

Although there are many effective diabetes medications, patients with diabetes may decide to use complementary therapies or nutrition supplements in addition to their conventional medications. The two case studies presented in this article review drug interactions and other issues that must be considered when patients decide to combine traditional medications with other therapies.

Interactions Between Complementary Therapies or Nutrition Supplements and Conventional Medications

Laura Shane-McWhorter, PharmD, BCPS, FASCP, CDE, BC-ADM, and Patti Geil, MS, RD, FADA, CDE

Approximately 15 million Americans concurrently take complementary medicines or nutrition supplements and conventional medications.¹ A recent article reported that patients with diabetes are 1.6 times more likely than patients without diabetes to use complementary and alternative medicines.² Recent surveys of patients treated in diabetes clinics indicate that 17–31% use complementary products.^{3,4}

The concurrent use of these agents raises a number of issues of which health care professionals must be aware. Approximately 40% of patients do not tell their health care providers they are taking these products.^{1,5} It is impossible to predict problems with drug interactions or side effects. Using nonjudgmental strategies to ask about or comment on complementary products patients may be taking will result in a more successful and productive exchange of information. It is also important to discuss product quality and variability with patients. Finally, clinicians who treat patients with diabetes should use appropriate references for obtaining information on complementary therapies.

Education Point: Consider the risk of potential interactions between complementary therapies or nutrition supplements and conventional medicines. Patients with diabetes frequently take complementary medicines and nutri-

tion supplements. These patients use such therapies not only for diabetes-related conditions but also for other disease states.^{2–4} Hence, one of the most important considerations for clinicians who treat these patients is the possibility of drug interactions.

The case studies on p. 263 and 264 offer examples of possible interactions involving complementary therapies or nutrition supplements and conventional medications.

Discussion of Case Study 1

In our first case, several potential interactions may be responsible for the problems T.R. is experiencing. These problems include elevated blood pressure, recurrence of atrial fibrillation (including subtherapeutic digoxin serum concentration), and subtherapeutic International Normalized Ratio (INR). Furthermore, he has experienced increased nervousness and agitation, and his diabetes is not well controlled.

First, T.R.'s blood pressure is not at goal. Two potential interactions may be responsible. Ginseng has been noted to increase blood pressure⁶ and may theoretically attenuate the efficacy of T.R.'s antihypertensive medication. St. John's wort has also been reported to interact with several medications. A constituent of St. John's wort, hyperforin, may affect metabolizing enzyme production. Hyperforin

Case Study 1: Possible Interactions Between Complementary and Conventional Therapies in a 72-Year-Old Man With Diabetes

T.R. is a 72-year-old man with type 2 diabetes that is not well controlled. His current hemoglobin A1c is 8.9% in spite of the fact that he takes three different oral diabetes agents. His history is significant not only for type 2 diabetes, but also for hypertension, atrial fibrillation, hyperlipidemia, osteoarthritis, and depression. His blood pressure, formerly well controlled at <130/80 mmHg is now 148/92 mmHg. Atrial fibrillation has recurred in this patient who had previously experienced good rate control with digoxin (Lanoxin). Serum digoxin concentration formerly was 1.0 ng/ml and now is 0.7 ng/ml. Furthermore, the INR has decreased from an appropriate therapeutic value of 2.5 to a subtherapeutic value of 1.7. The INR is the most widely used standardized test to monitor warfarin (Coumadin) therapy.

T.R. is taking the following medications:

- Metformin (Glucophage), 1,000 mg twice daily
- Nateglinide (Starlix), 120 mg three times a day with meals
- Rosiglitazone (Avandia), 4 mg twice a day
- Losartan (Cozaar), 50 mg daily
- Warfarin, 5 mg daily
- Digoxin, 0.125 mg daily
- Atorvastatin (Lipitor), 10 mg daily
- Paroxetine (Paxil), 20 mg daily
- Acetaminophen (Tylenol), 500 mg daily

