

An Appraisal of Herbal and Drug Interactions— Podiatric Implications

Here's what you need to know
about these common side-effects.

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Learning Objectives

- 1) Recognize the potential for herb-drug interactions.
- 2) List the known herb-drug interactions as reported in the medical literature
- 3) Recognize the main reasons for caution with herbs "in" or "before" podiatric surgical procedures

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Following this article, an answer sheet and full set of instructions are provided (pg. 180).—**Editor**

Introduction

Complementary medicines are widely available at many health food stores, pharmacies, and doctors' offices. The use of herbal remedies has been around for centuries, and their use in both eastern and western societies are well documented. As recent as 1890, 59% of the listings appearing in the US Pharmacopeia were created from herbal products.¹ In North America, alternative medicine can be

traced back to the teachings of Dr. Benedict Lust, founder of the American School of Naturopathy.² The term "drug" comes from the ancient word for "root." Until the 1930s, medical schools taught that plant drugs were the primary medicines available.

Analyses of the 2002 NIS/CAM report revealed that approximately 38 million North American adults (18.9% of the population) used natural herbs or supplements during the

preceding year.^{3,4} Over the last 15 years, the use of dietary supplements and herbal products in the United States has dramatically increased.^{5,6} In a 2011 publication, Wu, et al. concluded that herbal preparations and dietary supplements remain popular in the United States, but user population and patterns of use are changing. Further, they recommended that ongoing surveillance of this behavior is

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a public health priority.⁷ Recently, these authors reported that children in the United States appear to have a pattern of moderate and appropriate use of herbs or dietary supplements, and use them at a much lower rate than adults.⁸

The Dietary Supplement Health and Education Act (DSHEA) defined a dietary supplement as a vitamin, mineral, herb or other botanical, amino acid, or other substance (e.g., coenzyme, organ tissue, glandular, or metabolite). The DSHEA assumed that the history of use of a given supplement was evidence for its safety, thus grandfathering in all supplements on the market before the legislation. Herbal medications are classified as dietary supplements by the Dietary Supplement Health and Education Act of 1994.⁹ This law exempts herbal medications from the safety and efficacy requirements and regulations that prescription and over-the-counter drugs must fulfill (i.e., pre-clinical animal studies, pre-marketing controlled clinical trials, or post-marketing surveillance).

The current U.S. regulatory mechanism provides little assurance that commercial herbal preparations have predictable pharmacological effects and that product labels provide accurate information. The potency of herbal medications can vary from manufacturer to manufacturer and from lot to lot within a manufacturer.¹⁰⁻¹²

Plants may be misidentified or deliberately replaced with cheaper or more readily available alternatives.¹³⁻¹⁶ Currently, manufacturers of these products are not required to report adverse events, and the FDA has no regulatory authority to require labeling changes or to help in-

quality of multivitamin and mineral products is inadequate.

Investigators have determined that the incidence of alternative medicine supplement use in pre-surgical patients ranged from 7% in pregnant women to 39% in patients awaiting elective non-cardiac surgery.¹⁸⁻²¹

Despite these findings acknowledging and accepting these percentages, the podiatric physician will encounter those patients who are reluctant to disclose their use of herbal supplements prior to surgical intervention.

The medical literature reveals that 40% to 70% of respondents did not report complementary medicine use to their physicians.^{2, 22-24} Some reasons cited for this phenomenon include: many patients feel that their physician will not understand, approve of, or have interest in such modalities.² Further, other patients may feel their physician has little knowledge about herbal products, while other patients do not consider the dietary supplements to be medications, or feel

that supplements are not related to their current medical care.²⁵⁻²⁶

Finally, Heyneman relates other reasons for patients failing to disclose herbal usage: a belief that because such products are “natural” they must be entirely safe, a fear of how healthcare providers would respond to self-medication, and the patient’s fear that the physician may be pre-

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TABLE I
Perioperative Herbal Concerns

