (78%) also made appropriate decisions about managing their cholesterol over time. Based on follow-up, 61% persisted with the OTC statin for six months, and 17% discontinued for appropriate reasons. Twenty-two percent inappropriately discontinued using lovastatin (ie, they gave no reason for stopping use of the drug).

Heart-healthy lifestyle behaviors improved. At the outset of the study, 47% of users said they were following the American Heart Association Step II diet compared to 59% at the conclusion of the study. With regard to exercise, 24% of users reported that they had improved their exercise routine, while nine out of 10 users (94%) said they had maintained or enhanced their exercise programs.

As expected, LDL-C was reduced. Sixty-two percent achieved the target of LDL-C <130mg/dL. There was a 25% decline in LDL-C among users who fasted and

a 21% decline among all users (fasting and non-fasting). These reductions are consistent with observations from randomized placebo-controlled trials.[11,12]

As with the PREDICT and OPTIONS studies, the CUSTOM safety profile was confirmed. There were no reports of drug-related death, myopathy, rhabdomyolysis, or liver disease. There was one report of a serious allergic reaction to lovastatin in a participant with no known prior allergy to the drug.

DISCUSSION

The findings are consistent across the CUSTOM, PREDICT, and OPTIONS studies.

Across the three studies: about 90% of participants were told they had high levels of LDL-C; an average of 88% knew their total cholesterol was >200mg/dL, and about three-fourths (74%) posted LDL-C >130mg/dL; approximately one-fourth were using nonprescription therapy; and 7% to 15% were taking a prescription drug. Importantly, about 90% saw their physicians at least once a year *(Table 2)*. In the three studies, patterns of consumer behavior were also consistent. Depending on the criteria, across the three studies, appropriate self-selection and use was about 90%, maintaining or improving diet and exercise was above 80%, and over half of participants consulted their physicians.

These three studies, taken together, clearly demonstrate that consumers:

(1) Show a consistent pattern of appropriate behavior in opting to purchase a low-dose statin;

(2) Use the drug correctly, and consult their physicians;

(3) Involve their health care providers in self-management;

(4) Improve their lifestyle behaviors; and

(5) Achieve beneficial lipid-lowering in an OTC environment.

The findings of PREDICT, OPTIONS, and CUSTOM indicate that a low-dose OTC statin is an effective and reasonable option for millions of Americans who are at intermediate risk for CHD and eligible for statin therapy (ATP III Guidelines) but who are not currently on prescription therapy. The availability of a low-dose OTC statin may influence consumers to see their physicians, follow the recommended OTC regimen, and adopt better heart-healthy lifestyles. The risk of OTC-statin therapy is small when viewed against the benefits of reducing LDL-C and the associated potential for CHD risk reduction. ■

Characteristics of OTC Users

Summary of Three Studies

	CUSTOM N=1059	PREDICT N=720	OPTIONS N=404
Total Cholesterol >200mg/dL	87%	87%	89%
LDL Cholesterol >130mg/dL	68%	74%	79%
Taking CHD non-prescription therapies	N/A	23%	25%
Taking CHD prescription therapy	*15%	7%	12%
See doctor at least yearly	88%	82%	97%
Appropriately self-select & use	65-90%	93%	89%
Maintain or improve diet/ exercise	94-98%	85%	N/A
Consult physician during study	57%	82%	49%

* 65% of these users consulted with a doctor prior to OTC use

N/A = data unavailable

Table 2

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CHAPTER 5: Value-Added Services Provided by Pharmacists in an Environment of Over-the-Counter Statins

Janet P. Engle, PharmD, FAPhA

Health care providers in the United States are having increased discussions about statins becoming available over-the-counter (OTC). This attention is spurred by the recent prescription-to-OTC switch of simvastatin in Great Britain, continued desire among many consumers for greater control of their health care, and increased awareness by the media to the burden of heart disease in our country. The potential availability for an OTC statin presents an opportunity to consider new ways to support the consumer who wishes to pursue self-care approaches to coronary heart disease (CHD) risk-reduction. Research studies have demonstrated that pharmacists, working collaboratively with primary-care physicians to provide point-of-purchase services, can have an important impact on patients' compliance with therapy and achievement of treatment goals. Also, there is a recent proposal to create a new Pharmacy-Care OTC category through which a manufacturer can voluntarily make OTC products available only in retail environments that contain a pharmacy in return for the availability of supportive services from pharmacists when requested by consumers. These topics are reviewed in greater detail in this chapter.

