

Understanding Niacin Formulations

John A. Pieper, PharmD

Abstract

Niacin is an important therapeutic option for the treatment of dyslipidemias and is the only agent currently available that favorably affects all components of the lipid profile to a significant degree.

Niacin has consistently been shown to significantly reduce levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and lipoprotein (a), while having the greatest high-density lipoprotein (HDL) cholesterol-raising effects of all available agents. Niacin has also been shown to significantly reduce coronary events and total mortality. Niacin is available in 3 formulations: immediate-release (IR), sustained-release (SR), and a newer formulation, niacin extended-release (ER), all of which differ in their pharmacokinetic, efficacy, and safety profiles. Conventional niacin therapy has notable limitations that include flushing, most often seen with IR formulations, and hepatotoxicity, associated with SR formulations.

These side effects are related to the absorption rate and subsequent metabolism of niacin as delivered from the different products. Niacin ER has a delivery system allowing absorption rates intermediate to that of niacin IR and SR. As a result, niacin ER achieves the efficacy of niacin IR with a reduced incidence of flushing and without the hepatic effects seen with niacin SR. The pharmacist should be familiar with the differences among and the advantages and disadvantages of each formulation to educate patients and help them achieve the optimal therapeutic benefit of niacin while minimizing adverse effects.

(Am J Manag Care 2002;8:S308-S314)

Niacin, also known as nicotinic acid, was introduced in the mid 1950s as the first effective lipid-modifying agent. By inhibiting the mobilization of free fatty acids from peripheral tissues, niacin reduces hepatic synthesis of triglycerides (TG) and the secretion of very low-density lipoprotein (VLDL); niacin may also inhibit the conversion of VLDL into low-density lipoprotein (LDL).

Niacin increases high-density lipoprotein (HDL) cholesterol by blocking hepatic uptake of apolipoprotein A-1, decreasing clearance, and increasing the amount of HDL cholesterol available for reverse cholesterol transport.^{1,2} Niacin is unique in that it has favorable effects on the complete lipoprotein profile. It has been shown to significantly reduce levels of total cholesterol (TC), LDL cholesterol, and TG.

Furthermore, niacin is the only available agent that significantly lowers lipoprotein (a) and has the greatest HDL cholesterol-raising effects of all available agents.³ In addition, niacin was the first lipid-altering agent shown to significantly reduce coronary death and nonfatal myocardial infarction, as well as total mortality, in patients with documented coronary heart disease in the Coronary Drug Project (CDP), a large, prospective trial.^{4,5}

Despite the efficacy of niacin in improving lipid profiles and its demonstrated role in secondary prevention, several factors have limited its widespread use. The primary limitation of immediate-release (IR) (or plain) niacin is prostaglandin-mediated facial and truncal flushing, which is experienced by most patients during the initial days of treatment.⁶ Although symptoms diminish over time, many patients stop therapy before tolerance develops.⁷ Other unwanted effects include itching, mucous membrane irritation, and diarrhea.

Another limitation of niacin IR is the multiple-dosing requirement (ie, 2 or 3 times a day).⁷ Niacin IR has been approved by the US Food and Drug Administration (FDA) for the treatment of dyslipidemias and is available over the counter.

In an attempt to reduce flushing, sustained-release (SR) niacin formulations were developed in the 1960s. The clinical use of some of these products, however, has suggested an increased incidence of hepatotoxicity and gastrointestinal intolerance.⁸ The studies reviewed in this article demonstrate that although niacin SR reduces flushing and itching, it has inconsistent effects on lipoprotein parameters and is associated with an increased risk for various side effects. Sustained-release formulations, which are not FDA approved for the treatment of dyslipidemia, are usually sold over the counter as health food supplements.

