Current treatment options for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

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Nonalcoholic fatty liver disease is the leading cause of liver disease in western society. It is a cause of end-stage liver disease, with increased mortality secondary to cirrhosis and its complications. It is also recognized that cardiovascular disease is a significant cause of death in these patients. Significant work evaluating various treatments has been performed in recent years; however, to date, no ideal therapy exists. Lifestyle modification remains the cornerstone of management. The present article reviews the current status of various treatment modalities evaluated in nonalcoholic fatty liver disease.

Key Words: *Fibrosis; Hepatic steatosis; Metabolic syndrome; Treatment*

Les options thérapeutiques courantes pour soigner la stéatohépatose non alcoolique et la stéatohépatite non alcoolique

La stéatohépatose non alcoolique est la principale cause de maladie hépatique dans la société occidentale. Elle est responsable de maladies hépatiques en phase terminale, et une mortalité accrue est imputable à la cirrhose et à ses complications. Il est également convenu que les maladies cardiovasculaires sont une importante cause de décès chez ces patients. Ces dernières années, on a effectué des travaux importants afin d'évaluer les divers traitements, mais jusqu'à maintenant, il n'existe aucun traitement idéal. Les modifications au mode de vie demeurent la pierre angulaire de la prise en charge. Le présent article permet d'analyser l'état actuel des diverses modalités thérapeutiques évaluées en cas de stéatohépatose non alcoolique.

Nonalcoholic fatty liver disease (NAFLD) is currently the most common cause of liver disease in the western world (1). Thirty per cent of the Canadian population has hepatic steatosis, 10% to 25% of whom have steatohepatitis, fibrosis or cirrhosis (2). These numbers are significantly higher when applied to obese individuals, of whom 75% have steatosis and 20% to 35% have nonalcoholic steatohepatitis (NASH) (3,4). NAFLD is considered to be the hepatic manifestation of the metabolic syndrome (MS). Approximately 50% of patients with type 2 diabetes mellitus (DM2) have NAFLD and, regardless of body mass index, have more severe liver disease than nondiabetic patients (5-7). NASH is associated with both increased cardiovascular disease- (CVD) and liver-related mortality (8,9).

The impact of NAFLD on health care resource use is significant (10). Adults with hepatic steatosis have been reported to incur 26% higher overall health care costs (11). This is not solely attributable to liver disease. There is strong evidence for increased CVD morbidity and mortality, particularly in patients with coexistent DM2 (12-16). Given the current epidemic of obesity and DM2, the burden of NAFLD will continue to rise dramatically in the years to come.

Increased recognition of the importance of NAFLD in recent years has led to several studies of various treatment modalities. These have included lifestyle modification, pharmacological agents and surgical intervention (Table 1). The current status of NAFLD therapy and an approach to its management is reviewed. While the evaluation of measures of response to treatment is beyond the scope of the present review, the primary objective of any NAFLD therapy is improvement in steatohepatitis and fibrosis, with the ultimate goal of preventing CVD- and liver-related death.

DIET AND LIFESTYLE MODIFICATION

Nonpharmacological measures are aimed at reducing caloric intake and increasing physical activity levels. Weight loss and increased physical activity are effective in NAFLD treatment, and their role in CVD risk reduction is well established.

Modest weight loss (7% to 10%) and exercise improve liver histology, insulin resistance (IR) and quality of life, and should form the backbone of any treatment strategy (17,18). While total caloric intake is important, there is accumulating evidence supporting the specific role of fructose consumption in patients with NAFLD, with higher levels of ingestion associated with increased levels of fibrosis (19). Regarding activity level, it has recently been suggested that vigorous exercise is associated with greater histological improvement than modest activity (20).

Unfortunately, many patients are unsuccessful in instituting these changes and, among those who do, many find them difficult to sustain over the long term (21). Hence, it is advisable that a behavioural approach, such as cognitive behavioural therapy or, at the very least, involvement of a dietician, be part of this treatment plan. Furthermore, before initiating any significant increase in exercise level, patients at risk should be evaluated for underlying CVD.

