Management of Adults With Diabetes and Cognitive Problems

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IN BRIEF Cognitive dysfunction is common in people with diabetes, especially as they age. Few studies are available to inform the best treatment approaches for individuals with diabetes and cognitive impairment. In this article, the authors review the many challenges of managing adults with both diabetes and impaired cognition and discuss home-based strategies and medication recommendations to help guide their management.

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Management of diabetes involves a high degree of patient involvement and daily performance of many self-care tasks. These include monitoring of blood glucose; eating healthy meals; engaging in physical activity; taking medications as directed; recognizing and managing hypoglycemia; performing proper hygiene, including foot and dental care; attending medical appointments; and under-

standing sick-day management (1,2). Pharmacological therapy, particularly when insulin is needed, can be complex. Social, physical, and mental health challenges may hinder self-care and are associated with increased diabetes complications and poor quality of life (3).

Cognitive impairment is a common, underdiagnosed complication of diabetes that can interfere with the ability to adequately perform required daily self-management behaviors (Table 1) (4). Mild-to-moderate cognitive impairment and dementia are more frequently observed in older adults, but declines in cognitive function also have been described in younger people with diabetes (5,6). It is estimated that at least half of older people with diabetes will become cognitively impaired and functionally disabled (7). Deficiencies in memory capacity, attention to detail, planning, ability to reason, decision-making, and information processing speed are associated with deficits in diabetes self-care behaviors, including poor compliance with medication, diet, and exercise recommendations; failure to receive appropriate care; and worse glycemic control, including more hypoglycemia (7–12).

A three-stage classification of cognitive dysfunction in patients with diabetes has been proposed (13). In the first stage, there are mild, subtle changes in cognition that might represent normal cognitive aging. These deficits are unlikely to significantly interfere with activities of daily living or self-management of diabetes in adults with type 2 diabetes treated with oral medications, but they may cause difficulties for patients requiring complex insulin regimens (i.e., those with type 1 diabetes or advanced type 2 diabetes). This stage occurs in all age-groups and is likely only detectable on neuropsychological assessment. Patients in stage one should have periodic assessment of their ability to perform crucial self-management tasks.

The second stage is mild-to-moderate cognitive impairment, in which testing shows cognitive impairment in one or more domains that does not meet the criteria for dementia and involves only subtle impairment in activities of daily living. This stage most commonly appears in patients >60 years of age and can affect diabetes self-management.

Dementia (stage three) occurs primarily in people >60 years of age, generally progresses over time, and involves cognitive impairment in two or more cognitive domains and impairment in activities of daily living. Decline in executive function (i.e., reasoning, planning, and problem-solving) resulting in an inability to understand or remember instructions leads to poor diabetes self-management.

A guiding principle in helping older adults with cognitive impairment is to balance the importance of personal autonomy and independence with safety. This requires adequate assessment to determine which tasks a patient can safely perform independently, which tasks will require some assistance, and which tasks will be dependent on others to perform. Most patients maintain independence in some areas even when they are dependent in others.

It has been recognized that management plans need to reflect patients' stage of cognitive decline. Recent reviews and diabetes practice guidelines have recognized that stage of cognitive impairment, availability of assistance by caretakers, and use of assistive technologies are significant factors affecting care plans, including determining individualized A1C and other diabetes care targets (2,14–18). Avoidance of hypoglycemia and symptomatic hyperglycemia is emphasized when poor cognition is present. Because there are scant data to help guide the management of patients with diabetes and cognitive impairment, these recommendations are primarily based on expert opinion and limited published studies.

Lifestyle and Daily Self-Care Activities

The complexity of diabetes self-management is often poorly recognized by those indirectly involved in a patient's care. For many people with diabetes and cognitive impairment, self-care tasks become overwhelming.

Self-monitoring of blood glucose (SMBG) is particularly important for insulin-treated individuals with type 2 diabetes and for all adults with type 1 diabetes. The frequency of SMBG is dependent on a person's specific needs, risk of hypoglycemia, and personal goals. The accuracy and utility of SMBG results are reliant on appropriate use of a home blood glucose monitoring device, including both proper monitoring technique and proper timing of testing (2).

