Varying Cost and Free Nicotinic Acid Content in Over-the-Counter Niacin Preparations for Dyslipidemia

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Background: **Nicotinic acid is an effective treatment for dyslipidemia, but the content of over-the-counter niacin is not federally regulated. As a result, patients may use preparations of over-the-counter niacin that do not contain free nicotinic acid.**

Objective: **To characterize the types, costs, and free nicotinic acid content of over-the-counter niacin preparations and to review literature on the use of over-the-counter niacin for dyslipidemia.**

Data Sources: **Commonly used over-the-counter niacin preparations (500-mg tablets or capsules) from the 3 categories of immediate-release, sustained-release, and no-flush were purchased at health food stores and pharmacies and from Internet-based vitamin companies. Pertinent literature on the use of over-the-counter niacin was obtained by searching PubMed.**

Measurements: **For each preparation studied, the monthly cost of therapy (at 2000 mg/d) and the free nicotinic acid content (quantified by high-performance liquid chromatography) were reported.**

Data Synthesis: **On average, immediate-release niacin preparations cost $7.10 per month, sustained-release preparations cost $9.75 per month, and no-flush preparations cost $21.70 per month. The average content of free nicotinic acid was 520.4 mg for immediate-release niacin, 502.6 mg for sustained-release niacin, and 0 for no-flush niacin.**

Conclusions: **No-flush preparations of over-the-counter niacin contain no free nicotinic acid and should not be used to treat dyslipidemia. Over-the-counter sustained-release niacin contains free nicotinic acid, but some brands are hepatotoxic. Immediate-release niacin contains free nicotinic acid and is the least expensive form of over-the-counter niacin.**

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The essential role of nicotinic acid in human metabolism was first shown in 1937, when researchers found it prevented pellagra (1). Pellagra, which manifests as the triad of dermatitis, diarrhea, and dementia, is caused by an intracellular deficiency of the cofactor nicotinamide adenine dinucleotide. Nicotinic acid and its amide form, nicotinamide, prevent pellagra, as both are precursors of nicotinamide adenine dinucleotide. Initially called the pellagra-preventing, or PP, vitamins, nicotinic acid and nicotinamide were later classified as vitamin B_3. The term *niacin* (*nic*otinic *ac*id vitam*in*) was coined in 1942 and referred to both nicotinic acid and nicotinamide (2). The recommended daily allowance of niacin ranges from 14 to 18 mg (3); because bread and cereal are supplemented with niacin, pellagra is essentially nonexistent in the United States.

With the discovery in 1955 that nicotinic acid (but not nicotinamide) in daily doses of 1000 to 4000 mg reduced total cholesterol level in hyperlipidemic persons (4), it became the first agent used to treat dyslipidemia (5). Although how nicotinic acid lowers lipid levels remains unclear, it improves the clinical lipid profile in several ways: Total triglyceride levels are reduced by 20% to 50% (6, 7); low-density lipoprotein (LDL) cholesterol levels are reduced by 10% to 25% (6, 7), including a preferential decrease in the more atherogenic population of small dense LDL (8); high-density lipoprotein (HDL) cholesterol levels are increased by 10% to 30%, with a preferential increase in the more atheroprotective HDL-2 subclass (9, 10); and lipoprotein(a) levels are lowered by 10% to 30% (11, 12). Such broad-ranging effects make nicotinic acid an effective tool in the treatment of most lipid disorders, including dyslipidemia of the metabolic syndrome (13).

Nicotinic acid was also the first lipid-lowering medication to significantly reduce cardiovascular events in at-risk patients. The Coronary Drug Project (1969 to 1975), a randomized, placebo-controlled trial of 3908 men, showed that 6 years of nicotinic acid therapy reduced the occurrence of nonfatal myocardial infarction compared with placebo (14). After 9 more years of follow-up, patients receiving nicotinic acid also had an 11% reduction in all-cause mortality compared with those receiving placebo (15). More recent data have shown that nicotinic acid combined with a bile-acid sequestrant (16, 17) or a statin (18) causes angiographic regression of atherosclerosis and reduces clinical cardiovascular events.

