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ON THE
CUTTING EDGE
Diabetes Care and Education

THERE'S A PILL (OR INJECTION) FOR THAT: A DIABETES PHARMACOTHERAPY UPDATE

Message from the Theme Editor:

Susan Cornell, PharmD, CDE, FAPhA, FAADE
Downers Grove, IL

Receiving the diagnosis of diabetes can be devastating, and too many people believe that taking a prescribed medication can cure the disease. Despite this mindset, nearly 50% of people with diabetes do not adhere to their medication therapy regimen.

As most of us who practice in diabetes know, lifestyle modification, including diabetes self-management education, healthy eating, physical activity, monitoring, stress reduction, and weight management, forms the cornerstone of diabetes management. Pharmacotherapy is always adjunct to lifestyle modifications. Diabetes care providers must help patients understand that taking medication does not replace healthy lifestyle choices.

In the past 20 years, the number of available diabetes pharmacotherapy options has increased 300%. There are currently 12 different classes of prescription medications available for the treatment of type 2 diabetes mellitus (T2DM). Therefore, designing the appropriate diabetes management plan must be individualized and take into consideration numerous factors:

1) How long has the patient had T2DM? The person who is newly diagnosed may have some remaining β-cell function compared with the person who was diagnosed many years ago and has negligible β-cell function.

2) Which blood glucose level is not at target? Some medications target the fasting glucose, others reduce postprandial glucose levels, and a few address both.

3) How much hemoglobin A1c (HbA1c)-lowering effect is required to achieve goals? Most medications lower the HbA1c between 0.4% and 2.0% (even in combination), with the exception of insulin, which has greater HbA1c-lowering abilities compared to the other 11 classes of diabetes agents.

4) What is the patient's preference for prescribed medication and route of administration (e.g., oral or injectable)? Simply prescribing a drug to a patient does not mean he or she will take it or take it correctly.

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Print Communications Coordinator:
Lorena Drago, MS, RD, CDN, CDE

***News*FLASH Editor:**
Anna Henry, MPH, RD, LD, CDE

***On the Cutting Edge* Editor:**
Janis Roszler, MS, RD, LD/N, CDE, FAND

***On the Cutting Edge* Associate Editor:**
Susan Weiner, MS, RDN, CDE, CDN

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Linda Flanagan Vahl
DCE Administrative Manager
Academy of Nutrition and Dietetics
120 South Riverside Plaza, Suite 2000
Chicago, IL 60606-6995

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MISSION
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Optimizing the health of people impacted by diabetes using food, nutrition, and self-management education.

5) What adverse effects are common and what is the patient's tolerability? Educating patients on common adverse effects and implementing strategies to reduce or minimize the effects can be beneficial.

6) What coexisting conditions does the patient have? Often patients have more than just diabetes. A thorough review of coexisting diseases is necessary to prescribe optimal drug therapy that can improve and not worsen other conditions.

In this issue of *On the Cutting Edge,* we focus on drug therapy for diabetes and its related conditions. The contributing authors were chosen for their extensive knowledge of diabetes pharmacotherapy issues, specific to their subtopics. We are extremely fortunate and grateful that they shared their expertise for this edition.

Beginning with a brief and concise overview of the current diabetes medications, nationally recognized expert Nadia Shaikh, PharmD, and Jennifer Goldman, PharmD, CDE, BC-ADM, FCCP, share their knowledge with practical commentary from Melinda Maryniuk, MEd, RD, CDE, FADA.

Justin M. Schmidt, PharmD, BCPS, BC-ADM, offers a clear glance into the diabetes crystal ball by reviewing emerging medications and those in the development pipelines for the treatment of diabetes.

Thomas G. Wadsworth, PharmD, BCPS, and Alyssa Gallagher, RD, LD, CDE, provide a team-based approach to their discussion on weight loss drugs and lifestyle therapy. This is a relevant topic, especially with the global focus on the obesity epidemic and its relationship to T2DM.

Wendy Mobley Bukstein, PharmD, CDE, and Melissa Schleder, RD, present an overview and practical considerations for practitioners about common vitamins and minerals used to prevent and treat diabetes and its complications.

Because herbal therapies are of great interest to patients and providers alike, Lea E. dela Pena, PharmD, BCPS, and Katherine Snyder, MS, RD, CDE, discuss the use of common herbal products (in the "pill" form) that are claimed to aid in the prevention and treatment of diabetes.

STRATEGIC PRIORITY AREAS

GOAL 1: Sustain and enhance participation and retention among members.

- Use electronic technology to engage new and existing members
- Promote and support member professional development
- Maintain a high value of membership

GOAL 2: Advance DCE's member relationships among industry, media, professional and public education.

- Collaborate with organizations to promote RDs in diabetes care, education and prevention

Goal 3: Support and promote public policy and research efforts in nutrition and diabetes

- Address and support public policy efforts involving nutrition and diabetes and pre-diabetes
- Increase research efforts

Despite all the available therapies, we know that if the patient does not take the medication, it will not work. In their review of adherence specific to diabetes pharmacotherapy, Diana Isaacs, PharmD, BCPS, CDE, BC-ADM, and Janice Fisher, PhD, RD, LD, CDE, BC-ADM, FAADE, examine strategies to assess and address this problem.

Finally, with much media focus on immunizations, Valerie Clinard, PharmD, and Ann Constance, MA, RD, CDE, FAADE, explain the value of and rationale behind the current recommendations for immunizations for people with diabetes.

This issue of *On The Cutting Edge* would not have been possible without the support of several amazing and talented people. I'd especially like to express my gratitude to Janis Roszler, MS, RD, LD/N, CDE, FAND, who provided me with this fabulous opportunity to be theme editor. I truly value the support and guidance she provided. I'd also like to thank my wonderful theme team, who helped design the content and recommended the authors. I would like to acknowledge the authors, reviewers, and editorial team for their expertise, time, effort, and patience. Finally, thank you to the readers. I hope you find the information valuable and helpful as you improve the lives of people with diabetes.

Suggested Reading

1. Bunting B, Horton B. The Asheville Project: Taking a fresh look at the pharmacy practice model. *Pharmacy Times.* 1998;October (suppl 1):11–17.
2. American Association of Diabetes Educators. Standards for outcomes measurement of diabetes self-management education. *Diabetes Educ.* 2003;29:804–816.
3. Anderson RM, Funnell MM. *The Art of Empowerment: Stories and Strategies for Diabetes Educators.* 2nd ed. Alexandria VA: American Diabetes Association; 2005.
4. Burke SD, Cornell SA. Medication management in type 2 diabetes. *Clinician Reviews.* 2008;18(3):28–34.
5. Cornell S. Dorsey VJ. Diabetes pharmacotherapy in 2012: considerations in medication selection. *Postgrad Med.* 2012;124(4):84–94.

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THEME TEAM

Susan Cornell, PharmD, CDE, FAADE, FAPhA
Melissa Dobbins, MS, RDN, CDE
Jennifer D'Souza, PharmD, CDE, BC-ADM
Sarah Ferguson, RN, CDE
Janis Roszler, MS, RD, LD/N, CDE, FAND
Jennifer Smith, PharmD, CDE
Susan Weiner, MS, RDN, CDN, CDE

REVIEWERS

R. Keith Campbell, RPh, MBA, CDE
Lori Chong, MBA, RDN, LD
Paula Clinton, RD, CDE
Don DeBarbieris, RPh
Marlowe Djuric-Kachlic, PharmD
Jennifer D'Souza, PharmD, CDE, BC-ADM
Sarah Ferguson, RN
Svetlana Goldman, PharmD, BCACP
Starlin Haydon Greatting, MS, BSPharm, FAPhA
Cindy Halstenson, RDN, CDE
Lisa Kroon, PharmD, CDE
Sandra Leal, PharmD, MPH, CDE, FAPhA
Carole Mensing, RN, MA, CDE, FAADE
Michele Moore, RD, CDE
Staci Norman, PharmD, CDE
Sara (Mandy) Reece, PharmD, CDE, BC-ADM
Barbara Reis, RD, CDE
Laura Shane-McWhorter, PharmD, BCPS, BC-ADM, CDE, FASCP, FAADE
Sheri Stensland, PharmD, AE-C, FAPhA
Donna M. White RPh, BCACP, CDE
Julie Sease, PharmD, FCCP, BCPS, CDE, BCACP
Joel Thome, PharmD, BCACP
Laura Waite, PharmD, BCPS, CLS, BC-ADM

OTHER CONTRIBUTORS TO PRODUCTION

Feon Cheng, MPH, RD, CHTS-CP
Kathryn Mount, MS, RD
Marla Solomon RD, LD/N, CDE
Linda Flanagan Vahl

Current Therapy in Diabetes

Nadia Shaikh, PharmD
Fellow, Global Medical Affairs Becton Dickinson and Company Billerica, MA
MCPHS University Boston, MA

Jennifer Goldman, PharmD, CDE, BC-ADM, FCCP
Professor of Pharmacy Practice, MCPHS University Boston, MA
Clinical Pharmacist, Well Life, Peabody, MA

Abstract

In addition to lifestyle modifications, people who have type 2 diabetes mellitus (T2DM) often require complex medication regimens to attain optimal glycemic control. Many different classes of medications are available, and it is crucial for health care practitioners to be familiar with the primary characteristics of these drugs and their place in therapy. This article reviews the classes of diabetes medications and their therapeutic roles, based on both the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) guidelines and the American Association of Clinical Endocrinologists (AACE) algorithm.

Introduction

According to the International Diabetes Federation, approximately 382 million people worldwide live with diabetes (1). This number is expected to rise to 592 million by 2035 (1). As the number of people who are living with diabetes increases, so too does the need for pharmacologic agents to help control the disease. Fortunately, many medications are available with varying mechanisms of action that can be used as monotherapy or as combination therapy to act synergistically in lowering glucose concentrations.

The ADA guidelines recommend a goal hemoglobin A1c (HbA1c) of less than 7% for most patients. Based on the available evidence, metformin combined with lifestyle modifications is recommended as a first-line therapy for all patients with T2DM. ADA recommendations suggest that if target HbA1c is not met after 3 months of taking metformin, a second agent of the clinician's choice should be added. Beyond metformin, no outcome data support the superiority of one drug class over another (2). The next step is the addition of a third agent, and if goal HbA1c values are not achieved, insulin should be initiated. If basal insulin is already being used, a more complex insulin regimen should be initiated. The choice of second- and third-line agents should be based on multiple factors, including patient preferences, duration of the disease, coexisting medical conditions, adverse effects, the degree to which the drug lowers HbA1c, and cost (2,3). When choosing agents for therapy, individualization is key.

The AACE recommends a more stringent HbA1c goal of less than 6.5% for most patients. If a patient presents with an HbA1c greater than 7.5%, AACE recommends initiating metformin therapy, with the addition of a glucagon-like peptide-1 (GLP-1) agonist, followed by a dipeptidyl-peptidase-4 (DPP-4) inhibitor, thiazolidinedione (TZD), or sodium-glucose-linked transporter-2 (SGLT-2) inhibitor, and finally basal insulin to reach goal HbA1c values (4). As with the ADA guidelines, therapy should be individualized for each patient.

Biguanide

The only medication commercially available in the biguanide class is metformin. When combined with lifestyle modifications, metformin helps to lower HbA1c by about 1% to 1.5% (5). This medication is believed to reduce blood glucose by inhibiting hepatic glucose output. Adverse effects are minimal and primarily gastrointestinal. Lactic acidosis is a rare severe adverse effect. Renal dysfunction is one factor that may predispose a patient to lactic acidosis. Therefore, renal assessment is required for all patients, particularly the elderly, before initiating therapy. An elevated serum creatinine (>1.5 mg/dL in males and >1.4 mg/dL in females) suggests reduced estimated glomerular filtration rate (eGFR). Metformin may be used with caution in patients with eGFR of less than 60 mL/min, but it is contraindicated in those with eGFR of less than 30 mL/min (6). When used as monotherapy, metformin is associated with a low risk of hypoglycemia and has neutral effects in regard to weight (5). Metformin has been studied in many trials and is one of the only

medications for treating diabetes that has shown mortality benefits and demonstrated a beneficial effect on cardiovascular outcomes, such as heart attack and stroke (6).

Sulfonylureas

Sulfonylureas are among the oldest classes of oral diabetes medications and include two generations of agents. Their mechanism of action is stimulation of the pancreas to release insulin. They help reduce HbA1c by about 1% to 1.5%, but the drug effects are transient and efficacy is reduced over time (5).

The first-generation sulfonylureas (chlorpropramide, tolazamide, and tolbutamide) are longer-acting and are associated with a higher risk of hypoglycemia, which is the reason that they are not preferred by either the ADA/EASD or the AACE (2,4). The second-generation sulfonylureas include glyburide, glipizide, and glimepiride. All sulfonylureas are associated with weight gain and hypoglycemia (7). Second-generation sulfonylureas are included as one of the options for second-line therapy by the ADA. However, glyburide is not recommended by the ADA due to its increased risk of hypoglycemia related to an active metabolite that prolongs drug activity and weight gain (2). AACE lists glyburide as a last-line agent. Although newer agents are available with little or no hypoglycemia risk, many clinicians continue to prescribe this class of medications because they are relatively inexpensive.

Thiazolidinediones

TZDs work at the peroxisome proliferator-activated receptors. These receptors are found in tissues that are most important for insulin action, such as adipose tissue and skeletal muscle. The receptors help to enhance insulin sensitivity in these tissues. Because TZDs do not increase the amount of insulin released from the pancreas, they are associated with a low risk of hypoglycemia. However, they are associated with weight gain as well as the risk of fluid retention and exacerbation of chronic heart failure. The fluid retention and heart failure can occur in patients with no known heart disease. TZDs are also associated with an increase in transaminases and should be used in caution with patients with liver disease. They also should been avoided in patients with bladder cancer and elderly patients who are at increased risk of fractures. Patients who suffer from symptomatic chronic heart failure should not be given TZDs, and they are contraindicated in patients with class III or IV heart failure (8). The drugs in this class include pioglitazone and rosiglitazone. Rosiglitazone was previously restricted by the United States Food and Drug Administration because of suspected risks for myocardial infarction, but it is now commercially available through the REMS program. (9). TZDs are also available in various combinations with metformin, glimepiride, and alogliptin, and they reduce HbA1c by 1% to 1.5% (5).

Meglitinides

Similar to sulfonylureas, meglitinides work by stimulating pancreatic insulin secretion. Meglitinides have a shorter duration of action than sulfonylureas and target postprandial blood glucose concentrations. The drugs in this class include nateglinide and repaglinide, and they decrease HbA1c by about 0.5 % to 1%. They are associated with hypoglycemia but less so than the sulfonylureas. (5) Meglitinides are not commonly used since they are dosed three times a day and have higher costs compared to the other oral medications. .

Alpha-glucosidase Inhibitors

Alpha-glucosidase is an enzyme located in the brush borders of the intestine that aids in the digestion of complex carbohydrates. By inhibiting this enzyme, agents such as acarbose and miglitol reduce the rate of carbohydrate digestion, which helps lower postprandial glucose concentrations. Alpha-glucosidases are not commonly used due to their modest HbA1c-lowering effects of 0.5% to 0.8% and gastrointestinal adverse effects (5). Although they do not cause hypoglycemia themselves, when alpha-glucosidase inhibitors are combined with other agents, patients may experience hypoglycemia. Patients should be counseled to use pure forms of glucose (gel or glucose tablets) to treat hypoglycemia when taking these medications because alpha-glucosidase inhibitors slow the absorption of complex carbohydrates such as orange juice and white sugar.

Amylin Analogs

Amylin analogs can mimic the actions of amylin, a hormone cosecreted with insulin that helps to slow gastric emptying and reduces elevated glucagon levels postprandially. Because of the mechanism of action, patients may feel satiated earlier, which helps promote weight loss and decreases postprandial glucagon suppression (5). The drug available in this class is pramlintide, which is administered as a subcutaneous injection. Adverse effects include nausea and hypoglycemia, and it lowers HbA1c by 0.5% to 1% (5).

The ADA guidelines recommend amylinomimetics as third-line therapy, and the AACE guidelines do not list them in a specific therapeutic role (2,4). Amylin analogs can be used for patients with type 1 diabetes mellitus (T1DM) as well as patients with T2DM who require mealtime insulin.

GLP–1 Agonists

Incretins, such as GLP–1 and gastric inhibitory peptide, are hormones involved in the regulation of blood glucose. Both are released in the presence of glucose and they indirectly help stimulate insulin secretion. The hormones are short-lived in the system and are quickly broken down by enzymes such as DPP-4. The incretin effect is impaired in patients with T2DM, and these therapies can help increase insulin secretion with minimal hypoglycemia and decrease glucagon secretion (5). In addition, they decrease gastric emptying, suppress appetite, and increase satiety (5).

