You Asked for It! CE

Diabetes Care in the Pharmacy: Tech Talk, Immunization Insight, and Cognition Changes (And How to Handle Them)

ABSTRACT: Diabetes management seems to evolve constantly. Advancements in pharmacotherapy, changes to guideline recommendations, or improvements in glucose monitoring technologies can make it difficult to "keep up with the Jones." In addition, diabetes' contribution to the development of other comorbidities expands our concerns well beyond glucose control. Mitigation of cardiovascular risk, renal dysfunction, and adverse effects should be at the forefront of our minds. These complexities often mean aspects of optimal treatment may be overlooked. Filling in the necessary gaps in care is imperative to ensuring ideal diabetes management. Additionally, selection of and counseling on glucose monitoring technologies plays an important role. However, despite our best efforts, without effective communication these strategies are frequently for naught. It is up to pharmacists and pharmacy technicians alike to stay on top of these constant changes and make certain that they convey current information to the patient appropriately.

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FACULTY DISCLOSURE: Drs. Nigro and Boemio have no actual or potential conflicts of interest associated with this article.

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INTRODUCTION

It is quite the exciting time in diabetes care. Recently, the Food and Drug Administration (FDA) approved semaglutide (Rybelsus), the first oral glucagon-like peptide (GLP-1) agonist for the management of type 2 diabetes. Dapagliflozin now has an indication for reducing the risk of cardiovascular death and hospitalizations in patients with heart failure. New artificial pancreas technology is helping patients with type 1 diabetes maintain better glucose control. And yet, despite this excitement there is still confusion. Diabetes care remains complex. From differentiating between types of diabetes (See Technician Tutorial) to deciding on drug therapy, we all deal with diabetes dilemmas.

Perhaps things would be easier if our only task was optimizing blood glucose control. But when you couple glucose control with cardiovascular risk reduction, renal protection, and mitigation of adverse effects, it’s no wonder why continued diabetes education is sorely needed. In this continuing education program, you asked for additional clarity about immunization recommendations and tips on...
how best to help patients with impaired cognition. We’ve got you covered! You asked for insight into new technologies and how to identify clinical gaps in care. We’re on it! While we can’t make everyone a diabetes guru in the next two hours, we hope we can clear up these conundrums so that you feel more confident when providing care to patients with diabetes.

**Immunization Insights**

The administration of appropriate vaccinations remains an integral part of diabetes management. Patients with diabetes are at an increased risk for infection compared to the general population. Chronic hyperglycemia has been linked to immune system dysfunction. Evidence suggests hyperglycemia impairs the mobilization and function of leukocytes, and reduces the body’s response to cytokine release. Long-standing, uncontrolled diabetes can also impact the vascular system. Reduced blood perfusion hampers oxygen delivery to vital organs, which can slow the healing process and lessen the effects of antibiotics.

When patients with diabetes develop an infection, maintaining optimal glycemic control can be a challenge. Infections stimulate the release of the counter-regulatory hormones adrenaline and cortisol, which work in opposition to insulin. This increased state of “stress” can increase the risk for diabetic ketoacidosis. In addition, during times of acute infection, patients with diabetes may be prescribed certain antibiotics (e.g., fluoroquinolones) and/or adjunctive therapies (e.g., glucocorticoids), which further alter glycemic control. Preventing infections is therefore key.

It is critical that all patients with diabetes keep up-to-date with appropriate vaccinations. Both community and ambulatory care pharmacists (and technicians too!) are in a unique position to help lead this charge. Pharmacists can review vaccination records to identify gaps in care, administer appropriate vaccinations (check your state regulations), and educate patients how to create a “sick day plan” during times of acute infection and/or illness (See Table 1).

Current immunization schedules for children and adolescents and adults can be found at [https://www.cdc.gov/vaccines/schedules/index.html](https://www.cdc.gov/vaccines/schedules/index.html).

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### Technician Tutorial: Differentiating Diabetes Types

<table>
<thead>
<tr>
<th>Type 1 Diabetes (T1DM)</th>
<th>Type 2 Diabetes (T2DM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>● A cellular-mediated autoimmune disorder in which pancreatic beta-cells are destroyed</td>
<td>● A complex metabolic disorder caused (primarily) by impaired insulin secretion, increased insulin resistance, and enhanced hepatic gluconeogenesis</td>
</tr>
<tr>
<td>Gestational Diabetes (GDM)</td>
<td>● Impaired glucose tolerance that occurs for the first time during pregnancy</td>
</tr>
<tr>
<td>Latent Autoimmune Diabetes of Adulthood (LADA)</td>
<td>● A form of T1DM in which the progression of autoimmune beta-cell destruction is slower, often appearing in adulthood</td>
</tr>
<tr>
<td>Maturity Onset Diabetes of the Young (MODY)</td>
<td>● A non-autoimmune form of diabetes in which an inherited gene mutation interferes with insulin production and/or glucose utilization, often appearing in adolescents or young adults</td>
</tr>
<tr>
<td>Double Diabetes</td>
<td>● A form of diabetes in which patients exhibit characteristics of both T1DM (e.g., autoimmunity) and T2DM (e.g., insulin resistance, obesity)</td>
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</table>

