Counseling Patients with Chronic Hepatitis C

Over-the-Counter Pain Medications

Because many medications are metabolized through the liver, it is important for the medical provider to know all of the medications a patient is taking, including over-the-counter medications. A current medication list should be solicited frequently.

Acetaminophen

Acetaminophen can cause clinically important hepatotoxicity, either through an acute overdose or when taken on a regular basis (even at lower doses).[1,2,3] In one large study that examined acetaminophen-related acute liver failure, individuals taking less than 4 grams per day of acetaminophen accounted for 7% of the cases.[1] Among healthy adults taking 4 grams per day for 14 days, 38% developed alanine aminotransferase (ALT) values in excess of 3 times the upper limit of normal.[2] In contrast, healthy adults who took 1 gram of acetaminophen taken twice daily for 12 weeks had only minor elevations in aminotransferase levels.[4] Studies involving persons with chronic HCV have shown an increased risk of acute liver injury in patients with chronic hepatitis C following acetaminophen overdose.[5,6] Concurrent alcohol use further increases the chance of acute or chronic acetaminophen-induced hepatotoxicity in persons with chronic HCV infection.[6] Formal guidelines for the safe use of acetaminophen in persons with HCV infection do not exist, but some experts have issued general recommendations.[7,8,9]

Recommendation

- Low dosages of acetaminophen (up to two grams per day) can safely be used in most patients with chronic hepatitis C infection without cirrhosis
- Patients with chronic HCV infection and cirrhosis should limit their intake of acetaminophen to 1 gram per day.
- Individuals with chronic HCV who drink excess alcohol should avoid taking acetaminophen.
- Clinicians should remind patients that many narcotic combination pills and over-the-counter cold and flu medications may contain acetaminophen.
- Individuals with chronic HCV who are regularly taking acetaminophen should have laboratory monitoring for hepatotoxicity every 3 to 6 months.

Aspirin and Nonsteroidal Anti-inflammatory Medications

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) are generally safe for persons who have chronic HCV without cirrhosis, when taken at standard doses. For patients who have cirrhosis, NSAIDS and aspirin are best avoided, especially for those with decompensated cirrhosis.[10] The American Association for the Study of Liver Disease (AASLD) recommends avoiding NSAIDs in patients with cirrhosis and ascites, except in special circumstances.[11] In patients with
decompensated cirrhosis, the use of NSAIDS and aspirin may further increase the inherent risk these patients have for developing nephrotoxicity and gastrointestinal bleeding.\[12]\n
**Recommendation**

- Individuals with chronic HCV who do not have cirrhosis can take aspirin or NSAIDs at low or standard recommended dosages.
- Persons with chronic HCV infection and cirrhosis should, in general, avoid taking NSAIDs or aspirin.
- Patients with cirrhosis who have short-term, minor pain should take acetaminophen in this setting as long as the acetaminophen dose does not exceed 1 gram per day. In the unfortunate situation involving a patient with cirrhosis who has joint or musculoskeletal pain unresponsive to acetaminophen, NSAIDs can be used for a very brief period of time (less than 3 days), if given at the lowest daily dose possible.
- Patients with chronic HCV and decompensated cirrhosis should not take aspirin or NSAIDs.
Iron and Vitamins

Iron

In persons with chronic hepatitis C infection, mild to moderate hepatic iron overload is common.[13,14] In some studies excess hepatic iron in persons with chronic HCV has been associated with accelerated fibrosis, whereas other studies have not shown a correlation of iron and hepatic fibrosis progression in persons with chronic HCV.[15,16,17]

Recommendation

- Based on the potential negative impact of iron in patients with chronic HCV, many experts have recommended these patients avoid taking iron supplements or a daily multivitamin that contains iron, unless a compelling reason exists to regularly take iron, such as iron deficiency anemia from gastrointestinal bleeding.[12]

Vitamin A

Vitamin A is a fat soluble vitamin that can be obtained in the diet as provitamin A (mostly plant sources) and preformed vitamin A (animal sources or supplements). Intake of vitamin A at levels contained in a multivitamin does not cause hepatotoxicity. Vitamin A deficiency is often made on a clinical basis, but is supported by either a serum retinol level less than 20 micrograms/dL or a molar ratio of retinol to retinol-binding protein less than 0.8.[18] Vitamin A deficiency is uncommon in the United States. Chronic ingestion of mega-doses of vitamin A, especially in excess of 25,000 international units per day, can potentially cause severe hepatotoxicity.[19,20,21,22]

Recommendation

- Vitamin A is a fat-soluble vitamin and should only be taken at standard doses of less than 5,000 international units per day.
- Intake of high-dose (or megadoses) of vitamin A, such as a dose greater than 25,000 international units per day, is not recommended.