Hypotensive	Fish Oil Garlic Coenzyme Q 10 (ubiquinone)
Cardiac effects	Coenzyme Q 10 (ubiquinone) Saw palmetto Ginseng Green Tea
Prolongation of anesthetic effects Increase Sedative Effects	St John’s wort Ginseng Kava Valerian
Hypoglycemia	Glucosamine Garlic
Perioperative Bleeding	Fish Oil Garlic Flax seed Coenzyme Q 10 (ubiquinone) Saw palmetto Ginseng Chondroitin Green Tea
Water/electrolyte Disturbance	Saw palmetto Ginseng Green Tea
Volume Depletion	Milk Thistle

******ASA recommends that all herbal medications should be discontinued 2 to 3 weeks before an elective surgical procedure**

form the public of these issues and concerns. Although the methodology of herbal trials has improved, some studies cited in specific herbal compendia have specific limitations. Many results of herbal trials often do not reach statistical significance because these studies enroll fewer participants than trials of conventional medications.¹⁷ The current level of public assurance of the safety and

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diced against use of herbs.^{18,27}

Numerous herbal supplements are known to increase the risks associated with surgery and anesthesia. Adverse effects of particular concern

continue the use of herbal medications two to three weeks before surgery.^{5, 18, 29-31} However, patients are often unaware of this recommendation and, furthermore, may present for emergency surgery.

The purpose of this article is to

deadly adverse effects. Lastly, some potential perioperative complications associated with common herbal products will be offered as a narrative and graphically as easy-to-read tables to serve as relative quick reference for the podiatric physician (Table 1 & Table 2).

It has been established that chronic use of Echinacea may cause liver inflammation and even hepatic failure.

for patients undergoing anesthesia include cardiovascular instability and electrolyte disturbances, endocrine effects, hepatotoxicity, renal failure, prolonged bleeding, and excessive sedation.^{2,5,18,20, 27-29}

As pharmacokinetic and pharmacodynamic data are lacking, the American Society of Anesthesiologists recommends that patients dis-

attempt to list the most clinically relevant herbal alternative medications with the goal of preventing adverse outcomes and potential side-effects during the perioperative period. Additionally, an attempt will be made to enhance the podiatric physician's knowledge of the importance of facilitating patient disclosure of their herbal medications to avoid potential

Echinacea

Echinacea is the most popular herbal remedy currently being used both in the United States and the United Kingdom.²⁹ It is used to boost the immune system. It is believed to improve the immune system through modulation of cytokine signaling and is used for the prevention and treatment of viral, bacterial, and fungal infections. It has been established that chronic use of Echinacea may cause liver inflammation and even hepatic failure when used in conjunction with hepatic toxic drugs like methotrexate, anabolic steroids, aminodarone, and halothane.^{5,29}

Echinacea can inhibit the hepatic cytochrome P-450 isoforms, thus precipitating toxicity of drugs metabolized by the liver. An increase in oral midazolam plasma concentrations and conversely a decrease in intravenous plasma concentrations have been found in patients who chronically ingest Echinacea.

Ephedra Sinica

Ephedra sinica originated from China. Ephedra (Ma Huang) contains the alkaloids ephedrine, pseudoephedrine, methylephedrine, and norpseudoephedrine.^{27,29} It has been used for the treatment of asthma and fatigue and was the active ingredient in many diet, cold, and anti-fatigue remedies. It is also used in the illicit manufacture of methamphetamine.³²

In 2004, the FDA banned the sale of dietary supplements containing ephedra because of adverse cardiovascular effects.⁵ Ephedra causes dose-dependent increases in blood pressure and heart rate.²⁷ Dysrhythmias have been reported with concurrent administration of ephedra and cardiac glycoside drugs such as digoxin, as well as the inhalation agent halothane.^{5,32} Ephedra side-effects are predictable and in-

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St John's wort	Alprazolam	↓
	Oral Contraceptives	↓
	Cyclosporine (Neoral)	↓
	Digoxin	↓
	Imatinib	↓
	Indinavir	↓
	Irinotecan	↓
	Omeprazole	↓
	SSRI	(Serotonin syndrome)
	Verapamil	↓
	Warfarin	↓↓↓
Ginseng	Digoxin	↑
	MAO Inhibitors	Toxicity