The American Diabetes Association (ADA) provides three specific vaccination recommendations for all patients with diabetes:

- Annual vaccination against influenza for all patients six months of age or older.
- Vaccination against pneumococcal disease with the 13-valent pneumococcal conjugate vaccine (PCV13) for children younger than two. Patients with diabetes who are between two and 64 years of age should receive a dose of the 23-valent pneumococcal polysaccharide vaccine (PPSV23). After age 65, regardless of vaccination history, an additional dose of PPSV23 should be administered.
- A 2- or 3-dose series of the hepatitis B vaccine for unvaccinated adults aged 18 to 59 years with diabetes.

Clinicians can consider administering a 3-dose series of hepatitis B vaccine to unvaccinated adults 60 years of age or older with diabetes. This includes those who are likely to acquire the infection in their lifetime (e.g., resident of a long term care facility).

Other vaccines such as tetanus-diphtheria-pertussis (Tdap), measles-mumps-rubella (MMR), human papillomavirus (HPV), and zoster should be administered to patients with diabetes in accordance with the Center for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP) recommendations. This guidance is updated annually as new evidence and information becomes available. Current immunization schedules for all age groups can be found at [https://www.cdc.gov/vaccines/schedules/index.html](https://www.cdc.gov/vaccines/schedules/index.html).

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**PAUSE AND PONDER:** How do you stay current with evolving and ever-changing evidence and recommendations related to diabetes management?
PCV13-type disease in older adults is now lessened. From pediatric PCV13 use over recent years, the incidence of pneumococcal disease is more than three times higher in patients with diabetes and/or blood sugars that remain elevated over 250 mg/dL. Ketones form when your body uses fat, not glucose, for energy. Ketones make the blood more acidic, thus increasing your risk of diabetic ketoacidosis.

***Table 1. Planning for Sick Days***

**What is a sick day?**

Sick days refer to periods of acute illness (e.g., infection, fever) during which blood glucose (“sugar”) levels can fluctuate and be difficult to maintain.

**How can I help patients with diabetes manage sick days?**

Work with patients to help them create a “sick day plan” outlining steps they can take proactively to reduce their risk of acute complications. Tell them this:

- Test your blood sugar every two to four hours. This will help you monitor for both low (hypoglycemia) and high (hyperglycemia) blood sugars.
- Continue to take your diabetes medications, including insulin, as prescribed. This will help you prevent an acute hyperglycemic crisis.
- Drink plenty of sugar-free liquids to prevent dehydration.
- Eat your regular meal plan (if possible) to prevent hypoglycemia.
- Consider checking urine ketones if you have type 1 diabetes and/or blood sugars that remain elevated over 250 mg/dL. Ketones form when your body uses fat, not glucose, for energy. Ketones make the blood more acidic, thus increasing your risk of diabetic ketoacidosis.
- Notify your primary care provider (PCP) that you are sick. Your PCP can provide additional information about when to seek emergency care and how to adjust your medications safely if needed.

**When should I refer the patient to seek emergent care during a sick day?**

This will vary from patient to patient. Generally speaking, patients should seek emergency care if they experience the following:

- Persistent symptoms of nausea, vomiting, and/or diarrhea
- Signs and symptoms of severe dehydration (e.g., extreme thirst, confusion, low blood pressure, little to no urination)
- Presence of moderate to large amounts of urine ketones
- Persistently elevated blood sugar (as determined by patient’s PCP)
- Persistent low blood sugar (< 70 mg/dL)

**Influenza**

Patients with diabetes are at an increased risk for flu and its complications. These patients are six times more likely to be hospitalized for flu compared to those without diabetes. The CDC suggests that in recent years, 30% of adult hospitalizations related to the flu occurred in patients with diabetes. While these statistics appear dour, there is good news. Proper vaccination against influenza can reduce hospital admissions for patients with diabetes by 79%. Annual vaccination is recommended to combat waning immunity and to provide adequate protection against newly circulating virus strains. Any inactivated influenza vaccine (IIV) is recommended. Pharmacists should avoid administering the live attenuated influenza vaccine (LAIV) to patients with diabetes given the paucity of safety and efficacy data. Pharmacists can offer the inactive, high-dose formulation to adults older than 65. When compared to the standard trivalent vaccine, the high-dose trivalent formulation creates a stronger immune response and is 24.2% more effective at preventing the flu.