Despite the versatility of nicotinic acid in treating a range of lipid disorders and the compelling clinical evidence of mortality reduction, this medication has not become a first-line treatment. One reason for its underuse is the side effects. After administration of nicotinic acid in doses as low as 100 mg, cutaneous symptoms, including redness, itching, burning, and paresthesias, occur (19). This "niacin flush" begins as soon as 10 to 15 minutes after ingestion and lasts 30 to 60 minutes. The flushing is thought to be most intense when levels of free nicotinic acid are increasing in the serum (20). Fortunately, both the frequency and severity of flushing episodes decrease with repeated doses of nicotinic acid. Although many patients stop flushing within 1 week of initiating therapy, this side effect has contributed to discontinuance rates higher than 40% in some clinical series (21). Other less common but

serious side effects include hepatotoxicity (22), insulin resistance and hyperglycemia (23), and hyperuricemia (24).

A second reason for the underuse of nicotinic acid is confusion about the many prescription and over-the-counter preparations marketed as niacin. Niacin is classified as a dietary supplement, and therefore the production and marketing are not strictly regulated by the U.S. Food and Drug Administration (FDA). Without FDA regulation, over-the-counter niacin preparations are readily available and inexpensive, but the free nicotinic acid content is not guaranteed. Scores of companies sell hundreds of niacin products differing in name, appearance, formulation, dose, and cost. To add to the confusion, nicotinamide is also marketed as niacin, even though it has no lipid-lowering effects (4). The dizzying array of over-the-counter niacin products makes it difficult to know which preparations actually contain free nicotinic acid and might be efficacious in treating dyslipidemia.

Over the last several years, patients have been referred to the University of Washington Medical Center Lipid Clinic in Seattle, Washington, because of apparent failure to respond to over-the-counter niacin therapy. In reviewing these cases, we became suspicious that some over-the-counter niacin products did not contain free nicotinic acid. This study was designed to evaluate 3 aspects of over-the-counter niacin preparations: 1) What types of over-the-counter niacin preparation are generally available? 2) What are the costs of the various over-the-counter niacin preparations? 3) What is the content of free nicotinic acid in these over-the-counter niacin preparations?

Key Summary Points: Types of Niacin Preparations

No-flush (inositol hexaniacinate)

- Most expensive form ($21.70 per month); contains no free nicotinic acid
- Ineffective lipid lowering in humans; should not be used to treat dyslipidemia

Sustained-release

- Less expensive form ($9.76 per month); contains a full amount of free nicotinic acid
- Hepatotoxicity associated with several formulations; some brands are safe

Immediate-release

- Least expensive form ($7.10 per month); contains a full amount of free nicotinic acid
- Used safely for more than 40 years; shown to prevent cardiovascular disease and death

METHODS

Procurement of Niacin Preparations

Over-the-counter niacin preparations are divided into 3 categories: immediate release, sustained release, and no flush. Immediate-release niacin preparations are absorbed within 1 hour of ingestion and are marketed as "immediate-release," "crystalline," or "plain" niacin. Sustained-release preparations are absorbed slowly over several hours and are marketed as "sustained-release," "controlled-release," or "timed-release" niacin. No-flush niacin is marketed as "no-flush," "zero-flush," or "flush-free" niacin.

We studied 10 brands each of immediate-release and no-flush niacin and 9 brands of sustained-release niacin, for a total of 29 preparations. Commonly used brands of niacin were identified in 2 ways. First, we sent an informal e-mail survey to clinical lipidologists in the United States, asking which niacin brands they typically recommended to their patients. Second, after consulting national sales figures, we identified top-selling over-the-counter niacin brands. The niacin preparations were purchased at local health food stores and pharmacies as well as from Internet-based vitamin supply companies. We studied only preparations advertised as containing 500 mg of niacin. We did not test niacin preparations labeled "nicotinamide" or "niacinamide," nor did we evaluate prescription brands of niacin.