Vitamin D

Vitamin D deficiency is common in patients with chronic HCV infection, particularly in those individuals with cirrhosis.[23,24] Some experts have suggested that vitamin D has anti-inflammatory and antifibrotic properties in persons with chronic HCV infection.[25,26] Several studies have shown patients with low vitamin D levels have poorer responses to interferon-based therapy, suggesting an important immunomodulatory role for vitamin D in patients with chronic hepatitis C infection.[27,28,29,30] Other studies, however, have not shown a correlation with vitamin D levels and sustained virologic responses to interferon-based therapy.[31,32] A more recent study examined 25-hydroxyvitamin D levels in 218 persons receiving direct-acting antiviral (DAA) therapy and found no correlation of vitamin D levels and sustained virologic response (SVR) rates.[24] The Institute of Medicine defines vitamin D deficiency as a serum 25-hydroxyvitamin D level less than 20 ng/mL, but other societies, including the Endocrine Society, the National Osteoporosis Foundation, the International Osteoporosis Foundation, and the American Geriatric Society recommend using less than 30 ng/mL as the cutoff for vitamin deficiency.[33,34,35,36]

Recommendation

- There are no liver-specific reasons to take vitamin D supplementation, but persons with chronic HCV infection who are deficient in vitamin D should have vitamin D replacement therapy.
For otherwise healthy adults, the Institute of Medicine has a recommended vitamin D dietary allowance of 600 IU per day, with an upper level of intake of 4,000 IU/day.[33] Some experts recommend that persons who do not have regular sun exposure take 800 IU per day of vitamin D. There are no known hepatotoxic effects of excess vitamin D dosing.[37]

For patients with more severe vitamin deficiency (e.g. serum 25-hydroxyvitamin D level less than 10 ng/mL), many experts recommend initial replacement therapy consisting of 50,000 IU of vitamin D once weekly for 8 weeks, followed by a maintenance dose of 800 to 1000 IU per day. For milder vitamin D deficiency, a daily dose of 1000 IU per day is usually sufficient.
Complementary and Alternative Therapies

Approximately 25% of persons living with chronic HCV infection take complementary and alternative therapies.[38,39] Some of these complementary and alternative therapies, however, may have harmful effects on the liver or cause serious interactions with medications used for hepatitis C therapy.[40,41] At the initial visit for HCV care and at regular intervals thereafter, clinicians should obtain a complete list of the patient's prescription medications, over-the-counter medications, complementary and alternative therapies, and dietary and herbal supplements. For patients taking complementary or alternative therapies, clinicians should discuss whether it is wise for them to continue taking these alternative and complementary therapies. The list of complementary and alternative therapies should be reviewed again during therapy for hepatitis C, as some patients may seek out these options for relief of treatment-related side effects. The National Center for Complementary and Alternative Medicine (NCCAM) at the U.S. National Institutes of Health has information on the safety and efficacy of dietary and herbal supplements. The following summarizes some of the complementary and alternative therapies that have been used by persons living with chronic HCV infection.

General Recommendation

- Given the extremely high SVR rates with current DAA therapy, it is unlikely that any of the complementary and alternative therapies listed below would provide any significant benefit for HCV treatment. In addition, complementary and alternative medications may cause drug interactions with DAA medications. Accordingly, we do not recommend the use of any complementary or alternative therapies for persons with HCV infection.

Ginseng

Ginseng includes Asian ginseng (Panax ginseng) and American ginseng (Panax quinquefolius). Asian ginseng is purported to have hepatoprotective effects.[42] There are insufficient data with ginseng in patients with hepatitis C to make any recommendations on its use. Asian ginseng may lower blood glucose, so it should be used cautiously in patients with a history of hypoglycemia.