**Pneumococcal Disease**

The rate of invasive pneumococcal disease is more than three times higher in patients with diabetes with mortality rates estimated to be as high as 50%. In November 2019, ACIP made changes to the pneumococcal vaccine schedule. The ACIP no longer recommends routine vaccination with the PCV13 vaccine for adults 65 years of age or older. Through indirect effects from pediatric PCV13 use over recent years, the incidence of PCV13-type disease in older adults is now lessened. PCV13 is still safe and effective for older adults and can be used based on “shared clinical decision-making.” Shared clinical decision-making is a process in which patients and providers collaborate to make healthcare decisions after reviewing clinical evidence and weighing the benefits and risks of treatment. PCV13 is generally reserved for adults with immunocompromizing conditions, cerebrospinal fluid (CSF) leaks, and/or cochlear implants. However, PCV13 may be considered for older adults with diabetes not previously vaccinated with PCV13, if they:

- They reside in nursing homes or long-term care facilities
- They reside in areas with low pediatric PCV13 use
- They travel to areas with no pediatric PCV13 program

If the patient and provider agree on PCV13 through shared clinical decision-making, it should be administered before PPSV23, with PPSV23 administered at least one year later.

**Hepatitis B**

The hepatitis B virus (HBV) can be transmitted via the blood. Patients with diabetes are at an increased risk of developing this infection, especially if they share glucometers, lancet devices, and/or needles. Outbreaks of HBV associated with blood glucose monitoring were first identified in 1990. Since then, at least 18 additional HBV outbreaks have been documented in acute care hospitals, nursing homes, and assisted living facilities. Of the new cases identified during these outbreaks, 95% occurred in patients with diabetes.

In 2011, the CDC released their first set of recommendations that all unvaccinated patients with diabetes under the age of 60...
Managing diabetes is often a complex and delicate balance of preventing hyperglycemia without precipitating hypoglycemia. In older adults, manifestations of diabetes-related complications and geriatric syndromes further complicate matters. In particular, cognitive impairment presents a unique challenge. It leads to increased risk of hypoglycemia, limits regimen complexity, and functional impairment to name a few. Additionally, an accumulation of chronic comorbidities can worsen polypharmacy which may contribute to drug interactions and hypoglycemia risk as well.

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1. **Identify Reversible Causes of Cognitive Impairment:** The prevalence of reversible causes of cognitive impairment may be as high as 23% among older adults with dementia. Some of the most common causes of cognitive impairment include medications, alcohol, depression, and metabolic disorders. Pharmacists and pharmacy technicians can pay close attention to older adults’ prescriptions and over-the-counter medications. Many medications lurk in the pharmacy aisles and shelves that have potential to worsen cognitive impairment artificially (see Table 2). In particular, the total burden of anticholinergic drugs has correlated with worsening cognition and the precipitation of delirium. Furthermore, it is vital that pharmacists ensure patients undergo appropriate evaluation for other underlying conditions that may contribute to their cognitive decline. Assessment for thyroid dysfunction, depression, and vitamin deficiencies is necessary to identify potentially reversible causes of worsening cognition. Ultimately, the best defense against the ill effects of cognitive dysfunction is preventing it in the first place!

2. **Prevent Hypoglycemia:** In general, older adults are at increased risk of hypoglycemia due to age-related pharmacokinetic and pharmacodynamic changes and accumulation of multiple comorbidities. Any level of cognitive impairment, which can lead to issues with medication adherence and administration, further compounds risk. To prevent hypoglycemia, clinicians should individualize glycemic goals in older adults. Those with many comorbidities, cognitive impairment, or functional dependence may benefit from less stringent goal setting (i.e., A1c <7.5-8.5%). Guidelines recommend selecting medication classes with low-risks of hypoglycemia (see Table 3). Additionally, treatment regimens should be simplified, when possible, to ensure appropriate adherence and safety. Unfortunately, even with optimal pharmacotherapy, serious hypoglycemic events may still occur. In situations where the risk of hypoglycemia is high, focusing on optimization of cardiovascular risk factors may be preferred.
3. **Improve Communication with Patient and Caregivers:** Communication with older adults is already nuanced compared to communication with their younger counterparts. Their values tend to reflect years of additional experiences and their ability to identify insincerity is unrivaled.\(^{20}\) Existing communication barriers with older adults are exacerbated when coupled with underlying cognitive impairment.\(^{20,21}\) Furthermore, counseling patients is a two-way street and communication pitfalls among healthcare providers can also contribute detrimentally to patient interactions. In other words, healthcare providers can also be at fault for communication difficulties (see Table 4, next page).\(^{20}\)

**PAUSE AND PONDER:** What communication problems have you experienced with older adults? What realistic steps can you take to improve communication with older adults and their caregivers in the future?