GLP-1 agonists are currently only available as subcutaneous injections administered twice daily (exenatide), once daily (liraglutide), and once weekly (exenatide-extended release, albiglutide, and dulaglutide). The most common adverse events associated with these medications are gastrointestinal (primarily nausea). Sometimes, therapeutic recommendations for GLP-1 agonists include a taper to help overcome the nausea before achieving a therapeutic dose (10). These medications also come with a warning for pancreatitis, which is a rare but severe adverse effect. Therefore, they should be used cautiously among patients who have high triglyceride levels. GLP-1 agonists lower the risk of hypoglycemia because they only work in the presence of hyperglycemia. They also are associated with weight loss and lower HbA1c by 1% to 1.5% (5).

The ADA recommends GLP-1 agonists as one of the options for second-line therapy after metformin and as part of a third line therapy in combination with basal insulin. (2) However, not all GLP-1 agonists are approved for use with insulin; only liraglutide, albiglutide, and exenatide are approved for administration with basal insulin. None of the agents are approved for use with prandial insulin. AACE recommends GLP-1 agonists as second-line therapy after metformin or as first-line monotherapy if metformin is not tolerated (4).

DPP-4 Inhibitors

DPP-4 inhibitors inhibit the breakdown of incretins, which leads to endogenous insulin secretion and decreased glucagon secretion. DPP-4 inhibitors are oral agents that include alogliptin, linagliptin, saxagliptin, and sitagliptin. All of these medications also are available in combination with metformin, which may help reduce a patient's pill burden. With the exception of linagliptin, DPP-4 inhibitors must be dose-adjusted for patients with renal insufficiency. They lower HbA1c by about 0.5% to 1% and should not be used with GLP-1 agonists (5). These medications do not have a risk of hypoglycemia when used alone but may increase the risk when combined with other therapies such as secretagogues.

SGLT–2 Inhibitors

SGLT-2 inhibitors are among the newest oral agents for the treatment of T2DM. A transporter protein known as sodium glucose transporter-2 is located in the kidneys, where approximately 90% of glucose reabsorption occurs. By inhibiting these channels in the kidneys, SGLT-2 inhibitors allow for urinary excretion of glucose, and patients who excrete glucose also excrete calories, which promotes weight loss. Currently there are three agents in this drug class: canagliflozin, empagliflozin, and dapagliflozin. Dapagliflozin should not be used if the eGFR is less than 60 mL/min, and empagliflozin and canagliflozin should not be used if the eGFR is less than 45 mL/min (11-13). Other adverse effects include urinary tract infections, genital fungal infections, increased urination, hypotension, dehydration, and possible DKA. Clinicians should obtain a basic chemistry panel for patients before prescribing SGLT-2 inhibitors because these drugs may cause changes in electrolytes, such as potassium or magnesium, especially if patients are taking diuretics. Because these drugs do not increase insulin secretion from the pancreas, they are associated with a low risk of hypoglycemia.

Insulin

Insulin is the most effective medication for treating hyperglycemia and reduces any degree of elevated HbA1c to or near goal. Although insulin is the most effective at lowering HbA1c, it also carries a risk of hypoglycemia that can be severe. Patients with T2DM most often need larger doses of insulin compared to those with T1DM due to insulin resistance. Insulin is available in various formulations, including human and analog insulin. Human insulin (NPH and regular) has greater variability in effects among patients but is less expensive. Insulin analogs are newer formulations that mimic the physiologic release of insulin. Long-acting formulations, also known as

basal insulin (insulin glargine and insulin detemir), do not generally peak and circulate for 14 to 24 hours. Rapid-acting insulin (lispro, aspart, and glulisine) are generally given before meals and offer therapeutic effects for approximately 1 to 3 hours. All insulins are associated with some weight gain, which is generally dose-dependent.

Insulin is available in mixed formulations as well. The mixed formulations are most often dosed twice daily, and appear as a cloudy solution. A concentrated version is five times as concentrated as the regular insulin. The concentrated insulin should be administered via a tuberculin syringe, rather than a traditional insulin syringe, to avoid confusion. A new form of rapid-acting inhaled insulin has recently been approved and is now available in pharmacies. This rapid-acting insulin is approved for patients with T1DM, is available as 4 or 8 units, and must be used with a special inhaler. In addition to adverse events such as hypoglycemia, patients may experience acute bronchospasms, and the inhaled insulin is contraindicated in those who have asthma and chronic obstructive pulmonary disease (14).

Conclusion

Over the last two decades, treatment of T2DM has flourished, with new therapies targeting the primary defects in T2DM and newer insulins addressing both T1DM and T2DM. With the variety of therapeutic options available, clinicians should consider each patient's overall health, HbA1c goals, and potential adverse effects of each drug to tailor therapy. Using both the ADA/EASD and AACE recommendations can guide therapy and help patients reach their HbA1c goals. The most important aspect of drug therapy is to treat each patient individually to help achieve better outcomes.

References

1. *Diabetes: Facts and Figures.* Brussels, Belgium: International Diabetes Foundation. 2014. Available at http://www.idf.org/worlddiabetesday/toolkit/gp/facts-figures. Accessed October 14, 2014.
2. Inzucchi S, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2015;38:140–149.
3. American Diabetes Association. (7) Approaches to glycemic treatment. *Diabetes Care.* 2015;38(suppl 1):S41–S48.
4. Garber A, Abrahamson M, Barzilay JI, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement. *Endocr Pract.* 2013;19(suppl 2).
5. *PL Detail-Document,* Drugs for Type 2 Diabetes. *Pharmacist's Letter/Prescriber's Letter.* September 2014.
6. Nathan DM, Buse JB, Davidson MB, et al. American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2009;32:193–203.
7. *Product Information for Glucotrol.* New York, NY: Pfizer. Last Revised October 2013.
8. *Product Information for Actos.* Deerfield, IL: Takeda Pharmaceuticals. Last revised July 2011
9. *Product Information for Avandia.* Research Triangle Park, NC: GlaxoSmithKline. Last revised May 2014
10. *Product Information for Victoza.* Plainsboro, NJ: NovoNordisk. Last revised April 2013
11. *Product Information for Farxiga.* Princeton, NJ: Bristol Myers Squibb Company and AstraZeneca. 2014.
12. *Product information for Invokana.* Titusville, NJ: Janssen. May 2014.
13. *Product Information for Jardiance.* Ridgefield, CT: Boehringer Ingelheim. August 2014
14. *Product Information for Afrezza.* Danbury, CT: Mannkind. June 2014.

Four Lessons About Medicines From Forty Years in Diabetes Education

Melinda Maryniuk, MEd, RD, CDE, FADA
Director, Clinical and Education Programs at Joslin Diabetes Center
Boston, Massachusetts

As a long-time diabetes educator, I've witnessed many changes in the field. Following are four lessons I've learned about medicines for type 2 diabetes and suggestions for having more productive conversations with patients (and other clinicians).

- **Help patients understand that type 2 diabetes is progressive.**
  Talk about the typical progression of diabetes early in the course of the disease. Help patients understand that moving from one medicine to another and even to insulin is very common with a longer disease duration. This can help to mitigate feelings of failure and fear if (and when) insulin is introduced.

- **Focus on the numbers.**
  Reinforce the importance of patients knowing the results of their key diabetes biomarker tests (hemoglobin A1c, blood pressure, cholesterol) by asking them to report those numbers to you, track the numbers themselves, and learn to identify which medicines help to keep the numbers within target ranges. Recognize that although lifestyle always is the first step, the right medicines (in the right doses) are critical for keeping biomarkers on target.

- **Facilitate clear communication between patient and clinicians.**
  With so many medicines now available, patients may not need to struggle with hypoglycemia or weight gain as a medication adverse effect. Ensure that both patients and clinicians explore all options. Report your assessment of any barriers to a patient taking medicines and efforts (and results) with lifestyle changes to other clinicians on the health care team to facilitate decisions on whether to advance medications.

- **Befriend a pharmacist.**
  Identify a few pharmacists in your community who have an interest and expertise in diabetes. Can they offer targeted counseling sessions on medication therapy management to help your patients address some of the challenges they may face with their regimen? In return, the pharmacists may refer some of their customers to you for medical nutrition therapy or diabetes education.

Emerging Treatment for Diabetes Management and Medications in the Pipeline

Justin M. Schmidt, PharmD, BCPS, BC-ADM
Associate Professor of Pharmacy Practice I Clinical Pharmacy Specialist-Internal Medicine
Midwestern University Chicago College of Pharmacy I Edward Hines Jr VA Hospital
Downers Grove, IL

Abstract

In 2014, several new medications were approved for diabetes treatment. Dapagliflozin and empagliflozin increase urinary glucose excretion and have similar efficacy and safety profiles compared to their predecessor, canagliflozin. Albiglutide and dulaglutide are the latest glucagon-like peptide receptor-1 agonists to gain U.S. Food and Drug Administration (FDA) approval. Dulaglutide is more effective than others in this class, and albiglutide, which is slightly less effective, is better tolerated. Rapid-acting inhaled insulin has re-emerged on the market and could be useful in select patients without respiratory disease. Many medications in the pipeline offer even more options for the future of diabetes management.

Introduction

Five new medications gained FDA approval for the treatment of diabetes mellitus in 2014. Collectively, they affect weight, body fat, gastrointestinal motility, satiety, urinary excretion of glucose, and glucagon and insulin concentrations. A report generated by the Pharmaceutical Research and Manufacturers of America identified 180 medications in development for the treatment of diabetes and its complications, many of which represent innovative therapeutic modalities (1).

Sodium-Glucose Cotransporter 2 Inhibitors

A relatively new class of orally administered medications called sodium-glucose cotransporter 2 (SGLT-2) inhibitors, also known as glucuretics, works by increasing glucose excretion in the urine (approximately 80 g/day of glucose). The SGLT-2, located in the proximal renal tubules, is responsible for reabsorption of the majority of filtered glucose. Administration of SGLT-2 inhibitors results in a modest reduction in weight (2-3 kg), presumably due to the loss of calories in the urine (Table 1). A modest systolic blood pressure reduction (2-4 mm Hg) has been attributed to osmotic diuresis. Such osmotic diuresis can

Table 1. Efficacy Summary of Novel SGLT-2 Inhibitors and GLP-1 Receptor Agonists

Drug Class	Drug Name	Approved Dose, Formulation, and Frequency of Administration	Monotherapy: Reduction in HbA1c (%)*	Combination Therapy: Reduction in HbA1c (%)*	MACE + Hazard Ratio	Weight Loss*
SGLT-2 Inhibitors	Dapagliflozin	5-10 mg tablets by mouth daily	0.5-0.8	0.4-0.7	0.81 (0.59, 1.09)	0.8-2.2 kg
	Empagliflozin	10-25 mg tablets by mouth daily	0.7-0.8	0.5-0.7	Data withheld	2.0-3.0 kg
GLP-1 Receptor Agonists	Albiglutide	30-50 mg subcutaneous injection weekly via pen injector	0.8-1.0	0.8-0.9	0.93 (0.55, 1.58)	None
	Dulaglutide	0.75-1.5 mg subcutaneous injection weekly via pen or syringe	N/A	0.8-1.2	0.57 (0.30, 1.10)	1.0-2.5 kg

*Range of placebo-adjusted mean decreases in phase III studies (2-5).

MACE+ is the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina.

result in volume depletion and orthostatic symptoms, warranting caution in the elderly and monitoring of electrolytes, kidney function, and blood pressure. The glucose-enriched urine does provide a good substrate for bacteria and fungi, resulting in increased risk of genital fungal infections and urinary tract infections, especially among women. These medications should be avoided in patients with kidney disease due to decreased efficacy and increased toxicity in this population.

Although SGLT-2 inhibitors do not typically cause hypoglycemia independently, they do increase the risk of hypoglycemia among patients taking insulin or sulfonylureas. Morning administration is recommended for this class to avoid nocturia and before-breakfast administration is advised for canagliflozin due to delay in intestinal glucose absorption (believed to be due to SGLT-1 inhibition) that increases the risk for hypoglycemia (6). Available preliminary results suggest these medications have a neutral effect on cardiovascular risk, but confirmatory studies are ongoing.

Dapagliflozin was approved in early 2014 and was the second drug to be approved in this class (2). Indirect comparison suggests that the efficacy of dapagliflozin is slightly more modest than canagliflozin when used alone or as part of an oral regimen. The effects of dapagliflozin on body composition were evaluated using dual energy X-ray absorptiometry in an exploratory study, which revealed that two thirds of the body weight loss was due to a reduction of fat mass (7).

Empagliflozin was approved after dapagliflozin. Indirect comparison suggests similar efficacy as dapagliflozin (3). The effects of empagliflozin on body composition were compared to glimepiride in a phase III study, but detailed results have not been published.

Glucagon-like Peptide-1 Receptor Agonists

Glucagon-like peptide (GLP) is endogenously released by cells in the intestines in response to food consumption. Effects of this peptide include increased insulin release (in a glucose-dependent manner), decreased glucagon release (resulting in reduced hepatic glucose output), delayed gastric emptying (providing time for the body to accommodate the glucose load), and increased satiety. Synthetic GLP-1 receptor agonists are subcutaneously administered and have similar effects to endogenous GLP-1, resulting in reduced fasting and postprandial glucose and reduced hemoglobin A1c (HbA1c). The delay in gastric emptying is associated with several gastrointestinal adverse effects (most frequently nausea). Accordingly, this class of medication should be avoided in patients with gastroparesis. Similar to SGLT-2 inhibitors, GLP-1 receptor agonists increase the risk of hypoglycemia in patients taking sulfonylureas or insulin.

Three GLP-1 receptor agonist formulations have been available for some time, with the first introduced a decade ago. Exenatide and liraglutide are shorter-acting, requiring twice-daily and daily injections, respectively. The long-acting formulation of exenatide allows for weekly administration.

Albiglutide is a long-acting GLP-1 receptor agonist that was approved for use in April 2014 (4). Compared with liraglutide, albiglutide has slightly less of an HbA1c-lowering effect (0.2% difference) but is better tolerated initially in terms of gastrointestinal symptoms (8,9). Unlike other GLP-1 receptor agonists, albiglutide does not lower body weight. Preliminary data suggest a neutral effect on cardiovascular events.

Dulaglutide is another long acting GLP-1 receptor agonist that received approval several months after albiglutide (5). Dulaglutide possesses greater HbA1c-lowering effects and similar effects on weight loss compared to the twice-daily formulation of exenatide. An indirect comparison by the FDA suggests similar rates of nausea and vomiting compared with the weekly formulation of exenatide. A preliminary trend toward benefit in cardiovascular events is promising, but the definitive impact on such events is being determined in an ongoing trial.

Inhaled Insulin

A formulation of inhaled insulin entered the United States market in 2006, only to be removed one year later due to poor sales. There were also concerns about a slight increase in the risk of lung cancer and worsening lung function. More recently, a rapid-acting insulin for inhalation was approved for use in June 2014 (10,11). Doses are available in increments of 4- and 8-unit cartridges, which limits the ability to fine tune an insulin dose. Because of its very rapid action, this inhaled insulin should be administered at the beginning of a meal.

This formulation of inhaled insulin was compared to subcutaneous insulin aspart for use with basal insulin in patients with type 1 diabetes and was studied as an adjunct to antihyperglycemic regimens for patients with type 2 diabetes. Compared with insulin aspart, the inhaled insulin was slightly less effective at reducing HbA1c (0.2% difference) but had lower rates of hypoglycemia (4 fewer events/

patient/month) in patients with type 1 diabetes (10). This difference might be explained, in part, by an unpublished pharmacodynamic study (submitted to and evaluated by the FDA), which showed that although the onset of glucose-lowering effects was similar to that of a subcutaneous rapid-acting insulin analog, the glucose-lowering effect of inhaled insulin waned after 50 minutes. In comparison, the effects of the subcutaneous rapid-acting analog persisted for 5 to 6 hours.

Bronchoconstriction and reduced expiratory volume have been observed in patients with pre-existing asthma or obstructive lung disease. Accordingly, use of insulin powder for inhalation should be avoided in patients with chronic lung disease and active or recent smokers. Patients without chronic lung disease should undergo pulmonary function tests because of a slight decline in pulmonary function observed in patients without lung disease. A reduction of forced expiratory volume in 1 second of 20% from baseline warrants drug discontinuation.

Medications in the Pipeline

The degree of innovation of medications in clinical trials spans from biosimilar insulins (including several insulin glargine formulations) to "me-too" drugs (additions to an established class of medications) to entirely new, first-in-class entities (Table 2). The upcoming expiration of patents for insulin glargine has generated considerable interest in developing a biosimilar formulation (12). A biosimilar refers to a version of an originator biologic, which is a drug product derived from a living organism (13). A biosimilar insulin has the same amino acid sequence as the originator drug but is not an identical copy. In contrast, a small-molecule drug can be manufactured identically and exist as a generic version of the originator drug. Although legal maneuvers have delayed the first attempts at another formulation of insulin glargine, less expensive biosimilar insulins will become available in the United States (in September, a biosimilar insulin glargine was approved by the FDA).