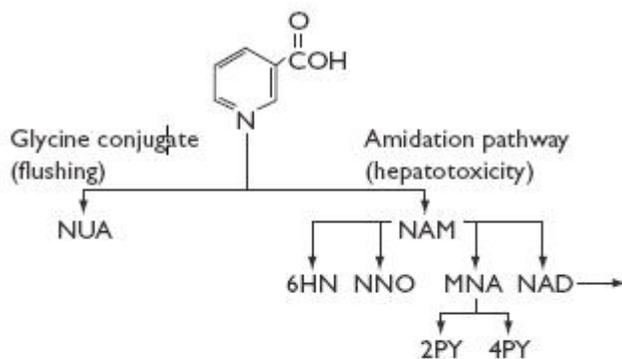
Niacin extended-release (ER), a recently introduced intermediate-release niacin formulation, has a unique delivery system that allows drug absorption over 8 to 12 hours. This formulation was developed in an attempt to achieve the lipid-lowering efficacy of niacin IR with a reduced incidence of flushing and to minimize the hepatotoxicity seen with longer-acting formulations.

Niacin ER is FDA approved for the treatment of dyslipidemia and is available by prescription only.⁹

Pharmacokinetics of Niacin

An understanding of the differences in side effect profiles of niacin IR, SR, and ER requires a review of the pharmacokinetics of niacin. Niacin undergoes extensive, saturable, first-pass metabolism in the liver, where it is metabolized by 2 hepatic pathways (**Figure 1**).

Figure 1. The Metabolic Pathways of Niacin



NUA indicates nicotinic acid; NAM, nicotinamide; 6HN, 6-hydroxynicotinamide; NAD, nicotinamide adenine dinucleotide; MNA, N-methylnicotinamide; NNO, nicotinamide-N-oxide; 2PY, N-methyl-2-pyridone-5-carboxamide; 4PY, N-methyl-4-pyridone-5-carboxamide.

Source: Used with permission from Piepho RW. The pharmacokinetics and pharmacodynamics of agents proven to raise high-density lipoprotein cholesterol. *Am J Cardiol.* 2000;86(suppl):35L-40L.

In one pathway, niacin is conjugated with glycine to form nicotinic acid. This conjugative pathway is a low-affinity, high-capacity pathway that generates metabolites that are associated with flushing. The second pathway involves several general oxidation-reduction metabolic reactions that produce nicotinamide and a series of related products, such as nicotinamide adenine dinucleotide, and ultimately several pyrimidine metabolites.

This amidation, or nonconjugative, pathway is a high-affinity, low-capacity pathway with metabolites that are associated with hepatotoxicity.⁹ Thus, the absorption rates of the different formulations dictate the extent of metabolism by each pathway, the type of metabolites generated, and the side effect profile. Niacin IR is usually completely absorbed within 1 to 2 hours; niacin SR absorption rates vary from product to product and even batch to batch, but generally exceed 12 hours.⁹ Niacin ER has an absorption rate of 8 to 12 hours.⁶

Niacin IR quickly saturates the amidation pathway, resulting in most of the drug being metabolized by the conjugative pathway and thereby causing a high incidence of flushing. Conversely, niacin SR is metabolized to a greater extent by the amidation pathway, saturating it more slowly.

As a result, niacin SR has a lower incidence of flushing, but a higher incidence of hepatotoxicity.⁹ Niacin ER, with its intermediate dissolution rate, better balances metabolism along the 2 pathways, resulting in a lower rate of flushing and hepatic effects compared with niacin IR and niacin SR, respectively.

The differences in metabolism and related side effects can be most clearly understood in a simulation model of drug metabolism after administration of either niacin IR or niacin SR. Niacin IR is absorbed at a rate of approximately 500 mg/hour, and, therefore, a 1-g dose of niacin IR would be completely absorbed and metabolized within 2 hours.

In contrast, niacin SR is released at an approximate rate of 50 mg/hour. Therefore, absorption of a 1-g dose of niacin SR would take >20 hours. The rate of metabolism of the amidation pathway (low capacity, high affinity) is fixed at approximately 40 mg/hour, and once this pathway is saturated, the remaining niacin must be metabolized by the higher-capacity, lower-affinity conjugative pathway.

For example, at 2 hours, niacin IR will generate approximately 80 mg of amidation metabolites and 920 mg of nicotinuric acid, the glycine conjugate of niacin. In contrast, niacin SR in the same time would form approximately 80 mg of amidation metabolites and 20 mg of the glycine conjugate.