PHARMACOLOGICAL THERAPIES

Insulin sensitizers

IR is a hallmark of NAFLD; therefore, targeting this pathway has been a major focus of many studies of its therapy. Insulin sensitizers, such as metformin and thiazolidinediones (TZDs), have been fairly well studied. Newer agents in this class include glucagon-like peptide-1 receptor (GLP-1) agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors (ie, incretins).

Metformin: Metformin has been evaluated in several small studies of nondiabetic NAFLD patients. It has been shown to improve transaminase levels and hepatic steatosis (22-24). However, its effect on inflammation was less robust, and fibrosis improvement was demonstrated in only one study (25). Most of these were small trials of relatively short duration and, unfortunately, histological follow-up was incomplete in many.

The results of the largest study of metformin, the Treatment of nonalcoholic fatty liver disease in children (TONIC) trial, which evaluated metformin, vitamin E and placebo in a pediatric population, were recently published (26). Metformin failed to demonstrate superiority to placebo in attaining the primary outcome of sustained reduction in transaminase levels. Liver histology was a secondary outcome in this study. Metformin was associated with improvement in hepatocellular ballooning, but not fibrosis, steatosis, inflammation or NAFLD activity score (NAS).

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TABLE 1
Evaluated treatments for nonalcoholic fatty liver disease

Lifestyle intervention
    Calorie restriction
    Exercise
Pharmacological therapy
    Insulin sensitizers: metformin, thiazolidinediones, incretin-based therapies
    Lipid-lowering agents: statins, fibrates, PUFA
    Cytoprotective and antioxidant agents: URSO, Vitamin E, silymarin,
        betaine
    Anti-TNF-α agents: Pentoxifylline, monoclonal antibodies
Phlebotomy
Surgical intervention and antiobesity drugs
    Bariatric surgery
    Orlistat

PUFA N-3 polyunsaturated fatty acids; TNF Tumour necrosis factor; URSO Ursodeoxycholic acid

TZDs: The TZD class of drugs has held promise in the treatment of NAFLD due to its beneficial impact on IR, hepatocyte fatty acid metabolism and adiponectin levels. As with metformin, many studies of TZDs are underpowered and differ with respect to histological and other outcomes. Reduction in transaminase levels and steatosis are almost universal, and the majority of trials have reported improvement in metabolic end points and steatohepatitis (27-30). However, regression of fibrosis has not been convincingly demonstrated.

Two drawbacks to treatment with this class of medications exist. One is the almost universal reversion of improvement after discontinuation of drug, making it likely that long-term therapy with these agents is necessary (31). The second is that TZD use is commonly associated with side effects of lower extremity edema and weight gain (average 2 kg to 5 kg), which may limit its beneficial effects. Both are unfortunate common causes of treatment discontinuation (32).

The results of the much anticipated Pioglitazone or Vitamin E for NASH Study (PIVENS) were published in 2010 (33). This large, multicentre randomized controlled trial evaluated pioglitazone versus vitamin E versus placebo in patients with NAFLD. Compared with placebo, pioglitazone improved insulin sensitivity and steatohepatitis. However, there was no significant difference between pioglitazone and placebo in improvement of fibrosis or the primary end point of composite score for steatosis, lobular inflammation, hepatocellular ballooning and fibrosis.

Overall, the results of trials of TZDs for NAFLD suggest some benefit from this class of drugs. However, prolonged therapy is likely necessary to achieve sustained histological improvement, which may be limited by their side effect profile, and the fact that the safety and efficacy of their long-term use in patients with NAFLD is currently unknown. Presently, TZDs should be reserved for second-line treatment in the majority of patients. One exception may be patients with DM2 and NAFLD, in whom TZD therapy may help both conditions (27,28).