Biosimilars are not the only formulations of insulin that are in the late stages of development. Insulin degludec, peglispro insulin, and the recently approved concentrated form of insulin glargine (U-300), known as Toujeo, are all in line as the next generation of basal insulin (1). Proposed benefits of these insulins include improved reduction in HbA1c and lower rates of hypoglycemia (depending on the product) compared to traditional insulin glargine. Several coformulations (or mixtures) of basal insulins and GLP-1 receptor agonists are also nearing approval. An ultrafast-onset subcutaneous insulin aspart and a prandial oral insulin spray formulation are in phase III studies, but data regarding safety and efficacy are not yet available.

Additional GLP-1 receptor agonists are also on the horizon (1). These include semaglutide (a weekly subcutaneous injection), lixisenatide (a daily subcutaneous injection), and a formulation of exenatide that requires a subcutaneous implant every 6 to 12 months. Reduction in HbA1c, gastrointestinal tolerability, effects on weight, and cardiovascular risk profile should determine their role in therapy if they are approved. A new addition to

Table 2. Medications in Phase III Trials or With Applications Submitted for U.S. Food and Drug Administration Approval

New Molecular Entity	Mechanism or Drug Class
Omarigliptin	DPP-IV inhibitor
Ertugliflozin	SGLT-2 inhibitor
Semaglutide	GLP-1 receptor agonist
Exenatide implant	GLP-1 receptor agonist
Lixisenatide	GLP-1 receptor agonist
Liraglutide (3-mg formulation) *just approved under trade name of Saxenda	GLP-1 receptor agonist (seeking obesity indication)
Lixisenatide/Insulin Glargine	GLP-1 receptor agonist /basal insulin
Liraglutide/Insulin Degludec	GLP-1 receptor agonist /basal insulin
Insulin Degludec	Basal insulin
Peglispro	Basal insulin
MK-1293	Basal insulin (glargine)
Insulin Degludec and Aspart	Basal insulin/rapid-acting insulin
Faster-acting Insulin Aspart	Rapid-acting insulin
Oral Insulin	Oral rapid-acting insulin
Alpha-1 Antitrypsin	Stabilizes the decline of insulin-producing cells

DPP=dipeptidyl peptidase, GLP=glucagon-like peptide

the dipeptidyl peptidase IV inhibitor class, omarigliptin, is also on the horizon. This medication class works, in part, by preventing enzymatic degradation of endogenous GLP-1. This class of medication is well tolerated, orally administered, and has slightly lesser effects on HbA1c reduction compared with GLP-1 receptor agonists. Omarigliptin offers the distinction of weekly administration.

Clinical Application

The 2013 American Association of Clinical Endocrinologists' diabetes management algorithm and the 2015 position statement by the American Diabetes Association and the European Association for the Study of Diabetes suggest roles for all medication classes currently available for the treatment of type 2 diabetes (14,15). The SGLT-2 inhibitors are used as adjunctive therapy for patients with type 2 diabetes who do not have kidney disease or hypovolemia. Although metformin is recommended as first-line therapy for most patients, SGLT-2 inhibitors can be considered (among other medication classes) as the next medication to add. The impact of GLP-1 receptor agonists on HbA1c and weight have resulted in their recommendation as second-line (behind metformin) drugs for monotherapy and a first-line consideration as an adjunct to combination therapy. Albiglutide may not be quite as effective as all available GLP-1 receptor agonists, but its favorable adverse effect profile should make it an alternative for patients who cannot tolerate other agents in the class. Albiglutide and dulaglutide should appeal to those who prefer less frequent administration. Inhaled insulin use probably will be relegated to patients without pulmonary disease who have significant objections to multiple daily injections.

Summary

Although none of the medications approved in 2014 introduce a new mechanism of action for reducing blood glucose and HbA1c, some offer distinctions that could benefit subgroups of patients. Some provide improved tolerability at the expense of efficacy; others offer enhanced efficacy and convenience of administration. The variable effects on HbA1c; weight; volume status; adverse effects; and considerations for gastrointestinal, kidney, and lung function among the classes emphasizes the continued need for patient-specific drug selection and monitoring.

References

1. Pharmaceutical Research and Manufacturers of America. *2014 Report: Medicines in Development for Diabetes.* Available at http://www.phrma.org/sites/default/files/pdf/diabetes2014.pdf. Accessed November 1, 2014.
2. U.S. Food and Drug Administration. *Drug Approval Package: Farxiga (dapagliflozin) Tablets.* 2014. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/202293Orig1s000TOC.cfm. Accessed November 1, 2014.
3. U.S. Food and Drug Administration. *Drug Approval Package: Jardiance (empagliflozin) Tablets.* 2014. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204629Orig1s000TOC.cfm. Accessed November 1, 2014.
4. U.S. Food and Drug Administration. *Drug Approval Package: Tanzeum (albiglutide) Injection.* 2014. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125431Orig1s000TOC.cfm. Accessed November 1, 2014.
5. U.S. Food and Drug Administration. *Drug Approval Package: Trulicity (dulaglutide) Injection.* 2014. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125469Orig1s000TOC.cfm. Accessed November 1, 2014.
6. U.S. Food and Drug Administration. *Drug Approval Package: Invokana (canagliflozin) Tablets.* 2013. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204042Orig1s000TOC.cfm.
7. Bolinder J, Ljunggren O, Johansson L, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Diabetes Obes Metab.* 2014;16:159-169.
8. Pratley RE, Nauck MA, Barnett AH, et al. HARMONY 7 study group. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. *Lancet Diabetes Endocrinol.* 2014;2:289-297.
9. Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care.* 2014;37:2159–2167.
10. U.S. Food and Drug Administration. *Label and Approval History: Afrezza (insulin recombinant human).* 2014. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022472lbl.pdf. Accessed November 1, 2014.

11. Endocrine and Metabolic Drugs Advisory Committee Meeting. *FDA Briefing Document: Afrezza (insulin recombinant human)*. 2014. Available at http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390864.pdf. Accessed November 1, 2014.
12. Rotenstein LS, Ran N, Shivers JP, Yarchoan M, Close KL. Opportunities and challenges for biosimilars: what's on the horizon in the global insulin market? *Clin Diabetes*. 2012;30:138–150.
13. Hoffman JM, Li E, Doloresco F, et al. Projecting future drug expenditures in U.S. nonfederal hospitals and clinics—2013. *Am J Health Syst Pharm*. 2013; 70:525–539.
14. Garber AJ, Abrahamson MJ, Barzilay JI, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement—executive summary. *Endocr Pract*. 2013;19:536–557.
15. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38:140–149.

Management of Obesity: Comprehensive Lifestyle Therapy and Weight Loss Medications

Thomas G. Wadsworth, PharmD, BCPS
Clinical Assistant Professor
Idaho State University
College of Pharmacy
Columbus, ID

Alyssa Gallagher, RD, LD, CDE
Registered Dietitian, Diabetes Educator
St. Luke's Humphreys Diabetes Center
Boise, ID

Abstract

Obesity is a widely recognized and challenging problem, particularly among patients with type 2 diabetes mellitus (T2DM). Comprehensive lifestyle therapy is the cornerstone of weight management treatment. In addition, many pharmacologic agents can assist with weight loss and weight maintenance. Some of these agents are approved by the U.S. Food and Drug Administration for general weight management; others are antidiabetic medications with weight-sparing effects. This article reviews comprehensive lifestyle therapy recommendations and available medications for weight management in overweight or obese patients.

Introduction

The majority of patients with T2DM are overweight or obese, which is a particularly deleterious combination that can result in worsening insulin resistance, blood pressure, cholesterol, depression, and cardiovascular events. Weight loss is a primary treatment strategy for T2DM, and those who succesfully lose weight may have prolonged survival through reductions in cardiovascular and diabetes mortality (1,2). Comprehensive lifestyle therapy is the cornerstone of treatment and involves reduced energy intake, physical activity, and behavior modification (3). Some patients eventually require the addition of pharmacologic therapy to assist in achieving or maintaining their weight loss goals. The purpose of this article is to review lifestyle therapy and weight-loss medications in the context of T2DM obesity.

Although most patients have a weight loss goal of 30% or more below their current weight, it is important to establish individual and realistic goals when discussing weight loss. Generally, the first goal for any overweight individual is prevention of further weight gain and stabilization of body weight to within 5 lb of current weight. Once this is established, clinicians can set a reasonable goal of 5% weight loss, although a goal of 3% body weight loss may be appropriate and realistic for select patients (4).

Comprehensive Lifestyle Therapy

Diet

Although low-fat and low-carb diets are highly marketed in the weight-loss world, there is not an "ideal" percentage of energy from carbohydrate, protein, and fat for all people with diabetes. However, certain general principles apply.

To achieve a weight reduction of 1 to 2 lb/wk, an energy deficit of about 500 to 1,000 kcal/day is required. This can be achieved through increased exercise, decreased energy intake, or both. For most women, this might equal 1,200 to 1,500-kcal/day

reductions, while men require a slightly greater reduction of 1,500 to 1,800 kcal/day (3). Registered dietitian nutritionists should use individualized self-monitoring, motivational interviewing, structured meal plans/portion control and/or meal replacements, goal setting, and problem-solving strategies to help patients achieve weight-loss goals (3).

Exercise

The American College of Sports Medicine and the American Diabetes Association both recommend a combination of aerobic and strength training exercise weekly to improve weight and diabetes control. Recommendations are for at least 150 min/wk of moderate exercise such as walking, with no more than 2 consecutive days without exercise. Additionally, strength training or resistance type exercises should occur at least 2 days weekly, on nonconsecutive days, with the ideal being three times per week (5,6).

Pharmacotherapy for Obesity

Even with the best lifestyle and behavioral treatments, many patients continue to struggle to achieve meaningful weight loss. A subset of patients requires additional assistance to meet their weight-loss goals. Pharmacotherapy should be considered in those who have demonstrated the inability to achieve weight-loss goals despite concerted effort and have enough health risks to justify an intensive approach. The American Heart Association/ American College of Cardiology/ The Obesity Society Guideline for the Management of Overweight and Obesity in Adults specifically recommends pharmacotherapy treatment for patients who have a body mass index of 30 or greater or those who have a body mass index of 27 and greater in addition to obesity-related comorbidities (e.g., hypertension, dyslipidemia, diabetes, sleep apnea) (4).

Currently five agents/classes have been approved by the U.S. Food and Drug Administration (FDA) for weight management: sympathomimetics, lorcaserin, combination topiramate/ phentermine, combination bupropion/ naltrexone, and orlistat (Table). Additionally, several medications approved by the FDA for diabetes treatment also possess weight-sparing properties and can be used to assist with weight loss in patients with T2DM. With the exception of glucagon-like peptide-1 GLP-1 agonists, these medications will not be discussed in this article.

Sympathomimetics

Sympathomimetics are appetite-suppressing drugs (also called anorectics or anorexigenics) that have been available for many years. Although their mechanism of action is not fully understood, drugs of this class are believed to suppress hunger or enhance energy metabolism through stimulation of the central nervous system via catecholamine or serotonin pathways. Suppression of hunger can increase adherence to reduced-calorie diets, resulting in weight loss. On average, obese patients treated with any anorectic and caloric restrictions lose more weight than those treated with placebo and caloric restrictions. The magnitude of weight loss, however, is modest (approximately 3 kg over 6 months), with greatest weight loss occurring in the first weeks of therapy (7).

Sympathomimetics are only approved for short-term use (weeks) and do have abuse potential. Historically, they have been used off-label for much longer durations, but the safety of this practice is questionable, given the potential for serious cardiovascular adverse effects. Common adverse effects include palpitations, increased blood pressure, insomnia, nervousness, and dizziness (8). More serious adverse effects such as myocardial infarction, valvular disease, psychosis, and seizure have all been reported. Therefore, sympathomimetics should not be used casually or long term, especially in patients with cardiovascular disease, history of psychiatric illness, seizures, or drug abuse.

Lorcaserin

Approved in June 2012, lorcaserin is the newest anorectic on the market. It is believed to decrease food consumption and promote satiety by selectively activating serotonin receptors (5-HT2C) in the central nervous system. Unlike its precursor, fenfluramine, lorcaserin does not affect serotonin receptors found on heart valves (5-HT2B). Fenfluramine was removed from the market in 1997 because its use was associated with an increased risk of valvular heart disorder. Lorcaserin differs from other anorectics in that it is tolerated very well and is FDA-approved for long-term use (1 year). Clinical trials demonstrate an average weight loss of 3.3 kg (placebo-adjusted) after 1 year (9). As with other anorectics, most of the weight loss occurs early in therapy, and patients who do not lose at least 5% of baseline body weight by week 12 are unlikely to benefit from continued treatment. Lorcaserin should be used cautiously or avoided in patients taking other serotonergic medications such as common antidepressants (selective serotonin reuptake inhibitors) and migraine medications (triptans).

Topiramate/phentermine–

The combination of low-dose phentermine plus extended-release topiramate and was approved in

Table.

Medication[a]	Weight Loss[b]	5%[c]	10%[d]	Common Adverse Effects	Contraindications	Average Wholesale Price[e]
Sympathomimetic Anorectics						
Phentermine **Diethylpropion** **Benzphetamine** **Methamphetamine** **Phendimetrazine**	~3 kg			• Cardiovascular • Central nervous system • Gastrointestinal • Allergic • Endocrine	• Cardiovascular disease • Hypertension • Hyperthyroidism • Glaucoma • History of drug abuse • Monoamine oxidase inhibitor (MAO) within 14 days	$45.66 - $412.43
Combination Products						
Phentermine/ Topiramate	9 kg	49%	40%	• Dizziness • Paresthesia • Dysgeusia • Insomnia • Constipation • Dry mouth • Suicidal ideation • Cognitive impairment • Kidney stones • Decreased sweating • Increased body temperature • Metabolic acidosis	• Pregnancy • Hyperthyroidism • MAO-I with 14 days • History of suicide attempt or active ideation	$239.40
Bupropion/ Naltrexone	3.2 kg	19%	12.6%	• Central nervous system: suicide ideation, mood changes, seizures, headache, dizziness • Cardiovascular: hypertension, tachycardia • Gastrointestinal: nausea, vomiting, constipation, dry mouth • Other: glaucoma, hepatotoxicity	• Uncontrolled hypertension • Seizure disorder • Bulimia/anorexia • Abrupt discontinuation of alcohol, benzodiazepine, or barbiturates • Avoid in patients taking opioids	$239.40
Serotonin 2C agonist						
Lorcaserin	3.3 kg	24%	22.4%	• Common: nausea, headache, dizziness, fatigue, dry mouth, diarrhea, constipation • Central nervous system: euphoria, cognitive impairment, hallucinations, dissociation, suicidal thoughts • Cardiovascular: bradycardia	• Pregnancy • Caution: other serotonergic drugs, depression	$239.40
Lipase inhibitor						
Orlistat	3.45 kg	28%	20%	• Gastrointestinal: oily spotting/ fecal incontinence/urgency/oily stool/abdominal/rectal pain/ nausea • Vitamin deficiency (A,D,E,K) • Gallstones • Pancreatitis	• Malabsorption syndrome • Gallstones • Caution: history of kidney stones	$563.80

[a] US Product Labeling
[b] Placebo adjusted mean weight loss after 1 year
[c] Percent of patients losing ≥5% body weight after 1 year; placebo adjusted
[d] Percent of patients losing ≥10% body weight after 1 year; placebo adjusted
[d] Estimated costs for 1 month supply; based on average wholesale price from September 2014

July 2012 for chronic weight management in adults. Topiramate is an anticonvulsant that was serendipitously discovered to have weight-reducing properties during clinical trials for epilepsy. The exact mechanism of action for weight loss is unknown but may be related to the agent's effects on both appetite suppression and satiety enhancement. Results from clinical trials to assess topiramate's efficacy as a weight-loss agent were very promising, with patients losing 5.6 to 8.3 kg (placebo-adjusted) over 60 months (10). Unfortunately, the higher doses used in these studies were not tolerated well. Patients experienced significant dizziness, sedation, and headaches.

Subsequently, lower doses of topiramate were combined with phentermine, which improved tolerability and enhanced the weight-sparing effect of either agent alone. In fact, clinical trials of this combination demonstrated the greatest weight-sparing effects of any single weight loss agent, with a mean weight loss of 9 kg (placebo-adjusted) after 1 year of treatment (11). More than 50% of studied patients achieved 5% weight loss goals and 40% achieved 10% weight loss goals (placebo-adjusted) . Despite these impressive results, many patients experienced significant adverse effects, most commonly dizziness, insomnia, tingling in hands/feet, taste disturbances, and impaired cognition.

Serious adverse events can also occur, such as kidney stones and metabolic acidosis. Topiramate is a known teratogen that can cause congenital malformations, specifically orofacial clefts, in infants exposed during the first trimester of pregnancy. For this reason, the drug has a risk management strategy to prevent its use during pregnancy. Prescribers are encouraged to undergo training and pharmacies must be certified to dispense this medication. A copy of the Medication Guide and a brochure detailing the risk of birth defects must be provided with each prescription.