### Table 3. Anti-Hyperglycemic Considerations in Older Adults\(^{14,15}\)

<table>
<thead>
<tr>
<th>Pharmacologic Class</th>
<th>Medications</th>
<th>Comorbidities of Concern</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Alpha-glucosidase Inhibitors | Acarbose, Miglitol | Cognitive impairment | • Low-risk hypoglycemia, but expensive  
• GI intolerance may be limiting  
• Frequent dosing contributes to regimen complexity |
| Biguanides | Metformin | Renal dysfunction  
Hepatic dysfunction  
Heart failure | • First-line in older adults  
• Requires dose adjustment with GFR <45 mL/min/1.72m\(^2\) and is contraindicated with GFR <30 mL/min/1.72m\(^2\) |
| Dipeptidyl peptidase 4 (DPP-4) inhibitors | Alogliptin, Linagliptin, Saxagliptin, Sitagliptin | Renal dysfunction | • Low-risk hypoglycemia, but expensive  
• Requires dose-adjustment with renal dysfunction |
| Glucagon-like peptide 1 (GLP-1) agonists | Exenatide, Dulaglutide, Liraglutide, Lithisenatide, Semaglutide | Cognitive impairment  
Neuropathy  
Renal dysfunction  
Vision impairment | • Low-risk hypoglycemia, but expensive  
• Prioritize in patients with ASCVD due to clinical benefit  
• Requires adequate vision and dexterity for appropriate administration |
| Insulins | Aspart, Degludec, Detemir, Glargine, Glulisine, Lispro, NPH, Regular | Cognitive impairment  
Neuropathy  
Vision impairment | • High-risk hypoglycemia (Rapid-acting >> Long-acting)  
• Adequate vision and dexterity is necessary for appropriate administration  
• Appropriate timing of administration is required  
• Once-daily basal insulin is preferred in older adults  
• Use of insulin pens may decrease difficulty of administration  
• Significant contributor to regimen complexity |
| Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors | Empagliflozin, Dapagliflozin, Canagliflozin | Peripheral vascular disease  
Renal Dysfunction  
Urinary Incontinence | • Low-risk hypoglycemia, but expensive  
• Prioritize in patients with ASCVD, HF, or CKD due clinical benefit  
• Contraindicated with GFR <30 mL/min/1.72m\(^2\)  
• Increased risk of urinary tract infection and amputations |
| Sulfonylureas (SU) | Glipizide, Glimepiride, Glyburide | Cognitive impairment  
Renal dysfunction | • Higher risk of hypoglycemia; may be worsened if not timed with meals  
• Glyburide should be avoided in older adults due to extended half-life |
| Thiazolidinediones (TZD) | Pioglitazone, Rosiglitazone | ASCVD  
Heart failure  
Falls/fractures  
Vision impairment | • Not preferred in older adults  
• May increase risk of fracture, heart failure exacerbation, and macular edema |

**ABBREVIATIONS:** ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; HF = heart failure; GFR = glomerular filtration rate; GI = gastrointestinal
When navigating a conversation with an older adult, especially one with cognitive impairment, it is important to try to practice the following:

- Ensure you have the patient’s attention before speaking. Reducing distractions and maintaining eye contact helps sustain engagement.
- Pay attention to non-verbal cues. Understanding a patient’s non-verbal communication can often be the difference between success and failure. Don’t forget that you are also projecting your own slew of non-verbal cues.
- Keep it simple, stupid! Use short and familiar words and avoid complicated medical jargon.
- Don’t overwhelm the patient. Provide only one message or ask one question at a time. Using positive language by suggesting what a patient “should do” rather than what “not to do” often elicits a better response. For example, instead of saying “Don’t stand up without using a walker or you may fall,” say, “Use your walker whenever standing up to prevent falls.”
- Be a good listener. Allow patients the time needed to formulate their response. Continue to encourage them, even if they are having difficulty.
- Always treat your patient and caregivers with respect. Even those with advanced dementia are not oblivious to demeaning or inconsiderate behaviors.
- Avoid “elderspeak.” Often likened to baby talk, elderspeak is hallmarkled by its slow rate, exaggerated tone, high pitch, loud volume, and simple vocabulary. Older adults may find this type of communication offensive or patronizing.

### Table 4. Communication Barriers

<table>
<thead>
<tr>
<th>Common in all Older Adults</th>
<th>Common in Older Adults with Cognitive Impairment</th>
<th>Communication Pitfalls of Healthcare Providers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distractions (i.e., background noise, television, music)</td>
<td>Difficulty with verbal communication (i.e., word finding, fluency)</td>
<td>Deficiencies in active listening skills</td>
</tr>
<tr>
<td>Cultural diversity</td>
<td>Increased reliance on non-verbal communication</td>
<td>Using close-ended questions (questions that can be answered with “yes” or “no.”)</td>
</tr>
<tr>
<td></td>
<td>Memory impairment</td>
<td>Using medical jargon</td>
</tr>
<tr>
<td></td>
<td>Decreased comprehension of both verbal and written communications</td>
<td>“Elderspeak” or patronizing speech</td>
</tr>
</tbody>
</table>

Identifying Duplicate Therapies and Gaps in Care

Pharmacists routinely screen for duplicate therapies and identify gaps in care when performing medication management, but as diabetes progresses, patients’ medical problems become more complex. Just as patients with diabetes are at greater risk for developing various diseases of infectious etiology, they are also significantly at risk for a number of metabolic comorbidities that further complicate their wellbeing. Managing these comorbidities without simultaneously worsening other conditions or organ systems is a balancing act that pharmacists must learn to juggle.

