

## **Wax-Matrix Sustained-Release Nicotinic Acid**

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### **INTRODUCTION:**

Today we have more options than ever for the pharmacological management of hyperlipemia. Some of the newer agents have unprecedented potency in lowering LDL cholesterol while others may be better at reducing triglycerides or improving HDL. Keeping track of which drugs are best for which lipid problems can be a challenge in the everyday practice of medicine. I offer here a simple rationale for selecting a first choice in lipid management. If you follow this rationale I think you will find that nicotinic acid or niacin is the best first choice, and that among the niacin preparations wax-matrix CNA (controlled release niacin) is by far the best available.

### **SELECTING A LIPID LOWERING DRUG:**

In selecting a lipid lowering drug, we must consider three important factors. First, the drug must have adequate efficacy and be proven to reduce the risk factors or health problems associated with the disease. Second, the drug must have a satisfactory safety profile and be well tolerated with few adverse side effects. Finally, the cost should be reasonable, as even the most efficacious and safe medications are worthless if few can afford them.

### **EFFICACY:**

In managing dyslipidemias we are actually managing risk for coronary vascular disease. Several well documented blood lipid markers are independently associated with risk for coronary vascular disease. Clearly, we want to select a drug that will target these lipid risk factors, and the more of them that are improved, the better the profile of that drug's action. Factors associated with increased risk for coronary vascular disease include 1) elevated total cholesterol, 2) elevated LDL cholesterol, 3) elevated triglycerides, 4) elevated Lp(a) lipoproteins, 5) decreased HDL cholesterol, and 6) small particle size of the LDL lipoproteins. The newer statin drugs are extremely potent in lowering LDL cholesterol. For example, atorvastatin can sometimes lower LDL by 50% or 60%. Fibric acid derivatives are effective at lowering triglycerides and raising HDL, but they are weaker drugs when it comes to total cholesterol and LDL. Only one lipid lowering drug can positively influence all of these six lipid risk factors, and that is nicotinic acid. None of the other drugs consistently

lower Lp(a), which is a serious risk factor for persons who have had angioplasty or coronary bypass surgery. Nicotinic acid is one of the most potent drugs available for increasing HDL cholesterol and promoting the HDL to total cholesterol ratios.

Perhaps a more important measure of efficacy is the actual decrease in coronary vascular events or morbidity from disease, and the decrease in cardiovascular mortality. Nicotinic acid was the first agent to demonstrate in long term follow-up trials both a reduction in coronary events and a decreased overall mortality from cardiovascular disease. In addition, nicotinic acid has been shown both as a single agent and in combination with other drugs to reverse atherosclerotic lesions in persons with coronary disease. Thus, nicotinic acid has demonstrated an optimal profile of action on lipid risk factors and has proven long term efficacy in reduction of disease morbidity and mortality.

#### SAFETY AND SIDE EFFECTS:

Nicotinic acid is the oldest of the lipid lowering drugs and has been in use since 1954. Despite its optimal action on blood lipids, it has been a difficult drug to use clinically because of its high incidence of side effects. Thirty to sixty percent of persons are intolerant of immediate-release nicotinic acid due to GI upset or severe flushing and itching of the skin. Sustained-release nicotinic acid preparations have been developed that do reduce the incidence of these side effects, but most of these preparations have been associated with an increased incidence of liver toxicity. Even though nicotinic acid has demonstrated an excellent efficacy profile, it has lost popularity with clinicians and patients due to these side effect and toxicity problems.

Wax-matrix CNA represents a recent breakthrough in the development of a safe and effective sustained-release nicotinic acid. Innovate, Inc. of Tigard, Oregon has created a wax-matrix delivery system for nicotinic acid that provides a smooth release of drug over a period of several hours. This sustained-release has effectively minimized the GI and cutaneous side effects and has been associated with remarkably little liver toxicity. Wax-matrix CNA has been studied at major research centers in the United States (University of Minnesota and Harvard) and at the National Research Centre for Preventive Medicine in Moscow. Multiple clinical trials have repeatedly shown excellent reductions in LDL cholesterol (26%), increases in HDL cholesterol (14%), and an overall patient tolerance of 96%. Clinical trials done at the National Research Centre for Preventive Medicine in Moscow have confirmed that wax-matrix CNA does significantly lower Lp(a). Generalizing from these clinical studies, we can predict that 85% to 90% of persons will reach their target lipid goals using wax-matrix CNA. The drug has shown minimal toxicity, and those liver

changes that have been noted in patients have been easily reversed by decreasing or stopping the medication. Furthermore, Dr. David Aronov with Moscow Centre has demonstrated in a recent study that liver enzyme changes can be prevented if methionine is given as a supplement to wax-matrix CNA. These studies show that wax-matrix CNA is unique among nicotinic acid products in that it is exceptionally well tolerated and offers efficacy in all six of the lipid risk factors.