Incretin-based therapies
A direct relationship between the gastrointestinal and endocrine systems has recently been appreciated with the discovery of neuroendocrine hormones known as incretins. Incretins are produced by the intestinal tract in response to food ingestion where they stimulate glucose-dependent insulin release, decrease glucagon release and prolong gastric emptying. These effects result in improved glycemic control, clinically significant weight loss and increased insulin sensitivity, which could benefit patients with NAFLD.

The two primary incretins are GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Circulating levels of GLP-1 and GIP are rapidly reduced following secretion by the enzyme DPP-4, and GLP-1 levels have been demonstrated to be decreased in patients with DM2 (34).

DPP-4 inhibitors have been developed and include sitagliptin, saxagliptin and vildagliptin. Both sitagliptin and saxagliptin are currently available in Canada for the treatment of DM2. DPP-4 inhibitors are administered orally, are weight-neutral and undergo little hepatic metabolism, making them an attractive candidate for use in NAFLD treatment (35,36). A clinical trial of sitagliptin treatment in NAFLD patients with DM2 is presently underway at the University of Western Ontario (London, Ontario) ClinicalTrials.gov Identifier: NCT01260246); however, to date, there are no published studies of these agents in NAFLD.

GLP-1 receptor agonists are a relatively new class of drugs, with one, liraglutide, available in Canada and the other, exenatide, expected to be available soon. They are administered as an injection and indicated for use as an adjunctive therapy for patients with DM2. Preliminary uncontrolled open-label studies suggest a potential benefit, but to date, there are no controlled trials of these agents in humans (37,38). Presently, incretin-based therapies should not be used outside of the context of a clinical trial.

Lipid-lowering agents
Statins, fibrates and omega-3 polyunsaturated fatty acids (PUFAs) are commonly used to manage dyslipidemia. This, in combination with their potential antioxidant properties and favourable effect on adiponectin levels, suggests a possible benefit in patients with NAFLD (39).

Possibly due to the unwarranted fear of hepatotoxicity of statins, there are few published studies of these drugs in NAFLD. In the prospective studies that have been performed, neither statins nor fibrates have been shown to improve liver fibrosis (40,41). However, a retrospective study of the effects of statin exposure on liver histology over 10 to 16 years (42) showed that, despite a higher baseline risk for liver disease progression, patients on statins had improved steatosis and slower fibrosis progression compared with controls.

A number of large studies have now demonstrated the safety of statins in patients with underlying NAFLD and dyslipidemia (43-45). In these patients, statins are an important part of the management of their metabolic risk factors and their use should be advocated by gastroenterologists seeing these patients.

To date, studies involving PUFAs have been heterogeneous and relatively small in size, with no published trials demonstrating well-defined histological outcomes (46,47). Thankfully, a number of such studies are presently underway (NCT00323414, NCT00681408, NCT01056133, NCT00760513). Until their results are known, the use of PUFAs to treat NAFLD is not recommended.

Cytoprotective and antioxidant agents
Oxidative stress is believed to play a role in the pathogenesis of NAFLD and, as such, potent antioxidants such as ursodeoxycholic acid (URSO), vitamin E, silymarin (milk thistle) and betaine are attractive therapeutic agents.
Bile acids: URSO is a hydrophilic bile acid with cytoprotective and antioxidant properties. Trials of moderate-dose URSO have failed to show significant benefit in NAFLD (48,49). Two randomized trials of high-dose URSO have recently been published (50,51). No improvement in the primary end point of liver histology was noted in one study. The other showed improvement in serological markers of fibrosis but unfortunately did not assess histology. Taken as a whole, it can be stated that moderate-dose URSO has no role in the treatment of NAFLD, and that high-dose URSO is unlikely to provide significant benefit to routinely advocate its use at this time.
Vitamin E: Vitamin E is a fat-soluble vitamin and a potent antioxidant. Until recently, it had only been assessed in small, heterogeneous studies. Two recently published, large, randomized controlled trials, PIVENS and TONIC, assessed its effect on adult and pediatric NAFLD populations, respectively (26,33). While each of these studies failed to achieve their primary end points, vitamin E treatment resulted in improvements in hepatocellular ballooning and NAS in

both trials (52). This is likely a clinically important result because ballooning confers a greater risk of disease progression and reflects cellular and cytoskeletal injury (53).