### Duplicate therapies

Recognizing duplications in therapy is a key first step that pharmacists and technicians can take to help decrease pill burden and cost, improve safety, and optimize patient adherence. Patients with diabetes often require more than one antidiabetic drug to maintain optimal glycemic control. When intensifying therapy, one of the many factors to consider is combining drugs with unique mechanisms of actions to promote synergy. Pharmacists should be on the lookout for these three inappropriate combinations:

- Sulfonylureas + glinides
- Sulfonylureas or glinides + insulin
- DPP-4 inhibitors + GLP-1 agonists

**Sulfonylureas combined with glinides.** Both sulfonylureas and glinides promote insulin secretion in the pancreatic beta cell. Glinides bind to the receptor with weaker affinity and dissociate more quickly, making them shorter acting compared to sulfonylureas. Combining the two has no therapeutic rationale.

**Sulfonylureas combined with insulin.** The combined use of sulfonylureas and insulin in patients with T2DM is not contraindicated, but whether the two should be combined has been a source of controversy among experts. Some suggest that the combination is associated with better glycemic control and reduces total daily insulin requirements. Others argue that the glycemic benefits of the combination are modest and do not justify use. Much of this data was published and in the 1990s before more contemporary and evidence-based treatments became available. For patients using this combination, pharmacists can monitor for additive weight gain and hypoglycemia. Insulin dose adjustments may be needed. For patients with T2DM who are taking both basal and bolus insulin (e.g., insulin-dependent), the use of sulfonylureas is unnecessary.

**Dual incretin therapy.** DPP-4 inhibitors and GLP-1 agonists should not be prescribed in combination due to limited efficacy data and an absence of safety data. In a small crossover study, the addition of sitagliptin combined with metformin and lira-
metformin resulted in a mere 0.3% reduction in A1c. Similarly, another study concluded that the addition of twice-daily exenatide in combination with sitagliptin and metformin resulted in a mere 0.3% reduction in A1c. Since both drug classes independently carry an increased risk of pancreatitis, it is plausible that the combination might further elevate this risk.

**Identifying Gaps in Care**

Central to management of diabetes is cardiovascular (CV) risk reduction. CV disease remains the leading cause of morbidity and mortality in patients with diabetes. Pharmacists and other health care providers must be vigilant about screening patients for CV risk factors at least annually. Pharmacists can assess individual patient risk factors or use risk calculators to forecast a patient’s 10-year probability of having a cardiac event. The American College of Cardiology (ACC)/American Heart Association (AHA) risk calculator is online at www.cvriskcalculator.com. Ensuring that patients are on appropriate antihypertensive drugs, lipid lowering therapies, and antiplatelet drugs is of utmost importance. Pharmacists can help close these gaps in care by screening for omissions in therapy and/or determining the appropriateness of existing therapies.

**Hypertension.** For patients with diabetes and co-morbid hypertension (HTN), shared decision-making should be employed to determine blood pressure goals. At minimum, patients with diabetes and HTN should be treated to a BP goal below 140/90 mmHg. A lower goal of less than 130/80 mmHg may be appropriate for patients with higher CV risk. Treatment with one antihypertensive drug is suitable for patients with BPs between 140/90 mmHg and 160/100 mmHg. Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), dihydropyridine calcium channel blockers (DH-CCB), and thiazide-like diuretics are recommended as first line agents. The BP lowering effects of ACE inhibitors and ARBs are considered less efficacious in Black patients due to their low-renin, salt-sensitive physiology. Therefore, thiazide diuretics and/or DH-CCBs are recommended as initial treatment choices for uncomplicated HTN in Black patients. For patients with albuminuria, preference should be given to ACE inhibitors or ARBs, regardless of race. For patients with BPs elevated above 160/100 mmHg, a two-drug combination is necessary. However, ACE inhibitors and ARBs should not be given together.

**Statins.** Statins continue to be the drugs of choice for CV risk reduction and LDL lowering. Findings from numerous studies illustrate the beneficial effects that statins have on CV outcomes in patients with and without pre-existing CV disease. In recent years, guideline recommendations have focused on statin intensity (see Table 5) over attainment of target LDL goals. For patients with diabetes aged 40 to 75 years without atherosclerotic cardiovascular disease (ASCVD), moderate-intensity statin therapy should be initiated for primary prevention. For older adults aged older than 75 years, the evidence of primary prevention is less robust, so shared decision making should be employed. If statins are recommended, moderate-intensity statins should be considered. High-intensity statin therapy is recommended for patients with established ASCVD (secondary prevention) or for those with multiple atherosclerotic cardiovascular disease risk factors and/or aged 50 to 70 years. Low-intensity statins are not routinely used due to a lack of efficacy in preventing CV disease. However, low-intensity statins may be appropriate for patients who are intolerant to side effects and/or those who are on medications known to inhibit statins’ metabolism. Pharmacists can therefore screen patients on low-intensity statins to ensure appropriate dosing.