**COST:**

The third factor to consider in choosing a lipid lowering drug is cost. Nicotinic acid has always been one of the least expensive drugs for treating dyslipidemia. Table 1 shows comparative retail costs for some of the popular lipid lowering drugs. Wax-matrix CNA is less than one tenth the cost of most of the statin drugs and has a better overall profile of efficacy than any of the drugs on this list. Thus, using our rationale for choosing a lipid lowering drug based on efficacy, safety and cost, wax-matrix CNA clearly emerges as the obvious first choice in lipid management.

Table 1.

**Retail Cost Per Month - U.S. • \$•**

Pravastin - 40 mg

\$109.09

Simvastatin - 40 mg

\$108.09

Lovastatin - 40 mg

\$117.29

Atorvastatin - 20 mg

\$ 86.69

Gemfibrosil - 600 mg

\$ 23.49

Atromid - S - 2,000 mg

\$160.76

Wax-matrix CNA - 2,000 mg

\$ 9.60

**COMBINATION THERAPY:**

Using wax-matrix CNA as a first choice in the management of dyslipidemia will allow most patients to reach their target lipid goals. Ten to fifteen percent of patients, however, will need more aggressive management. If a patient has primarily an elevation of LDL cholesterol, then perhaps a single agent from the • statin• group of drugs would be appropriate. Most patients with resistant dyslipidemia, however, have multiple lipid risk factors and would likely benefit from the combination of wax-matrix CNA with one of the other available agents. The combined approach often allows you to use a significantly lower dose of the more expensive drug and still get very effective lipid management. This would be especially useful in patients with low HDL or high Lp(a) as part of their dyslipidemia pattern since nicotinic acid is the most effective drug in managing those risk factors. Combinations of wax-matrix CNA with statin agents can be expected to have a dramatic impact on LDL cholesterol and be a good combination to attempt reversal of lesions in patients with known coronary artery disease. Since both statins and nicotinic acid can cause liver toxicity, persons on combination therapy should have their liver function monitored regularly.

#### HOW TO PRESCRIBE AND MANAGE WAX-MATRIX CNA:

Nicotinic acid has gotten the reputation over the years of being a difficult drug to use clinically because of its high incidence of side effects in patients. A significant part of this problem, however, has been iatrogenic. Many physicians do not know how to prescribe or manage Nicotinic Acid therapy, and they either cause side effects by improper dosing or by failure to manage treatment in a way that avoids side effects.

Most of us were taught in medical training to try to achieve therapeutic blood levels of a drug as quickly as possible in initiating therapy. This is not the proper way to prescribe a nicotinic acid product. A sudden rise in the blood level of nicotinic acid in a person who is not acclimated to that medication will trigger a prostaglandin release that causes flushing and itching. Similarly, local increase in concentration of nicotinic acid in the bowel causes prostaglandin release and smooth muscle contraction with GI upset and irritability. These side effects can be minimized by gradually increasing the dose of wax-matrix CNA for a period of three to four weeks as shown in Figure 1, with a goal of achieving the usual therapeutic blood level of 1500 mg per day over that period of time.

Figure 1.

Initial Dosing:

- Start with a low dose (250 - 500 mg/day for one week)

- Increase by 250 - 500 mg each week, if tolerated well, to 1,500 mg/day (split dose into bid or tid)

After Six Weeks, Recheck Blood Lipids, Blood Chemistries:

- If lipid target reached and no chemical abnormalities - maintain dose at 1500 mg/day (recheck blood work in three months)

- If lipids still too high - gradually increase dose to 2000 mg/day (recheck in six weeks)

- If lipids are normal but chemistries abnormal cut dose to 1000 mg (recheck in 3 to 4 weeks).

wax-matrix CNA is usually well tolerated in the gut because of its smooth and gradual release of nicotinic acid. However, giving the medication with food also helps to prevent a local build-up of the drug in the bowel. Most patients will tolerate a 500 mg per day initial dose without distressing side effects and generally tolerate a weekly incremental increase of wax-matrix CNA 500 mg per day, up to an initial target dose of 1500 mg per day. Wax-matrix CNA is a sustained-release product, but should still be dosed in a bid or tid fashion to spread the delivery of the medication over the course of the whole day.