Lactoferrin

Lactoferrin, also known as apolactoferrin or lactotransferrin, is a protein found in milk and other body fluids that binds and transports iron. The highest concentration of lactoferrin is in colostrum. Bovine lactoferrin is the formulation of lactoferrin most often used when taken as a dietary supplement, with a typical dose of 1.8 to 3.6 grams per day; lactoferrin can also be produced via recombinant technology. Several small studies suggested that lactoferrin may lower HCV RNA levels.[43,44,45] In a placebo-controlled trial in patients with chronic HCV, orally administered bovine lactoferrin at a dose of 1.8 g daily for 12 weeks had no greater impact on HCV RNA levels than placebo.[46] In a randomized placebo-controlled trial of interferon alpha-2b plus ribavirin, with and without lactoferrin, for treatment of chronic HCV, lactoferrin did not increase SVR rates.[47] Although lactoferrin appears to be safe, there is no compelling reason to use it in patients with hepatitis C infection.

Licorice Root (Glycyrrhiza glabra)

Licorice root contains a compound called glycyrrhizin (or glycyrrhizic acid). Several preliminary studies suggested intravenous glycyrrhizin had some beneficial effects for patients with hepatitis C.[48,49] The intravenous formulation, however, is not available outside of the research setting. There are minimal reliable data on oral licorice root for hepatitis C, so no specific recommendations can be made regarding its use. When taken in large amounts, however, licorice root containing glycyrrhizin can cause high blood pressure, salt and water retention, low potassium levels, and alterations in serum cortisol levels.[50,51] Because of lack of convincing benefit and potential adverse effects, it is not recommended for patients on diuretics or those with cirrhosis or
cardiovascular problems.

**Red Yeast Rice Extract**

Red yeast rice extract is a dietary supplement commonly used in Asia to lower blood cholesterol.[52, 53] It contains a compound (monacolin K) that is biochemically similar to the HMG-CoA-reductase inhibitor lovastatin. Some red yeast rice extract contains citrinin, a chemical that can cause nephrotoxicity. In addition, red yeast rice extract can potentially cause the same adverse effects that occur with statins, such as acute hepatitis, myopathy, and rhabdomyolysis. For these reasons, we recommend strongly against using red yeast rice extracts in persons with chronic HCV infection.

**S-Adenosyl-L-Methionine (SAMe)**

S-adenosyl-L-methionine (also called S-adenosyl methionine, S-adenosylmethionine, SAMe, or SAM-e) is a molecule involved in multiple cellular reactions, acting as the principal methyl donor.[54] Animal models have shown that SAMe depletion may favorably impact liver function.[55] *In vitro* models of hepatitis C demonstrated that SAMe enhances the antiviral effect of interferon, although SAMe does not have any direct antiviral activity. Patients with hepatitis C who took SAMe in conjunction with peginterferon and ribavirin had improved viral kinetics (improved early response), but this did not translate into better sustained virologic response rates.[56, 57] Most often, SAMe is taken at a dose of 1200 mg per day. There are no large, high-quality studies to date demonstrating a treatment outcome benefit of taking SAMe for patients with chronic hepatitis C.[58] A meta-analysis of SAMe concluded that it is superior to placebo in controlling pruritus in patients with chronic liver disease.

**Silymarin**

The alternative medication silymarin is an extract produced from the seeds of the flowering milk thistle plant (*Silybum marianum*). *In vitro* and animal studies suggest silymarin and its derivatives protect liver cells from injury and have antiviral activity.[59, 60, 61] Although oral silymarin is a frequently taken supplement by persons living with chronic HCV infection, clinical studies have not shown a convincing benefit.[59, 62, 63, 64] A randomized study with high-dose oral silymarin found no significant improvement in ALT or decreases in HCV RNA levels.[62] There are data that suggest intravenous silymarin may produce antiviral effects in persons with chronic HCV who receive a liver transplant.[59] Oral milk thistle can be purchased in health food stores without a prescription; the most frequently studied dose is 420 mg per day. The intravenous form of silymarin is available only in a research setting. The most common side effects with oral silymarin are gastrointestinal (laxative effect, nausea, and epigastric discomfort) and arthralgias.[60] Silymarin may also rarely cause hypoglycemia. Patients who have allergies to ragweed, chrysanthemum, marigold, or daisy may have a similar reaction to silymarin. Oral preparations of silymarin do not appear to cause hepatotoxicity, but it can decrease bilirubin conjugation and inhibit the cytochrome P450 enzyme system.[65, 66] In summary, milk thistle taken orally does not appear to have any beneficial or toxic effects on the liver and it does not significantly alter HCV RNA levels.