It is important for diabetes educators to instruct the caretakers of cognitively impaired patients with diabetes about the signs and symptoms of hypoglycemia and hyperglycemia, proper SMBG technique, pattern recognition, and problem-solving to help these patients avoid acute complications, emergency room visits, and hospitalizations. However, it is also important to recognize that caregivers are often spouses who may themselves be older adults with changing cognitive skills and medical concerns. Some informal assessment of caregiver competence with diabetes care tasks is important. Paid caregivers may be necessary in some cases. Setting achievable goals together with the patient, family, and other caregivers and providing praise and encouragement for advances in meeting personal goals confers positive reinforcement and promotes patient safety (3).

For individuals with severe insulin deficiency who are at risk of developing diabetic ketoacidosis (DKA), testing for blood or urine ketones is also occasionally needed. There is a risk of DKA for anyone with type

TABLE 1. Daily Diabetes Self-Management Tasks Affected by Cognitive Impairment

Task	Impairment
Glycemic monitoring	• Cannot remember how to perform a fingerstick blood glucose test • Cannot remember at what time a blood glucose test is required • Unable to recognize or communicate hypoglycemia or signs of hyperglycemia • Unable to access the glucose testing device memory to recall the last blood glucose value • Forgets to wash hands before a blood glucose test, leading to an inaccurate result • Cannot remember the blood glucose test value to accurately transcribe it on a log sheet or use it to direct insulin dosing • Unable to determine the appropriate actions to take based on a determined blood glucose level (e.g., for hypoglycemia or sick-day management) • Unable to use a continuous glucose monitoring device • Unable to determine when or how to check urine or blood for ketones
Nutrition	• Forgets to eat, frequently misses meals, or eats smaller meals than anticipated, resulting in a higher risk of hypoglycemia • Eats too frequently or too much, resulting in hyperglycemia • Has unpredictable eating, resulting in wide glycemic excursions • Unable to perform meal planning or meal preparation tasks • Cannot determine carbohydrate content of food (if applicable)
Mobility and physical activity	• Cannot remember to engage in prescribed physical activity such as taking a walk or performing wheelchair exercises • Cannot remember how to return home after taking a walk • Cannot remember how to prevent or treat hypoglycemia when active • Forgets to carry carbohydrate during physical activity (to treat hypoglycemia, should it develop) • Unable to incorporate physical activity into a daily regimen • Has slower gait or speed, shortened strides, and poor balance; prone to falling • Does not use assistive devices (e.g., a cane or walker) when needed • Lacks initiative to engage in prescribed physical activity
Medication management	• Cannot remember when to take medications • At risk of inaccurate dosing, resulting in overdose or double-dosing • Unable to determine the correct dose of insulin to take at a designated time • Unable to track when refills are needed and obtain refills or new medications • Cannot remember how to properly store insulin or other diabetes supplies • Unable to use insulin administration devices, including insulin pens, insulin syringes, or an insulin pump
Personal hygiene	• Cannot remember to bathe, resulting in an increased risk for skin breakdown and infections • Has poor foot care, resulting in increased risk of ulcers, infections, and amputation • Has ineffective oral hygiene
Coordination of health care services and appointments	• Unable to schedule and track medical appointments • Unable to navigate through a complex health care system • Has difficulty using an automated telephone service • Unable to travel independently to appointments

1 diabetes and, less commonly, for those with type 2 diabetes during times of illness, infection, or injury (2). Patients with cognitive difficulties may be unable to determine when ketone testing is needed and incapable of taking the necessary steps to avoid life-threatening DKA.

Monitoring blood glucose through the use of a continuous glucose monitoring (CGM) device is of particular benefit for people with frequent hypoglycemia or hypoglycemic unawareness. As adults with type 1 diabetes are living longer, CGM use is becoming more prevalent. Those who develop cognitive impairment may become challenged by the use of this technology and have a reduced ability to interpret the data to make appropriate self-management decisions (2). However, the CGM devices' alarm features (for hypoglycemia and hyperglycemia) and ability to transmit glucose data to caregiver devices have the potential to help caregivers better assist in a patient's management. The use of CGM to reduce hypoglycemia in adults with cognition difficulties has not been studied.