Baseline lipids and blood chemistry should be obtained before starting wax-matrix CNA, and persons with an elevated baseline level of liver transaminases, fasting blood glucose, or uric acid should perhaps be considered for a different medication that doesn't effect these blood chemistries. If there is a strong reason for considering wax-matrix CNA (such as a very low HDL, or high Lp(a)) over other forms of therapy in a patient with abnormal chemistries, close monitoring is warranted.

Repeat blood chemistries and lipid profile should be obtained after the patient has been on wax-matrix CNA therapy for four to six weeks. If lipid goals have been obtained and blood chemistries are within normal limits, a person should be maintained on the 1500 mg of wax-matrix CNA daily in either a bid (750 mg day) or tid (500 mg, three times day). Repeat blood lipids and chemistries should be obtained in three to six months.

If lipid goals have not been reached and the person's blood chemistries are within normal limits, an additional 500 mg of wax-matrix CNA should be added to bring the person to the maximal dose of 2000 mg per day. That person should then be rechecked again in six to eight weeks for lipid results and blood chemistries.

If lipid goals have been achieved but the patient is showing evidence of blood chemistry abnormalities, then the dose of wax-matrix CNA should be cut in half, and blood chemistries rechecked in three to four weeks. If the blood chemistry abnormalities are severe or if there are symptoms of hepatitis, gout, or overt diabetes, then wax-matrix CNA should be stopped. In the past, these individuals were considered intolerant of nicotinic acid and switched to other medications. Research from the University of Minnesota indicates that there is a sub-group of individuals who are highly sensitive to the effects of nicotinic acid and can often be maintained with good therapeutic response and low toxicity on much lower doses of wax-matrix CNA, as low as 250 mg per day. The physician must also consider other causes of blood chemistry abnormalities, especially if the abnormalities don't resolve themselves in two to three weeks off of wax-matrix CNA. Alcohol abuse is often the cause of liver enzyme elevations in patients with nicotinic acid and patients should be cautioned to use alcohol moderately if at all when on wax-matrix CNA therapy.

#### HOW TO AVOID SIDE EFFECTS WITH WAX-MATRIX CNA THERAPY:

Patients should be instructed that nicotinic acid therapy is often associated with some skin or GI effects, but that these can usually be prevented or minimized by some simple management techniques. Clinical experience has shown that taking a large glass of water with the wax-matrix CNA dose helps to minimize skin flushing and itching. GI side effects can be reduced by taking the medication with a meal. Sensitive individuals may still experience some flushing or tingling in the skin, and these can be further minimized by taking a single adult aspirin tablet 325 mg with the wax-matrix CNA dose. The aspirin blocks the prostaglandin release associated with increasing blood levels of nicotinic acid.

Since wax-matrix CNA is formulated in a wax-matrix tablet for sustained-release, it is important that the patient does not drink a hot beverage with this medication which would cause the tablet to melt down quickly. Similarly, vigorous exercise should be avoided immediately following dosing with wax-matrix CNA since the increased core body temperature can cause a more rapid melt down and release of nicotinic acid.

Using these prescribing methods, over 95% of patients should be able to tolerate wax-matrix CNA without distressing side effects. If a patient does complain of new or persisting side effects, it's useful to review his or her own dosing schedule to be sure that poor dosing habits are not inadvertently causing their side effects. One common problem leading to periodic side effects is the patient who misses doses for a period of time and loses some of the initial tolerance that they built up with the graduated introductory dose. Finally, if patients complain of palpitations,

dysrhythmias, or visual changes, they should be evaluated for some of the more rare but potentially serious side effects of nicotinic acid, namely atrial dysrhythmias and toxic retinal changes. Patients should simply be advised that if they experience any unusual heart beats or new difficulties with vision, they should report them immediately.

**SUMMARY:**

In summary, I have offered a rationale for selecting a drug for the management of dyslipidemias, and I feel that most clinicians would concur that wax-matrix CNA is a logical first choice. Much of the success of good lipid management lies in the proper dosing and management of side effects. It is important for the physician not only to choose the right drug, but also to prescribe and manage therapy to optimize beneficial outcomes.