**St. John’s Wort (Hypericum perforatum)**

The St. John’s wort plant (*Hypericum perforatum*), and its derivative hypericin and hyperforin, are commonly used herbal medicines for the treatment of depression. The evidence for its effectiveness in depression is mixed, with several large studies showing no benefit over placebo for major depression.[67, 68] Although sometimes taken by persons living with chronic HCV infection, St. John’s wort does not have anti-HCV activity. In a small phase 1 study that examined the safety and efficacy of oral St. John’s wort in persons with chronic HCV, investigators reported no detectable antiviral activity, but significant problems with phototoxicity.[69] St. John’s wort is a strong CYP3A inducer and thus can significantly lower the levels of medications that are substrates of CYP3A.[68, 70] This effect on CYP3A can potentially impact all of the recommended DAA regimens to treat HCV infection.
Thus, it is very important that persons receiving HCV DAA therapy avoid concomitantly taking St. John’s wort. Other significant drug interactions with St. John’s wort include digoxin, warfarin, oral contraceptives, and anti-epileptics. Due to lack of antiviral activity, potential adverse effects, and major problematic drug interactions, persons with chronic HCV infection should not take St. John's wort.

**Thymus Extract**

Produced from the thymus gland of cows, thymus extract contains lymphocytopoietic factors, referred to as thymosins, some of which have pleiotropic immunomodulatory effects, including augmentation of T-cell activity. One member in the family of thymosins, thymosin alpha-1, is a 28-amino acid peptide that stimulates T-cell maturation, antigen recognition, and stimulation of native interferons.

Studies involving thymosin alpha-1 in persons with chronic HCV have primarily focused on its use as an adjunctive immune modulatory with interferon-based therapy. Overall, these studies suggested that thymosin alpha-1 might improve SVR rates in interferon-based therapy, but thymosin alpha-1 was never recommended as part of the standard of care for HCV treatment. Since current HCV therapy has moved completely away from interferon-based therapy, there is no longer significant need or interest in using thymosin alpha-1 to augment HCV treatment. Further, some have raised concerns of contamination of thymus extract products as well as the potential for zoonotic disease transmission given its bovine source.
Coffee, Diet, and Sodium Intake

Coffee

Coffee consumption may provide a benefit to patients with chronic hepatitis C infection by slowing fibrosis progression, decreasing the risk of developing hepatocellular carcinoma, and increasing the rates of sustained virologic responses with therapy.\[76,77,78,79\] A large, NIH-sponsored study (referred to as the HALT-C Trial) found that patients who consumed 3 or more cups of coffee per day were half as likely to have progression of their liver disease and twice as likely to respond to peginterferon and ribavirin therapy.\[80\] In addition, a subsequent meta-analysis of 16 studies concluded that coffee consumption can significantly reduce the risk for hepatic fibrosis and cirrhosis.\[81\]

Recommendation

- Patients living with chronic HCV infection should be advised that consuming 3 cups of coffee per day may have a beneficial effect on their liver.

Diet

In general, patients with hepatitis C should choose nutritious foods from each food group: fruits, vegetables, dairy, meat, and grains. A well-balanced diet can help patients receive appropriate amounts of all the vitamins, minerals, and other nutrients. All patients receiving therapy for hepatitis C should drink an adequate amount of water (at least 2 liters per day) to prevent dehydration. It is important to emphasize that protein restriction has not been shown to reduce the risk of hepatic encephalopathy in patients with advanced liver disease and is associated with increased mortality. Patients living with chronic hepatitis C, especially those with cirrhosis, should consume enough protein (1.2 gm of protein per kg weight per day) to avoid muscle wasting and to promote tissue healing. In particular, patients with cirrhosis are often malnourished and should be encouraged to optimize their protein intake. Examples of high quality protein include chicken, fish, lean beef, pork, tofu, nuts, beans, milk, yogurt, and eggs.