Bupropion/naltrexone–

The combination of a well-known antidepressant, bupropion, with naltrexone, a pure opioid antagonist used to treat alcohol or opioid dependency, obtained recent approval. The exact neurochemical effects of naltrexone/bupropion that lead to weight loss are not fully understood but are believed to result from action on appetite (hypothalamus) and reward centers (mesolimbic dopamine circuit) of the brain.

The average weight loss demonstrated in clinical trials of bupropion/naltrexone was 3.3 kg (placebo-adjusted) over 56 weeks, which is very similar to that of other weight-loss medications (12). Of note, more than half of patients discontinued treatment during clinical studies, indicating a high degree of intolerance; the most common complaints were nausea, vomiting, headache, dizziness, constipation, dry mouth, and mood changes. More serious adverse effects include suicide ideation/suicidality, seizures (due to bupropion component), and liver disease. Bupropion/naltrexone should not be used in patients with uncontrolled hypertension or increased propensity for seizures (i.e., seizure disorder; abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs). Additionally, it should not be used by patients taking opioid pain medications.

To minimize nausea and the seizure risk, the dose should be slowly escalated over 4 weeks according to the following schedule: 1 tab every morning for 1 week; 1 tab BID for 1 week; and 2 tabs every morning and 1 tab every evening for 1 week to increase to the full dose.

Orlistat

Orlistat is an irreversible inhibitor of pancreatic and gastric lipases, which are required for systemic absorption of dietary triglycerides. Failure to hydrolyze ingested fat to absorbable free fatty acids and monoacylglycerols results in a net increase in fecal fat excretion. With administration of orlistat, up to 30% of dietary fat is not absorbed and the resulting energy deficit has a weight-sparing effect (13). Orlistat is approved for obesity management, including weight loss and weight maintenance, as well as to reduce the risk for weight regain after prior weight loss.

The magnitude of weight loss experienced by orlistat users has been studied in a number of long-term clinical trials (1-2 years), including the 4-year XENDOS study. In these studies, mean weight loss at 1 year was significantly greater than with placebo by 3.5 to 4 kg (12). In the XENDOS trial, weight savings remained significantly greater than placebo by 2 kg ($P<0.001$) after 4 years of treatment (14).

Orlistat is taken as a 60-mg or 120-mg capsule up to three times daily during or up to 1 hour after a fat-containing meal. The dose is omitted if the meal is skipped or contains little or no fat. Orlistat is primarily known for its prominent gastrointestinal disturbances, which include fecal urgency and incontinence, oily spotting, flatulence with discharge, oily evacuation, and increased defecation. These effects are a result of drug-induced steatorrhea and are directly related to the amount of fat consumed with each dose. Patients

should be advised to spread out their daily fat intake and avoid exceeding 16 g of fat in any single meal. Rare but more serious adverse effects include increased risk of gallstones and kidney dysfunction. Additionally, orlistat-induced steatorrhea can impair absorption of fat-soluble vitamins and patients should be advised to supplement their intake with a multivitamin containing fat-soluble vitamins (A,D,E, and K) once daily at least 2 hours before taking orlistat.

Incretin Mimetics (GLP-1 Agonists)

Incretin mimetics stimulate the GLP-1 receptor to increase insulin secretion in response to high blood glucose levels, inhibits glucagon release, slows gastric emptying, and increases satiety. Although indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, these agents are primarily used for their weight-sparing properties. Liraglutide recently received approval from the FDA Advisory Committee for the treatment of obesity and will soon be available as a once-daily subcutaneous injection (15).

Weight loss is generally attributed to improved satiety and decreased appetite and varies among patients, depending on dose and length of use. On average, patients treated for 1 year lose 0.6 to 4.4 kg (16). As a class, GLP-1 agonists are being administered as subcutaneous injections. Their use is often limited by excessive gastrointestinal adverse effects, including nausea, vomiting, and diarrhea. However, these treatment effects can be minimized with proper dose titration and wane with extended use. GLP-1 agonists should not be administered to patients with gastroparesis, pancreatic disease, or moderate-to-severe renal impairment.

Clinical Application

No head-to-head studies have demonstrated the superiority of any weight-loss agent. Accordingly, medications should be selected based on potential adverse effects and the individual patient's past medical history, comorbidities, and concurrent medications. Cost and availability also should be considered. All of these medications reinforce the intention to adhere to a diet and, therefore, should always be used as an adjunct to comprehensive lifestyle interventions. The patient's particular adherence problem or diet type might also be considered when selecting the most appropriate medication. For example, anorectics might be more useful in those having difficulty adhering to caloric restrictions because of preoccupation with food, cravings, persistent thoughts of eating, or serious difficulty in the presence of food. Orlistat is probably most appropriate for patients adhering to low-fat or balanced diets rather than high-protein diets because these diets tend to be higher in fat and could increase intolerable gastrointestinal disturbances.

Although some patients can sustain their weight loss, weight is often regained after discontinuation of medication, especially if the patient does not maintain dietary/lifestyle changes. Conversely, some patients may not respond adequately to treatment, and medications should be discontinued if 5% of body weight loss is not achieved after 12 weeks or if patients experience intolerable adverse effects.

Summary

Obesity is a particular problem in the management of T2DM. Weight loss may prolong survival through reducions in cardiovascular and diabetes mortality. Comprehensive lifestyle therapy is the cornerstone of weight management treatment, but many pharmacologic agents can assist with weight loss and weight maintenance. These moderately effective agents have significant adverse effects and should be used only when obese/overweight patients fail to meet their weight loss goals. The medications should be selected after careful consideration of potential adverse effects, past medical history, comorbidities, concurrent medications, diet, and adherence problems.

References

1. Lean ME, Powrie JK, Anderson AS, Garthwaite PH. Obesity, weight loss and prognosis in type 2 diabetes. *Diabet Med.* 1990;7:228–233.
2. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care.* 2000;23:1499–1504.
3. Academy of Nutrition and Dietetics. Adult weight management. *Evidence Analysis Library.* 2014. Available at: http://www.andeal.org/topic.cfm?menu=5276&cat=4690. Accessed March 30, 2015.
4. Jensen MD, Ryan DH, Apovian CM, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation.* 2014;129(25 suppl 2):S102–S138.

5. Colberg SR, Sigal RJ, Fernhall B, et al; American College of Sports Medicine; American Diabetes Association. Exercise and Type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care.* 2010; 33:e147–e167.
6. American Diabetes Association. Executive summary: standards of medical care in diabetes-2014. *Diabetes Care.* 2014;37(suppl 1): S5-S13.
7. Haddock CK, Poston WS, Dill PL, Foreyt JP, Ericsson M. Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials. *Int J Obes Relat Metab Disord.* 2002;26:262–273.
8. *ADIPEX-P (R)[package insert).* Teva Pharmaceuticals USA, Sellersville, PA; 2012
9. *Belviq® Package Insert*. Zofingen, Switzerland: Arena Pharmceuticals; 2012.
10. Wilding J, Van Gaal L, Rissanen A, Vercruysse F, Fitchet M; OBES-002 Study Group. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of topiramate in the treatment of obese subjects. *Int J Obes Relat Metab Disord.* 2004; 28:1399–1410.
11. *Qsymia® Package Insert.* Mountain View, CA: VIVUS, Inc; 2012.
12. *Contrave® Package Insert.* La Jolla, CA: Orexigen Therapeutics;2014.
13. *Xenical® Package Insert.* South San Francisco, CA: Genetech USA: 1999 http://www.gene.com/download/pdf/xenical_prescribing.pdf. Accessed October 15, 2014.
14. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care.* 2004;27:155–161.
15. Tucker ME. FDA Panel endorses liraglutide as obesity treatment. *Medscape Medical News.* 2014. Available at: http://www.medscape.com/viewarticle/831609. Accessed March 30, 2015.
16. Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ.* 2012;344:d7771.

Vitamin and Mineral Deficiencies in the Person With Diabetes

Wendy Mobley-Bukstein, PharmD, CDE
Assistant Professor of Pharmacy
Drake University
Des Moines, IA

Melissa Schleder, RDN, LDN, CDE
Nutrition Care Systems
Elgin, IL

Abstract

Several potential for vitamin and mineral deficiencies related to drug therapy may develop in those who have diabetes and other related health conditions (e.g., celiac disease). Evidence from the literature and guidelines provides the rationale for recommendations for vitamin or mineral supplementation for patients with diabetes. The article also provides information about selecting appropriate supplements at the pharmacy and quick reference tables for vitamin and mineral supplementation via diet and pharmacotherapy.

Introduction

The 2015 American Diabetes Association (ADA) Diabetes Standards of Medical Care (1) state that clinical evidence supporting the use of multivitamins or minerals in patients with diabetes is insufficient. The ADA recommends individualized meal planning to helps patient meet the recommended daily allowance of important micronutrients that are essential for normal daily function. Nutrient disturbances affecting patients with diabetes may result from the type, dose, or duration of medication used or from complications related to other disease states/conditions commonly associated with diabetes (2).

Pharmacists and registered dietitian nutritionists (RDNs) can collaborate to prevent secondary complications associated with micronutrient deficiencies in their patients via supplements and diet. According to the Academy of Nutrition and Dietetics, "medical nutrition therapy (MNT) is a cost effective approach, one that alters or prevents the course of diabetes and other chronic disease" (2). One of the first steps that an RDN should take in working with patients with diabetes is to perform an in-depth assessment that serves as the foundation for developing an individualized nutrition plan (2). MNT based on this assessment should support individuals at high risk of nutrient deficiency through dietary modification.

Although evidence is insufficient to prove that people with or without diabetes benefit from supplementation with vitamins, minerals or other micronutrients, such as chromium, magnesium, and vitamin D, health professionals must monitor and treat such deficiencies when they occur in high-risk patients. One example involves the risk of underlying deficiencies in patients who have used blood glucose-lowering medications such as metformin for long periods of time. Recent studies show that even short-term use of metformin can cause folic acid and vitamin B_{12} deficiencies (3). Clinicians also should have heightened concern for those treated with blood glucose-lowering medications who suffer from additional disease states that can parallel diabetes, such as celiac disease, gastroparesis, hypertension, chronic kidney disease, lipid disorders, osteoporosis, and obesity. Women with gestational diabetes who are taking oral agents for glycemic control also should be monitored carefully.

Without proper monitoring, those with diabetes may develop anemia or osteopenia, possibly related to restricted diets or underlying deficiencies. Such situations could be intensified by nutrient-drug interactions. Nutrients of particular concern include vitamin B_{12}, folic acid, iron, calcium, and vitamin D (2,4).

Drug Therapy

Drug information resources indicate that long-term use of metformin in patients with diabetes results in depletion of vitamin B_{12} and folic acid in 7% of the population (3). Recent investigations suggest that these micronutrient changes are of concern even with short-term use of metformin (5-9). The pharmacist and RDN can educate patients on appropriate supplementation required for repletion of essential vitamins and minerals that are lost to the body's absorption of metformin. This is growing concern for patients with polycystic ovarian syndrome and gestational diabetes because of increased use of metformin in these conditions. Folic acid supplementation is required for all women before and during pregnancy for prevention of neural tube defects in infants, but health professionals should pay special attention in this population of patients when considering the nutrient-drug interaction with metformin (8).

The patient's current health status has an impact on MNT, but the RDN must also consider the individual's food preferences and lifestyle to promote diet adherence and achieve synergy between nutrition therapy and medication use. In short, RDNs can support and recommend the use of supplementation when deficiencies result from unavoidable diet inadequacies and the malabsorption related to disease or nutrient-drug interactions (1).

Celiac Disease

Celiac disease is a chronic malabsorption syndrome related to an immune reaction to gluten, a storage protein found in wheat, barley, and rye, in a person's diet (10). The overall prevalence of celiac disease in the United States population is 0.5% to 1%, with an incidence of 1 per 133 for individuals who are not at risk. Research has shown that a person with symptoms of celiac disease may not be diagnosed for 8 to 10 years and may require up to 2 years for symptomatic resolution once a gluten-free diet is initiated (11,12,13). In an effort to reduce the complications of celiac disease, clinicians need to institute early screening and treatment, especially among those with type 1 diabetes in whom the prevalence of celiac disease is nearly 16% (11). Screening should be considered in patients with type 1 diabetes to prevent micro- and macronutrient deficiencies due to malabsorption, which could result in suboptimal growth in children and reduced glycemic control in all patients related to inconsistent carbohydrate absorption (13).

Early treatment of celiac disease involves education about a gluten-free diet for life. This eating pattern includes gluten-free grains that may not be fortified with sufficient vitamins and minerals to prevent nutrient deficiencies. Elements of concern include iron, folate, niacin, vitamin B_{12}, phosphorus, and zinc. Calcium and vitamin D also may be at risk if transient lactose deficiency occurs. It is not uncommon for the patient with undiagnosed celiac disease to present with anemia and/or bone disease. Accordingly, regular screening for nutrient deficiencies in this population appears imperative.

Health care professionals should encourage a well-balanced diet and the use of a wide range of gluten-free foods to balance and ensure nutrient adequacy. In addition, consultation with an RDN for MNT and a pharmacist for recommendations on appropriate choices of gluten-free vitamin and/or mineral supplements is appropriate (13). The website www.glutenfree drugs.com is one resource for patients to investigate prescription, nonprescription, and other supplements.

Supplementation

Choosing the proper vitamin and mineral supplement for each patient requires several considerations. First, it is imperative that chosen products are reputable. Over-the-counter vitamins, minerals, and other supplements are not regulated by the U.S. Food and Drug Administration for standardization. The same pharmaceutical manufacturers that create prescription products make many of the vitamin and mineral brands, which may mean that the same good manufacturing procedures and quality control are used to ensure high-quality products. The United States Pharmacopeia (USP) (14) has a voluntary program, termed "USP Verified", that allows manufacturers to enhance the quality of their product. The USP verifies the ingredients used to make the product and performs quality control verification on the manufactured product. After such review, the product is allowed to bear the "USP Verified" logo. Patients should be told to read the label to see who the manufactures the product or if the manufacturer participates in the USP program.

The second consideration is that the formulation must be appropriate for the patient. One factor is the dosing schedule. For example, will the patient be adherent with an immediate-release formulation that may require multiple ingestions during the day or does the deficiency warrant once-daily supplementation in the form of an extended-release formulation? Product ingredients also must be examined, such as requiring a gluten-free product for the patient with celiac disease. Finally, it is important to determine the appropriate dose needed to address the patient's deficiency. Communication between the pharmacist and RDN is imperative when choosing the proper dose to determine how much of the vitamin or mineral that needs to be replaced is being taken in through the diet (Table 1). Most excess vitamins and minerals are excreted in the urine or the feces, but some can accumulate and cause additional medical problems. Finding the fine line for each patient is critical. Table 2 reviews dosing, formulations, and special considerations of vitamins and minerals discussed in this article.

Conclusion

Routine supplementation with multivitamins and minerals is not recommended in the current standards of medical care for diabetes, but drug therapy, comorbid conditions, and special diets can cause vitamin and mineral deficiencies. Recognizing the deficiencies and recommending increased dietary intake of foods rich in the specific vitamin or mineral is important. If the patient is unable to tolerate the food sources, supplementation with pharmacotherapy is appropriate.