Diminished cognition with deterioration of executive function may make planning activities, preparing meals, and shopping difficult or even impossible (4,19). Memory loss can lead to forgetting to eat or eating insufficient carbohydrates, which can cause hypoglycemia in adults who require insulin therapy or take insulin secretagogues. Poor meal planning can also lead to food choices high in processed sugar, resulting in hyperglycemia. Forgetting whether a meal was consumed and eating twice can also result in hyperglycemia.

Following a rigid "diabetic diet" may lead to poor dietary intake and unintentional weight loss (20). Registered dietitians play a significant role in patient care by assessing nutritional status and providing medical nutrition therapy when needed. A safe, realistic diet takes into account a patient's cultural and personal preferences, food availability and affordability, and personal goals (2). Quality of life can be enhanced through effective nutritional management. Caregivers should join patients in meeting with nutritionists and medical providers so that realistic meal planning is coordinated with appropriate pharmacological therapy.

Regular physical activity is recommended for people with diabetes. Exercise has been shown to improve glycemic control, reduce cardiovascular risk factors, help with weight management, maintain muscle mass and mobility, and improve overall health (2). For adults with diabetes and cognitive impairment, who may also have problems with vision, mobility, and balance, incorporating a structured exercise program can be difficult. Physical therapists and occupational therapists, in collaboration with the diabetes team and caretakers, can help design and implement safe activities to help individuals with various functional or mobility limitations maintain their highest possible level of function.

The risk of hypoglycemia during physical activity is also a major concern for patients with executive dysfunction who are taking insulin or insulin secretagogues because of their poor ability to adjust their carbohydrate intake and medication dosing to compensate for activity (2,4). Caretakers should be instructed about the prevention, recognition, and treatment of hypoglycemia associated with exercise.

Cognitive limitations can lead to poor personal hygiene, further compromising glycemic control and patient health (2). Poor dental care can result in oral infections, gum disease, difficulty eating solid foods, and deterioration in glycemic control. Foot care, including well-fitting shoes, orthotics when indicated, and assistance in nail care and daily foot examination can help prevent foot infections and ulcerations and improve mobility. Specific instructions for caregivers and patients regarding when to seek specialty care also may be needed. Podiatry follow-up is particularly helpful for patients with a history of foot ulcers, peripheral arterial disease, peripheral neuropathy, or foot deformities.

Depression is common in adults with diabetes. It is important to recognize and treat depression to improve emotional well-being. It is also important to consider depression as a reversible cause of cognitive impairment in older adults. Diabetes-related distress is associated with regimen nonadherence and poor glycemic control and may advance diabetes complications (1). Diabetes complications can further increase emotional distress, which in turn can exacerbate the symptoms of such disorders. The inability to care for oneself due to psychosocial factors is compounded by cognitive impairment. The assistance of a case manager, mental health professional, or social worker may be appropriate when there is evidence of depression, physical neglect, or unsafe medication adherence (2,19).

Coordination of health care services, including scheduling appointments and tests, renewing and obtaining needed medicines and supplies, and paying medical-related bills, is necessary for diabetes management. Navigating our complex medical system is overwhelming for many adults, but can be virtually impossible for people with cognitive impairment. For a person with cognitive impairment, scheduling and remembering medical appointments, ensuring transportation, and recording or understanding instructions may not be possible without assistance.

Adults with diabetes and cognitive impairment who live alone are at particular risk of self-neglect and harm due to potential inadequate food and drink intake, poor medication adherence, and poor hygiene (21). Home care services may be able to provide additional care and support to allow patients to safely remain in their own living environment. For stage one or

two cognitive impairment, training in the use of cognitive compensatory strategies and external memory aids (e.g., memory notebooks, alarms, calendars, and written instructions) may be sufficient to maintain functioning. In addition, the use of environmental supports (e.g., a consistent daily routine, visual cues, and caregiver prompts) may help maintain functioning and keep older adults in their homes and managing their diabetes longer.