This simulation indicates that with the use of niacin IR, large amounts of nicotinuric acid (920 mg) are produced and excreted in the urine, and, as such, niacin IR is likely to produce flushing. However, 12 hours after niacin SR administration, approximately 480 mg of amidation metabolites, but only 120 mg of nicotinuric acid, are generated. Following the simulation to 24 hours, approximately 800 mg of amidation metabolites are generated with niacin SR, along with approximately 200 mg of nicotinuric acid.

These amounts are in stark contrast to the 80 mg of amidation metabolites and 920 mg of nicotinuric acid, (~92% of the original niacin dose) generated with niacin IR over the same time period. Thus, approximately 10 times more amidation metabolites are excreted when niacin SR is administered, while 4.6 times more nicotinuric acid is excreted with niacin IR versus SR administration. Therefore, the side effects observed with niacin are determined by the absorption rate of niacin from different formulations: flushing with niacin IR and hepatotoxicity with niacin SR.

Niacin ER has an absorption rate that falls between the values for niacin IR and SR. Theoretically, this intermediate profile should lead to the production of less nicotinuric acid than niacin IR, and therefore to a lower incidence of flushing, and fewer amidation metabolites than niacin SR, thus minimizing the risk of hepatotoxicity.

Using the simulation model described above, if 1 g of niacin ER is added to the simulation at an absorption rate of approximately 100 mg/hour, niacin ER would generate 400 mg of amidation metabolites compared with 800 mg with niacin SR, and 600 mg of nicotinuric acid compared to 920 mg with niacin IR. Furthermore, the delivery system of niacin ER makes it suitable for once-daily dosing at bedtime, which also helps to minimize the flushing side effects by allowing any flushing to occur while the patient is asleep.⁶ This simulation is supported by limited experimental data. In a 1992 crossover study, 10 healthy volunteers received a 0.5-g dose of niacin IR and then, after a washout period, a 0.5-g dose of niacin SR.

The urinary metabolites of niacin were measured and expressed as the mean (\pm SD) amounts excreted in mg/24 hours. After niacin IR administration, 78 ± 14 mg of nicotinuric acid and 171 ± 12 mg of 2-pyridone, a major amidation metabolite, were excreted. However, when niacin SR was administered, 19 ± 4 mg of nicotinuric acid and 130 ± 11 mg of 2-pyridone were excreted.¹⁰ The amount of nicotinuric acid excreted was 4.1 times more in patients receiving niacin IR than niacin SR, whereas the ratio of the amounts of 2-pyridone in the IR group compared with the SR group was 1.3.

Clinical Studies Comparing Niacin Formulations

Although the absorption profiles and resultant metabolism of niacin from differing formulations help explain the differences in side effect profiles, clinical studies that have compared these products clarify the actual and relative incidence of adverse effects as well as the relative efficacy of niacin formulations.

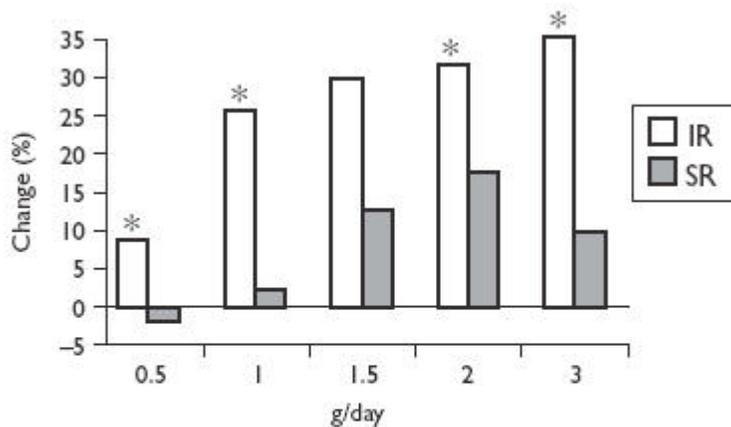
The first published comparative trial enrolled 71 hypercholesterolemic patients who were randomized to either niacin IR or niacin SR.¹ During the first month, each formulation was administered at a dose of 1.5 g/day, which was then increased to 3 g/day and maintained for 6 months. Total cholesterol, LDL cholesterol, TG, and HDL cholesterol were recorded and compared among treatment groups, as were aspartate transaminase (AST) and alkaline phosphatase levels, symptomatic side effects, and adherence to therapy. Mean (\pm SD) LDL cholesterol levels were 208 ± 51 mg/dL in the IR group and 201 ± 45 mg/dL in the SR group at baseline. Over 2 to 6 months, mean LDL cholesterol was reduced by 21.1% and 12.8% in the IR and SR groups, respectively; this difference was only significant between groups at month 6 ($P < .05$). Mean baseline HDL cholesterol levels were approximately 49 mg/dL in both groups.