Table 1. Medical Nutrition InterventionTreating Vitamin/Mineral Deficiencies with Food

Nutrient	Food Source	Deficiency Symptoms
B_{12}	Meat, Blue/Camembert/Gorgonzola cheese	Unsteady gait, chronic fatigue, dizziness, mood swings, nerve disorders, pernicious anemia
Folic Acid	Fortified cereal, pinto beans, navy beans, asparagus, spinach, broccoli, Brussels sprouts, barley, beef, bran, brewer's yeast, whole grains, green leafy vegetables.	Anemia, irritability, weakness, sleep disturbances, pallor, sore & red tongue
Vitamin D	Sun exposure, sardines, salmon, mushrooms, eggs, fortified milk, fortified cereals, herring, liver, tuna, cod liver oil, margarine	Osteomalcia, osteoporosis, hypocalcemia
Chromium	Brewer's yeast, broccoli, grape juice, brown rice, cheese, whole grains, dried beans, chicken, corn, eggs, potatoes, mushrooms, wine and beer	Alterations in metabolism of fats, carbohydrates and proteins
Selenium	Lobster, Brazilian nuts, shellfish, whole grains, organ meat, brown rice, broccoli, dairy products, onions, salmon, wheat germ, tuna	Muscle weakness, may be linked to heart disease, fatigue, elevated cholesterol, susceptibility to infection, sterility
Magnesium	Brown rice, avocados, spinach, navy beans, broccoli, yogurt, bananas, baked potatoes, apples, apricots, brewer's yeast, cantaloupe, nuts	Sleep disturbance, irritability, rapid heartbeat, confusion, muscle spasm, GI upset
Iron	Iron fortified cereals, beef, baked potatoes, eggs, fish, nuts, avocados, beets, brewer's yeast, dates, peaches, pears, lentils, dried prunes, raisins, sesame seeds	Anemia, dry, coarse hair, dysphasia, dizziness, fatigue, hair loss, cracked lips or tongue, slowed mental response, pallor
Zinc	Oysters, beef, lamb, eggs, whole grains, nuts, yogurt, fish, legumes, lima beans, liver, mushrooms, yogurt, sunflower seeds, poultry, sardines	Change in taste and smell, nails thin and peel, acne, hair loss, elevated cholesterol, impaired night vision, increased susceptibility to infection

References for Tables

1. American Diabetes Association Standards of Medical Care in Diabetes- 2014 Available at http://care.diabetesjournals.org/content/37/Supplement_1/S14.extract. Accessed 10/30/2014.
2. Position of the American Dietetic Association: Integration of Medical Nutrition Therapy and Pharmacotherapy. The Academy of Nutrition and Dietetics, Journal of the American Dietetic Association, June 2010, Volume 110 Number 6.
3. Alison B. Evert, MS, RD, CDE, Jackie L. Boucher, MS, RD, LD, CDE, Marjorie Cypress, PHD, C-ANP, CDE, et al. Nutrition Therapy Recommendations for the Management of Adults With Diabetes. Diabetes Care. Published online before print October 9, 2013, doi:10.2337/dc13-2042 *Diabetes Care* November 2013 vol. 36 no. 11 3821–3842
4. Lexicomp. Metformin drug monograph. Available at http://www.lexicomp.com Last updated 11/7/14. Accessed 10/30/14.
5. Dynamed. "Celiac Disease." Available at http://web.b.ebscohost.com/dynamed. Last updated 10/06/14. Accessed on 11/5/14.
6. Mackenzie M. Celiac Disease. Practical Diabetology 2014; Sept/Oct: 10–12.
7. Mosby's Pocket Guide Series Nutrition Care by Mary Courtney Moore, Fourth Edition. Page 267, Chapter Gastrointestinal Disorders
8. American Dietetic Association. Nutrition Care Manual . Normal Pregnancy, Vegetarian, Celiac Diet. http://www.nutritioncaremanual.org. Accessed 11/3/2014
9. Winston J. Craig, PhD, MPH, RD (Andrews University, Berrien Springs, MI); Ann Reed Mangels, PhD, RD, LDN, FADA (The Vegetarian Resource Group, Baltimore, MD). Position of the American Dietetic Association: Vegetarian Diets. Journal of the American Dietetic Association, July 2009 Volume 109 Number 7.
10. United States Pharmacopeia. "USP Verified" Available at http://www.usp.org/usp-verification-services/usp-verified-dietary-supplements. Accessed 11/7/2014.
11. Krinsky D, Berardi R, et al. Chapter 22. Essential and Conditionally Essential Nutrients. In: Handbook of Nonprescription Drugs An Interactive Approach to Self Care, 17th Edition. Washington, DC: American Pharmacists Association; 2012.

References

1. American Diabetes Association. Standards of Medical Care in Diabetes-2015. *Diabetes Care.* 2015;38(suppl 1). Available at http://care.diabetesjournals.org/content/38/Supplement_1. Accessed January 13, 2015.
2. McCabe-Sellers BJ1, Skipper A; American Dietetic Association. Position of the American Dietetic Association: integration of medical nutrition therapy and pharmacotherapy. *J Am Diet Assoc.* 2010;110:950–956.
3. Metformin drug monograph. Lexi-Comp. 2014. Available at http://www.lexicomp.com Accessed October 30, 2014.
4. Evert AB, Boucher JL, Cypress M, et al; American Diabetes Association. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care.* 2013; 36:3821–3842.
5. Ko SH, Ko SH, Ahn YB, et al. Association of vitamin B_{12} deficiency and metformin use in patients with type 2 diabetes. *J Korean Med Sci.* 2014;29:965–972.
6. Niafar M, Hai F, Porhomayon J, Nader ND. The role of metformin on vitamin B_{12} deficiency: a meta-analysis review. *Intern Emerg Med.* 2015;10:93–102.

Table 2. Vitamin and Mineral Supplementation Pharmacotherapy Guide (11)

Vitamin/Mineral	Recommended Daily Dose	Formulations	Special Considerations
Calcium	1,200-1,500 mg daily	Calcium Carbonate: more naturally occurring calcium, can cause constipation, most difficult to absorb, take with food Calcium Citrate: easier on the stomach, easier to absorb, constipation neutral	Because the body can only absorb 600 mg of calcium at any one time, doses must be divided. Because calcium absorption can be affected by iron and other metals, calcium and iron ingestion must be separated by at least 2 hours. Calcium needs vitamin D to aid with absorption if the person is not exposed to sunlight.
Vitamin D	800-1,000 IU daily	D_3 (cholecalciferol)	
Magnesium	300-400 mg daily	Magnesium citrate or found in combination with zinc and potassium	
Iron	Ferrous Sulfate: 325 mg daily (contains 65 mg elemental iron) Ferrous Gluconate: 225 mg daily (contains 27 mg elemental iron)	Ferrous Sulfate: can cause constipation and stomach upset; reference product Ferrous Gluconate: well tolerated	Can interfere with many prescription and nonprescription medications. Check with the pharmacist about potential drug interactions before beginning therapy.
Vitamin B_{12}	500-1,000 mcg daily	Cyanocobalamin or vitamin B_{12} tablets over the counter or injection by prescription	Poor oral absorption; subcutaneous or intramuscular injection may only require weekly administration.
Folic Acid	400-1,000 mcg daily	Folate or Folic Acid	400 mcg for women of childbearing age, 1 mg (1,000 mcg) for those who have deficiency. Absorption of folic acid from food is poor; oral supplementation is better
Zinc	10-15 mg daily 50 mg elemental zinc three times daily for deficiency	Zinc sulfate 220 mg (50 mg elemental zinc)	Can induce copper deficiency if used chronically. Used to help treat wounds.

7. Aghamohammadi V, Gargari BP, Aliasgharzadeh A. Effect of folic acid supplementation on homocysteine, serum total antioxidant capacity, and malondialdehyde in patients with type 2 diabetes mellitus. *J Am Coll Nutr.* 2011;30:210–215.
8. Lautatzis ME1, Goulis DG, Vrontakis M. Efficacy and safety of metformin during pregnancy in women with gestational diabetes mellitus or polycystic ovary syndrome: a systematic review. *Metabolism.* 2013; 62:1522–1534.
9. Centers for Disease Control and Prevention. *Manifestations of Low Vitamin B_{12} Levels.* 2009. Available at: http://www.cdc.gov/ncbddd/b12/manifestations.html. Accessed January 13, 2015.
10. Dynamed. "Celiac Disease." Available at https://dynamed.ebscohost.com. Last updated 10/06/14. Accessed on 11/5/14.
11. Mackenzie M. Celiac disease. *Practical Diabetology.* 2014; 33:10–12.
12. Moore MC. Gastrointestinal, pancreatic, and liver dysfunction. In: *Mosby's Pocket Guide Series Nutritional Assessment and Care.* 6th ed. St. Louis, MO: Mosby Elsevier; 2009:302–332.
13. Academy of Nutrition and Dietetics. Normal pregnancy, vegetarian, celiac diet. In: *Nutrition Care Manual.* Chicago, IL: Academy of Nutrition and Dietetics; 2014. http://www.nutritioncaremanual.org. Accessed November 3, 2014.
14. United States Pharmacopeial Convention. *USP Verified Dietary Supplements.* 2014. Available at http://www.usp.org/usp-verification-services/usp-verified-dietary-supplements. Accessed November 7, 2014.

Complementary and Alternative Medicine Products for Diabetes in Pill Form

Lea E. delaPena, PharmD, BCPS
Associate Professor and Clinical Pharmacist
Midwestern University
Downers Grove, IL

Katherine Snyder, MS, RD, CDE
Registered Dietitian
Dreyer Medical Clinic
Aurora, IL

Abstract

Millions of Americans use complementary and alternative medicine (CAM) products for a variety of reasons. Because of the paucity of well-designed clinical trials on CAM products, clinicians have a difficult time providing sound advice about these agents to patients. Systematic reviews and/or meta-analyses may be used to form more substantive conclusions and recommendations. Several CAM products have been used to aid in glycemic control for diabetes through different mechanisms of action. This review addresses five such CAM products: alpha-lipoic acid, chromium, ginseng, resveratrol, and vitamin D.

Introduction

CAM uses non-mainstream approaches to health either along with or in place of conventional medicine. There are three primary areas of CAM: natural products, which include vitamins, minerals, probiotics, and herbals; mind and body practices, which include acupuncture, massage, meditation, and spinal manipulation; and other practices, which do not fit into the first two areas and include homeopathy, traditional Chinese medicine, and Ayurvedic medicine (1).

Access to CAM has greatly increased since the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994. DSHEA states that the manufacturer of the supplement, not the U.S. Food and Drug Administration (FDA), must ensure that the supplement is safe to use and that any claims made about the supplement are not false or misleading (2). The manufacturer is not obligated to show the FDA any evidence supporting the safety or efficacy of its supplement (2). Labeling on dietary supplements is not allowed to state that the supplement can be used for the treatment, prevention, or cure of any disease state or condition. Labeling that describes how the supplement affects the structure or function of the body is allowed if the manufacturer also includes a disclaimer that states "This statement has not been evaluated by the Food and Drug Administration (FDA). This product is not intended to diagnose, treat, cure, or prevent any disease" (2).

Studies and surveys have tried to determine the characteristics of a typical CAM user. The 2002 National Health Interview Survey found that almost 19% of United States adults had used an herb or dietary supplement in the previous 12 months, which is almost double the amount reported in 1999 (9.6%) (3). According to this survey, the following factors were associated with an increased likelihood of using CAM: female gender, middle age (45-64 years old), certain races, higher education levels, higher income levels, those with private insurance, patients who described their overall health as "excellent" or "very good," and those who had issues that required at least one prescription medication (3). The 2007 National Health Interview Survey update showed similar findings except that older adults (≥65 years old) showed an increase in CAM usage compared to middle-aged adults (4).

Among the reasons for patients using CAM products are dissatisfaction with conventional medicine practitioners; costs associated with conventional medical care, including prescription and over-the-counter medications; and an interest in holistic models of health and healing (3). Patients may perceive CAM as an avenue to greater control over their health and the ability to improve or maintain their health. Additionally, because many CAM products are found in nature, patients may believe that "natural" is associated with increased safety. However, patients may not realize that CAM products may cause harm either due to a medical condition, interactions with concomitant medications, or the fact that CAM is largely unregulated.

Alarmingly, less than 50% of all CAM users report their usage to their health care providers (3,4). Nahin and associates (5) studied the use of CAM among patients with severe diabetes, which was defined as at least three of the following six measures: at least 5 years since diabetes diagnosis, use of

Table 1. Commonly Used Complementary and Alternative Medicine Products for Glycemic Control (6,7)

Product	Other Names or Types	Common Doses Used in Studies	Possible Adverse Effects	Warnings/ Precautions
Alpha-lipoic acid	Thioctic acid	300-1,800 mg/day in single or divided doses	Nausea, vomiting, diarrhea, dizziness, fullness, skin rash, changes in blood pressure, angina, contact dermatitis	• Patients with or at risk for cardiovascular disease because adverse cardiovascular events have been reported • Patients with thiamine or element deficiencies
Chromium	Glucose tolerance factor Trivalent chromium	200-1,400 mcg/day	Headache, nausea, , vomiting diarrhea, insomnia, mood changes, contact dermatitis	• Allergy to chromate or leather because cross-reactivity may occur • Caution in patients with cardio-vascular disease or renal/hepatic dysfunction because adverse effects have been reported • Caution in patients taking levothyroxine or iron supplements due to potential for interactions
Ginseng	American ginseng *(Panax quinquefolius)* Asian or Korean ginseng *(Panax ginseng)*	1-9 g/day in divided doses	Headache, nausea, vomiting, diarrhea, constipation, changes in blood pressure, rash, mastalgia, insomnia	• Patients taking medications that affect blood pressure • Patients with mental health issues • May increase risk of bleeding
Resveratrol	Grape seed extract Grape skin	5-2,000 mg	Allergic dermatitis, diarrhea, immune changes	• Allergies to grapes or red wine • Patients taking anticoagulants or antiplatelets due to increased risk of bleeding • Patients on antihypertensives due to possible additive effects • Patients on estrogen therapy because resveratrol may act as either an agonist or antagonist
Vitamin D	Vitamin D2 (ergocalciferol) Vitamin D3 (cholecalciferol)	Vitamin D3: 400 units daily up to 40,000 units weekly or up to 200,000 units x 1 dose	Diarrhea, constipation, abdominal cramping, gastrointestinal upset, vomiting	• Use with caution in patients with cardiovascular disease, skin disorders, liver disorders, or hypercalcemia due to possible adverse effects

prescription medications to control diabetes, functional limitation due to diabetes, kidney damage, vision problems, or coronary heart disease. They found that such patients were more likely to use CAM than those without severe diabetes (5). This article examines some CAM products that have been used to help manage blood glucose levels (Table 1).

Literature Review

Alpha-lipoic Acid

Alpha-lipoic acid is a natural antioxidant produced in the body that has been used to help with both glycemic control and diabetic neuropathy. It is believed to aid glycemic control by increasing insulin release, amplifying glucose uptake, and improving insulin sensitivity (6).

Porasuphatana and colleagues (8) found that administration of 300 to 1,200 mg/day of alpha-lipoic acid in Thai patients resulted in statistically significant decreases in fasting plasma glucose (FPG) ($p<0.05$), but nonsignificant decreases in hemoglobin A1c (HbA1c) values for each dosing group over 6 months. When results were pooled, the

decrease in HbA1c became significant ($p<0.05$) and both FPG and HbA1c decreased dose-dependently ($p=0.004$ and $p=0.011$, respectively) (8). Adverse events included anorexia, skin rash, and bitter taste. de Olivera and colleagues (9) examined Brazilian patients with well-controlled type 2 diabetes (HbA1c <7%) who received one of the following agents for 16 weeks: alpha-lipoic acid (600 mg), vitamin E (800 mg), vitamin E plus alpha-lipoic acid (800 mg + 600 mg), or placebo. None of the groups exhibited any effect on lipid parameters or insulin sensitivity; adverse events due to the interventions were not reported. Udupa and colleagues (10) studied patients receiving the following agents: alpha-lipoic acid (300 mg), vitamin E (400 mg), fish oil (180 mg eicosapentaenoic acid + 120 mg docosahexaenoic acid), or placebo over 90 days. They documented nonsignificant reductions in FPG, but statistically significant reductions in HbA1c ($p<0.05$ for alpha-lipoic acid, $p<0.001$ for fish oil, $p<0.001$ for vitamin E), total cholesterol ($p<0.001$), body mass index (BMI) ($p<0.001$), and waist circumference ($p<0.001$). However, the results were not clinically significant and adverse events were not reported (10).

Chromium

Chromium is an essential trace element that is commonly found in either the trivalent (chromium III) or hexavalent (chromium VI) form. Trivalent chromium is found in foods such as rye bread, brewer's yeast, and calf liver as well as in dietary supplements such as chromium picolinate (7). Chromium deficiency, although rare in humans and difficult to measure, has been linked to glucose intolerance and insulin resistance. Chromium is believed to have a positive effect on glycemic control by increasing the quantity of insulin receptors, promoting insulin binding, and increasing insulin sensitivity (6,7).

Suksomboon and colleagues (11) conducted a systematic review and meta-analysis of chromium in diabetes patients that included 25 trials. Chromium doses were 200 to 1,000 mcg/day for 3 to 24 weeks. Statistically significant improvements were seen in both HbA1c (mean decrease of 0.55%; $p=0.001$, 95% CI 0.22-0.88) and FPG (mean decrease of 21 mg/dL; $p=0.001$, 95% CI 8.5-33mg/dl). Reported adverse events included watery stool, dizziness, headache, nausea, constipation, and flatulence, but there was no difference in risk of adverse events from chromium compared to placebo. (11) The authors noted significant heterogeneity in the studies, which can limit the applicability of these results (11). Abdollahi and associates (12) conducted a meta-analysis that included seven randomized clinical trials with a minimum chromium dose of 250 mcg/day and a duration of therapy of at least 2 months (12).There was a statistically significant decrease in FPG of 17 mg/dL ($p<0.0001$) but no significant differences in HbA1c, lipid parameters, or BMI .

Ginseng

Two primary types of ginseng relate to glucose control: Asian ginseng *(Panax ginseng)* and American ginseng *(Panax quinquefolius)*. The root of the ginseng plant contains ginsenosides that are believed to be the active part of the plant. Ginseng purportedly works by enhancing beta-cell function; stimulating insulin release; improving insulin binding and resistance; and positively affecting glucose absorption, transport, and disposal (6,10,13,14).