Cost Analysis

We recorded the retail purchase price to the investigator for each niacin preparation. Then we calculated the cost of each preparation from the purchase price and expressed it as U.S. dollars per milligram. The cost of a month's supply of niacin therapy (at a dose of 2000 mg/d, the maximum recommended dosage for sustained-release niacin preparations) was calculated as follows:

$$\text{monthly cost} = (\$/\text{mg}) \times (2000\ \text{mg/d}) \times (30\ \text{d/mo}).$$

Measurement of Free Nicotinic Acid

We analyzed in duplicate the free nicotinic acid content of each niacin preparation as follows. Individual niacin pills (tablets or capsules) were weighed and then ground to a fine powder. One mg of the resulting powder was dissolved in 1 mL of water and filtered through a syringe nylon filter to yield a sample solution of 1 mg/mL. An aliquot (100 μL) of the sample solution was combined with 50 μL of 6-methyl nicotinic acid in water (1 mg/mL) and 850 μL of high-performance liquid chromatography (HPLC) mobile phase to yield 1 mL in final volume. This mixture was then transferred to an autosampler vial and analyzed by HPLC.

We did the chromatographic separation as previously described by Miyauchi, with minor modifications (25). In brief, we performed HPLC using an HP 1050 LC system (Hewlett Packard, Wilmington, Delaware) equipped with an ultraviolet detector at 245 nm. Separation was achieved on a Microsorb-mv C18 column (Rainin, Oakland, California) using an isocratic elution with 93% of 10-mmol sodium phosphate per L and 7% of acetonitrile containing 10 mmol of octane sulfonate per L (pH, 2.1). The mobile phase was delivered at 1 mL/min. We estimated the free nicotinic acid content in each solubilized aliquot from a

calibration curve that was constructed using a known nicotinic acid standard. We calculated the total nicotinic acid content in each preparation by multiplying the amount of free nicotinic acid measured in the 1-mg sample aliquots by the total weight of the individual sample pill. We noted the expiration dates of each product, and all analyses took place well before the expiration dates.

Statistical Analysis

We used Prism statistical software (GraphPad Software, San Diego, California) for data compilation and statistical analysis. We calculated monthly cost and free nicotinic acid content as described and compared them using the unpaired Student *t*-test, with a *P* value for statistical significance set at less than 0.05. All data are presented as means (± SE).

DATA SYNTHESIS

Cost of Niacin Preparations

We analyzed 29 over-the-counter niacin preparations (**Table**). We purchased 16 niacin preparations from health food stores and pharmacies and 13 preparations from Internet-based suppliers. The average cost of niacin samples purchased from health food stores or pharmacies compared with the cost of those purchased over the Internet did not differ (data not shown).

Table. **Over-the-Counter Niacin Preparations**

Name of Manufacturer	Location of Manufacturer	Formulation	Monthly Cost, $
Immediate-release			
Rugby	Westbury, NY	Tablet (scored)	1.48
Bartell's	Seattle, WA	Tablet	4.19
Natural Factors	Everett, WA	Tablet	5.19
Carlson	Arlington Heights, IL	Tablet	6.62
Solaray	Park City, UT	Capsule	6.74
Twinlab	Ronkonkoma, NY	Capsule	6.74
Major	Livonia, MI	Tablet	6.95
Country Life	Hawppauge, NY	Tablet	8.48
Solgar	Leonia, NJ	Capsule	9.58
Squibb	Princeton, NJ	Tablet	14.99
Sustained-release			
Trader Darwin's	Monrovia, CA	Tablet	3.59
NOW	Bloomingdale, IL	Tablet	4.79
Sundown	Boca Raton, FL	Capsule	6.01
Major	Livonia, MI	Tablet	6.01
Carlson	Arlington Heights, IL	Tablet	9.11
Source Naturals	Scotts Valley, CA	Tablet	9.94
Enduracin	Tigard, OR	Capsule	14.39
Nature's Bounty	Bohemia, NY	Tablet	15.97
Slo-Niacin	Minneapolis, MN	Tablet (scored)	17.99
No-flush			
Vitamin Shoppe	North Bergen, NJ	Capsule	13.64
Solaray	Park City, UT	Capsule	16.70
Natural Factors	Everett, WA	Capsule	17.59
AOR	Calgary, Alberta, Canada	Capsule	18.07
Natrol	Chatsworth, CA	Tablet	21.84
Source Naturals	Scotts Valley, CA	Tablet	22.36
Solgar	Leonia, NJ	Capsule	22.85
KAL	Park City, UT	Capsule	23.34
Twinlab	Ronkonkoma, NY	Capsule	29.40
Country Life	Hawppauge, NY	Capsule	31.20