Upon further probing, T.R. stated that he had also started taking certain products that he hoped would improve his diabetes and overall health, especially since he had also felt somewhat “down.” He stated that these feelings, along with the realization that he is growing older, had prompted him to use additional products to help him feel better and improve his chances of seeing his grandson graduate from law school. He stated that, since starting these “natural products,” he has felt better, although he also has felt increasingly nervous and agitated. The products he is taking include:

- St. John’s wort, 300 mg three times a day, for a “positive attitude”
- Asian ginseng, 200 mg daily, for diabetes and to increase energy
- Glucosamine sulfate, 500 mg three times a day, for discomfort secondary to joint pain

binds to the pregnane X receptor, a nuclear receptor.^{7,8} This increases CYP3A4 activity and may increase the metabolism of drugs that are substrates in this isoenzyme system, including the angiotensin receptor blocker losartan. Thus, taking St. John’s wort could reduce the blood pressure-lowering effect of losartan.

The second problem for T.R. is the recurrence of atrial fibrillation and decreased digoxin serum concentration. St. John’s wort may be responsible for decreasing digoxin effects because it is a P-glycoprotein modulator. St. John’s wort has been reported to decrease digoxin serum concentrations by 18–25%.^{9,10} This could result in the recurrence of atrial fibrillation and diminished serum digoxin concentration.

Yet another problem in T.R.’s case is a subtherapeutic INR, which places him at risk for a thromboembolic event. A potential cause is the induction of warfarin metabolism by St. John’s wort, which has been reported to induce CYP2C9, the enzyme system for which warfarin is a substrate.^{6,11} Ginseng has also been reported to interact with warfarin with a resultant decrease in INR.¹²

T.R. also reports feeling “down” and somewhat nervous even though he is taking an antidepressant. He may be experiencing an interaction between St. John’s wort and paroxe-

tine.^{13,14} Concurrent use of these two agents may increase adverse effects such as the serotonin syndrome, which is characterized by nervousness, hyperactivity, and other symptoms. Patients who are elderly, such as T.R., are particularly predisposed to serotonin syndrome when combining St. John’s wort with a selective serotonin reuptake inhibitor.¹⁵

In addition, an elderly patient with diabetes who is feeling “down” is likely to experience a declining appetite and lack of interest in food. This may lead the patient to try medical nutritional supplements in an effort to improve diabetes control and overall health. Specific medical nutritional supplements are promoted for patients with diabetes as snacks, supplements, and meal replacements. They are available in standard carbohydrate (50%) or lower-carbohydrate (33–40%) versions in the form of beverages, shakes, or snack bars. Although many patients do not consider such supplements to be “food,” these products may be fortified with at least 25–50% of the daily value of select vitamins and minerals. Some products contain 100% of the daily value of Vitamin C and E, as well as small amounts of chromium.

Health care providers should carefully question patients with diabetes about their use of medical nutritional supplements to determine the amount and types of products being con-

sumed. Because these products contain calories and carbohydrate, their effect on body weight and blood glucose should be monitored. In addition, it is important to note the potential for excessive ingestion of vitamins and minerals when these products are combined with patients’ usual food and supplement intake.

The last problem in Case Study 1 is that T.R.’s diabetes is not well controlled. This may be caused in part by a drug-disease interaction. The patient is taking a glucosamine supplement, which may theoretically contribute to insulin resistance. A small study¹⁶ showed that glucosamine sulfate decreased glucose tolerance. Another in vitro evaluation¹⁷ showed that glucosamine may increase insulin resistance. This may result in the need to increase doses of diabetes medications or possibly add insulin.