**Antiplatelet therapy.** The efficacy of aspirin at reducing CV morbidity and mortality in patients with previous myocardial infarction or stroke (e.g., secondary prevention; using an intervention AFTER an event occurs) is well established and highly recommended. However, the recommendations for aspirin for primary prevention (using an intervention to PREVENT an event) of CV events are less robust. The 2018 “A Study of Cardiovascular Events in Diabetes” (ASCEND) study was the largest randomized trial to date to explore low-dose aspirin’s safety and efficacy for primary prevention in patients with diabetes without evident CV disease. More than 15,000 patients were randomized to either aspirin 100 mg daily or placebo. After a mean duration of 7.4 years of follow-up, serious vascular events were significantly lower in the aspirin group compared to the placebo group (8.5% vs. 9.6%; rate ratio 0.88; 95% CI 0.79-0.97; p = 0.01). However, major bleeding events, most

### Table 5. Statin Intensity by Dose

<table>
<thead>
<tr>
<th></th>
<th>High-intensity</th>
<th>Moderate-intensity</th>
<th>Low-intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower LDL cholesterol by &gt; 50%</td>
<td>Atorvastatin 40-80 mg, Rosuvastatin 20-40 mg</td>
<td>Atorvastatin 10-20 mg, Fluvastatin XL 80 mg, Fluvastatin 40 mg BID, Lovastatin 40 mg, Pravastatin 40-80 mg, Pitavastatin 2-4 mg, Rosuvastatin 5-10 mg, Simvastatin 20-40 mg</td>
<td>Lovastatin 20 mg, Fluvastatin 20-40 mg, Pitavastatin 1 mg, Pravastatin 10-20 mg, Simvastatin 10 mg</td>
</tr>
<tr>
<td>Lower LDL cholesterol by &gt; 30% to 49%</td>
<td>较低</td>
<td>较低</td>
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<tr>
<td>Lower LDL cholesterol &lt; 30%</td>
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commonly gastrointestinal and extracranial bleeding, were higher in the aspirin group compared to placebo (4.1% vs 3.2%; rate ratio 1.29; 95% CI 1.09-1.52; p = 0.003). Currently, the ADA recommends using low-dose aspirin (75-162 mg daily) for primary prevention for patients with diabetes who are 50 years old or older and have at least one additional major risk factor (family history of ASCVD, hypertension, dyslipidemia, smoking, chronic kidney disease/albuminuria) who are not at an increased risk of bleeding (older age, anemia, renal disease). 28

Antidiabetic drugs with CV benefit. Since 2008, the FDA has mandated all new antidiabetic drugs coming to market must demonstrate CV safety. In the past decade, much has been learned about the cardiac benefits in patients with established CV disease and those who are at highest risk for developing it. Based on such findings, the ADA recommends use of GLP-1 receptor agonists and/or SGLT-2 inhibitors with proven CV benefit in patients with diabetes who have ASCVD. 28 Such drugs include liraglutide, semaglutide, dulaglutide, canagliflozin, empagliflozin and dapagliflozin. For patients with co-morbid heart failure, SGLT-2 inhibitors have been shown to reduce heart failure admissions 31-34 and should therefore be used in patients with heart failure unless contraindications exist. In addition to recommending evidence-based antidiabetic regimens, pharmacists can also ensure that patients are not taking any antidiabetic drugs that could potentially worsen or exacerbate preexisting cardiac conditions. For example, both saxagliptin and alogliptin have been found to increase hospitalizations related to heart failure. 35,36 Pioglitazone can cause fluid retention and worsen heart failure in patients with the disease. Moreover, sulfonylureas, notably glyburide, may impair myocardial ischemic preconditioning. 37

Renal considerations. It is estimated that 20% to 40% of patients with diabetes are at risk for developing diabetic kidney disease. 38 Appropriate management of renal disease helps slow disease progression and reduce overall CV risk. 38 The presence of albuminuria and/or declining glomerular filtration rate signals impaired renal function and necessitates appropriate lifestyle changes and pharmacotherapy. ACE inhibitors or ARBs should be part of the treatment armamentarium for patients with kidney disease, unless contraindicated. Both classes have been shown to decrease the progression of diabetic nephropathy. 39,40 The SGLT-2 inhibitors are also renoprotective, independent of their blood glucose effects. They decrease renal tubular glucose reabsorption, intraglomerular pressure, body weight, and systolic blood pressure. 31,32,37 When possible, they should be used preferentially as add on therapy to metformin for patients with T2DM and co-morbid renal disease.

Many antidiabetic drugs need renal dose adjustments in patients who have kidney disease. Pharmacists can help ensure that doses are safe and effective. While SGLT-2 inhibitors help treat diabetic nephropathy, they need to be used with caution to prevent any initial acute kidney injury. Generally speaking, SGLT-2 inhibitors should not be initiated if the eGFR is less than 45 mL/min/1.73m² and are contraindicated if the eGFR is less than 30 mL/min/1.73m².

Metformin is first-line therapy in T2DM, but in patients with renal disease, its metabolism and excretion are impaired, potentially causing accumulation of toxic metabolites and lactic acidosis. Although lactic acidosis is rare, it can be fatal in many cases. 41 Metformin should not be initiated if the eGFR is less than 45 mL/min/1.73m² and is contraindicated if the eGFR is less than 30 mL/min/1.73m².