↓ = Decrease in Drug Activity
↑ = Increase in Drug Activity

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clude palpitations, hypotension, tachycardia, stroke, and seizures.²⁹ Long-term use of ephedra may decrease the effectiveness of certain agents used to treat intra-operative hypotension.^{5,18,27,29,32} The effects of ephedra on anesthesia are partly predictable. In combination with other sympathomimetic drugs, it can result in life-threatening arrhythmias, hypertension, and hyperthermia.^{2,5,18,27,29}

Garlic

Garlic (*Allium sativum*) has also been used for centuries for its medicinal properties. Users of garlic claim it is beneficial in cardiovascular disease, diabetes, infection, and even tumors. Garlic does seem to have significant effects on both systolic and diastolic blood pressure.² Garlic's actions on platelets are believed to be because of the cysteine contained in garlic, which decreases thromboxane formation and alters arachidonic acid metabolism.²⁹ Garlic has been implicated in the development of spontaneous epidural hematoma.^{5,33} Garlic is thought to have been the cause of a spontaneous epidural hematoma in an elderly man who ingested approximately 2,000 mg of garlic daily for an unspecified period.^{18,34} Theoretically, patients using garlic may demonstrate increased intra-operative blood loss.

Ginger

Ginger (*Zingiber officinale*) is marketed as an anti-inflammatory and an anti-emetic. In addition to direct stimulation of the gastrointestinal tract, it is postulated to inhibit peripheral and central serotonergic pathways. A systematic review of randomized controlled trials showed no significant difference in the incidence of post-operative nausea and vomiting between the ginger and placebo groups.^{29,35}

Ginkgo Biloba

Ginkgo biloba is used to treat cerebral insufficiency, dementia, and to help improve memory. Also it has been marketed and used to treat intermittent claudication, tinnitus, and vertigo. Episodes of increased bleeding to include subdural hematoma

and sub-arachnoid hemorrhage have been reported in patients taking ginkgo biloba alone, or in conjunction with aspirin or ergotamine.^{33,36}

Though ginkgo biloba is considered safe, the podiatric physician should consider in the peri-operative period that its platelet inhibitory effect may be of some concern. This supplement should be avoided in patients taking anticoagulant drugs, or drugs that inhibit platelet aggregation.^{5,18,27,32,33,36}

Ginseng

Ginseng is used to support overall health and boost the immune system. Ginseng may also be used to increase stamina, promote a sense of well-being, control blood pressure, and lower blood glucose levels.³⁶ Excessive use

meadowsweet which contain high concentrations of salicylates.¹⁸ These herbal products should be considered theoretical risks for prolonged bleeding at this point. Until more information becomes available, it would be wise that the podiatric physician discourages the use of any of these herbs in patients taking warfarin or who are undergoing any type of surgical procedure.

Herbal Diuretics

Herbal diuretics include dandelion, green tea, goldenseal (*Hydrastis canadensis*), saw palmetto berries, and spearmint.^{29,38,39} They are often marketed in combination as natural weight loss remedies and are readily available on the streets and the Internet without prescription. Their mechanism of action is uncertain, but in-

One component of this licorice is carbenoxolone which can elevate blood pressure and cause hypokalemia.

may cause hypertension and central nervous system (CNS) stimulation, potentially necessitating an increase in administration of anesthetic agents.^{5,32} This product may cause hypoglycemia in patients taking insulin or oral anti-diabetic agents.^{5,18,27,33}

Ginseng may induce hypoglycemia, which is significant particularly in the perioperative time period because patients are likely in the fasting state before surgery.² Therefore, serum blood glucose levels should be closely monitored in surgical patients with diabetes who have been taking ginseng. In addition, ginseng may decrease the efficacy of warfarin. It is recommended that clotting studies be closely monitored in patients who combine ginseng with warfarin therapy.^{5,27,33}

Herbs believed to contain coumarin or coumarin derivatives include angelica root, arnica flower, anise, celery, chamomile, fenugreek, horse chestnut, licorice, lovage root, parsley, passionflower herb, quassia, red clover, and rue.^{18,37}