Recommendation

- Persons living with chronic HCV infection should have a balanced diet and choose nutritious foods from each major food group.
- Patients with cirrhosis should not have protein restriction; we recommend a protein intake of approximately 1.2-1.5 g/kg/day.
- For patients with cirrhosis and hepatic encephalopathy, the American Association for the Study of Liver Diseases (AASLD) recommended protein intake is 1.2-1.5 g/kg/day.\[82\]

Sodium Intake

Patients with cirrhosis and ascites should limit sodium intake to less than 2000 mg per day (88 mEq per day) because excessive sodium intake can lead to fluid retention in the form of lower extremity edema and ascites.\[11\] As a rough guide, one teaspoon of table salt contains about 2000 mg of sodium. Patients should not add salt to their food, but instead should replace salt with herbs or spices that can add flavor to the food, without the sodium load. Advise patients to choose fresh, unprocessed foods instead of salted, smoked, cured, canned, or dried meats, since these processed meats often contain large amounts of sodium.

Recommendation

- Persons with chronic HCV, cirrhosis, and ascites should limit sodium intake to less than 2000 mg per day.
mg per day.
Modifying Obesity

In the United States and other Western nations, obesity is a growing problem. Obesity is defined as a body mass index (BMI) of 30 or greater and overweight as a BMI of 25 or greater. Concurrent with the obesity epidemic, the prevalence of non-alcoholic fatty liver disease (NAFLD) has risen substantially, as has the more severe form of NAFLD, known as non-alcoholic steatohepatitis (NASH). The prevalence of NAFLD and NASH in the United States population is estimated at 30% and 5%, respectively. Even in the absence of hepatitis C infection, NASH can cause cirrhosis and end-stage liver disease. In persons living with chronic HCV, NAFLD accelerates hepatic fibrosis, particularly with genotype 3 HCV infection. In addition, among persons living with chronic HCV and cirrhosis, the presence of hepatic steatosis is an independent risk factor for developing hepatocellular carcinoma. Further, in HCV treatment clinical trials using interferon-based therapy, obesity, insulin resistance, and hepatic steatosis consistently predicted a poorer response to therapy. In contrast, with DAA therapy for HCV, patients with obesity and hepatic steatosis appear to have responses similar to non-obese patients who receive the same therapy. There are, however, concerns that patients successfully treated for HCV, but who have continued NAFLD or NASH, could develop further liver disease and liver complications.

Recommendations

- Any patient with a BMI greater than 30 should be referred to a nutritionist for diet and weight loss counseling, with a goal of decreasing their BMI to less than 25.
- Obese patients should limit total caloric intake from fat to less than 30% (about 50 to 60 grams of fat per day) and they should receive counseling that any kind of weight loss can benefit them, even if they lose as little as 3 to 5% of their baseline weight.
- A combination of exercise and diet often produces the best long-term results.

- Patients with steatosis who undergo HCV treatment and achieve an SVR should have their liver monitored with liver function tests every 6 to 12 months to ascertain ongoing liver inflammation.
Alcohol, Cannabis, and Tobacco

Alcohol

In the United States, excessive alcohol consumption is one of the most common causes of cirrhosis and liver failure. The combination of excessive alcohol use with hepatitis C infection causes accelerated fibrosis progression, thereby significantly increasing the risk of developing cirrhosis and liver complications, including hepatocellular carcinoma. \([93,94,95,96]\) Available data show that consumption in excess of 30 grams of alcohol per day is hazardous to liver health. \([97,98]\) Note that one alcoholic beverage typically contains about 14 grams of alcohol. In addition, an exact “safe” level of alcohol consumption has never been clearly established for persons with chronic HCV. The Alcohol Use Disorders Identification Test Consumption questionnaire (AUDIT-C) is a useful screening test for estimating a patient's alcohol consumption. \([99]\) Studies that have evaluated the influence of past or current excessive alcohol use on SVR rates with interferon-based therapy have been mixed. \([100,101,102,103]\) Data on the impact of alcohol on DAA HCV treatment are limited, but one study suggested excellent SVR rates with DAA therapy, regardless of alcohol use. \([104]\) Individuals who clear HCV with treatment, but continue to drink excessive amounts of alcohol, may nullify any treatment-related benefit in terms of long-term hepatic complications and liver-induced mortality. \([105]\)

**Recommendation**

- Ideally, persons with chronic HCV infection should abstain from alcohol. The highest priority is in persons with a history of excessive alcohol use (including alcohol use associated with legal, working, or relationship problems); these individuals should abstain completely from alcohol.
- Women who have never had an alcohol problem should have no more than one alcoholic drink per day, and men with no history of alcohol problems should have no more than two alcoholic drinks per day.
- Patients with past or present alcohol use should not be excluded for consideration of HCV treatment. Nevertheless, those with ongoing alcohol use should be encouraged to discontinue alcohol prior to, during, and after therapy for HCV, since continued alcohol use will nullify the fibrosis regression benefit that usually occurs following successful HCV therapy.