Niacin IR increased mean HDL cholesterol levels to a significantly greater extent at 2, 3, and 4 months (to 62, 64, and 64 mg/dL, respectively) compared with values in the SR group ($P < .05$).

Concentrations of TG, which averaged approximately 167 mg/dL in the IR group and 180 mg/dL in the SR group at baseline, were reduced by an average of 27% in the IR group versus 8% in the SR group ($P<.05$). Alkaline phosphatase levels increased significantly from baseline ($P<.05$) and there was a trend toward increasing levels of AST in the SR group, but not in the IR group.¹ Flushing was reported in 100% of patients in the IR group, but also in a surprisingly high 82% of the SR group. Indigestion (12% vs 0%), nausea (38% vs 8%), vomiting (18% vs 0%), diarrhea (45% vs 22%), male sexual dysfunction (22% vs 3%), and fatigue (24% vs 3%) were all more common in the SR versus the IR niacin group ($P<.05$).

Additionally, over months 2 to 6, a higher dose of niacin IR was tolerated (~2.7 g), compared with niacin SR (~2.0 g).¹ These data confirm that flushing is more common with niacin IR than niacin SR, and that, even with lower daily doses, niacin SR compared with niacin IR shows a trend towards increased liver enzyme levels.

Figure 2A. Percent Change in HDL Cholesterol: Niacin IR Versus Niacin SR



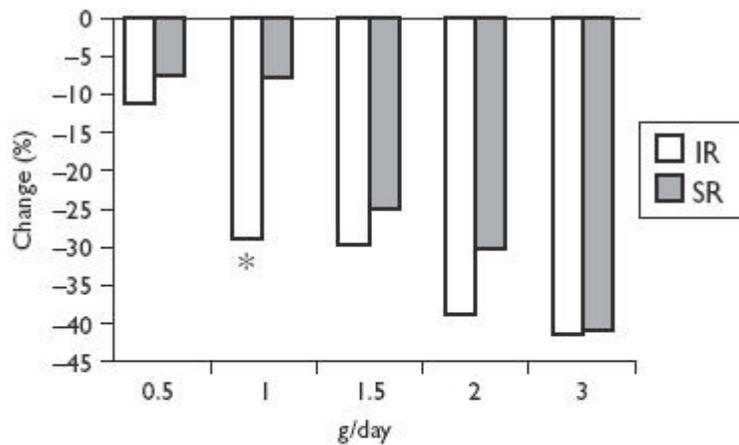
* $P<.05$; HDL indicates high-density lipoprotein; IR, immediate-release niacin; and SR, sustained-release niacin.

Source: Adapted from McKenney JM, Proctor JD, Harris S, Chinchilli VM. A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA*. 1994;271:672-677. Used with permission from the American Medical Association.

The relative safety and efficacy of niacin products was also compared in an important study published in 1994 by McKenney and colleagues.⁸ In this study, 46 dyslipidemic patients were randomized to either niacin IR (Rugby Laboratories) or SR (Goldline Laboratories) for 30 weeks. Escalating doses of 0.5, 1, 1.5, 2, and 3 g/day were sequentially administered in 6-week intervals.

Patients were advised to take an adult aspirin tablet 30 minutes before the morning niacin dose and to take each dose with food to minimize adverse effects. Outcome measures included lipid values, liver enzyme levels, symptomatic side effects, and withdrawal rates as a measure of adherence to therapy.