Monthly costs in the immediate-release category varied widely, with a 10-fold difference between the least expensive brand ($1.48 per month) and the most expensive brand ($14.99 per month). The **Table** lists the manufacturer names, location, formulation type, and monthly cost of the 10 immediate-release niacin preparations studied. Variability in the monthly cost of the sustained-release niacin preparations was similar (**Table**) and ranged from a low of $3.59 per month to a high of $17.99 per month.

No-flush over-the-counter niacin (**Table**) was the most expensive, ranging from a low of $13.64 per month to a high of $31.20 per month. The cost of the most expensive brand of no-flush niacin was 20 times greater than that of the least expensive immediate-release niacin brand ($1.48 per month).

The average cost of 1 month of niacin therapy (at 2000 mg/d) was calculated for each of the 3 niacin categories (**Figure 1**, *top*). The least expensive category was immediate-release niacin, which averaged $7.10 ± $1.13 per month. Sustained-release niacin was somewhat more expensive, averaging $9.76 ± $1.74 per month. No-flush niacin was the most expensive, averaging $21.70 ± $1.95 per month, or more than double the average cost of either immediate-release or sustained-release niacin. The price differences between no-flush niacin and the other preparations were statistically significant ($P < 0.001$ for both immediate-release and sustained-release niacin compared with no-flush niacin).

Free Nicotinic Acid Content of Niacin Preparations

On average, the immediate-release niacin preparations contained 520.4 ± 12.6 mg of free nicotinic acid per pill (range, 457 to 570 mg). The bottom panel of **Figure 1** shows the average free nicotinic acid content per pill. Preparations of sustained-release niacin contained an average of 502.6 ± 19.3 mg of free nicotinic acid per pill (range, 423 to 620 mg). No statistically significant difference in the average free nicotinic acid contents existed between the immediate-release and sustained-release categories.