Cannabis

Several studies in persons with chronic HCV monoinfection have shown that individuals who frequently smoked cannabis had an increased risk of developing cirrhosis, even after controlling for other factors, such as alcohol use and obesity. \([106,107,108]\) In addition, elevated plasma levels of endocannabinoids provide a biologically plausible mechanism for how cannabis use could accelerate hepatic fibrosis. \([109]\) Whether other routes of cannabis use (e.g. ingestion) or sporadic use have a similar impact on liver fibrosis remains unknown. Several studies in persons coinfected with HIV and HCV have not shown any adverse effect of cannabis use on hepatic fibrosis. \([110,111]\) There are insufficient data on the impact of cannabis on HCV treatment outcomes.

**Recommendation**

- Clinicians should inform all patients of the potential hazards of cannabis, but total abstinence should not be a requirement for HCV treatment.
- Past or present cannabis use should notexclude a person with chronic HCV from receiving HCV treatment.
- For individuals under consideration for a liver transplantation, most programs require complete abstinence from cannabis, due to the increased risk of pulmonary infections associated with cannabis smoking in immunosuppressed patients.
Tobacco

The effects of tobacco smoking on the liver are controversial.\cite{112,113,114,115} In a study involving 244 patients with chronic hepatitis C infection, patients who were smokers had increased hepatic inflammation when compared with non-smokers, but no differences in rates of fibrosis were observed.\cite{114} In addition, other studies involving patients with chronic liver disease have shown increased rates of steatosis and advanced fibrosis, but those studies were retrospective and difficult to control for concurrent alcohol use and obesity.\cite{113,116,117} One study in persons with HIV and HCV coinfection did not show any adverse effect of smoking.\cite{112} It is clear, however, that tobacco use significantly increases the risk of hepatocellular carcinoma, irrespective of HCV status.\cite{118,119,120}

Recommendation

- Clinicians should counsel all tobacco smokers with chronic HCV infection to quit tobacco completely for the following three reasons: (1) smoking may potentially accelerate hepatic fibrosis, (2) smoking clearly increases the risk of developing hepatocellular cancer, and (3) smoking is associated with numerous nonhepatic adverse health outcomes.
Summary Points

- Patients with chronic HCV infection without cirrhosis may take up to 2 grams per day of acetaminophen, but individuals with cirrhosis should limit daily intake of acetaminophen to 1 gram per day. Those with excessive alcohol intake should not take acetaminophen.
- In general, NSAIDS are safe for patients with hepatitis C, except for those with cirrhosis, in which case they should be avoided.
- Patients can take a multivitamin without iron, but excess iron intake in the absence of iron deficiency can promote hepatic injury.
- Vitamin D levels should be checked and replenished if less than 20 ng/mL.
- No complementary or alternative medications have shown a definite benefit for patients with hepatitis C. St. John’s wort should be avoided in persons receiving treatment for HCV given its potential to interact with DAA medications.
- Drinking 3 or more cups of coffee per day may have beneficial effects for the liver.
- A balanced, low-fat (less than 30% of total calories) diet is recommended. Patients with cirrhosis should limit sodium intake to less than 2 grams per day and consume at least 6 ounces per day of protein.
- Obese patients are encouraged to lose at least 3 to 5% of their body weight, with a goal body mass index of less than 25, primarily to reduce the risk of fatty liver disease, but also for general health benefits.
- Ideally, persons with chronic HCV infection should abstain from alcohol for liver health, but persons with past or present alcohol use should not be excluded for consideration of HCV treatment.
Citations


86. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA. 2015;313:2263-73.


99. Dawson DA, Grant BF, Stinson FS, Zhou Y. Effectiveness of the derived Alcohol Use Disorders...
[PubMed Abstract] - 

[PubMed Abstract] - 

[PubMed Abstract] - 

[PubMed Abstract] - 

[PubMed Abstract] - 

[PubMed Abstract] - 

[PubMed Abstract] - 

[PubMed Abstract] - 

[PubMed Abstract] - 

[PubMed Abstract] - 

[PubMed Abstract] - 

[PubMed Abstract] - 

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

References

[PubMed Abstract]

[PubMed Abstract]

