As the U.S. population ages there will be substantial increases in the number of older adults who have type 2 diabetes mellitus. Older adults with diabetes often will be taking many other medications. Health care professionals who coordinate care for older patients with diabetes must not only be able to treat hyperglycemia to target individualized goals of care but also anticipate and recognize the adverse effects of various pharmacologic agents prescribed.
Prescriber knowledge about drug pharmacodynamics and pharmacokinetics and their interaction with normally aging physiology is critical in treating the elderly patient with diabetes. This knowledge is needed to minimize and even avoid the potentially adverse effects of hypoglycemia and the side effects associated with polypharmacy. When medications become necessary to the management of diabetes in an older patient, informed practitioners can correctly and safely write a prescription for the proper drug, dose and frequency.

**Pharmacodynamics**

When evaluating the pharmacodynamic effects of a drug on a body, the patient’s age, comorbid conditions and concurrent medications should be considered. An older patient may exhibit alterations in receptor affinity or number and signal transduction mechanisms, and impairment of cellular response in affected organs that influence the pharmacodynamics of a particular medication.

Pharmacodynamic effects commonly encountered with regard to neurologic and cardiac functioning via the autonomic and central nervous system also play a role in pharmacotherapy for diabetes. Drug sensitivity may increase in older patients when the cellular response to a given pharmaceutical concentration is enhanced. Physicians must realize that enhanced concentration of some medications, such as the sulfonylureas, can increase the incidence of hypoglycemia in older patients more than in younger patients.

Evaluating each diabetic medication and its respective pharmacodynamic properties is imperative to reduce the risk of these potential effects.

**Pharmacokinetics**

Pharmacokinetics involves the effect of body on a drug during the course of travel from absorption, bioavailability, distribution and metabolism through excretion. Many classes of diabetic medications are taken orally and absorbed via the gastrointestinal tract. A net neutral absorption effect of decreased intestinal motility is likely in the older patient, which increases the time for drug absorption in the otherwise normal gastrointestinal tract that may be offset by the patient’s increasing pH level. With normal aging, there is a decrease in lean body mass, water volume and organ blood flow, with a concomitant increase in adipose tissue, making it imperative that the practitioner choose the lowest possible effective dose for the patient.

Renal and hepatic elimination of diabetic medications is certainly a main concern of providers caring for older inpatient and outpatient populations. Some of the most common disease-induced changes can affect both liver and kidney function, further leading to varying pharmacokinetics and drug elimination. These issues make treating the older adult with diabetes even more challenging.

**Adverse drug reactions**

The most common and one of the most devastating side effects of pharmacologic treatment of older patients is hypoglycemia. The risk of severe or fatal hypoglycemia exponentially increases with age. The landmark trial Action to Control Cardiovascular Risk in Diabetes, or ACCORD, was discontinued early when interim results indicated a statistically significant increase in mortality in patients who received intensive therapy with the goal of achieving a glycated hemoglobin level of 6% or less. Further analysis of data from this trial showed that individuals in this group used more medication and had more hypoglycemic events, greater weight gain and greater fluid retention than individuals in the group that received standard therapy with the goal of a glycated hemoglobin level of 7% to 7.9%.

Although the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, or ADVANCE trial, which similarly compared intensive blood sugar control to standard therapy, did not show a difference in mortality between the two groups, it did demonstrate an increase in the number of hypoglycemic events and hospitalization in those who were more intensively treated. In light of these findings, the American Diabetes Association has recommended that goals be individualized, with more flexible goals for older adults, those with advanced disease and complications or those with limited life expectancy.

Older patients also may experience delayed psychomotor responses as a result of interventions designed
to correct hypoglycemia. Glucagon, one of the main counter-regulatory responses to hypoglycemia, is impaired in older people and, to a greater extent, older patients with diabetes. Altered psychomotor and impaired counter-regulatory responses must be balanced with the functional and cognitive status of the individual. In addition to being aware of and recognizing hypoglycemia, patients must be able to access food or drink to reverse this iatrogenic condition.

Hypoglycemia manifests through an easily recognizable adrenergic constellation of symptoms, most notably tremor, sweats or weakness. However, older patients commonly demonstrate a primarily neuroglycopenic syndrome (i.e., confusion, delirium, dizziness and falls) that can be misdiagnosed as a neurologic event such as a transient ischemic attack or syncope.

Listed below are some common classes of medications prescribed for diabetes. Although this is not a comprehensive list of medications and corresponding adverse events, notes are provided on the potential for adverse reactions in this population. Clear provider instructions and patient (or caregiver) comprehension are essential to ensure directed drug dosing, timing and administration.