Adults living in long-term care or assisted-living environments have unique, individualized needs that should be assessed at intake and at regular intervals thereafter. Realistic diabetes care plans need to be formulated and carefully communicated to patients, family members, and facility staff members. Facility staff may require additional diabetes-related education. Glycemic control (including glucose monitoring), dietary intake, nutritional status, and medication administration require periodic review, with adjustments made as needed. To improve care, it has been recommended that facilities develop diabetes-specific policies and procedures (2). Guidance is provided by the American Diabetes Association (ADA) (2).

Table 2 lists health care professionals, including medical providers, nurses, dietitians, social workers, counselors, pharmacists, and certified diabetes educators, who play crucial roles in identifying needs, supporting people with diabetes, and educating patients, family members, and other caretakers. Diabetes educators, for example, work with health care team members, patients, and caregivers to provide ongoing education and support (22). Table 3 and Table 4 identify support systems, strategies, and assistive devices used to improve diabetes management. Having discussions with patients and their families to better understand their concerns and incorporating, when possible, their preferences in relation to their diabetes care are crucial. This holistic approach can increase patients' willingness to accept assistance from members of the care team and obtain necessary services to be safe and maintain the highest possible degree of independence.

Glycemic Targets

Hypoglycemia, which is more common with intensive glycemic treatment, has been linked to long-term impairment of cognition (23,24). Not only is hypoglycemia associated with worsening cognition, but also cognitive impairment is associated with a higher risk of hypoglycemia (25–28). Impaired cognition, including poor performance on numeracy-based diabetes self-management tasks, also has been associated with higher risk

TABLE 2. Role of Health Care Professionals in Supporting the Needs of People With Diabetes and Cognitive Impairment

Health Care Professionals	Services
Diabetes medical providers	1. Screen patients for cognitive impairment, determine etiology of cognitive decline, and/or refer to a specialty provider (neurologist or neuropsychologist) for further evaluation and provide for treatment of cognitive impairments, as indicated; screening might include using the Montreal Cognitive Assessment, asking patients about cognitive changes, and asking family about cognitive changes
	2. Make appropriate referrals for ongoing diabetes care management to a:
	a. Nurse for home care needs such as medication management, glucose monitoring or wound care
	b. Dietitian for nutritional needs
	c. Physical therapist to address mobility and balance issues
	d. Occupational therapist to address home safety needs
	e. Diabetes educators to address educational needs of the patient, family, and other caregivers
	f. Podiatrist for foot care
	g. Mental health provider or social worker to address psychosocial needs
	h. Pharmacist for coordination of medication needs and refill management
	i. Specialty care provider (e.g., cardiologist, neurologist, optometrist, ophthalmologist, dentist, nephrologist, or endocrinologist), as needed
	3. Foster a collaborative relationship among patients, their family members, and other members of the health care team
	4. Seek opportunities to simplify regimens
	5. Adjust medical regimens to minimize hypoglycemia and symptomatic hyperglycemia

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TABLE 2. Role of Health Care Professionals in Supporting the Needs of People With Diabetes and Cognitive Impairment, *continued from p. 228*

Health Care Professionals		Services
Registered nurses	1.	Discuss with patients (and families) their concerns and preferences in relation to their diabetes and move to incorporate nursing care to meet these, as appropriate
	2.	Help patients (and/or their caregivers) who perform SMBG to interpret results and encourage autonomous decision-making where possible
	3.	Provide instructions in simplified terms
	4.	Obtain assistive devices such as an automatic pill dispenser, as needed
Registered dietitians	1.	Ascertain and maintain patients' nutritional needs and food preferences
	2.	Review nutrition, establishing realistic carbohydrate, protein, and caloric goals
	3.	Provide realistic meal plans
	4.	Refer to outside agencies as needed (e.g., Meals on Wheels)
Physical therapists, occupational therapists, and speech therapists	1.	Assess patients' functional abilities and limitations
	2.	Establish a safe activity regimen
	3.	Establish a safe home environment
	4.	Recommend assistive devices as needed
Certified diabetes educators or other diabetes educators	1.	Educate patients, families, caregivers, and staff how to best manage diabetes and meet diabetes-related needs, including prevention, recognition, and treatment of hypoglycemia
	2.	Provide behavioral, educational, psychosocial, and clinical support
	3.	Recommend assistive devices as needed (e.g., use of syringe magnifiers or change from use of insulin syringes to insulin pens)
Mental health providers and social workers	1.	Assess patients' mental health status and needs
	2.	Provide emotional and behavioral therapies, as needed
	3.	Refer as needed to ensure patients receive appropriate care and ongoing support
Neuropsychologists	1.	Determine whether patients' cognitive impairment is of sufficient severity to affect diabetes self-management tasks
	2.	Provide recommendations for strategies to mitigate the impact of cognitive impairment on diabetes tasks
	3.	Support and educate family members on the nature of cognitive impairment and how they can support the patient
	4.	Make targeted recommendations for cognitive rehabilitation
	5.	Consult with other members of the medical team regarding best practices given a patient's specific profile of cognitive strengths and weaknesses (e.g., suggest a simplified treatment regimen, suggest written versus oral communication, or indicate the need for caregiver support in medical management)