These results for vitamin E are quite promising and suggest that patients with biopsy-proven steatohepatitis associated with hepatocellular ballooning (NAS ≥4) may benefit from its use. However, widespread use in all NAFLD patients cannot yet be recommended. This is due, in part, to concerns regarding its long-term safety because doses of ≥400 IU/day have been associated with an increase in all-cause mortality in some but not all studies (54,55). As well, indefinite use is likely required because these studies demonstrated worsening of transaminase levels following drug discontinuation.

Silymarin: Silymarin (milk thistle) is a lipophilic extract with antioxidant properties from the seeds of the *Silybum marianum* plant. Its use among patients with liver disease is popular because it is viewed as a 'natural' substance and, to date, has not been associated with significant adverse effects (56). While a pilot study demonstrated some promising results with respect to serological end points, well-designed, randomized controlled trials are lacking. As well, standardization of silymarin in its formulations and effective dosages remain lacking (57).

Betaine: Betaine is a naturally occurring metabolite of choline and has been shown to increase S-adenosylmethionine levels and reduce oxidative stress. Unfortunately, when compared with placebo in a randomized controlled trial, betaine failed to improve steatosis or other histological outcomes (it was concluded, however, that it may protect against worsening steatosis) and, as such, its use is not currently recommended (58).

Antitumour necrosis factor-alpha agents

Pentoxifylline: Inflammatory activation plays a significant role in NAFLD progression, with tumour necrosis factor-alpha (TNF-α) possibly playing a direct role in obesity and IR (59). Pentoxifylline is a TNF-α antagonist with an established safety profile. It has been studied in a number of small NAFLD trials, two of which have assessed histological response and demonstrated improvement in steatosis, inflammation and ballooning (60,61). A double-blind randomized controlled trial of pentoxifylline (NCT00590161) has recently been completed and it is hoped that its results will further clarify its role in NAFLD therapy.

Infliximab/adalimumab/certolizumab: TNF-α monoclonal antibodies are another class of agents well known to gastroenterologists given their important role in the treatment of inflammatory bowel disease. As yet, they have not been studied in NAFLD, but two studies are underway evaluating their effect in hepatitis C (NCT00237484, NCT00512278).

PHLEBOTOMY

Elevated serum ferritin levels and increased hepatic iron deposition is a common finding in patients with NAFLD and MS, independent of *HFE* genotype (62,63). Iron is a potent catalyst of oxidative stress, and serum ferritin may also reflect oxidative stress and hepatocyte damage (64-66). Iron depletion has been demonstrated to improve metabolic indexes and transaminase levels in NAFLD; however, its impact on hepatic steatohepatitis and fibrosis is largely unknown (67,68). A prospective study evaluating pre- and postliver histology is currently underway at the University of Western Ontario to address this important question (NCT00641524).

SURGICAL INTERVENTION AND ANTIOBESITY DRUGS

Bariatric surgery
Bariatric surgery is an increasingly popular therapeutic option among morbidly obese patients. To date, a number of studies, most retrospective or observational in nature, have evaluated bariatric surgery for NAFLD. Overall, surgical results have been positive, with improved liver histology and amelioration of many aspects of the MS, including resolution of DM2 in many patients (69). However, advanced fibrosis has not been demonstrated to consistently regress, and one five-year prospective study found that while steatohepatitis decreased, fibrosis actually worsened slightly (70). As well, the presence of cirrhosis is a relative contraindication to bariatric surgery due to increased short- and intermediate-term mortality (71). A recently published Cochrane review (72) concluded that the lack of randomized and quasirandomized trials precludes the assessment of bariatric surgery as a therapeutic option for patients with NAFLD.