Additionally, all DPP-4 inhibitors require renal dose adjustments except for linagliptin. Glipizide is the preferred sulfonylurea to be used in patients with kidney disease. On the other hand, glyburide has a long serum half-life and active metabolites that can accumulate increasing the risk of hypoglycemia. 42 Pharmacists are encouraged to consult drug information resources to identify medications that require renal dose adjustments or strict avoidance in kidney disease.

PAUSE AND PONDER: When do you recommend self monitoring of blood glucose testing for patients on non-insulin-based therapies?
Monitoring Mayhem: When Technology Meets Clinical Practice

Enormous leaps in diabetes technology have changed the landscape of both the treatment and monitoring of T1DM and T2DM. The emergence of new devices and software has provided many avenues for patients, but unfortunately there is no “one-size-fits-all” approach. Overall, diabetes technology can be broken down into three main categories: Self-Monitoring Blood Glucose (SMBG), Continuous Glucose Monitors (CGM), and Insulin Pumps.

Self-Monitoring Blood Glucose (SMBG): Self-monitoring of blood glucose relies on capillary blood samples analyzed by glucometers to produce results. Capillary blood samples correlate well with blood glucose and provide insight into a patient’s glycemic control. Glucose monitoring offers individualized guidance on the effects that diet, physical activity, and medications have on glucose control. Most importantly, SMBG can help identify and prevent hypoglycemia. However, despite all of the potential positives of SMBG, not all patients benefit (see Table 6). In particular, patients on oral antihyperglycemics only have shown limited improvement in outcomes despite glucose assessment with SMBG. Overall, regardless of treatment regimen, SMBG is most effective when used to inform pharmacotherapy decisions or elicit patient behavior change.

Many patients and providers assume that all FDA-approved glucometers consistently provide accurate readings. However, both improper use and variability between technologies can contribute to inaccuracies. Since glucometer results rely on enzymatic reactions, results can potentially be altered by oxygen saturation, temperature, and interfering substances (e.g., acetaminophen, ascorbic acid). It is also important to ensure patients use only FDA-approved test strips and ensure proper hand hygiene to improve glucometer accuracy.

Unfortunately, despite a patient’s best efforts to use the glucometer correctly, not all glucometers are created equal. For example, an independent analysis of 16 of the most popular glucometers deemed that only six met strict accuracy thresholds. This reinforces the fact that appropriate glucometer selection and training are essential. All patients should be provided proper instruction on performing SMBGs at home. As pharmacists and pharmacy technicians, it is imperative we are well-versed on this process. Patients can be counseled to:

- Gather supplies. This includes a glucometer, test strip, lancet, and an alcohol prep pad
- Clean their hands. Wash hands thoroughly in a sink and dry them well
- Prepare the glucometer. Turn on the device and insert the test strip
- Disinfect the finger. Use the alcohol prep pad to wipe the selected area and allow to dry
- Obtain the blood sample. Use the lancet to pierce the side of the finger and place drop of blood on test strip. AVOID piercing the pads of the finger as this may be more painful
- Record the result. Once the glucometer generates the result, make note of it. These values will help individualize the treatment plan and identify glucose patterns/trends

Continuous Glucose Monitors (CGM): Continuous glucose monitors use interstitial glucose rather than capillary blood samples to estimate plasma glucose levels. In addition to the differences between CGM and SMBG, there is also some variability between CGM devices (see Table 7). The main types of CGM devices include the following:

- Real-time CGMs measure glucose levels continuously and can provide the user with automated alarms and alerts at certain glucose levels.
- Intermittently-scanned CGMs measures glucose continuously but only report glucose level when swiped by a reader or smart phone.
- Blinded CGMs are typically interpreted by the provider after a period of time. They do not display any glucose information to the patient.

<table>
<thead>
<tr>
<th>Table 6. Recommendations for Glucose Monitoring</th>
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<tbody>
<tr>
<td><strong>Treatment Regimen</strong></td>
<td><strong>Daily SMBG Recommended?</strong></td>
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<tr>
<td>Intensive insulin regimen (multiple daily injections; insulin pump)</td>
<td>Yes</td>
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<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Basal insulin with or without oral medications</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>Oral medications only</td>
<td>No</td>
</tr>
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</table>

*Can be individualized based on patient’s needs
Not all CGM devices replace the need for SMBG monitoring due to the need for calibration of the glucose sensor. The main advantage of CGM devices over SMBG is that it provides more detailed information related to the patient’s glucose control. This additional data translates to reductions in A1c and hypoglycemic episodes when tested in clinical trials.\(^{43}\) Furthermore, benefits are sustained across the spectrum of diabetes, including T1DM and T2DM in both adults and pediatric patients.\(^{43}\) However, it should be noted that patients must actually use the technology to derive its benefits. Which elicits an important question: who is a good candidate for CGM and what are potential barriers to its use?