of severe hypoglycemia in older adults with a long duration type 1 diabetes (12,29). Although there is evidence that poor glycemic control can worsen cognition in people with diabetes, there is no evidence that tight glycemic control improves cognitive impairment or prevents or slows cognitive decline in those already affected (30–32).

Over-treatment of diabetes has been reported in adults with cognitive impairment (33). In a study of veterans with significant comorbid conditions, including cognitive impairment and dementia, 50% had evidence of intensive control based on A1C levels <7.0% while being treated with insulin and/or a sulfonylurea (34). Management of the complex medication regimens that are commonly required to achieve tight control of blood glucose in diabetes can be difficult for patients with cognitive impairment and contribute to errors and hypoglycemia. Patients with cognitive impairment might not be able to express or recognize symptoms of hypoglycemia and therefore might be at increased risk for serious events when using insulin or insulin secretagogues. In these cases, treatment regimens should be evaluated and possibly altered to reduce hypoglycemia risk.

ADA, the American Association of Clinical Endocrinologists, and the American Geriatric Society (AGS) all have released diabetes practice

TABLE 3. Support Systems and Strategies to Improve Diabetes Management

Support Systems	Strategies
Family, friends, and caregivers	1. Determine degree of involvement in diabetes management by family, friends, and caretakers in collaboration with patients (when possible)
	2. Provide diabetes education and self-management skills to family, friends, and caretakers who help care for patients' needs
Home care services	1. Evaluate patients' needs for home- and community-based services
	2. Consider referral options, including nutrition counseling, physical and occupational therapy, social services, and mental health services
Case management	1. Use case managers to evaluate patients' care needs and help in coordination of and transportation to appointments, delivery and administration of medications, food preparation or delivery, and other services
	2. Access community agencies offering programs designed to help individuals with special needs
	3. Identify resources and support systems for patients and their families
Long-term care and skilled nursing facilities	1. Prepare a realistic diabetes management plan for patients
	2. Provide education for facility staff and caregivers
	3. Involve facility administration, nursing, dietary, and other staff members
Hospice/palliative care	1. Care for patients with an emphasis on comfort and symptom control
	2. Preserve patients' dignity
	3. Prevent patients' discomfort and hospitalizations
	4. Respect patients' right to refuse treatment

guidelines that recognize cognitive impairment as an important factor to be considered when prescribing glycemic control medications (2,17,18). The ADA's 2016 guidelines provide the most specific recommendations related to cognitive impairment and specifically recommend an A1C goal of <7.5% for older adults with intact cognition, <8.0% for those with mild-to-moderate cognitive impairment, and <8.5% for those with moderate-to-severe cognitive impairment. Unfortunately, although raising A1C targets may be helpful in reducing hypoglycemia, it is insufficient in preventing hypoglycemia, especially in the elderly and in those with type 1 diabetes of long duration or with hypoglycemia unawareness (12,35,36). Therefore, raising A1C targets cannot be the sole means of preventing hypoglycemia in patients with poor cognition.