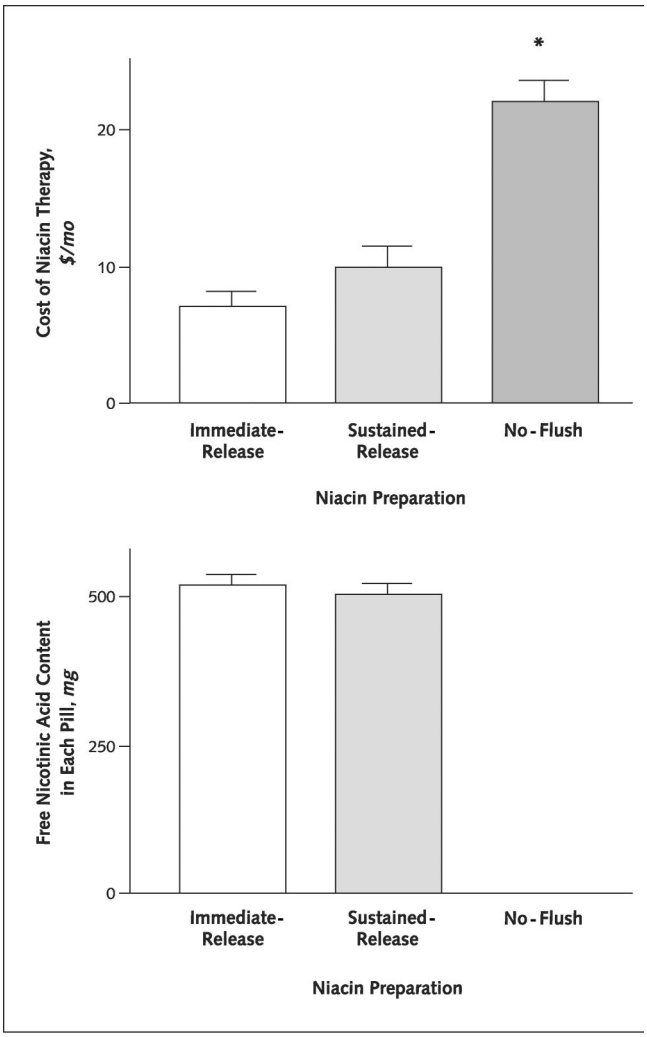
None of the 10 no-flush niacin preparations contained detectable free nicotinic acid, even when samples were dissolved by using a variety of solvents (water, dimethyl sulfoxide, ethyl acetate, or acetonitrile) and acid–base conditions (pH, 2.0 to 10.0). Several of the no-flush preparations were further tested for levels of nicotinamide, which was also not detected. The labels of the no-flush preparations showed that the form of nicotinic acid supplied in each was inositol hexaniacinate.

DISCUSSION

No-Flush Niacin (Inositol Hexaniacinate)

To make nicotinic acid therapy more tolerable, researchers have studied the effect of several synthetic prodrug esters of nicotinic acid in humans, albeit with discouraging results (26). It was hoped that these intact esters would be absorbed into the bloodstream, then slowly hy-

Figure 1. **Cost and content of over-the-counter niacin preparations.**



Top. Monthly cost (in U.S. dollars per month) for 2000 mg of over-the-counter niacin per day (*$P < 0.001$ for both immediate-release and sustained-release compared with no-flush niacin). **Bottom.** Content of free nicotinic acid (in milligrams per pill) in over-the-counter niacin preparations. Free nicotinic acid was measured by using high-performance liquid chromatography.

drolyzed, releasing enough free nicotinic acid to reduce lipid levels without causing flushing. One such ester is inositol hexaniacinate, a chemical containing 6 molecules of nicotinic acid esterified to 1 molecule of the inositol. Although treatment with inositol hexaniacinate showed promising lipid-lowering effects in a rabbit model of hyperlipidemia (27), this agent has little if any effect on lipid levels in humans (28). To our knowledge, no randomized, placebo-controlled trials have shown the efficacy of inositol hexaniacinate in lowering lipid levels, and several studies suggest the treatment has no effect on lipoprotein levels (26, 29).

Gastrointestinal absorption of inositol hexaniacinate varies widely, with an average of only 70% of an orally ingested dose absorbed into the bloodstream (30). Once inositol hexaniacinate is present in human serum, hydrolysis of the ester bonds and release of free nicotinic acid take more than 48 hours, significantly longer than when inositol hexaniacinate is incubated in rat or dog serum (31). This finding may explain why inositol hexaniacinate is effective in some animals (27) but not in humans (26). After an oral dose of 1600 mg of inositol hexaniacinate in humans, plasma levels of free nicotinic acid peak at around 0.6 μmol/L (32). In contrast, after an oral dose of 1000 mg of crystalline niacin, plasma levels of free nicotinic acid peak at 244 μmol/L (33), whereas with sustained-release niacin (at 2 g/d), plasma levels of free nicotinic acid reach a steady state between 22 and 40 μmol/L (34).

The vitamin and supplement industry continues to market inositol hexaniacinate as no-flush niacin (35). Although vendors of inositol hexaniacinate may not explicitly claim beneficial lipid-lowering effects, uninformed patients may purchase and use these preparations to treat dyslipidemia. Use of inositol hexaniacinate may be detrimental in 2 ways: Patients waste resources on an unproven therapy, and they miss the opportunity to take a beneficial form of lipid therapy. Therefore, we recommend that inositol hexaniacinate not be used to treat dyslipidemia.