Shishtar and colleagues (13) conducted a systematic review and meta-analysis of 16 studies of at least 30 days duration that included either American or Asian ginseng.There were statistically significant reductions in FPG (mean decrease of 5.6 mg/dL; $p=0.03$, 95% CI -0.59 to -0.03) but no significant reduction in HbA1c, plasma insulin levels, or homeostasis model assessment of insulin resistance (HOMA-IR), which is a measure of insulin resistance. Adverse events were not reported in most trials (13). One of the limitations of this analysis is the short duration of most studies (≤12 weeks), so a lack of significant effect on HbA1c is not surprising. Further, the median baseline HbA1c was 7.1%, indicating that patients already had relatively good glycemic control. Finally, the ginseng preparations were not standardized (13). Mucalo and associates (14) reviewed studies of primarily American ginseng administered in doses of 1 to 9 g/day. Results showed beneficial effects on postprandial glucose, HbA1c, and FPG after 8 weeks. Adverse effects were seen at higher doses and included headache, gastrointestinal issues, insomnia, and nervousness. Shishtar and colleagues (15) performed a multiple crossover study using Korean ginseng *(Panax ginseng C.A. Meyer)* in patients with type 2 diabetes at doses of either 1, 3, or 6 g. They did not find any significant effects on postprandial glucose. Shergis and colleagues (16) reviewed six studies of glucose metabolism and ginseng in which only two of the trials enrolled patients with type 2 diabetes; the other four enrolled healthy adults. Of the two trials with patients with diabetes, one showed benefits in HOMA-IR and FPG, while the other did not show any benefits in glycemic parameters (16).

Resveratrol

Resveratrol is a naturally occurring polyphenol compound found in the skin of grapes, red wine, and certain nuts and berries. Resveratrol became popular when it was associated with the "French paradox" in which coronary heart disease deaths are lower in France compared to other industrialized nations, despite a high-fat diet. The paradox was believed to be due to increased consumption of red wine in France (6). The mechanism of action of resveratrol is multifaceted: it is purported to stimulate glucose uptake, attenuate beta-cell degradation in the pancreas, enhance insulin sensitivity, and prevent inflammation (17,18).

A meta-analysis conducted by Liu and colleagues (17) reviewed 11 randomized clinical trials of patients who received a resveratrol supplement for at least 2 weeks for whom FPG, insulin concentrations, HbA1c, or HOMA-IR was assessed. Eight of 11 studies were performed in patients without diabetes. Statistically significant reductions were seen in FPG ($p<0.001$, 95% CI -52.13 to -18.30), insulin concentrations ($p<0.01$, 95% CI -6.54 to -2.56μIU/mL, HbA1c ($p=0.02$, 95% CI -1.48 to -0.11%), and HOMA-IR ($p<0.01$, 95% CI -3.58 to -0.93) in patients with diabetes; no significant effect was seen in patients without diabetes (17). Limitations of this meta-analysis include nonstandardized dosing, duration, and patient population; concurrent medication usage; and overall quality of studies.

Vitamin D

Vitamin D is a fat-soluble vitamin that maintains normal concentrations of calcium and phosphorus. There are two primary forms of vitamin D: D2 (ergocalciferol) and D3 (cholecalciferol). Humans synthesize D3 in the skin when exposed to sunlight. Food sources of vitamin D include fortified milk, fatty fishes such as salmon and sardines, mushrooms, and eggs. The mechanism of action of vitamin D in glycemic control is not well-defined and may be attributable to several possibilities, including stimulating insulin release from beta cells, decreasing parathyroid hormone levels, modulating carbohydrate metabolism, increasing glucose uptake, and increasing insulin sensitivity (19,20).

Three recent systematic reviews or meta-analyses have evaluated the effects of vitamin D on type 2 diabetes. Mitri and colleagues (21) found no significant changes in HbA1c, FPG, or insulin resistance for patients receiving vitamin D compared to placebo. George and associates (19) found that vitamin D administration was associated with a small significant decrease in FPG (-5.8 mg/dL; $p=0.01$, 95% CI -10.3 to -1.3) and insulin resistance (-0.25; $p=0.03$, 95% CI -0.48 to – 0.03) when compared to placebo but no significant difference in HbA1c. In a systematic review, Thomas and coworkers (20) found no benefit with vitamin D compared to placebo on glycemic measures or insulin resistance, although two small studies did document improved insulin secretion. Authors of all three analyses stated that dosing used in the individual trials varied widely and the duration of treatment primarily ranged between 7 days and 2 years. Their consensus was that current data are insufficient to recommend vitamin D supplementation as a means to improve glycemic control in patients with type 2 diabetes (19-21).

Clinical Application

The absence of well-designed clinical trials involving CAM products makes it hard for the clinician to definitively recommend such therapies to patients. Systematic reviews and/or meta-analyses are sometimes used to pool data obtained from smaller trials to provide more substantive conclusions and recommendations. The American Diabetes Association does not currently support the use of CAM due to insufficient evidence (22). Despite the lack of reliable data, if patients want to use a CAM product, clinicians should advise them to buy one that has had its

Table 2. Internet Resources for More Information About Complementary and Alternative Medicine

Organization/Title	Websites
National Center for Complementary and Alternative Medicine (NCCAM)	http://www.nccam.nih.gov
U.S. Food and Drug Administration (FDA)	http://www.fda.gov/Food/DietarySupplements/default.htm
National Institutes of Health Office of Dietary Supplements (NIH ODS)	http://ods.od.nih.gov
US Pharmacopeial Convention (USP)	http://www.usp.org/dietary-supplements/overview
Natural Standard*	http://naturalmedicines.therapeuticresearch.com
Natural Medicine Comprehensive Database*	http://naturaldatabase.therapeuticresearch.com
Consumer Lab*	http://www.consumerlab.com

*requires paid subscription service

quality verified by organizations such as the US Pharmacopeia Convention or Consumer Lab (Table 2).

Patients using any CAM products in conjunction with conventional prescriptions or over-the-counter medications for diabetes should be told to monitor their blood glucose levels closely, especially when starting new CAM products or conventional medications or with any dosage changes, due to the possibility of hypoglycemia. Before starting any new CAM products, patients should be encouraged to ask a pharmacist how the product may interact with any prescription or over-the-counter medications or other CAM products they may already use. Clinicians can also encourage patients to report their CAM usage to their prescribing health care providers, including the name, dose, indication, and duration of therapy. Just because a CAM product may seem more "natural" than conventional medication does not mean it is without risk; adverse effects can still occur. If a patient wishes to report an adverse effect or other issue related to a CAM product, he or she can either call the FDA MedWatch Hotline (1-800-FDA-1088) or use the online Safety Reporting Portal (http://www.safetyreporting.hhs.gov) (2).

Summary

Many patients have an interest in or are currently using CAM products. Clinicians can help patients by reminding them that these products are not regulated by the FDA and encouraging them to inform all of their health care providers of any herbal products they are using. Clinicians also should be aware of some common CAM products that patients may use for diabetes as well as good sources of information about CAM. At this time, no CAM products have demonstrated any benefits in glycemic control for type 2 diabetes in well-designed randomized clinical trials.

References

1. National Institutes of Health. National Center for Complementary and Alternative Medicine Website. Available at: http://nccam.nih.gov. Accessed November 7, 2014.
2. U.S. Food and Drug Administration. *Dietary Supplements.* 2014. Available at: http://www.fda.gov/Food/DietarySupplements/default.htm. Accessed November 7, 2014.
3. Kennedy J. Herb and supplement use in the US adult population. *Clin Ther.* 2005;27:1847–1858.
4. Wu CH, Wang CC, Kennedy J. Changes in herb and dietary supplement use in the US adult population: a comparison of the 2002 and 2007 National Health Interview Surveys. *Clin Ther.* 2011; 33:1749–1758.
5. Nahin RL, Byrd-Clark D, Stussman BJ, Kalyanaraman N. Disease severity is associated with the use of complementary medicine to treat or manage type 2 diabetes: data from the 2002 and 2007 National Health Interview Survey. *BMC Complement Altern Med.* 2012;12:193–210.
6. *Natural Standard.* Available at: http://naturalmedicines.therapeuticresearch.com. Accessed November 7, 2014.
7. *Natural Medicine Comprehensive Database.* Available at: http://naturaldatabase.therapeuticresearch.com. Accessed November 7, 2014.
8. Porasuphatana S, Suddee S, Nartnampong A, Konsil J, Harnwong B, Santaweesuk A. Glycemic and oxidative status of patients with type 2 diabetes mellitus following oral administration of alpha-lipoic acid: a randomized double-blinded placebo-controlled trial. *Asia Pac J ClinNutr.* 2012;21:12–21.
9. de Olivera AM, Rondo PHC, Luzia LA, D'Abronzo FH, Illison VK. The effects of lipoic acid and α-tocopherol supplementation on the lipid profile and insulin sensitivity of patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. *Diabetes Res ClinPract.* 2011;92:253–260.
10. Udupa AS, Nahar SH, Shah MJ, Kshirsagar MJ, Ghongane BB. Study of comparative effects of antioxidants on insulin sensitivity in type 2 diabetes mellitus. *J Clin Diagn Res.* 2012;6:1469–1473.
11. Suksomboon N, Poolsup N, Yuwanakorn A. Systematic review and meta-analysis of the efficacy and safety of chromium supplementation in diabetes. *J Clin Pharm Ther.* 2014;39:292–306.
12. Abdollahi M, Farshchi A, Nikfar S, Seyedifar M. Effect of chromium on glucose and lipid profiles in patients with type 2 diabetes; a meta-analysis and review of randomized trials. *J Pharm Pharm Sci.* 2013;16:99–114.
13. Shishtar E, Sievenpiper JL, Djedovic V, et al. The effect of ginseng (the genus Panax) on glycemic control: a systematic review and meta-analysis of randomized controlled clinical trials. *PLoS One.* 2014;9:e107391
14. Mucalol, Rahelic D, Jovanovski E, et al. Effect of American ginseng (Panaxquinquefolius L.) on glycemic control in type 2 diabetes. *Coll Antropol.* 2012;36:1435–1440
15. Shishtar E, Jovanovski E, Jenkins A, Vuksan V. Effects of Korean white ginseng (Panax ginseng C.A. Meyer) on vascular and glycemic health in type 2 diabetes: results of a randomized, double blind, placebo-controlled, multiple-crossover, acute dose escalation trial. *Clin Nutr Res.* 2014;3:89–97.

16. Shergis JL, Zhang, AL, Zhou W, Xue CC. Panax ginseng in randomised controlled trials: a systematic review. *Phytother Res.* 2013;27:949–965.
17. Liu K, Zhou R, Wang B, Mi MT. Effect of resveratrol on glucose control and insulin sensitivity: a meta-analysis of 11 randomized controlled trials. *Am J Clin Nutr.* 2014;99:1510–1519.
18. Szkudelski T, Szkudelska K. Anti-diabetic effects of resveratrol. *Ann NY Acad Sci.* 2011;1215:34–39.
19. George PS, Pearson ER, Witham MD. Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. *Diabet Med.* 2012; 29:e142–e150.
20. Thomas GN, Scragg R, Jiang CQ, et al. Hyperglycaemia and vitamin D: a systematic overview. *Curr Diabetes Rev.* 2012;8:18–31.
21. Mitri J, Muraru MD, Pittas AG. Vitamin D and type 2 diabetes: a systematic review. *Eur J Clin Nutr.* 2011;65:1005–1015.
22. Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care.* 2014;37(suppl 1):S120–S143.

Improving Medication Adherence in Patients with Diabetes

Diana Isaacs, PharmD, BCPS, CDE, BC-ADM
Clinical Assistant Professor
Chicago State University
Oak Lawn VA Clinic
Chicago, IL

Janice Fisher, PhD, RD, LD, CDE, BC-ADM, FAADE
Clinical Dietitian Specialist, Retired
Veterans Affairs Medical Center
Iowa City, IA

Abstract

Medication adherence is defined as filling medications on time and taking medications exactly as directed. Consequences of poor medication adherence include worsening glycemic control and increases in hospitalizations and mortality. Many barriers exist to medication adherence. Successful strategies to overcome such barriers are patient-specific and include interdisciplinary teams, social support, motivational interviewing, patient engagement, shared decision--making, and planned follow-up. A combination of these strategies in addition to traditional methods such as simplifying dosing regimens, using pillboxes, and setting reminders are most effective. Diet adherence and the relationship to the medication regimen should also be evaluated on a continuous basis.

Introduction

Adherence is defined by the World Health Organization as the extent to which a person's behaviors, such as taking medication and following lifestyle changes, correspond with agreed recommendations from his or her health care provider (2). Adherence is preferred over the term compliance, which may suggest passively following doctor's orders instead of active patient involvement in his or her own care (1). In this context, adherence means filling prescriptions on time and taking medications exactly as directed, including any special dosing instructions such as "with food." Intentional nonadherence involves choosing not to take medications for reasons such as adverse effects or believing they are not needed, and unintentional nonadherence is missing medications for reasons such as forgetting or having low health literacy (Table 1). Patients are often considered

Table 1. Unintentional and Intentional Causes of Medication Nonadherence (1)

Unintentional Nonadherence	Intentional Nonadherence
• Forgetfulness	• Inconvenient dosing schedule
• Misunderstanding instructions	• Poor relationship with the prescriber or health care team
• Low health literacy	• Asymptomatic illness
• Cognitive or visual impairment	• Cultural beliefs
• Financial issues	• Adverse effects
• Language barriers	• Poorly perceived benefit
• Poor dexterity	
• Lack of social support	
• Psychiatric disorders	
• Substance abuse	

adherent if they take at least 80% of doses correctly (2). Actual adherence rates for chronic conditions are closer to 50% (1). Evaluation of barriers to medication adherence and strategies to improve adherence should be reviewed at every visit.

Consequences of Poor Medication Adherence

Achieving blood glucose, blood pressure (BP), and blood cholesterol goals reduces the risk of microvascular and macrovascular complications in patients with diabetes. Poor medication adherence is directly linked with higher hemoglobin A1c (HbA1c), BP, and cholesterol levels (3). Poor adherence has also been associated with a 58% increase in all-cause hospitalization and an 81% increase in all-cause mortality (4). In a retrospective study that evaluated 229,848 electronic health records, patients poorly adherent to their oral diabetes medications (<50%) were nearly three times more likely to have poor glycemic control compared to those who were adherent (>80%) (5). However, older patients with longstanding diabetes were more likely to have poor glycemic control despite good medication adherence, suggesting that medication adherence is only one component of many affecting glycemic control (5).

Assessing Medication Adherence

Objective methods to measure medication adherence include direct observation, pill counts, pharmacy refill records, electronic medication tracking systems, and drug levels in the urine or blood (2). Pharmacy refill records can be used to calculate the proportion of days covered (PDC), which measures the number of doses dispensed in relation to the dispensing period, expressed as a percentage. The PDC is increasingly being used as a quality improvement indicator by health insurance programs. A PDC greater than 80% is considered highly adherent for most chronically administered medications (6).

Objective methods may be challenging to obtain. Therefore, subjective measurements are often used in practice, including survey tools, asking patients about medication-taking behaviors, or monitoring response to therapy (2). Many survey tools were created for clinical research. The Morisky Scale, which is short and may be useful in clinical settings, poses questions that help identify the patient's specific barriers to adherence such as "When you feel like your symptoms are under control, do you sometimes stop taking your medicine? (3). Clinicians should use nonjudgmental and empathetic statements when talking to patients such as "It can be challenging to take medications every day. How many doses do you think you may have missed over the last two weeks?" (7).

Barriers to Medication Adherence

Many barriers to medication adherence are described in the literature. A cross-sectional study of 77 patients with poorly controlled diabetes indicated that the most common barriers were paying for medications (34%), remembering doses (31%), reading prescription labels (21%), and obtaining refills (21%) (8). Other barriers include poor provider-patient communication, poor interaction with the health-care system, complexity of the treatment regimen, adverse effects, substance abuse, low health literacy, lack of education about how the medication should be taken, poorly perceived benefits, and suboptimal social support (2,9). The patient's emotional state can also be a barrier and may include psychological insulin resistance (PIR), regimen-related distress, and comorbid conditions such as depression and dementia (7). In addition, taking diabetes medications more than twice daily or taking five or more different medications are risk factors for nonadherence (8).

Psychological Insulin Resistance

Specific barriers to starting insulin can include: fear of needles or injection pain, fear of hypoglycemia, fear of weight gain, fear of dependence, perceived interference with daily activities, and the belief that taking insulin is a sign of treatment failure. Prior clinician communication that insulin will be initiated because of low medication/diet adherence may be perceived as threatening and result in less patient cooperation when insulin is actually necessary. Strategies to overcome PIR include educating patients about diabetes progression, introducing the concept of insulin treatment from the onset, not "threatening" patients with insulin as a punishment, and explaining insulin action times to avoid hypoglycemia (Table 2). Shared medical appointments and support groups, where patients can hear from others who have had success with injecting insulin, are also good strategies (10).

Social Support

Strong social support is associated with higher medication adherence. This especially includes having a partner, family, or friends provide practical support such as filling pillboxes, paying for medications, administering medications, and providing transportation to appointments. Social support also improves adherence when it involves addressing unmet emotional needs, such as reassurance of worth (13).