**Biguanide**

Patients will commonly experience gastrointestinal side effects that tend to improve after the first few weeks of treatment with metformin. Metformin should not be used in individuals older than age 80 until renal function has been established. Lactic acidosis is a potential side effect of metformin, yet evidence is scant that it will occur with contraindications to metformin. The biguanide class is also contraindicated in patients with renal disease, renal dysfunction or abnormal creatinine clearance rates.

**Sulfonylureas**

As previously mentioned, hypoglycemia is a notable adverse event that can occur with the sulfonylurea class of drugs. There are conflicting data on whether the sulfonylurea class increases the risk of cardiovascular events, and further research is needed. Older patients should be instructed about the potential for weight gain as more insulin is produced and glucose is utilized.

**Meglitinides**

Weight gain is a common feature of this class that includes the medications repaglinide and nateglinide. Although hypoglycemia is a possible side effect, nighttime dosing of meglitinides enables older patients to be flexible with their dosing schedule. Repaglinide may also be a good choice for an older patient or a patient with renal disease, as 90% of the drug can be recovered in the feces.

**Insulin therapy**

Insulin is often an underutilized therapeutic modality in the older patient with diabetes because of the practitioner’s, patient’s or family’s concerns about administration and the risk of hypoglycemia. Weight gain is another common adverse effect of insulin products. Patients should be appropriately educated on the proper administration, dosing and effects of the various insulin products. Visual and cognitive acuity should be assessed prior to initiating and tailoring products to ensure that patients can easily administer the amount of insulin prescribed. Specifically, the use of insulin pens can greatly assist older adults who may have issues with vision or dexterity. In some of the pens the correct dose can be achieved even with clicks of the pen, ensuring more accurate dosing.

**Commonly prescribed medications**

**Thiazolidinediones**

Adverse events associated with the thiazolidinediones are weight gain, edema, macular edema, congestive heart failure, increased bone fracture risk and, when combined with other diabetic medications, hypoglycemia. Of notable mention are several studies that suggest the potential for adverse cardiovascular events with rosiglitazone and potential for benefits in cardiovascular risk reduction from pioglitazone. Further studies are needed regarding these events and how they affect the older population with diabetes. Ongoing concerns about fluid retention limit the utility of these studies for older patients with diabetes.
Dipeptidyl Peptidase-4 Inhibitors
Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, has a favorable safety profile, and a low incidence of hypoglycemia. Nausea generally resolves with dosing strategies during the introduction of the medication.27 Sitagliptin is being investigated to determine whether it is linked to acute pancreatitis.28, 29 Abdominal pain and substantially decreased appetite should be cause to discontinue this medication.

Saxagliptin has a similar adverse effect profile but is associated with a decrease in the absolute lymphocyte count (this was not observed at the 2.5 mg dose).30 Although the clinical importance of this laboratory finding has not been firmly established, saxagliptin has been associated with an increased number of upper respiratory infections, as well as urinary tract infections.31 Repeated infections should prompt a review of saxagliptin’s clinical utility in the individual’s case. Despite an increased financial burden for the elderly, DPP-4 inhibitors may be particularly useful in older adults, since they exhibit few drug-to-drug interactions. In addition, these medications can be used in adults with all stages of renal disease, including end-stage renal disease (but dosage adjustment is needed).

Incretin mimetics
Exenatide has a favorable safety profile, with adverse events of dizziness, headache and gastrointestinal discomfort.27 Incretin mimetics is being investigated to determine whether it is linked to acute pancreatitis and thyroid cancer.28, 29, 32 Liraglutide has a similar safety concern but carries the benefit of once daily dosing administered in a pre-filled pen. Since weight loss can be substantial in patients using this medication, the role of incretin mimetics is limited in the vulnerable or frail elderly population.33

Polypharmacy
The administration of multiple pharmaceutical products in concert (known as polypharmacy) may potentiate or decrease the effects of common diabetes medications in the older population. Such patients commonly have other systemic, related chronic conditions; the physician must recognize the variety of medications the patient may be taking and the potential interactions among these medications. In one study of 18,968 patients with diabetes, at least 16% were dispensed a medicine that is associated with adverse interactions, and 22.7% were dispensed at least one potentially inappropriate medicine.34

Every six to 12 months, physicians should request that their older patients bring their medications with them to their appointments as an audit for usage and also as an educational opportunity. This “brown bag” medication review is one method to avert potential polypharmacy.35 Physicians should also strive to partner with family members who are often caregivers for these patients.

Final notes
As aging is a risk factor for chronic care conditions such as diabetes, physicians are faced with a growing population of older patients with this disorder. Ensuring that patients are educated on both their medications and potential adverse events is a necessity in every care plan to limit potential treatment complications.
References