Sustained-Release Niacin

A more successful strategy to improve the tolerability of nicotinic acid has come with the development of sustained-release formulations, which appear to cause less flushing and have higher adherence rates than immediate-release niacin (36, 37). However, several sustained-release niacin preparations have been shown to be more hepatotoxic than immediate-release niacin (38, 39), and the use of some preparations has resulted in fulminant hepatic failure (40, 41). Because of this danger, we believe that the use of over-the-counter sustained-release niacin should be limited to products that have been objectively shown to be safe and effective.

Clinical data have been published for 2 over-the-counter sustained-release niacin brands. A retrospective study of 969 patients treated with Slo-Niacin (Upsher Smith, Minneapolis, Minnesota) and followed for an average of 13 months showed favorable lipoprotein changes, although nearly half the study sample discontinued therapy because of adverse effects (21). Probable niacin-induced hepatotoxicity occurred in only 2.2% of the study sample, primarily occurring in patients with preexisting liver disease or alcohol use. In a recent randomized, controlled trial involving 160 patients, Slo-Niacin, in combination with simvastatin, substantially improved LDL and HDL cholesterol levels and promoted regression of arteriographic atherosclerosis regression (18). Enduracin (Endurance Products Co., Tigard, Oregon), a wax matrix–based form of over-the-counter niacin, also has some published evidence of efficacy and safety. In 2 randomized, controlled trials involving a total of 290 patients (42, 43), Enduracin, when

Figure 2. **Patient information for initiation of immediate-release niacin therapy.**

Purchase plain or crystalline niacin (nicotinic acid) — 500-mg tablets

Week	Breakfast	Lunch	Dinner
1	–	–	1/2 tablet
2	1/2 tablet	–	1/2 tablet
3	1/2 tablet	1/2 tablet	1/2 tablet
4	1/2 tablet	1/2 tablet	1 tablet
5	1 tablet	1/2 tablet	1 tablet
6	1 tablet	1 tablet	1 tablet

Helpful Hints

1. Flushing and itching are the major side effects of this medicine.
2. Flushing symptoms may be reduced by:
   a. Taking niacin after meals.
   b. Taking aspirin (81 mg) 30 minutes before niacin.
   c. Avoiding hot drinks and alcohol with niacin.
3. Do not use "no-flush" or "flush-free" niacin, or nicotinamide.
4. Never interchange plain niacin with sustained-release niacin unless under physician supervision.

compared with placebo, was shown to improve lipoprotein profiles without increasing the frequency of abnormal findings on liver function tests.

In 1998, the FDA approved the first extended-release prescription form of nicotinic acid for the treatment of dyslipidemia—Niaspan (Kos Pharmaceuticals, Miami, Florida). This formulation has proven to be safe and effective in several patient populations, including those with type 2 diabetes (44, 45). Niaspan appears as effective as immediate-release niacin on a gram-for-gram basis, with fewer (albeit more severe) flushing episodes (8). Despite its tolerability and convenient once-a-day dosing, Niaspan is relatively expensive compared with over-the-counter forms of niacin, with an average wholesale price of $84.89 per month at 2000 mg/d (46).

Immediate-Release Niacin

Immediate-release over-the-counter niacin has several advantages over other forms of nicotinic acid. First, immediate-release niacin has been used safely for more than 40 years. Second, it is the only monotherapy form of niacin shown to prevent cardiovascular events and death (14, 15). Third, it is inexpensive, available for less than $10 per month at 2000 mg/d (**Table**). Fourth, if needed, immediate-release niacin may be titrated to dosages of 6000 mg/d, allowing more flexibility and power in achieving lipid-level goals than does sustained-release niacin.