Antiobesity drugs
Medical treatment of obesity has been viewed as a potentially promising option for NAFLD therapy given the established benefit of weight loss for this condition. However, drug therapy has not shown a direct beneficial effect on the liver independent of the effect of weight loss (73,74). As well, there have been concerns regarding the safety of some of these agents with sibutramine withdrawn from the United States and Canadian markets in 2010, and rimonabant production discontinued in 2008. Orlistat, an inhibitor of pancreatic lipase, remains available despite rare reports of hepatotoxicity (75).

CONCLUSION

Presently, the mainstay of treatment for NAFLD is the adoption of lifestyle changes aimed at increased physical activity and moderate, sustained weight loss. In addition, all patients should be screened for concomitant MS risk factors including hypertension, dyslipidemia and IR. Given the excess CVD-related mortality in this population, each of these require regular monitoring and should be treated aggressively, including the use of statins in patients who require them (Box 1).

The controversy regarding vitamin E continues. It likely has a role in selected NAFLD patients; however, its widespread use will likely be tempered by the as yet uncertain relationship between vitamin E and all-cause mortality. The results of ongoing trials of existing and novel agents are hoped to add to the treatment options available for this important disease.

There are no guidelines in terms of monitoring response to treatment in NAFLD. This is, however, recommended in patients in whom drug therapy has been initiated (ie, vitamin E, pioglitazone, etc) to determine whether that agent is effective. While noninvasive markers such as transient elastography and serum CK-18 levels are promising, their role in measuring treatment response remains to be clarified (76,77). Presently, treatment response is best achieved with liver biopsy. The timing of biopsy can be guided by whether there has been improvement in liver enzyme levels and metabolic indexes. Generally, sampling after 12 months of therapy can be considered to confirm histological improvement. If there is no improvement or a worsening of these markers, biopsy should be considered at six months to determine whether treatment should be discontinued or changed.

Given our ever increasing obesity rates, NAFLD will continue to be a significant cause of liver-related morbidity and mortality. Effective and safe treatments for this disease are desperately needed. Challenges facing future studies of therapeutic agents include the need to demonstrate improvement of liver disease and long-term safety because it appears that most agents will need to be used indefinitely. Because liver biopsy, the current gold standard, is a relatively invasive procedure, it is hoped that the validation of noninvasive markers of steatohepatitis and fibrosis in NAFLD will greatly aid future studies in this field.

Box 1: Current recommendations for treatment of nonalcoholic fatty liver disease (NAFLD)

● Screening for and treating associated features of the metabolic syndrome: Regular monitoring of weight (waist to hip ratio or body mass index), blood pressure, fasting lipids and glucose. Statins are preferred agent in patients who meet fasting lipid criteria.

● Moderate (10% current weight), sustained weight loss. Total caloric intake reduction with focus on decreasing refined carbohydrates (ie, high fructose corn syrup).

● Regular exercise, at least 30 min 3 to 5 times per week following evaluation for underlying cardiovascular disease.

● In patients with diabetes, consider metformin or pioglitazone with decision to use either agent based on the potential risks and benefits in that individual. This is best achieved in consultation with an endocrinologist.

● Vitamin E (800 IU/day) should be considered in patients with significant histological disease activity (hepatocyte ballooning and NAFLD activity score ≥4)

● Bariatric surgery must be considered on a case by case basis in patients who meet criteria. A preoperative liver biopsy is recommended to exclude the presence of cirrhosis.

● For NAFLD cirrhosis, there is no evidence to support initiation of drug therapy. Lifestyle measures and management of complications of cirrhosis is recommended.

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ᴾ OLESTYR®

Light and Regular Powder
(Cholestyramine for Oral Suspension USP)
(Cholestyramine Resin)

ⓘ PRESCRIBING SUMMARY

👤 PATIENT SELECTION CRITERIA

THERAPEUTIC CLASSIFICATION
Antihypercholesterolemic and Antidiarrheal

INDICATIONS AND CLINICAL USE
OLESTYR® is indicated as a symptomatic control of bile acid induced diarrhea due to short bowel syndrome. OLESTYR® is indicated for the relief of pruritus associated with partial biliary obstruction.