Discussion of Case Study 2

There are two main issues in the case of E.M. First, she has experienced bleeding reactions and has a supratherapeutic INR. Second, she may also be exhibiting a phototoxic reaction. Several potential interactions with warfarin may have resulted in the bleeding reaction. All of the products E.M. is taking, including the supplemental vitamin E and the complementary therapies Ginkgo biloba, vanadium, and dong quai, may have

Case Study 2: Possible Interactions Between Complementary and Conventional Therapies in a 52-Year-Old Woman With Diabetes

E.M. is a 52-year-old postmenopausal woman with type 2 diabetes and a history of deep vein thrombosis (DVT) 2 months ago. Before the DVT, E.M. was taking medications for diabetes and hormone replacement therapy for menopausal symptoms. During workup for the DVT, she was found to have the Factor V Leiden mutation. This indicates that she has an inherited hypercoagulability disorder that makes her more predisposed to a thromboembolic event. Estrogens are thought to increase thromboembolic potential, so she was taken off hormone replacement therapy when she experienced the DVT. She now presents to the hospital emergency department with a chief complaint of hematuria and severe nosebleeds in the past 24 hours.

E.M. stated that she is taking the following medications:

- Glipizide (Glucotrol), 10 mg daily
- Warfarin (Coumadin), 7.5 mg daily
- Glargine (Lantus), 20 units at bedtime

Laboratory evaluation in the emergency department shows the INR is supratherapeutic at 29. When questioned about any changes that E.M. has made in her diet regarding foods or nutritional products that may interact with warfarin, she stated that she has been taking some “natural products” to try and deal with the menopausal symptoms since she is no longer able to use hormone replacement therapy. Upon the advice of her friends, she has also started other products that she thinks may help her diabetes and diabetes-related complications. She stated that in addition to her prescription medications she is also taking the following nutrition supplements and complementary medicines:

- Vitamin E, 1,000 IU daily, for hot flashes
- Ginkgo biloba extract, 40 mg three times a day, for intermittent claudication
- Vanadium (vanadyl sulfate), 50 mg twice a day, for diabetes
- Dong quai, 520 mg three times a day with meals, for hot flashes and other menopausal symptoms

In addition to the bleeding reaction and supratherapeutic INR, the emergency physician notes that E.M. seems to have dermatological irritation and erythema, particularly on the face, neck, arms, and legs.

antiplatelet effects⁶ and may therefore interact either with warfarin or with one another.

Doses >400 IU/day of vitamin E may interact with warfarin to enhance its antiplatelet effects.^{6,18,19} Vitamin E is a fat-soluble vitamin that has been used for a variety of disorders including menopausal symptoms and mastalgia. However, in high doses it may increase the risk of bleeding by inhibiting platelet aggregation and interfering with production of vitamin K-dependent clotting factors.^{6,18,19} Vitamin E may also interact with the other complementary products E.M. is taking to produce additive antiplatelet effects.

She is taking Ginkgo biloba for a possible diabetes complication—intermittent claudication. There are several reports of antiplatelet effects of Ginkgo biloba, and there is a potential for additive antiplatelet effects when it is combined with warfarin.⁶ Ginkgo biloba use has been associated with intracerebral²⁰ and cerebral²¹ hemorrhage, subdural hematoma,²² subarachnoid hemorrhage,²³ and spontaneous hyphema.²⁴

Vanadium is a trace element used for a variety of reasons, including diabetes and bodybuilding, although there are only a few published trials with a small number of patients evaluating its use in diabetes.⁶ The recommended dietary intake of vanadium is unknown,²⁵ and the National Academy of Sciences has indicated that there is insufficient evidence to set a recom-

mended daily allowance or an adequate intake level.²⁶ An upper intake level based on renal toxicity in laboratory animals has been set at 1.8 mg.²⁶ Because vanadium may possess anticoagulant activity,²⁷ a theoretical interaction between vanadium and warfarin is potentiation of warfarin's anticoagulant effects. This may be yet another factor that has contributed to E.M.'s elevated INR.

Dong quai is a botanical product used to treat menopausal symptoms.⁶ In a case report,²⁸ dong quai doubled the INR in a woman also taking warfarin. In vitro data²⁹ show that dong quai may inhibit cyclooxygenase activity and platelet aggregation. Furthermore, E.M. may also be exhibiting photosensitivity secondary to combined use of dong quai and the sulfonyleurea. Dong quai contains the photoactive compounds, psoralens and bergapten, which may produce additive phototoxicity when combined with other photosensitizing agents³⁰ such as sulfonyleureas.

Education Point: Ask patients what they are taking.