Categories of Medicines in UK

- POM (Prescription-only medicine)
  - Requires medical monitoring because of health risks, etc.
  - Cannot be promoted to public
- P (Pharmacy-only medicines)
  - Sold only from registered pharmacies under supervision of a pharmacist
  - No self-selection
  - Restrictions on use by labeling
- GSL (General Sales List)
  - Can be sold from any lockable shop - superstores, drug stores, health food shops, gas stations, etc.
  - Self-selection allowed

Figure 1

THE UNITED KINGDOM EXPERIENCE

Unlike the US, Great Britain offers three classes of drugs *(Figure 1)*: POM, prescription-only medicine; P, available from a pharmacist without prescription but behind the counter; and GSL, general sale list (ie, over-the-counter). In May 2004, the British Department of Medicines and Healthcare Products Regulatory Agency/Committee on Safety of Medicines reclassified a statin, for the first time, from POM to P, thus making this class of drug more easily available to more people in the UK who are at risk for cardiovascular disease. Before the switch, the UK health system provided medical treatment only for those individuals with a >30% 10-year risk of experiencing a CHD event. On the advice of medical authorities, the health system was also willing to provide medical treatment for individuals with a 15% to 30% risk as long as resources were available. Individuals with <15% risk were not offered a treatment option even though studies have shown a benefit in treating this patient population. With simvastatin's move to P class in the UK, patients in the 10% to 15% risk category now have a treatment option. In many cases, drugs become accessible GSL (over-the-counter) after they are first reclassified to P from POM, and experience has demonstrated consumers' safe and effective use of the drug. Both supporters and skeptics of making more types of drugs available OTC in the US await data from Great Britain's experience with simvastatin.

BACKGROUND ON A THIRD CLASS OF DRUGS IN THE US

Since the mid-1970s, there has been intermittent discussion in the US about creating a third class of drugs similar to the UK model of drug classification.

Supporters of this approach cite benefits deduced from the UK experience (ie, increased number of OTC drugs available to consumers, reduced misuse of drugs, and lower costs associated with physician visits for disorders treatable with OTC medication).

At present, it is unlikely that the US government will create a third class of drugs comparable to class P. The most recent GAO study, "Pharmacist-Controlled Nonprescription Drugs," published in December 1995 (GAO/PEMD-95-12), did not support formally establishing a pharmacist class of drugs in the US, stating that evidence was not sufficient to endorse such action and that the current classification system worked well.

PHARMACY-CARE OTC: AN ATTRACTIVE MODEL

The health care environment in the US continues to evolve at a rapid pace. Increased numbers of drugs are moving from prescription to OTC status, there are increased discussions about permitting more types of drugs to be available OTC (eg, weight control, osteoporosis prevention, birth control, blood pressure management, and cholesterol management drugs), and consumers continue to seek increased authority over decisions about their health care.

With the prospect of drugs becoming available OTC to treat asymptomatic conditions like high cholesterol, some manufacturers are exploring the concept of distributing various OTC drugs on the open-shelf with current OTC products, but only in outlets with a pharmacy. Given the trend of increased numbers of prescription-to-OTC switches and manufacturers' consideration of limiting certain OTC drugs to sales in stores with pharmacies, the American Pharmacists Association is exploring an approach called Pharmacy-Care OTC *(Figure 2)*. In light of the changing health care environment, this approach merits serious consideration.

Pharmacy-Care OTC medications could offer significant benefits to consumers, pharmacists, and drug manufacturers. Today consumers are exposed to a plethora of oftentimes complex information about health conditions and treatments. Pharmacy-Care OTCs would create opportunities for consumers to speak with their pharmacists, gain information, ask questions, raise concerns, obtain monitoring (eg, point-of-care testing for lipid profile), and gain support to make long-term compliance more likely. In sum, consumers would be able to have increased dialogue with another professional partner in their health care, and pharmacists would have additional education and training around the introduction of these particular OTC products. As Pharmacy-Care OTC evolves, it is reasonable to expect that pharmacists would offer support services for a product, such as cholesterol-control management programs that might include on-site cholesterol testing, statin monitoring and counseling, dietary and lifestyle counseling, etc., in the case of the OTC-statin option.

Pharmacists, too, benefit from Pharmacy-Care OTC. Pharmacists would have greater opportunities to counsel consumers, distribute literature, provide diagnostic tests and monitoring for attainment of therapeutic endpoints, and collaborate with physicians and patients on the customers' current drug therapies.

What is Pharmacy-Care OTC?

- OTC medication distributed only in retail stores with a pharmacy
  - Expands consumer access to valuable medications
  - Facilitates consumer access to pharmacists
    - Allows coordination of prescription medication use
    - Increases availability of support services
- Does not require pharmacist intervention, but supports it
- Especially beneficial for potential first-time users and chronic users with questions

Figure 2

Project ImPACT: Hyperlipidemia

- 397 patients collaborated with pharmacists in 12 states
- Goals of project included:
  - Improve persistence/compliance of prescribed medications
  - Improve cholesterol levels of patients over time
  - Increase population of patients who reach and maintain their lipid treatment goals

Figure 3

BENEFITS OF PHARMACIST INVOLVEMENT WITH LIPID-LOWERING THERAPY

Many studies have been published documenting the benefit of pharmacists working collaboratively with patients with dyslipidemia. One study, "Pharmaceutical Care Services and Results in Project ImPACT: Hyperlipidemia," *(Figure 3)* describes a demonstration project completed in 16 community-based pharmacies that included 397 patients.[1] These patients were followed by community pharmacists for a period of approximately two years. Point-of-care testing was used to obtain objective information about the patients' progress. The model also established a process for documentation of lipid management interventions and for the flow of patient care data between the pharmacist, patient, and the primary physician. Of the 397 patients enrolled in the study, 87% were treated with medications and lifestyle modifications. At the end of the two-year study period, the project documented a persistence rate of 93.6% and a compliance rate of 90.1% *(Figure 4)*. These rates exceeded all historical norms. In addition, enrolled patients demonstrated a 22.1% reduction in LDL-C and a 14% mean increase in HDL-C. At the end of the study, 62.5% of patients were at or below National Cholesterol Education Program (NCEP) goals. The model described in this demonstration project suggests that pharmacists provide value to the patient taking lipid-lowering agents, such as statins, in terms of enhancing persistence and compliance with medications as well as reaching NCEP goals.