Table 2. Interventions to Address Barriers to Medication Adherence (2, 7,9,10-12)

Barriers	Interventions
Adverse effects	• Determine if patient is taking correctly (e.g., metformin with food) • Switch to other therapeutic alternatives if possible (e.g., dipeptidyl peptidase 4 inhibitors instead of sulfonylurea for less hypoglycemia) • Consider dose adjustment
Cognitive impairment	• Caregiver, friend, family involvement • Provide visual aids and written instructions

Cost of prescriptions	• Patient Assistant Programs
	  • Partnership for Prescription Assistance (http://www.pparx.org)
	  • NeedyMeds (http://www.needymeds.com)
	• Work within formularies
	• Free samples
	• Consider lower-cost options
	• Prescription savings cards

Cultural beliefs	• Ask about cultural beliefs and attitudes • Provide individualized, culturally competent care
Emotional barriers, including regimen-related distress	• Motivational interviewing and motivational communication • Elicit patient's feelings about his/her ability to follow the regimen • Help patient create a specific plan to address stressors • Patient empowerment • Collaborative, interdisciplinary team with all members communicating the same message to patients
Lack of perceived benefit	• Education about complications of uncontrolled diabetes and benefits of the medication • Motivational interviewing and motivational communication • Shared medication appointments • Self-monitoring to see effects (e.g., glucose, blood pressure)
Low health literacy	• Ask patients to demonstrate or "teach back" how they will take the medication • Empower patients to ask questions • Visual, interactive education • Pictorial medication schedule or "pill card" • Language barriers: use interpreters and translated educational materials
Physical limitations	• Dexterity issues: insulin pens instead of vials, prefilled medication packaging • Visual impairment: insulin syringe magnifier, audio prescription labels • Prescription delivery service • Follow-up appointments via phone
Psychological comorbidities	• Mental health referrals • Frequent follow-up • Caregiver, friend, family involvement
Psychological insulin resistance	• Introduce the concept of insulin treatment from diabetes onset • Educate patients about diabetes progression • Avoid threatening patients with insulin as a punishment • Explain insulin action times to avoid hypoglycemia • Use of smaller needles or insulin pens • Shared medical appointments or support groups
Refilling medications	• Medication synchronization • Mail-order pharmacies • Prescription delivery service • Pharmacy phone call reminders and text messaging services
Remembering to take medications	• Pillboxes • Pair medication taking with daily activities (e.g., with brushing teeth or morning coffee) • Simplify regimen by minimizing number of doses or injections per day • Use combination pills • Switch to long-acting medications • Discontinue medications that are not needed • Set alarms • Involve caregivers, friends, family • Electronic packaging • Mobile applications
Social support	• Diabetes support groups • Caregiver, friend, family involvement
Understanding medication instructions	• Large print prescription label clearly stating dosage information • Patient counseling upon receiving the prescription • Visual aids and written educational materials using clear, simple language • Call-back number for patient questions

The Link Between Diet and Medication Adherence

Patients with type 2 diabetes may have comorbid conditions that require specialized diets. For example, warfarin, an anticoagulant, is commonly prescribed for patients with diabetes and atrial fibrillation or venous thromboembolism. Increasingly complex regimens that may necessitate coordination of diet and medications may contribute to poor adherence to one or both entities (14).

Another dietary consideration is seen in patients with celiac disease and type 1 diabetes. As discussed in a recent issue of *On The Cutting Edge* (15), the complexity of the gluten-free diet and the limited resources available to assist in incorporating carbohydrate counting into the food plan contribute to patient confusion and frustration. The challenge of adjusting insulin dosages based on carbohydrate intake and blood glucose readings without detailed diet labeling information may reduce diet and medication adherence or result in errors in medication dosage.

Interventions to Improve Medication Adherence

Several interventions can improve medication adherence (Table 2). For example, patients who forget to take medications frequently respond to simplifying the regimen, introducing a pillbox, and setting watch or cell phone alarms. For patients who have difficulty picking up refill medications, the strategies of mail-order pharmacy, medication synchronization (refilling all medications at the same time), and home delivery services can be of help.

A Collaborative Interdisciplinary Team Communicating the Same Message

Multiple health care professionals may advise patients on their care. Therefore, a unified health care team communicating the treatment plan is important. Studies confirm the benefits of close teamwork, including collaboration between physicians, pharmacists, nurses, registered dietitian nutritionists, and health care technicians (16). The use of team "huddles," shared electronic progress notes, and interdisciplinary literature reviews can help to standardize the messages given to patients. Pharmacists can be an invaluable resource to the team regarding medication formulation, dosing, and cost considerations. Advising patients to use just one pharmacy can allow pharmacists to maintain a record of all of the patient's medications and monitor for medication-related problems such as drug interactions and duplication of therapy.

Strategies for Interviewing Patients

Motivational Interviewing

Patients require more than knowledge and facts to be motivated to adhere to medications, diet, exercise, and other self-management behaviors. Motivational interviewing has been reported to improve adherence (17), although successful implementation has been viewed as time-consuming. Behavioral psychologist Kim Lavoie, PhD, has trained more than 7,000 physicians and other clinicians in a form of motivational interviewing called Motivational Communication (17). The clinician partners with the patient and asks the patient's permission to discuss adherence issues. Once permission is granted, questions are carefully designed to help direct the patient to reflect on and verbalize barriers to change. When the clinician asks if he or she can offer an opinion, the patient feels engaged rather than being lectured. Using simple questions can encourage patients to define the issues affecting their self-care regimen.

Patient Engagement

Patient engagement turns the individual into a partner with the health care team, thereby improving appropriate self-care behaviors. Key recommendations from a consensus report (18) for clinicians to improve patient engagement include the team framing collaborative goal-setting in the context of the patient's clinical status while considering comorbidities; culture and values; and family, social, and community environment. Additional recommendations are for the team to be open-minded to patient choices, ensure that the patient receives adequate training and support to engage in self-management behaviors, encourage participation in community programs, review laboratory and biometric data with the patient as part of goal-setting and support, assess and revise the treatment plan yearly, and recognize the many behaviors involved in managing diabetes.

Shared Decision-making

To ensure shared decision-making, patients need to understand why they are taking medications and agree to take them. A health care professional should explain key information to patients, family, or caretakers when a new medication is prescribed, including the name of the medicine, its purpose and role in reducing

diabetes complications, the number of tablets or units per injection, timing and frequency of dosing, any special dosing instructions, and common adverse effects. Clearly written, easy-to-understand instructions should be provided. Visual aids may be helpful (6). Specifically, "pill cards" can address low health literacy by providing an image of all medications the person takes and including simple phrases to describe the medication purpose, how much to take, and when to take it. The Agency for Healthcare Research and Quality provides a template for such a pill card (19).

Electronic Medication Packaging

Electronic medication packaging is a form of health information technology integrated into containers in which pills, inhalers, or other products are dispensed. This technology can greet patients, remind them to take their medications, provide adherence data to patients and their health care team, and alert the team when doses are missed. While it does not guarantee the patient took the medication correctly, adherence has been improved with features showing the last time the container was opened along with audible reminder alarms. (20).

Telephone Outreach

Telephone outreach to improve medication adherence has had mixed results. A recent trial of 2,378 adults with type 2 diabetes who were prescribed a new medication to treat elevated HbA1c, BP or low-density lipoprotein cholesterol did not significantly improve adherence after six months (11). Telephone follow-up may work best once a strong relationship is established with the diabetes educator through the previously mentioned interviewing techniques.

The Strength of Planned Follow-up

Regular follow-up by a team member following initial diabetes self-management education has improved adherence to medications (21). Research has shown that adherence declines 6 months after attending diabetes self-management education training and that patients tend to be more adherent 5 days before and 5 days after an appointment with a health care professional (9). Therefore, it is important for the health care team to use regular follow-up opportunities with the patient to support ongoing adherence to medication and self-care behaviors.

Summary

Nonadherence to medication regimens is a problem in diabetes that can lead to worsening glucose control and health outcomes. Patients may not adhere to their medications for both intentional and unintentional reasons. Interventions should be individualized to address patient-specific barriers. Interdisciplinary teams that communicate the same message, motivational interviewing, patient engagement, shared decision-making, planned follow-up, and strong social support are proven effective interventions. The traditional methods of simplifying dosing regimens, using pillboxes, and setting reminders have also proven to be helpful. Diet adherence and the relationship to effectiveness of the medication regimen should be evaluated on a continuous basis to achieve optimal glycemic control.

References

1. Sabaté E, ed. *Adherence to Long-term Therapies: Evidence for Action.* Geneva, Switzerland: World Health Organization; 2003. Available from: http://whqlibdoc.who.int/publications/2003/9241545992.pdf. Accessed January 3, 2014.
2. Brown MT, Bussel JK. Medication adherence: WHO Cares? *Mayo Clin Proc.* 2011;86:304–314.
3. DiBonaventura M, Wintefeld N, Huang J, Goren A. The Association between nonadherence and glycated hemoglobin among type 2 diabetes patients using basal insulin analogs. *Patient Pref Adherence.* 2014;8:873–882.
4. Ho MP, Rumsfeld JS, Masoudi FA et al. Effect of medication nonadherence on hospitalization and mortality. *Arch Intern Med.* 2006;166:1836–1841.
5. Feldman BS, Cohen-Stavi CJ, Leibowitz M et al. Defining the role of medication adherence in poor glycemic control among a general adult population with diabetes. *PLoS One.* 2014;9:e108145.
6. Nau D. *Proportion of Days Covered (PDC) as a Preferred Method of Measuring Medication Adherence.* Springfield, VA: Pharmacy Quality Alliance. 2015. Available from: http://pqaalliance.org/resources/adherence.asp. Accessed January 3, 2015.
7. Lin EHB, Ciechanowski P. Working with patients to enhance medication adherence. *Clin Diabetes.* 2008;26:17–19.
8. Odegard PS, Gray SL. Barriers to medication adherence in poorly controlled diabetes mellitus. *Diabetes Educ.* 2008;34:692–697.
9. Osterberg I. Blascke T. Adherence to medication. *N Engl J Med.* 2005;353:487–497.

10. Gherman A, Veresiu IA, Sassu RA, Schnur JB, Scheckner BL, Montgomery GH. Psychological insulin resistance: a critical review of the literature. *Pract Diabetes Int*. 2011;28:125–128.
11. O'Connor PJ, Schmittdiel JA, Pathak RD, et al. Randomized trial of telephone outreach to improve medication adherence and metabolic control in adults with diabetes. *Diabetes Care*. 2014;37:3317–3324.
12. Kripalani S, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. *Arch Intern Med*. 2007; 167:540–550.
13. Scheurer D, Choudhry N, Swanton K, Matlin O, Shrank W. Association between different types of social support and medication adherence. *Am J Manag Care*. 2012;18:e461–e467.
14. Smith MB, Christensen N, Wange S, et al. Warfarin knowledge in patients with atrial fibrillation: implications for safety, efficacy, and education strategies. *Cardiology*. 2010;116:61–69.
15. McLarney M. Celiac disease, type 1 diabetes, and considerations for carbohydrate counting. *On the Cutting Edge*. 2014;35(2):27–32.
16. Willens D, Cripps R, Wilson A, Wolff K, Rothman R. Interdisciplinary team care for diabetic patients by primary care physicians, advanced practice nurses, and clinical pharmacists. *Clin Diabetes*. 2011;29:60–68.
17. Chesanow N. For noncompliant patients, a fix that works. *Medscape*. June 26, 2014.
18. Marrero DG, Ard J, Delamater AM, et al. Twenty-first century behavioral medicine: a context for empowering clinicians and patients with diabetes: a consensus report. *Diabetes Care*. 2013:36:463–470.
19. Agency for Healthcare Research and Quality. *How to Create a Pill Card*. 2014. Available from: http://www.ahrq.gov/patients-consumers/diagnosis-treatment/treatments/pillcard/index.html. Accessed January 3, 2015.
20. Checchi KD, Hambrechts DF, Avorn J, Kesselheim AS. Electronic medication packaging devices and medication adherence: a systematic review. *JAMA*. 2014;312:1237–1247.
21. Aliiha JM, Asgari M, Kahayeri F, Ramazani M, Farajzadegan Z, Javaheri J. Group education and nurse-telephone follow-up effects on blood glucose control and adherence to treatment in type 2 diabetes patients. *Int J Prev Med*. 2013;4:797–802.

Diabetes and Immunizations

Valerie Clinard, PharmD
Vice Chairman, Experiential Education
Associate Professor, Pharmacy Practice
Campbell University College of Pharmacy & Health Sciences
Buies Creek, NC

Ann Constance MA, RD, CDE, FAADE
Director, Upper Peninsula Diabetes Outreach Network
Marquette, MI

Abstract

Vaccines are important for patients with chronic health conditions, including those living with diabetes, to prevent a variety of infectious diseases. The use of vaccines has reduced hospitalizations and deaths due to influenza and pneumococcal disease in patients with diabetes. Such patients also are at increased risk of hepatitis B infection. Therefore, in addition to the vaccines recommended for all persons, the Centers for Disease Control and Prevention (CDC) specifically recommends that patients with diabetes receive annual influenza vaccines, pneumococcal vaccine, and the hepatitis vaccine series.

Introduction

Immunization practices were followed in China more than 1000 years ago, but vaccines became accepted more widely among medical practitioners after 1798, when Edward Jenner developed a vaccination to eradicate small pox. Since then, a substantial number of other infectious diseases have been prevented or, in the most successful situations, nearly eradicated through the use of vaccinations (1).

Vaccination is especially important for patients with chronic health conditions, such as type 1 and type 2 diabetes (2). According to the Advisory Committee on Immunization Practices (ACIP), people with diabetes may have changes in immune function that could increase their risk for morbidity and mortality from infections. In addition, ACIP cites sufficient evidence that people with diabetes generally have the expected protective effect of vaccines. Vaccinations have effectively reduced hospitalizations and deaths due to influenza and pneumococcal disease in patients with diabetes (3). Members of the health care team should assess each patient's immunization status, educate patients about vaccines, and provide the immunization or refer the patient for recommended vaccinations when appropriate (4).

Guidelines and Literature Review

The ACIP periodically publishes recommendations for all patients regarding appropriate vaccinations. The most current versions of these recommendations identify diabetes as a specific indication in adults for hepatitis B virus (HBV), influenza, and pneumococcal vaccines.

Hepatitis B

The ACIP recommendations published in 2011 recommended the HBV vaccine series for all adults age 59 and younger who have diabetes (5). Additionally, patients age 60 years and older with diabetes may receive the HBV vaccine at the discretion of the clinician. This recommendation was prompted by outbreaks of HBV infection in practice settings that provide assisted blood glucose monitoring (5). One explanation for the outbreak in this patient population is that current basic infection control practices are not adequate to prevent the spread of HBV, making vaccination critical to prevent an increased incidence of this infection (6).

Patients with diabetes may be at increased risk of HBV infection. In one population-based study, persons 23 to 59 years of age with diabetes were approximately twice as likely to be infected with HBV compared to patients without diabetes (7). This trend was also observed in patients 60 years of age and older. In a study that examined HBV serology data from the National Health and Nutrition Examination Survey, the overall prevalence of previous or current infection was statistically higher in patients with diabetes compared with persons without diabetes (8.3% and 5.2 %, respectively) (7). In a national evaluation, hospitalizations associated with HBV occurred three times more frequently in persons with diabetes than without diabetes (8).

The HBV vaccine series should be initiated and completed as soon as feasible after the patient is diagnosed with diabetes. The recommendation does not extend to women with gestational diabetes.

Influenza

Influenza is the most frequent cause of vaccine-preventable death in the

United States (9,10). Additionally, seasonal influenza results in greater than 200,000 hospitalizations each year. The risks of complications, hospitalizations, and mortality are greatest in persons 65 years of age and older, children younger than 5 years, and patients who have medical conditions that place them at increased risk for complications, which includes diabetes. Thus, although the CDC recommends annual seasonal influenza vaccination for all patients 6 months of age and older, those with an increased risk of complications should be targeted (6). Annual influenza vaccine administration has been documented to decrease diabetes-related hospitalizations for influenza during "flu epidemics" by up to 79% (11). In a population-based cohort study in Spain, influenza vaccination reduced all-cause mortality by 33% among patients with diabetes during the study period (12). Per the ACIP, patients with diabetes who currently control the disease strictly with diet still should receive the influenza vaccine yearly (9).

Pneumococcal Disease

Pneumococcal disease is caused by *Streptococcus pneumoniae*. This bacterium has greater than 90 serotypes, but only a few of these cause most invasive pneumococcal disease (9,10). Pneumococcal disease may include bacteremia, meningitis, and pneumococcal pneumonia presenting in combination or as individual syndromes. The risk for mortality is highest among patients older than 65 years and those who have underlying medical conditions, including diabetes (9,10).