Figure 2B. Percent Change in TG: Niacin IR Versus Niacin SR

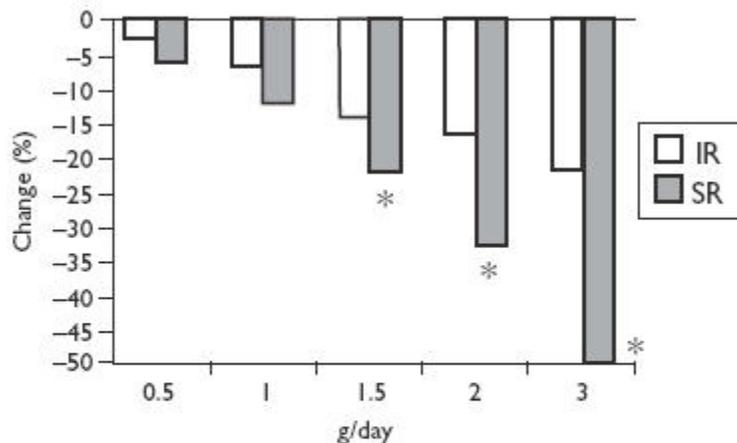


* $P < .05$; TG indicates triglycerides; IR, immediate-release niacin; SR, sustained-release niacin.

Source: Adapted from McKenney JM, Proctor JD, Harris S, Chinchilli VM. A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA*. 1994;271:672-677. Used with permission from the American Medical Association.

Niacin IR was associated with significantly greater increases in HDL cholesterol levels than niacin SR at all doses ($P_{.02}$) (**Figure 2A**). Niacin IR (1 g/day) caused significantly greater reductions in TG than niacin SR ($P = .009$) with a nonsignificant trend at doses ≥ 1.5 g/day (**Figure 2B**). In contrast, niacin SR reduced LDL cholesterol levels significantly more at ≥ 1.5 g/day compared with niacin IR ($P_{.04}$) (**Figure 2C**).

Figure 2C. Percent Change in LDL Cholesterol: Niacin IR Versus Niacin SR



* $P < .05$; LDL indicates low-density lipoprotein; IR, immediate-release niacin; SR, sustained-release niacin.

Source: Adapted from McKenney JM, Proctor JD, Harris S, Chinchili VM. A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA*. 1994;271:672-677. Used with permission from the American Medical Association.

At 1 g/day of niacin IR, the HDL cholesterol levels of all 23 patients were increased, while with the same dose of niacin SR, levels were increased in only 15 of the 23 patients. As expected, the IR group reported a higher incidence of flushing, ranging from 29% to 53% compared with 13% to 22% in the SR group, and the incidence of gastrointestinal (GI) intolerance and fatigue was higher in the SR group than in the IR group (56% vs 14% and 33% vs 14%, respectively, at the 3 g/day dosage).

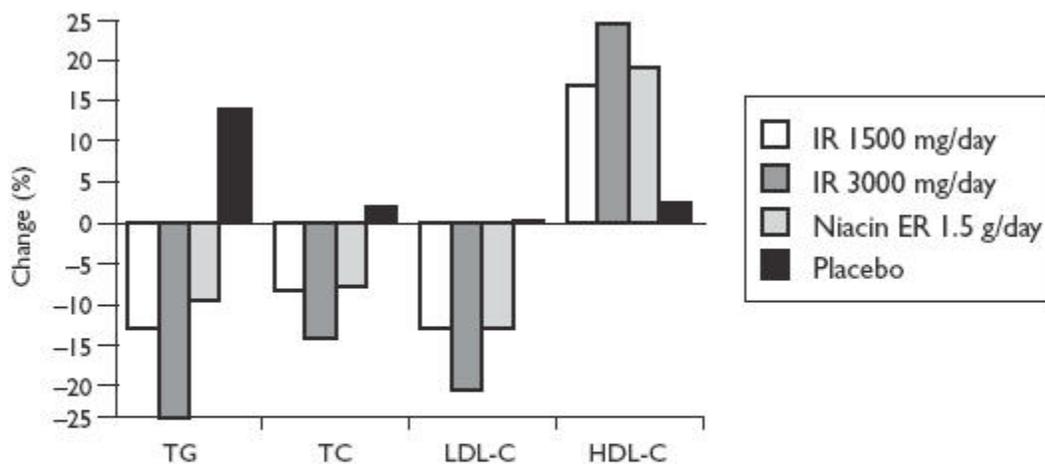
Perhaps most important, mean levels of AST and alanine aminotransferase (ALT) were significantly elevated over baseline levels ($P < .05$) in patients receiving ≥ 1.5 g/day of niacin SR, while no significant increases were observed in the IR group. Of the 23 patients receiving the SR formulation, 18 (78%) were withdrawn from the study, as compared with 9 of 23 (39%) patients in the IR group.