CONTRAINDICATIONS
Known hypersensitivity and in patients with complete biliary obstruction where bile is not excreted into the intestine (see PRECAUTIONS in Supplemental Product Information Section).

✋ SAFETY INFORMATION

WARNINGS
OLESTYR® (cholestyramine resin) should not be taken in its dry form. Always mix OLESTYR® with water or other fluids before ingesting.

Since OLESTYR® may bind other drugs given concurrently, patients should take other drugs at least one hour before or 4-6 hours after OLESTYR® (or at as great an interval as possible) to avoid impeding their absorption.

Pregnancy: Since OLESTYR® is not absorbed systemically, it is not expected to cause fetal harm when administered during pregnancy in recommended dosages. There are, however, no adequate and well controlled studies in pregnant women, and the known interference with absorption of fat soluble vitamins may be detrimental even in the presence of supplementation.

Nursing Mothers: Caution should be exercised when OLESTYR® is administered to a nursing mother. The possible lack of proper vitamin absorption described in the Pregnancy Section may have an effect on nursing infants. Use in pregnancy or lactation requires that the potential benefits of drug therapy be weighed against the possible hazards to the mother and the child.

Use in Children: The effects of long term drug administration, as well as its effect in maintaining lowered cholesterol levels in pediatric patients, are unknown.

Geriatrics: Appropriate studies on the relationship of age to the effects of cholestyramine have not been performed in the geriatric population. However, patients over 60 years of age may be more likely to experience gastrointestinal side effects.

PRECAUTIONS
There is a possibility that prolonged use of cholestyramine resin, since it is a chloride form of anion exchange resin, may produce hyperchloremic acidosis. This would especially be true in younger and smaller patients where the relative dosage may be higher. (For more details, see PRECAUTIONS in Supplemental Product Information).

Drug interactions
Since cholestyramine resin is an anion-exchange resin, it may have strong affinity for anions other than the bile acids. Drugs that are affected by co-administration of bile acid sequestrants vary widely in pharmacologic effect and mechanisms, magnitude of doses, and chemical characteristics. It should be assumed that concomitantly administered drugs have the potential interacting with cholestyramine unless clinical studies have shown otherwise (see Drug Interactions in Supplemental Product Information Section).

◊◊ ADVERSE REACTIONS
The most frequent adverse effect of cholestyramine resin is constipation. When used as a cholesterol-lowering agent predisposing factors for most complaints of constipation are high dose and increased age (more than 60 years old). Most instances of constipation are mild, transient, and controlled with conventional therapy. Some patients require a temporary decrease in dosage or discontinuation of therapy (For more details on adverse events, see ADVERSE REACTIONS in Supplemental Product Information).

🝆 ADMINISTRATION

DOSAGE AND ADMINISTRATION
To familiarize the patient with OLESTYR® Light and Regular Powders and to minimize gastrointestinal side effects, it is desirable to begin all therapy with one dose daily. Dosage is then increased within a day or two to the desired level for effective control. The recommended adult dose is 4 grams of cholestyramine resin, one to six times daily. Dosages may be adjusted as required to meet the patient's needs. A pediatric dosage schedule has not been established.

OLESTYR® Light and Regular Powders (cholestyramine resin) are administered orally and should not be taken in their dry form (see WARNINGS). Always mix the powder with water or other fluids before ingestion (see Preparation Instructions in Supplemental Product Information).

📖 REFERENCES

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SUPPLEMENTAL PRODUCT INFORMATION
PRECAUTIONS
Cholestyramine resin may produce or worsen pre-existing constipation. Dosage should be reduced or discontinued in such cases. Fecal impaction and aggravation of hemorrhoids may occur. Every effort should be made to avert severe constipation and its inherent problems in those patients with clinically symptomatic coronary artery disease.

Cholestyramine potentially may cause steatorrhea or accentuate pre-existing steatorrhea and this may require reduction and adjustment of dosage.