Anti-platelet activity has been reported for turmeric, clove, onion, and bromelain, willow bark, poplar, and

terference with the renin-angiotensin-aldosterone system is postulated. Hence, there have been reports of significant electrolyte disturbances associated with their use.^{18,38}

Kava

Kava (*piper methysticum*) is derived from the dried root of the pepper plant family. It is used as an anxiolytic and sedative with effects mediated by potentiating gamma-aminobutyric acid (GABA) transmission.^{5,18,27} It potentiates the effects of barbiturates and benzodiazepines. There is a single case report of an interaction between kava and alprazolam that purportedly resulted in a semi-comatose state.⁴⁰ The podiatric physician should consider if muscle relaxants are used during surgery; dosage adjustments of reversal agents may be required in patients who have recently ingested kava. This supplement may also increase the potency of CNS depressants, dopamine antagonist anti-emetics (metoclopramide), and antipsychotics.^{5,32} In addition, kava may cause liver damage.^{2,5}

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Licorice

Licorice (*Glycyrrhiza glabra*) is used as a cough suppressant and expectorant. This herb promotes prostaglandin synthesis in the stomach, which protects the gastric mucosa and supports the healing of gastric ulcers.^{5,32,41} When taken in excessive amounts, 50 grams per day or prolonged use greater than six weeks, pseudaldosteronism results in potassium depletion, sodium retention, edema, hypertension, and weight gain. Licorice contains glycyrrhizic acid, which increases blood glucose levels and causes hypokalemia. One component of this herb is carbenoxolone, which can elevate blood pressure and cause hypokalemia.⁴¹ Drug interactions have been noted with licorice ingestion and thiazide and loop diuretics, cardiac glycosides, anti-hypertensives, and amiloride.

St John's Wort

St John's wort (*Hypericum perforatum*) is widely used in western societies as an antidepressant and for other mood disorders. Similar to more conventional antidepressants, its effects are thought to be because of the inhibition of serotonin, norepinephrine, and dopamine re-uptake by neurones. The efficacy of St John's wort was found to be equivalent to tricyclic antidepressants in the treatment of mild to moderately severe depressive disorders.²⁹

There are numerous important interactions between conventional drugs and St John's wort.^{2,5,18,27,29} It can lead to a serotonergic syndrome characterized by muscle rigidity, autonomic dysfunction, and altered mental state when used in combination with drugs which also increase plasma serotonin concentrations. It is also a potent inducer of hepatic cytochrome P450 CYP3A4 isoform. Hence, it may significantly increase the metabolism of many concomitantly administered drugs such as alfentanil, midazolam, and lidocaine. St John's wort significantly reduces the area under the plasma concentration-time curve (AUC) and blood concentrations of midazolam. It also

induces the P450 2C9 isoform that results in the reduction in effect of warfarin and NSAIDs.

P-glycoprotein (Pgp) is involved in multidrug resistance and acts as a pump to remove drugs from cells. St John's wort has been found to induce this process and thus remove drugs from cells. It also regulates MDR-1 (multidrug resistance gene) and other drug transporters and may contribute to recent multi-drug resistance bacterial organisms. The sedative properties of St John's wort may potentiate or prolong an anesthetic agent's effect.²⁹

Sympathetic nervous system stimulants used to increase heart rate or blood pressure intra-operatively, when taken in conjunction with St. John's wort, can cause an exaggerated increase in blood pressure.^{2,5,18,27,29} Further, St. John's wort is known to induce photosensitivity; therefore, the treatment with a laser or intense pulsed light should be avoided while patients are taking St. John's wort.²

Valerian

Valerian (*Valeriana officinalis*) has been used as an anxiolytic and a sedative. It produces dose-dependent sedation and hypnosis, and is believed to inhibit GABA breakdown and re-uptake. This supplement is a CNS depressant with hypnotic and sedative effects, and may potentiate the effects of prescription sedatives and opioids.^{2,18,27,29} The concomitant use of opioid analgesics with sedative herbs to include valerian, kava, and chamomile may lead to increased CNS depression. Adverse effects reported include tremor, headache, hepatic dysfunction, and cardiac disturbances. Caution should be taken with abrupt discontinuation of valerian use in patients who may be physically dependent on valerian because of the risk of benzodiazepine-like withdrawal. Tapering the dose may be a more prudent strategy.²⁹