Although many clinical trials show the benefit of immediate-release niacin (4–7, 9–12, 15), we know of only 2 trials that specifically mention the brand name. In 1 retrospective study, 101 patients treated with either Squibb (Princeton, New Jersey) immediate-release or sustained-release niacin had beneficial changes in lipid levels, albeit with a 19% occurrence of abnormal findings on transient liver function tests (47). Because analysis was pooled, the beneficial or detrimental effects cannot be attributed to either the immediate-release or sustained-release preparation alone. A randomized, controlled trial involving 46 patients showed that 2000 mg of Rugby (Westbury, New York) immediate-release niacin per day lowered triglyceride levels by 39%, lowered LDL cholesterol levels by 16%, and increased HDL cholesterol levels by 31%, without increasing liver function test results (7). With a relative paucity of clinical trial data, other criteria must be used to help decide which over-the-counter brands of immediate-release niacin to use.

There are several reasons to consider the use of Rugby immediate-release niacin. In addition to the efficacy and safety shown in the clinical trial (7), Rugby is the least expensive brand of immediate-release niacin we studied. It effectively treats dyslipidemia for less than $3 per month. The tablets are scored, making dosing titration easier. With any form of immediate-release niacin, patients must be willing to tolerate more flushing and 3-times-daily dosing. But in those patients able to tolerate immediate-release niacin, drug costs can be lower than $50 per year, representing a substantial savings compared with any prescription lipid-altering drug.

The FDA has approved 1 prescription brand of immediate-release nicotinic acid for the treatment of dyslipidemia—Niacor (Uspher-Smith, Minneapolis, Minnesota). A recent placebo-controlled trial of 468 patients has shown that Niacor is safe and effective (48). The cost of Niacor, with an average wholesale price of $33.80 per month at 2000 mg/d (46), is higher than over-the-counter brands of immediate-release niacin.

Summary and Recommendations

In summary, over-the-counter niacin preparations are marketed under many names and have a wide range of costs; some products contain no free nicotinic acid (Key Summary Points). No-flush niacin is the most expensive of the niacin preparations, yet contains no free nicotinic acid and should not be used to treat dyslipidemia. Sustained-release brands are inexpensive and contain a full amount of free nicotinic acid, but several preparations have been associated with increased hepatotoxicity. Immediate-release niacin brands are the least expensive preparations, with some brands costing less than $5 per month. Furthermore, immediate-release niacin contains a full amount of nicotinic acid and is the only form of niacin shown to prevent cardiovascular disease and death.

We recommend immediate-release niacin (Rugby), which comes in scored 500-mg tablets. The patient begins therapy with 250 mg after dinner for the first week. Additional 250-mg doses after breakfast and lunch are added each week, and the dose is titrated up to 500 mg 3 times a

day over the course of 6 weeks. The patient must be told that they will flush with the first dose of niacin. The flushing can be markedly lessened with a few simple steps: 1) Take niacin at the end of a meal; 2) take aspirin (81 mg) before the meal; and 3) avoid hot drinks and alcohol around the time of niacin ingestion. **Figure 2** is a helpful information sheet distributed to our patients who are beginning niacin therapy. In our experience, patient education is vital, and most patients can tolerate this 6-week titration schedule.

Baseline laboratory tests (fasting glucose, liver aminotransferase levels, and uric acid) should be done on all patients before niacin therapy begins. Tests should be repeated 6 to 8 weeks after niacin therapy is begun as well as after any dose increases. Once the patients are receiving a stable dose of niacin, these tests should be done less frequently or as clinically indicated. Patients should not increase niacin dose without physician supervision and should never substitute immediate-release niacin with sustained-release niacin at an equivalent dose because of the risk for hepatotoxicity (38).

APPENDIX

The articles cited herein were taken from a larger pool of literature on niacin obtained by searching PubMed using the identifiers *dyslipidemia*, *niacin*, *nicotinic acid*, and *inositol hexaniacinate* and by reviewing the reference lists of germane articles on niacin. Citations were selected for inclusion in this manuscript on the basis of the authors' subjective assessments of their pertinence.

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