Diabetes Medication Management

No glycemic control medications have been proven to improve cognitive function independent of their glucose-lowering effects. There is evidence from animal studies that metformin, thiazolidinediones (TZDs), incretin-based therapies, and insulin have direct positive effects on the brain, but clinical trials are needed to establish benefit in humans (13,37–39). No clinical trials have evaluated the efficacy and safety of different diabetes treatment regimens in adults with diabetes and cognitive impairment.

An individualized, patient-centered approach is recommended when choosing a medication regimen for adults with cognitive dysfunction. As cognition declines, patients' wishes should be respected to ensure quality of life (20). Other considerations include the type of diabetes a patient has, the patient's degree of cognitive impairment, and the patient's living situation (i.e., living alone, living with involved caregivers, or living in a skilled nursing facility). In general, regimen simplification is suggested as cognitive function declines, with the primary goals of avoiding hypoglycemia and symptomatic hyperglycemia. Noninsulin glycemic control medications used to treat type 2 diabetes are discussed below and in Table 5.

Metformin remains the mainstay of treatment of type 2 diabetes because it is safe, effective, and inexpensive; has a low risk of hypoglycemia; and is generally well tolerated. Low doses are recommended to minimize gastrointestinal (GI) symptoms. In the absence of GI side effects, this is a good choice for patients with cognitive impairment. Low-to-moderate doses of metformin can be used with care in people with a glomerular filtration rate (GFR) of 30–45 mL/min/1.73 m^2 regardless of age. It is recommended that, for patients such as the elderly who are at increased risk for the development of renal impairment, renal function be assessed more frequently than the usual standard of once yearly.

The oral insulin secretagogues associated with the greatest risk of hypoglycemia are sulfonylureas and

TABLE 4. Assistive Devices for People With Diabetes and Cognitive Impairment and Their Caregivers

Device	Description
Recording and alarming devices	1. Multi-memo voice recorder: records reminder messages 2. Talking recordable products (e.g., photo album programmed to create audio and visual reminders of photos, important information, or medications 3. Reminder clocks: records messages and allows set times for playback 4. Automated pill dispensers: beep (alarm) and open or vibrate to remind caregivers and those with dementia to take their medication 5. Vibrating or audio watch: provides reminder alarms 6. Diabetes Sentry wrist alarm: worn to monitor perspiration or a decrease in skin temperature in the event of a hypoglycemic reaction Information about products above can be found at: • http://www.acmaweb.org • http://shop.alzheimers.org.uk/product/multi-memo-voice-recorder • http://www.alzheimers.net/9-22-14-technology-for-dementia • http://www.talkingproducts.com/recordable-cards-gifts/talking-photo-albums-gifts/talking-photo-albums-deluxe.html • http://www.alzstore.com/reminder-rosie-voice-controlled-25-alarm-clock-p/0044.htm
Insulin and injectable devices	1. Insulin pens that provide memory of time and dose of previous insulin injections such as the NovoPen Echo or the Timesulin pen cap memory device 2. Insulin pump: may be appropriate if caregiver is available and well educated in its use 3. Choice of injectable device that is easiest to use for the individual patient
GPS tracking and emergency alert/alarm devices	1. GPS tracking devices: worn or attached to the patient to alert caregivers if the patient has left a certain area 2. Alert necklace or bracelet: alerts emergency personnel of patient's diagnoses or impairments in case of emergency
Picture phones	Help patients who struggle to remember names or phone numbers by incorporating programmable, large buttons with clear covers in which to insert pictures (i.e., elder phones)
Electrical use monitors	Devices that can be plugged into a wall outlet or power strip and will monitor a person's use of electrical appliances and alert caregivers if commonly used appliances have not been turned on or off (e.g., Evermind)
Talking glucose meters	Voice-activated blood glucose meters that allow patients to audibly track their blood glucose level and history of readings (e.g., Prodigy Voice no code talking glucose meter, Gmate VOICE Speaking Meter, or SOLUS V2)
CGM devices	1. CGM devices for personal wear (e.g., Dexcom G5, Medtronic Enlite, or Medtronic Guardian): alert patients or caregivers to fluctuating blood glucose levels and blood glucose levels that are above or below preset parameters. The share feature of the Dexcom G5 might be particularly useful in patients with cognitive impairment. 2. mySentry Remote Glucose Monitor: a device that displays a patient's blood glucose levels but can be set up in a caretaker's room. Customizable alarms can be set to alert the caregiver to dangerous glucose levels. 3. CGM devices for professional use (e.g., Dexcom G4 Platinum professional or Medtronic iPro2 Professional CGM: used to track a patient's glucose levels for a designated number of days; data downloading allows the medical provider to see glucose trends, glycemic excursions, and problematic glucose patterns and direct changes in therapy to address them.