Although generally considered safe by the FDA as a food additive, caution is warranted because of the potential for excessive sedation when surgical patients consume valerian.²⁸

Yohimbe

This supplement has demonstrated effectiveness as a treatment for

male impotence. It is available by prescription (yohimbine hydrochloride), since it has been shown to be of poor quality when purchased at health food stores and other specialty shops; in some cases, it's completely lacking the active substance yohimbine.³² Excessive doses may cause hypertension and tachycardia, potentially necessitating an increase in anesthetic requirements.³² Paresthesias and manic or psychotic episodes are also associated with yohimbine.³²

Aloe Vera and Sevoflurane

One interesting case study involves a 35-year-old woman who lost five liters of blood during surgery as a result of a possible herb-drug interaction between Aloe vera and sevoflurane.⁴² Aloe vera is a common herb used for anti-inflammatory and hypoglycemic effects, and lipid-lowering effects. The patient admitted to ingesting four tablets of aloe vera per day for 14 days before her admission for leg pain. Compounds contained within aloe vera can cause a reduction in prostaglandin synthesis, which may inhibit secondary aggregation of platelets. Sevoflurane inhibits thromboxane A² formation by suppression of cyclooxygenase activity, impairs platelet aggregation, and prolongs bleeding. The patient was discharged 25 days after her admission without ill effects.⁴²

Conclusion

A significant percentage of surgical patients use dietary supplements on a regular basis; however, many users are reluctant to reveal their use to their healthcare providers. Podiatric physicians should be aware of the potential adverse effects that herbal products may have on patients undergoing lower extremity surgical intervention. The American Society of Anesthesiologists recommends that patients should discontinue the use of their herbal medications two to three weeks before surgery. **PM**

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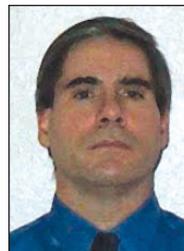
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SEE ANSWER SHEET ON PAGE 181.

- 1) The Dietary Supplement Health and Education Act of 1994 exempts _____ medications from the safety and efficacy requirements and regulations.
 - A) legend
 - B) scheduled
 - C) herbal
 - D) over-the-counter
- 2) The American Society of Anesthesiologists recommends that patients should discontinue the use of their herbal medications _____ before surgery
 - A) 3–4 weeks
 - B) 2–3 months
 - C) 2–3 days
 - D) 2–3 weeks
- 3) The medical literature reveals that _____ of respondents during investigations did not report complementary medicine use to their physicians.
 - A) 25% to 50%
 - B) 15% to 25%
 - C) 10% to 30%
 - D) 40% to 70%
- 4) It has been established that chronic use of echinacea may cause _____.
 - A) kidney inflammation.
 - B) liver inflammation
 - C) muscle inflammation
 - D) brain inflammation
- 5) Long-term use of ephedra may decrease the effectiveness of certain agents used to treat intraoperative _____.
 - A) hypotension
 - B) electrolyte imbalance
 - C) bleeding
 - D) bradycardia
- 6) Some reasons cited for patients not reporting complementary medicine use to their physicians include:
 - A) feelings their physician will not understand
 - B) feelings their physician will not approve
 - C) feelings their physician has no interest
 - D) all of the above
- 7) Garlic has been implicated in the development of spontaneous _____.
 - A) epidural hematoma
 - B) hypoglycemia
 - C) hypertension
 - D) hypocalcemia
- 8) With ginkgo biloba, the podiatric physician should consider in the perioperative period that its _____ may be of some concern.
 - A) hypoglycemic effect
 - B) wound healing properties
 - C) hypertensive effect
 - D) platelet inhibitory effect
- 9) Serum blood glucose levels should be closely monitored in surgical patients with diabetes who have been taking _____.
 - A) kava
 - B) ginseng
 - C) St John’s wort
 - D) valerian
- 10) Angelica root, arnica flower, anise, celery, chamomile, fenugreek, horse chestnut, and licorice are believed to contain _____.
 - A) midazolam derivatives
 - B) pentobarbital derivatives
 - C) coumarin derivatives
 - D) digoxin derivatives
- 11) Significant electrolyte disturbances are associated with _____.
 - A) dandelion
 - B) green tea
 - C) goldenseal
 - D) all the above
- 12) _____ mediates by potentiation of gamma-aminobutyric acid (GABA) transmission.
 - A) Piper methysticum
 - B) Hypericum perforatum
 - C) Ma Huang
 - D) Zingiber officinale
- 13) One component of licorice is carbenoxolone that can elevate blood pressure and cause _____.
 - A) hyperkalemia
 - B) hypokalemia
 - C) hyponatunemia
 - D) hypercalcemia
- 14) St John’s wort is a potent inducer of which hepatic cytochrome P450 isoform?
 - A) CYP2B5
 - B) CYP4A3
 - C) CYP2E7
 - D) CYP3A4
- 15) The sedative properties of St John’s Wort may potentiate or prolong _____ agent’s effect.
 - A) anesthetic
 - B) plasma
 - C) antibiotics
 - D) colloidal