In another study, "Effect of Community Pharmacist Intervention on Cholesterol Levels in Patients with High Risk of Cardiovascular Events: The Second Study of Cardiovascular Risk Intervention by Pharmacists" (SCRP-plus), 42 community pharmacies in six provinces of Canada followed approximately 400 patients with a >30% 10-year risk for cardiovascular events for six months.[2] At the end of six months, 27% of patients attained their target LDL-C levels, which was an improvement as no patient met target levels at the onset of the study. Adherence to lipid-lowering medications was 84%. In a forerunner study, the "Study of Cardiovascular Risk Intervention by Pharmacists" (SCRIP), 675 patients at high risk of cardiovascular events were enrolled at 54 centers and randomly assigned to enhanced pharmacist care or usual care.[3] The trial was terminated early due to the marked enhanced outcomes of the patients in the pharmacist care group.

Project ImPACT: Hyperlipidemia Results

- Achieved 93.6% persistence and 90.1% compliance with lipid modifying therapy – exceeded all historical norms; results were achieved over a two-year period – longer than any other study
- 62.5% achievement of NCEP goals
- 22.1% LDL-C reduction and 14% mean increase in HDL-C
- Pharmacists' services were well received by patients and their primary physicians

Figure 4

These studies and others provide documentation that pharmacists can add value to the care of patients with dyslipidemias. Patients working closely with their pharmacist generally have improved persistence, compliance, and attainment of their target lipid goals.

AN EXPANDED ROLE FOR PHARMACISTS

A Pharmacy-Care OTC system of distribution would offer pharmacists increased opportunities to use their higher education and skills, which, currently, are too often insufficiently employed beyond dispensing drugs. To understand more clearly the current pharmacy environment surrounding new trends in OTC-patient care, the National Lipid Association, in cooperation with the American Pharmacists Association, sponsored a survey of pharmacists,[4] conducted online in March 2004. The survey revealed the following:

- *Pharmacists are optimistic about the consumers' ability to manage self-care.*

  The vast majority of pharmacists surveyed (90%) believe that, when people participate actively in their own health management, the results are often very positive.

- *Pharmacists believe there is a need to educate consumers about the risks of high LDL-C.*
  Only 9% agree that the public clearly understands the link between high cholesterol and CHD, and only one in five pharmacists (21%) believes there is sufficient public attention paid to the risks of high LDL-C. However, fully two-thirds (67%) agree that new approaches should be tried to reach untreated consumers with high cholesterol who are at risk for CHD.
- *Pharmacists want to do more to support wise consumer self-care.*
  Three out of four (75%) say they would like to play a greater role in advising patients about OTC treatments and self-care, but only 15% agree they have sufficient support materials to educate patients about the risks of high cholesterol.
- *However, pharmacists see obstacles to successfully supporting consumers of OTC statins.*
  Seventy-nine percent of pharmacists say they are concerned about side effects, drug interactions, and patients discontinuing use of their medication, but only 32% agree that they are able to obtain the needed health information about patients to advise them adequately about OTC treatments and self care.

In response to discussions about a potential OTC statin and a Pharmacy-Care OTC system that would increase consumer access to and understanding of sometimes complex information, the American Pharmacists Association created a Taskforce on Pharmacy-Care OTC Products in August 2004. The taskforce has presented a set of recommendations addressing how Pharmacy-Care OTCs would function in the marketplace. Some of these recommendations address the training and education of pharmacy personnel to support consumers and collaborate with their physicians (ie, the provision of consumer support materials, in-pharmacy services including point-of-care testing, documentation, and follow-up), and cooperation with physicians in sharing appropriate and pertinent patient information. The full report can be found at: http://www.aphanet.org.

SUMMARY

In the UK, the pharmacist provides important services to consumers including CHD risk assessment, triage to primary-care physicians, and counseling on lifestyle modification and OTC statins.

The proposed Pharmacy-Care OTC category in the US would allow manufacturers the option to voluntarily distribute their OTC products only through retail environments that contain a pharmacy and thereby provide consumers the opportunity to speak with their pharmacists to gain information, ask questions, raise concerns, obtain monitoring, and gain support for medication compliance.

When pharmacists work collaboratively with primary physicians to support and encourage patients receiving prescriptive lipid-lowering therapy, the rates of compliance and persistence with therapy, and the percent of patients reaching treatments goals are substantial.

A 2004 NLA survey of pharmacists indicated that 75% would like to play a greater role in advising patients about OTC treatments and self-care. ■

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