Of the patients withdrawn from the SR group, 12 (67%) had liver aminotransferase elevations >3 times the upper limit of normal, of which 5 also had symptoms of hepatic dysfunction (ie, fatigue, nausea, and anorexia).⁸

The efficacy and safety of niacin ER has been compared with that of niacin IR (research formulation) in a double-blind trial enrolling 223 dyslipidemic patients randomized to niacin ER (n = 76), niacin IR (n = 74), or placebo (n = 73) for 25 weeks.⁷ The niacin dose was titrated over 4 weeks to 1.5 g/day of niacin IR (500 mg tid) and 1.5 g/day at bedtime of niacin ER.

After week 8 of the study, the dose of niacin IR was increased to 3.0 g/day (1 g tid). Lipid values, liver enzyme levels, symptomatic side effects, and adherence to therapy were recorded. At a daily dose of 1.5 g/day, niacin IR and niacin ER produced similar reductions in TG, TC, and LDL cholesterol and similar increases in HDL cholesterol (**Figure 3**).⁷

Figure 3. Percent Change in TC, LDL-C, TG and HDL-C Levels from Baseline in Patients Treated with Niacin ER Versus Niacin IR



All values $P < .05$ versus baseline and placebo. IR indicates immediate-release; ER, extended-release; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Source: Adapted with permission from Knopp RH, Alagona P, Davidson M, et al. Equivalent efficacy of a time-release form of niacin (Niaspan) given once-a-night versus plain niacin in the management of hyperlipidemia. *Metabolism*. 1998;47:1097-1104.

As compared with both niacin ER (1.5 g/day) and niacin IR (1.5 g/day), niacin IR at 3 g/day produced significantly greater reductions in levels of TG (16%, 18%, and 29%, respectively), TC (8%, 8%, and 15%, respectively), and LDL cholesterol (12%, 12%, 22%, respectively).

High-density lipoprotein cholesterol levels were similarly elevated by all 3 niacin formulations (20%, 17%, and 24%, respectively). Liver enzyme levels were not significantly elevated, either clinically or statistically, over the course of the trial in either treatment group. The number of patients reporting flushing events during the titration phase in weeks 1 and 2 was greater in the niacin IR group than in the niacin ER group (54 vs 26, $P<.001$).

Fewer patients experienced flushing as the study progressed; by week 16, only 33% of niacin ER and 44% of niacin IR-treated patients continued to report flushing episodes. The total number of flushing events was significantly higher in the niacin IR group compared with the niacin ER group (1905 vs 576 episodes; $P<.001$), and GI side effects were similar in both treatment groups, as was the incidence of pruritus and the percent of patients who withdrew from the study.⁷

The results of these studies highlight the potential advantages and disadvantages of each niacin formulation. Niacin IR is associated with greater increases in HDL cholesterol, greater decreases in TG, and comparable lowering of LDL cholesterol compared with equivalent doses of niacin SR.

A greater incidence of flushing is seen with niacin IR, yet niacin SR can produce unacceptably high levels in liver enzymes and more frequent GI side effects.^{1,8} Niacin ER has demonstrated comparable efficacy to niacin IR and is associated with a significantly lower incidence of flushing without the increased hepatic risk seen with niacin SR.⁷

The Pharmacists' Role

The pharmacist is in a unique position to appropriately counsel patients when selecting a niacin product, especially over-the-counter formulations. To assist health practitioners, both the American Society of Health-System Pharmacists and the Center for Drug Evaluation and Research within the FDA released position statements in 1997 that discourage patients from taking niacin for dyslipidemia without medical supervision. The American Society of Health-System Pharmacists position statement is as follows:

“Because a variety of nonprescription niacin products with various potentials for toxicity are available, pharmacists should actively monitor patient selection of niacin products and discourage patient self-treatment with niacin.”¹¹

The FDA recommendation is as follows:

“Drug treatments for hypercholesterolemia should not be sold over the counter in the United States because treatment requires both accurate diagnosis and clinical testing and careful practitioner-directed medical management.”¹²

In addition, pharmacists can recommend several strategies for minimizing the incidence and severity of flushing episodes. Aspirin or other nonsteroidal prostaglandin inhibitors can be taken approximately 30 minutes before taking niacin. Patients also should avoid spicy foods, hot beverages, or hot showers soon after dosing, and interruption in therapy should be avoided to maintain any tolerance to flushing that develops.

Furthermore, niacin ER, which is taken once daily at bedtime, may be a favorable option, as most flushing will occur while the patient is sleeping, and the once-daily dosing may increase adherence.^{6,13,14}

Conclusion

Niacin is a safe and effective therapeutic agent for the management of patients with dyslipidemias. Achieving the most therapeutic benefit from niacin therapy with minimal adverse effects is best done under the supervision of a healthcare practitioner.

Pharmacists can play a particularly important role in educating patients about the differences in available niacin formulations. Greatest efficacy and tolerability appears to be optimally attained with niacin ER, which has an efficacy profile similar to niacin IR, a reduced incidence of flushing compared with niacin IR, and no increased risk of hepatotoxicity as is seen with niacin SR.

In summary, niacin is the only lipid-modifying agent available that favorably affects all aspects of the lipid profile, and should be considered an important therapeutic option for patients with dyslipidemias.

... REFERENCES ...

1. **Knopp RH, Ginsberg J, Albers JJ, et al.** Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues to mechanism of action of niacin. *Metabolism*. 1985;34:642-650.
2. **Grundy SM, Mok HY, Zech L, Berman M.** Influence of nicotinic acid on metabolism of cholesterol and triglycerides in man. *J Lipid Res*. 1981;22:24-36.
3. **Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.** *National Cholesterol Education Program: Adult Treatment Panel III Report*. Bethesda, Md: National Heart, Lung, and Blood Institute; 2001. Publication No. 01-3095.
4. **The Coronary Drug Project Research Group.** Clofibrate and niacin in coronary heart disease. *JAMA*. 1975;231:360-381.
5. **Canner PL, Berge KG, Wenger NK, et al, for the Coronary Drug Project Research Group.** Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986;8:1245-1255.
6. **Knopp RH.** Evaluating niacin in its various forms. *Am J Cardiol*. 2000;86(suppl):51L-56L.
7. **Knopp RH, Alagona P, Davidson M, et al.** Equivalent efficacy of a time-release form of niacin (Niaspan) given once-a-night versus plain niacin in

the management of hyperlipidemia. *Metabolism*. 1998;47:1097-1104.

8. McKenney JM, Proctor JD, Harris S, Chinchili VM. A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA*. 1994;271:672-677.

9. Piepho RW. The pharmacokinetics and pharmacodynamics of agents proven to raise high-density lipoprotein cholesterol. *Am J Cardiol*. 2000;86(suppl):35L-40L.

10. Stern RH, Freeman D, Spence JD. Differences in metabolism of time-release and unmodified nicotinic acid: explanation of the differences in hypolipidemic action? *Metabolism*. 1992;41:879-881.

11. American Society of Health-System Pharmacists.

ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm*. 1997;54:2815-2819.

12. Center for Drug Evaluation and Research.

Guidance for Industry. OTC Treatment for Hypercholesterolemia. Rockville, Md: US Food and Drug Administration; 1997.

13. Wilkin JK, Wilkin O, Kapp R, et al. Aspirin blocks nicotinic acid-induced flushing. *Clin Pharmacol Ther*. 1982;31:478-482.

14. Capuzzi DM, Morgan JM, Brusco OA, Jr., Intenzo CM. Niacin dosing: relationship to benefits and adverse effects. *Curr Atheroscler Rep*. 2000;2:64-71. **S314** THE