Note: With the exception of GPS tracking and emergency alert devices, most devices included in this table are only appropriate for patients with stage one or stage two cognitive impairment and are unlikely to be effective in those with dementia.

meglitinides. Sulfonylurea drugs, which are inexpensive, need to be used with care in patients with severe cognitive dysfunction because of their potential to cause hypoglycemia (2,40). Glipizide, the sulfonylurea with the lowest risk of hypoglycemia and lowest dependence on renal function, can be a reasonable choice in patients with cognitive impairment. Long-acting glyburide should be avoided. The short-acting meglitinides are associated with less hypoglycemia than sulfonylureas, but they need to be given with each meal. This dosing regimen is more difficult for adults with poor memory but may be preferable for patients who only eat one large meal daily.

Oral incretin-based medications (i.e., dipeptidyl peptidase-4 [DPP-4] inhibitors) are expensive but have several possible advantages in people with cognitive impairment. Importantly, they carry a very low risk of hypoglycemia, are taken only once daily, and are well tolerated. Linagliptin does not require dose adjustment for poor renal function. In contrast, glucagon-like peptide 1 (GLP-1) receptor agonists are administered by injection twice daily, daily, or weekly. GI side effects, cost, and potential for weight loss can limit their use. Adults with cognitive impairment might have difficulty operating the more complex pen delivery devices used to administer some of these medications; assistance from a caregiver or visiting nurse may be required.

TZDs have the advantage of once-daily dosing but should not be used in patients with congestive heart failure. Adverse effects on bone health, in addition to fluid retention and weight gain, need to be considered. α-Glucosidase inhibitors have GI side effects that limit their use. They need to be taken with each meal, which can also be difficult for people with cognitive impairment.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors, the newest oral glycemic control agents, are expen-

TABLE 5. Oral and Noninsulin Injectable Medications for Type 2 Diabetes and Considerations Related to Cognitive Impairment

Medication	Advantages in Cognitive Impairment	Possible Disadvantages in Mild Cognitive Impairment	Possible Disadvantages in Dementia	Other Considerations
Metformin	• Oral medication; easy to use; inexpensive • Once-daily dosing (with extended release preparations) • Very low risk of hypoglycemia	• None specific to cognitive impairment • May cause GI side effects, reduced appetite	• None specific to dementia • May cause GI side effects, reduced appetite	• Vitamin B_{12} deficiency possible • Use with caution if age is >80 years, with attention to need for dose adjustment for renal insufficiency; do not use if GFR <30 mL/min/1.73 m^2
Sulfonylureas (glipizide, glimepiride, glyburide)	• Oral medication; easy to use; inexpensive • Once-daily dosing possible	• Risk of hypoglycemia • Glipizide is associated with lowest risk of hypoglycemia • Avoid glyburide because of increased risk of prolonged hypoglycemia	• Risk of hypoglycemia increased with unreliable food intake (low-dose glipizide preferred) • Hypoglycemia risk increased with poor or unreliable intake of food • Avoid glyburide because of increased risk of prolonged hypoglycemia	

TABLE 5. Oral and Noninsulin Injectable Medications for Type 2 Diabetes and Considerations Related to Cognitive Impairment