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16) Valerian produces a dose-dependent sedation and hypnosis which is believed to be because of inhibition of _____ breakdown and re-uptake.

- A) Gamma-histimine acid
- B) Gamma-glycemic acid
- C) Gamma-aminobutyric acid
- D) Gamma-globulin

17) Adverse effects of herbal ingestion of particular interest to the podiatric surgeon include:

- A) Electrolyte Disturbances
- B) Excessive Sedation
- C) Peri-operative/Prolonged Bleeding
- D) all the above

18) Excessive doses of yohimbine may cause hypertension and tachycardia, potentially necessitating an increase in _____ requirements.

- A) glucose
- B) anesthetic
- C) fluid
- D) suture

19) One recent case report examined the possible drug herb interaction between Sevoflurane and _____.

- A) Gingko biloba
- B) Ginseng
- C) St John's wort
- D) Aloe Vera

20) The concomitant use of opioid analgesics with sedative herbs including _____ may lead to increased CNS depression)

- A) valerian
- B) kava
- C) Chamomile
- D) all the above

SEE ANSWER SHEET ON PAGE 181.

PM's CME Program

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(3) All answers should be recorded on the answer form below. For each question, decide which choice is the best answer, and circle the letter representing your choice.

(4) Complete all other information on the front and back of this page.

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2. The answers to the test
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Charge to: Visa MasterCard American Express

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Signature _____ Soc. Sec. # _____ Daytime Phone _____

State License(s) _____ Is this a new address? Yes _____ No _____

Check one: I am currently enrolled. (If faxing or phoning in your answer form please note that \$2.50 will be charged to your credit card.)

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EXAM #4/14
An Appraisal of Herbal and Drug Interactions—
Podiatric Implications (Smith)

Circle:

- | | |
|-------------|-------------|
| 1. A B C D | 11. A B C D |
| 2. A B C D | 12. A B C D |
| 3. A B C D | 13. A B C D |
| 4. A B C D | 14. A B C D |
| 5. A B C D | 15. A B C D |
| 6. A B C D | 16. A B C D |
| 7. A B C D | 17. A B C D |
| 8. A B C D | 18. A B C D |
| 9. A B C D | 19. A B C D |
| 10. A B C D | 20. A B C D |

Medical Education Lesson Evaluation

Strongly agree [5]	Agree [4]	Neutral [3]	Disagree [2]	Strongly disagree [1]
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- 1) This CME lesson was helpful to my practice ____
- 2) The educational objectives were accomplished ____
- 3) I will apply the knowledge I learned from this lesson ____
- 4) I will make changes in my practice behavior based on this lesson ____
- 5) This lesson presented quality information with adequate current references ____
- 6) What overall grade would you assign this lesson?
A B C D

How long did it take you to complete this lesson?
____ hour ____ minutes

What topics would you like to see in future CME lessons?
Please list :