The first pneumococcal vaccine available in the United States was a polysaccharide vaccine that contained antigen from 14 serotypes of pneumococcal bacteria (9). In 1983, a 23-valent polysaccharide vaccine was licensed (PPSV23) (9). In 2000, the first polyconjugate pneumococcal vaccine that contained seven serotypes was licensed (9). The new 13-valent product (PCV13) was licensed in 2010.

As of September 2014, the ACIP recommends that all adults 65 years and older receive both pneumococcal vaccines (PCV13 and PPSV 23) (9,10). The series of four PCV13 vaccinations are recommended for all children younger than 2 years (Fig. 1). In addition, those with diabetes ages 2 to 64 years should receive PPSV23. Ideally, PPSV23 is administered at least 8 weeks after PCV13 if both are indicated. If the patient received PPSV23 before age 65, PCV13 should be administered after age 65 and at least 1 year after PPSV23 was given (Fig. 2). Another dose of PPSV23 is required after the age of 65 years and after a period of 5 years since the previous PPSV23 vaccination.

Figure 1. Pneumococcal vaccine recommendations for children (10,12).

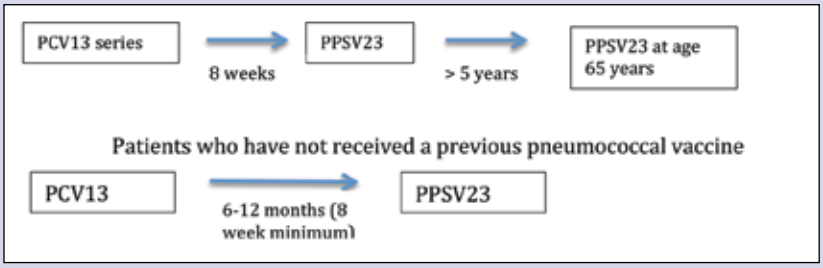
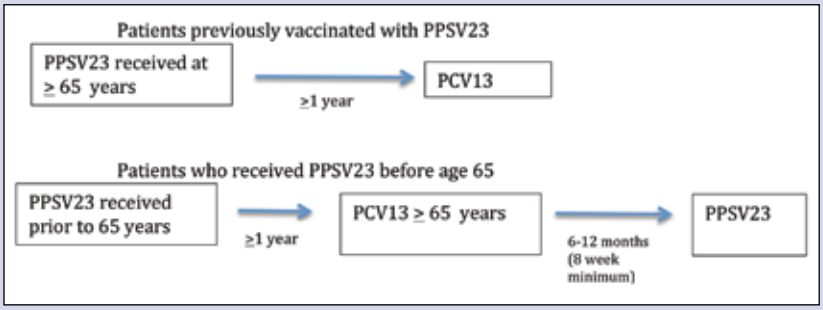


Figure 2. Pneumococcal vaccine recommendations for adults 65 years of age and older (10,13).



In addition to HBV, influenza, and pneumococcal vaccines, patients with diabetes should follow general vaccine recommendations provided by the CDC. The Table lists all vaccines recommended for adults with diabetes.

Clinical Application

Patients with diabetes are six times more likely to be hospitalized and three times more likely to die from influenza and pneumococcal complications compared to patients in the general population (6). Patients with diabetes also are at an increased risk of developing HBV infection. Accordingly, it is imperative for clinicians to understand and communicate the benefits of immunizing this patient population.

Further, clinicians should review and understand the CDC recommendations for other vaccinations because they also can help prevent serious health

illnesses for those living with diabetes (Table). In general, practitioners should be aware of precautions, contraindications, and adverse effects of the various vaccines. For example, patients with diabetes should not receive the live attenuated flu vaccine. The CDC considers diabetes and other underlying medical conditions that place a patient at increased risk for serious complications resulting from flu to be a precaution for the live attenuated flu vaccine (10). The safety of this vaccine has not been established in this patient population.

Summary

Evidence indicates the importance of appropriate vaccination of patients with diabetes. The most effective method of disease prevention is immunization. Because patients with diabetes are at increased risk of morbidity or mortality from influenza, pneumococcal disease, and HBV infection, their clinicians must identify if specific vaccinations are needed in individual patients, provide needed vaccines, or refer patients to other clinicians for vaccination. Finally, clinicians must work with patients to overcome barriers to care and make certain that systems are in place to identify and provide needed vaccinations (3).

Table. Recommended Vaccines for Adults Living With Diabetes (13,14)

Vaccine	Ages 19 to 64 Years	Ages 65 Years and Older	Pregnant Women
Influenza	Annually	Annually	Annually
Tdap (Tetanus, Diphtheria, Pertussis)	One dose, If not given at younger age	One dose, if not given at younger age	One dose during each pregnancy
Td (Tetanus, diphtheria)	Give every 10 years following Tdap	Give every 10 years following Tdap	Not given during pregnancy
PCV 13 (pneumococcal)	One dose as adult, only if other high risk conditions	One dose if have diabetes and have not received as an adult	Not given during pregnancy
PPSV23 (Pneumococcal)	One to three doses	One dose at least (5 years after last dose before age 65) Give 6 to 12 months after PCV13	One dose, if never given
Zoster (Shingles)	One dose after age 60 years	One dose if not given before age 65 years	Contraindicated
MMR (Measles, Mumps Rubella)	May need one to two doses if born after 1957	Not needed	Contraindicated
Hepatitis B	Give, if not previously vaccinated	Assess need for	Assess need for
Human papillomavirus	Before age 26 years if female and age 21 years if male	Not indicated	Not indicated

Hepatitis A and meningococcal vaccines are recommended for children but are not needed for unvaccinated adults with diabetes unless other risk factors are present. The varicella vaccine is recommended for all children and is only needed by nonpregnant adults who have not been vaccinated or infected with chickenpox.

References

1. The College of Physicians of Philadelphia. *The History of Vaccines.* 2015 Available at: http://www.historyofvaccines.org/content/timelines/all. Accessed October 19, 2014.
2. Centers for Disease Control and Prevention. *Diabetes Type 1 and Type 2 and Adult Vaccination.* 2014. Available at: http://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/diabetes.html. Accessed October 19, 2014.
3. Advisory Committee on Immunization Practices, American Diabetes Association. Influenza and pneumococcal immunization in diabetes. *Diabetes Care.* 2004;27(suppl 1): S111–S113.
4. National Vaccine Advisory Committee. Recommendations from the National Vaccine Advisory Committee: standards for adult immunization practice. *Pub Health Rep.* 2014;129:115–123.
5. Centers for Disease Control and Prevention. Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2011;60:1709–1711.
6. American Association of Diabetes Educators. Vaccination practices for hepatitis B, influenza, and pneumococcal disease for people with diabetes. *Diabetes Educ.* 2014;40:122–124.

7. Byrd KK, Lu P, Murphy TV. Baseline hepatitis B vaccination coverage among persons with diabetes before implementing a U.S. recommendation for vaccination. *Vaccine.* 2012;30:3376–3382.
8. Byrd KK, Holman R, Mehal J, Murphy TV. Chronic liver disease-associated hospitalizations among adults with diabetes-United States, 2001-2008. *Hepatology.* 2011;54(suppl 1):1177A.
9. Immunization Action Coalition. Ask the Experts. 2015. Available at; www.immunize.org/ask experts/. Accessed November 1, 2014.
10. Centers for Disease Control and Prevention. *Vaccines & Immunizations.* 2015: Available at: www.cdc.gov/vaccines/. Accessed November 1, 2014.
11. Looijmans-Van den Akker I, Verheij TJ, Buskens E, Nichol KL, Rutten GE, Hak E. Clinical effectiveness of first and repeat influenza vaccination in adult and elderly diabetic patients. *Diabetes Care.* 2006;29:1771–1776.
12. Rodriguez-Blanco T, Vila-Corcoles A, de Diego C, et al. Relationship between annual influenza vaccination and winter mortality in diabetic people over 65 years. *Hum Vaccin Immunother.* 2012;8:363–370.
13. Tomczyk S, Bennett NM, Stoecker C, et al; Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2014;63:822–825.
14. Centers for Disease Control and Prevention. *Adult Immunization Schedules, United States, 2015.* Available at: http://www.cdc.gov/vaccines/schedules/hcp/adult.html. Accessed November 12, 2014.

CPE CREDIT
ANSWER KEY

See the CPE credit self-assessment questionnaire on page 42.

1. C
2. B
3. D
4. A
5. B
6. C
7. A
8. A
9. D
10. D

Diabetes Management & Medication

Instructor's Plans	Objectives	Student's Assignment
• Discuss the progression of diabetes from the early stages of beta cell destruction to the insulin deficiency state. • Provide case studies of patients with diabetes (pre-diabetes and type 2) who use both oral medications and insulin. Demonstrate the medication regimen changes from oral prescription to insulin administration.	The student will identify patient concerns and diabetes self-management barriers that influence the diabetes health status.	A group of students (two or more) will write a mock patient dialogue/skit between a patient and a registered dietitian which includes pointers listed in the article. The skit includes patient's concerns with identified solutions.

Lifestyle Therapy and Weight Loss

Instructor's Plans	Objectives	Student's Assignment
• Use of this article will be included into the established obesity lecture of a dietetic didactic program. • During the second day of this lesson, student discussion on the medication charts found within the article will be addressed. • Identified guest speaker and/or a primary care physician will present patient case studies of individuals with BMI of at least 30. • Identified guest speaker to present how to use motivational interviewing when talking with obese patients.	After the class assignment and discussion, the student will have adequate knowledge on the oral medications used for weight reduction to be a patient resource.	Develop a patient chart of medications listed in the article with selected categories (i.e., dose, percentage body weight loss, etc.) From the primary care physician case study presentation, the student will develop a list of appropriate open-ended questions to use when obtaining dietary and medical history (motivational interviewing)

Complementary & Alternative Medicine Products

Instructor's Plans	Objectives	Student's Assignment
Instruct the students on the nutritional information and the physiological pathway of the following: alpha-lipoic acid, Chromium and Vitamin D, Addresss nutritional benefits of ginseng and resveratrol.	After this session the student will have basic knowledge and awareness of CAM that will be helpful during a patient counseling session.	Research and write a short paper about the following organizations and their involvement with dietary supplements. DSHEA and FDA Investigate and research product claims of health food(s) found at a local health food shop or national chain. Determine the accuracy of the claim and present findings to the class.

Pharmacotherapy of Vitamins & Minerals

Instructor's Plans	Objectives	Student's Assignment
Attend an interactive presentation with a pharmacist at the local hospital or a community pharmacy. Pharmicst presents education materials on drugs and nutrieint deficiencies.	The student will understand importance of a patient/client's medication needs and supplement with necessary food needs for nutrients lacking.	2-3 students identify a class of drugs for one type of condition, such as cardiac, renal/kidney, asthma. Research the class and identify which drug you would like and its corresponding nutrient deficiencies. List corresponding food sources that supply these nutrient deficiencies. Make a chart or graph to demonstrate how the nutrient shortage is present as fewer increased beverages are consumed

Diabetes and Immunization

Instructor's Plans	Objectives	Student's Assignment
Discuss medication position/ algorithim of medication changes of the following organizations: • American Diabetes Association • Juvenile Diabetes Research Foundation • American Association of Clinica Endocrinologists	The student will have a strong understanding of vaccinations and be able to state the health benefits.	Each student will interview a public health specialist, an epidemiologist or an infectious disease physician to identify the health trends of people with and without diabetes and their use of immunizations. Conduct a literature search to find one article about diabetes and vaccinations; present findings to the class in a fifteen to twenty minute presentation.

Current Therapy in Diabetes

Instructor's Plans	Objectives	Student's Assignment
Invite a pharmacist to present diabetes medications and their pharmalogical actions to the class. Sources: local pharmacy with Pharm-D, CDE, pharmacy professor, or a local American Diabetes Association office	After this lesson, the student will be able to recite the medications' positive or negative impact on glycemic control and/or body weight.	Research one type of oral diabetes medication and present it in a fifteen minute discussion, and prepare a pediatric patient handout that can be used during your clinical rotation.

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ACADEMY/DCE STAFF

Administrative Manager
Linda Flanagan Vahl
312-899-4725 / Fax: 312-899-5354
lflanagan@eatright.org

DCE SUPPORT SERVICES

DCE Webmaster
Aurimas Adomavicius
aurimas@devbridge.com

DCE Web address
www.dce.org

DCE Copy Editor
Deborah Kuhlman dkedits@speakeasy.net

After reading this issue of *On The Cutting Edge*, "There's a Pill (or Injection) for That: A Diabetes Pharmacotherapy Update," DCE members can earn 4.0 hours of free continuing professional education units (CPEUs level 1) approved by the Commission on Dietetic Registration (CDR). CPE eligibility is based on active DCE membership status from June 1, 2014 to May 31, 2015.

DCE members must complete the post-test of the CPEs page on the DCE website: http://www.dce.org/resources/cpeus by 2/13/18. For each question, select the one best response. After passing the quiz, to view/print your certificate, access your CPEU credit history or view the learning objectives, go to: http://www.dce.org/account/history.

Please record 4.0 hours on your Learning Activities log and retain the certificate of completion in the event you are audited by CDR. The certificate of completion is valid when the CPE questionnaire is successfully completed, submitted, and recorded by DCE/Academy of Nutrition and Dietetics.

CPE Credit Self-Assessment Questionnaire

Select the one best answer for each question below.

1) Which of the following statements about complementary and alternative medicine (CAM) is FALSE?
   a. There are three primary areas of CAM.
   b. Females are more likely to use CAM.
   c. There is an abundance of well-designed clinical trials on CAM products.
   d. Some of the CAM products, such as alpha-lipoic acid, chromium, ginseng, resveratrol, and vitamin D, are commonly used for glycemic control.

2) According to the National Health Interview Survey in 2001, approximately what percentage of United States adults had used dietary supplements or herbs in the previous 12 months, which doubled the number observed in 1999?
   a. 9%.
   b. 19%.
   c. 29%.
   d. 39%.

3) Which of the following actions can help to enhance diabetes education?
   a. Communicate with patients on the importance of knowing key diabetes biomarker test results.
   b. Assist patients in understanding that type 2 diabetes is progressive.
   c. Collaborate with pharmacists in offering counseling sessions on medication therapy management for patients.
   d. All of the above.

4) Studies show that the use of diabetes drug treatment, specifically metformin, can cause deficiencies of which of the following factors?
   a. Folic acid and vitamin B12.
   b. Folic acid and vitamin E.
   c. Vitamin B12 and vitamin E.
   d. Vitamin B12 and vitamin B6.

5) What medication, in combination with lifestyle changes, is considered first-line of therapy for individuals with type 2 diabetes?
   a. Insulin.
   b. Metformin.
   c. DPP-4 inhibitor.
   d. Sulfonylurea.

6) Which vaccines are recommended for adults living with diabetes who are 65 years and older?
   a. Annual influenza, PCV13 every 5 years, single dose of zoster, single dose of hepatitis B.
   b. Annual influenza, single dose of Tdap combined with Td, annual PPSV23, single dose of zoster, MMR every 10 years.
   c. Annual influenza, single dose of Tdap if not given at a younger age, Td every 10 years following Tdap, single dose of zoster.
   d. Annual influenza, Tdap every 5 years, single dose of PPSV23, MMR two doses 6 months apart.

7) Which of the following statements about weight control in those with type 2 diabetes (T2DM) is correct?
   a. Comprehensive lifestyle therapy is the cornerstone of T2DM treatment and includes reducing energy intake, physical activity, and behavior modification.
   b. Exercise recommendations for obese patients with T2DM are for 60 minutes of moderate exercise daily.
   c. Recommendations for strength training or resistance type exercises for obese patients with T2DM are for 30 minutes on 3 consecutive days each week.
   d. Because most obese patients with T2DM have a weight loss goal of at least 30% below their current weight, their first goal should be a 10% weight loss.

8) Which of the following statements about weight-loss medications is correct?
   a. Lorcaserin is an anoretic medication that decreases food consumption and promotes satiety by selectively activating serotonin receptors in the central nervous system but not on heart valve receptors.
   b. Orlistat, with its ability to inhibit pancreatic and gastric lipases, is best used in obese patients who consume high-fat diets.
   c. Sympathomimetics are appetite-suppressing medications that have the greatest potential for both initial and sustained weight loss.
   d. The combination of topiramate and phentermine as a weight management regime has shown modest weight reduction with very few adverse effects.

9) Which of the following statements about sodium-glucose cotransporter 2 (SGLT-2) inhibitors (glucuretics) is true?
   a. They are best used in elderly patients with T2DM who have high blood pressure.
   b. They are recommended for patients with T2DM and kidney disease.
   c. They are effective appetite suppressants that promote weight loss.
   d. They work by increasing glucose excretion in the urine.

10) Inhaled insulin may be effectively used in patients who:
   a. Need a longer-lasting insulin.
   b. Need a slower-acting insulin.
   c. Need fine-tuning of their insulin dose.
   d. Do not have pulmonary disease and express significant objection to multiple daily injections.

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