Less than 40% of patients tell their health care providers they are taking complementary therapies.^{1,5} Different surveys have reported varying reasons why patients do not provide this information. One survey³¹ indicated the following reasons:

- “It wasn't important for the doctor to know.”

- “The doctor never asked.”
- “It was none of the doctor's business.”
- “The doctor would not understand.”

It is imperative for clinicians to ask their patients whether they are taking any complementary products.

One reason patients may not let their providers know they are using these products is because patients often do not regard these products as medications.³² Or, they may not consider these products as potentially harmful since mandatory product labeling may suggest beneficial although nonmedical claims, such as St. John's wort “helps to maintain a positive attitude” or “helps support healthy emotional balance.”³³

Education Point: Use nonjudgmental, evidence-based strategies to comment on products your patients are taking.

Patients are often reticent about admitting to using complementary therapies, and clinicians may not ask about specific use of these products.³² Effective provider-patient relationships require providers to have a nonjudgmental attitude. Without this, there may be a lack of trust, and patients may not be willing to tell providers what they are taking.

Using potentially toxic therapies may put patients at risk for adverse events. Cases have been reported in which individuals use unorthodox treatments to treat their diabetes. For

instance “urine therapy” to prevent or treat diabetes is based on using patients’ own urine to develop an “autoimmune” solution that purportedly produces antibodies against patients’ own glucose without increasing pancreatic insulin production.³⁴ Another example is substitution of complementary therapies for conventional diabetes medications. Diabetic ketoacidosis occurred in a patient with type 1 diabetes who was advised to stop insulin.³⁵ Another patient was also advised by a reflexologist to stop insulin and was subsequently admitted to the hospital with acute hyperglycemia.³

Education Point: Consider product quality and variability.

Many complementary products are on the market. There are >1,500 herbal products alone.³⁶ Product ingredients and quality may vary considerably. Although use of standardized products is recommended, standardization is difficult to accomplish when active ingredients are unknown and there are no appropriate assays.³⁷ For example, St. John’s wort has been standardized according to hypericin content. However, hypericin content may vary. Some products having labels that state that they contain 0.3% hypericin may have differing amounts of hypericin, such as 300 or 450 mg. Other formulations may be liquid preparations for which the label states the product “contains hypericins.” Other agents may not state contents at all other than that the product “contains St. John’s wort.”³⁷

Furthermore, hypericin has never been verified as the active ingredient. Hyperforin, another component of St. John’s wort, has been thought to be a more potent antidepressant than hypericin³⁸ and is theorized to be the ingredient responsible for drug interactions.^{7,8}

Other products may contain a variety of different components, such as a combination of St. John’s wort, echinacea, kava, and other substances. Patients may believe that a combination product may provide the most value because they are obtaining many different ingredients for a single price.

Product variability may result in harm from a toxic product replacing a traditional product³⁹ or from inadvertent contaminants.⁴⁰ In 2000, the California Health Department announced that the sulfonylurea gly-

buride and the biguanide phenformin had been found as contaminants in some complementary products aimed at treatment of diabetes.⁴¹ Other publications have also reported lead contamination in Indian herbal remedies used for diabetes.^{42,43}

Educational point: Use appropriate references for obtaining information on complementary therapies and nutrition supplements.

There are myriad products that patients with diabetes may use, and it is of utmost importance for clinicians to stay up to date on information regarding these products. Some references and web sites that may be useful for clinicians include:

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Summary

Many patients with diabetes may take complementary therapies or nutrition supplements and conventional medicines concomitantly. Some of these combinations may lead to potentially harmful interactions. The education points listed throughout this article can help health care providers navigate these issues with their patients with diabetes.

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Laura Shane-McWhorter, PharmD, BCPS, FASCP, CDE, BC-ADM, is associate professor (clinical) at the University of Utah College of Pharmacy and an adjunct faculty member at the University of Utah School of Medicine in Salt Lake City. Patti Geil, MS, RD, FADA, CDE, is a nutrition consultant in private practice in Lexington, Ky.

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