Effect on Vitamin Absorption: Because cholestyramine binds bile acids, it may interfere with normal fat digestion and absorption and thus may prevent absorption of fat soluble vitamins such as A, D and K. When OLESTYR® is given for long periods of time, concomitant supplementation of water-miscible parenteral forms of vitamins A and D should be considered.

Chronic use of OLESTYR® may be associated with increased bleeding tendency due to hypoprothrombinemia associated with vitamin K deficiency. This will usually respond promptly to parenteral vitamin K_1 deficiency. This will usually respond promptly to parenteral vitamin K_1 deficiency, and recurrences can be prevented by oral administration of vitamin K_1.

Reduction of serum or red cell folate has been reported over long term administration of cholestyramine resin. Supplementation with folic acid should be considered in these cases.

Laboratory Tests: Serum cholesterol levels should be determined frequently during the first few months of therapy and periodically thereafter. Serum triglyceride levels should be measured periodically to detect whether significant changes have occurred.

Use in Children: Because bile acid sequestrants may interfere with absorption of fat-soluble vitamins, appropriate monitoring of growth and development is essential if cholestyramine is used in children.

Drug Interactions: Cholestyramine resin may delay or reduce the absorption of concomitant oral medication such as thyroid and thyroxine preparations, warfarin, chlorothiazide (acidic), phenylbutazone, phenobarbital, tetracycline, penicillin G, and digitalis. The discontinuance of cholestyramine could pose a hazard to health if a potentially toxic drug such as digitalis has been titrated to maintenance level while the patient was taking cholestyramine. The concomitant drug should be re-titrated to avoid over-dosage when cholestyramine is discontinued. Also, OLESTYR® may interfere with the pharmacokinetics of drugs (e.g., estrogens) that undergo enterohepatic recirculation.

Drug Interaction studies have been conducted with cholestyramine and various HMG-CoA reductase inhibitors. Although cholestyramine has been shown to reduce the bioavailability of HMG-CoA reductase inhibitors, the clinical cholesterol-lowering effects of an HMG-CoA reductase inhibitor and cholestyramine have been shown to be additive.

ADVERSE REACTIONS
Less Frequent Adverse Reactions: Abdominal discomfort, flatulence, nausea, vomiting, diarrhea, heartburn, anorexia, dyspepsia and steatorrhea, bleeding tendencies due to hypoprothrombinemia (Vitamin K deficiency) as well as Vitamin A (night blindness has been reported rarely) and D deficiencies, hyperchloremic acidosis in children, osteoporosis, rash and irritation of the skin, tongue and perinatal area.

Occasional calcified material has been observed in the biliary tree, including calcification of the gallbladder, in patients to whom cholestyramine resin has been given. This may be manifestation of the liver disease and not drug related.

DOSAGE AND ADMINISTRATION
Motivation of the patient to continue the prescribed regimen in spite of gastrointestinal problems is important.

Preparation Instructions: The color of cholestyramine resin may vary somewhat from batch to batch but this variation does not affect the performance of the product.

Place the contents of one pouch or one level scoop of OLESTYR® Light or Regular Powder on the surface of 120 mL - 180 mL of water, or non-carbonated beverage such as milk or fruit juice. After 1-2 minutes mix thoroughly by stirring.

OLESTYR® Light and Regular Powders may also be mixed in highly fluid soups or pulpy fruits with high moisture content such as applesauce or crushed pineapple.

SYMPTOMS AND TREATMENT OF OVERDOSE
One case of overdosage with cholestyramine resin has been reported in a patient taking 150% of the maximum recommended daily dosage for several weeks. No ill effects were observed. Should overdosage occur, the chief potential harm would be obstruction of the gastrointestinal tract. The location of such potential obstruction, the degree of obstruction, and the presence or absence of normal gut motility would determine treatment.

For management of drug overdose, contact the regional poison control centre.

STORAGE AND STABILITY
Store at room temperature (15-30°C). Protect from moisture.

The Full Product Monograph is available by contacting PENDOPHARM, a division of Pharmascience Inc., at 1-888-550-6060 or e-mail at medinfo@pendopharm.com.

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