Researchers believe several patient groups benefit from CGM use. This includes patients with T1DM, patients with T2DM requiring three or more daily insulin injections, pregnant women, and/or patients with hypoglycemia unawareness.\(^{48}\) Patients with T2DM on only oral therapies do not generally need CGM monitoring. Additional barriers to CGM use may include cognitive impairment, poor aptitude for self-care, and non-adherence. These could negatively impact the patient’s ability to use the technology appropriately and prevent meaningful data points from which pharmacotherapy can be optimized. CGM may also be cost-prohibitive for some patients, which limits its utility. Once patients are determined to be good candidates for CGM, it is crucial to provide the necessary diabetes education and training to ensure proper use. Patients requesting additional information can be directed to diabeteswise.org as it contains a plethora of patient-centered information on CGM devices and their use.

**Insulin Pumps:** Relative to the newer CGM devices, insulin pumps have a longer history in diabetes management. They are designed to administer rapid-acting insulin subcutaneously throughout the day to maintain continuous glucose control. Insulin pumps can also be programmed to deliver boluses of insulin to cope with carbohydrates associated with meals and snacks. Glucose monitoring sensors are often used to augment insulin pump therapy and allow real-time modification of insulin administration. These sensors are oftentimes the same or similar as the CGM devices listed earlier, but are integrated into an insulin delivery system. Typically, these types of insulin delivery systems are reserved for those with T1DM, though select patients with T2DM and significant insulin deficiency may also benefit. Currently, there is no consensus on when to use an insulin pump rather than more standard methods of insulin administration (e.g., multiple daily injections). Clinicians should always consider patient-specific factors and barriers to care when determining therapy appropriateness.

**CONCLUSION**

While the treatment of diabetes has been around for decades, it’s easy to forget management intricacies (see Figure 1). Since diabetes contributes to numerous complications and consistently undergoes clinical management updates, gaps in care can be easy to miss. Ensuring proper adherence to vaccine recommendations and adjunctive therapies mitigates multiple risk factors that could be detrimental to a patient’s quality of life. Understanding both drug-drug and drug-disease interactions can prevent polypharmacy and exacerbations of comorbidities or geriatric syndromes. Additionally, diabetes is unique, in that its management can be heavily influenced by breakthroughs in technology, not just pharmacotherapy. It’s up to pharmacists and pharmacy technicians alike to remain abreast of the ever-changing landscape of diabetes management and guide patients to optimal care. Whether it be reviewing guideline updates, participating in journal clubs and online forums, or completing continuing education, there is no wrong way to stay informed.

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### Table 7. Available CGM Monitors\(^{43,46,47}\)

<table>
<thead>
<tr>
<th>CGM Device</th>
<th>Type</th>
<th>Use with Insulin Pump</th>
<th>Fingerstick Calibration</th>
<th>Alerts/Alarms</th>
<th>Sensor Life Span</th>
<th>Body Attachment</th>
<th>Technology Integration</th>
</tr>
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<tbody>
<tr>
<td>Dexcom G6</td>
<td>Continuous</td>
<td>Yes, but not required</td>
<td>No</td>
<td>Yes, customizable and sharable</td>
<td>10 days</td>
<td>One step insertion; integrated adhesive</td>
<td>Android, Apple, Pebble watch, Dexcom receiver</td>
</tr>
<tr>
<td>Medtronic Guardian</td>
<td>Continuous</td>
<td>Required</td>
<td>2 per day</td>
<td>Yes, customizable</td>
<td>7 days</td>
<td>Multi-step insertion; outer adhesive required</td>
<td>Apple</td>
</tr>
<tr>
<td>Freestyle Libre</td>
<td>Intermittent</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>10-14 days</td>
<td>One step insertion; integrated adhesive</td>
<td>Android, Freestyle Libre receiver</td>
</tr>
<tr>
<td>Eversense</td>
<td>Continuous</td>
<td>No</td>
<td>2 per day</td>
<td>Yes, customizable</td>
<td>90 days</td>
<td>Requires minor procedure by physician</td>
<td>Android, Apple, Pebble watch</td>
</tr>
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</table>
Best
1. **BE COMMUNITY CHAMPIONS.** Identify barriers to good diabetes care in sub-populations in your community, and help improve diabetes care—REACH OUT!
2. Take glucose monitors out of their boxes and read the directions; show patients how to use them.
3. Communicate in quiet areas using clear, positive sentences.

Better
1. Refine your communication skills, and pay particular attention to your older adults with diabetes.
2. Know specifically what type of diabetes each patient has, and ensure patients are on appropriate medications.
3. Screen each patient’s immunization record at every visit, and offer necessary vaccinations.

Good
1. Provide individualized care to your patients who have diabetes
2. Stay current with changing technology and know how each products differs.
3. Look for opportunities to discuss patients’ medications and blood glucose monitoring.
REFERENCES


37. Riddle MC. Editorial: sulfonylureas differ in effects on ischemic preconditioning—is it time to retire glyburide? J Clin Endocrinol Metab. 2003;88(2):528-530.