Meglitinides (repaglinide, nateglinide)	• Oral medication; easy to use • Mealtime dose can be held if the patient skipped the meal or ate a small meal	• Risk of hypoglycemia (but less than with sulfonylureas) • May be difficult to remember multiple daily dose regimen	• Risk of hypoglycemia • Three-times-daily mealtime dosing; would require involvement of a caretaker • Possible advantage of flexibility in patients with irregular eating habits; would require involvement of a caretaker	
DPP-4 inhibitors (sitaglipitin, saxagliptin, linagliptin, alogliptin)	• Oral medication; easy to use • Once-daily dosing • Very low risk of hypoglycemia	• None specific to cognitive impairment	• None specific to cognitive impairment	• Expensive • May need to adjust dose based on renal function
GLP-1 receptor agonists (exenatide, liraglutide, albiglutide, dulaglutide)	• Twice-daily, daily, or weekly dosing • Weekly dosing in particular might help simplify medication regimen	• Injectable only; delivery devices may be difficult to use • Weekly dosing can be hard to remember • Can contribute to hypoglycemia when used with insulin or a sulfonylurea • GI side effects, especially nausea, and weight loss may limit use	• Injection devices would likely require involvement of a caregiver • Can contribute to hypoglycemia when used with insulin or a sulfonylurea • GI side effects, especially nausea, and weight loss may limit use	• Expensive
TZDs (pioglitazone, rosiglitazone)	• Oral medication; easy to use • Once-daily dosing possible • Low risk of hypoglycemia	• None specific to cognitive impairment	• None specific to cognitive impairment	• Use with caution in the elderly due to possible increased fluid retention, exacerbation of heart failure, and increased risk of fractures
α-Glucosidase inhibitors (acarbose, miglitol)	• Oral medication; easy to use • Low risk of hypoglycemia	• May be difficult to remember multiple daily dose regimen	• Possible advantage of flexibility in patients with irregular eating habits; would require involvement of a caretaker	• GI side effects of diarrhea, flatulence, and abdominal pain may limit use
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin	• Oral medication; easy to use • Once-daily dosing • Low risk of hypoglycemia	• Dehydration may worsen cognition and cause dizziness or lightheadedness, increasing fall risk • Risk of UTIs, which may worsen cognition	• Decreased fluid intake could lead to intravascular volume depletion (increasing fall risk) and renal impairment • Risk of UTIs and addition of delirium to dementia	• Expensive • Worsening of urinary incontinence • Risk of DKA (especially if insulin is also required)

TABLE 6. Basal Insulins

Insulin	Length of Action (hours)	Peak of Action (hours)	Dosing
NPH (least expensive)	14–24	4–10	Once or twice daily; care must be taken with timing to avoid hypoglycemia because of significant peak in action
Detemir	6–24	4–8	Once or twice daily
Glargine U-100	22–30	None	Once daily
Glargine U-300	36	None	Once daily
Degludec U-100 and U-200	14–42	None	Once daily

sive, taken once daily, and have not been studied in patients with cognitive impairment. In elderly patients or adults with severe dementia who might not have good or reliable oral intake, the potential for intravascular volume depletion limits their use. These agents also carry an increased risk for urinary tract infections (UTIs), which may go unrecognized in the elderly or people with dementia, and can exacerbate urinary incontinence. There is also a risk of DKA.

All patients with type 1 diabetes and many with type 2 diabetes require insulin therapy. Insulin regimens need to be individualized and will depend on the type of diabetes and, in part, on the degree of cognitive dysfunction, as well as a patient's particular living situation and support system. When used properly, insulin therapy is safe and effective for patients with cognitive impairment and dementia.

In people with type 2 diabetes, insulin therapy is often initiated with the use of a basal insulin in addition to oral or noninsulin injectable medications. Factors to consider when starting or continuing basal insulin include the risk of hypoglycemia, cost, duration of action, and ease of use (Table 6).

Insulin glargine has been shown to have a lower risk of nocturnal and overall hypoglycemia than NPH insulin (40). This is likely because of the peak in action that occurs 4–10 hours after NPH insulin is taken. Therefore, when using NPH insulin, it is prudent to check blood glucose during the peak of action to monitor for impending hypoglycemia. Nonetheless, NPH insulin might be preferred as the least expensive basal insulin. Insulin detemir in low doses has a shorter duration of action than insulin glargine. Therefore, 24-hour coverage may require twice-daily dosing. However, compared to NPH insulin, it usually does not have any significant peak in action. A newer formulation of insulin glargine (300 units/mL) is reported to have a lower risk of hypoglycemia than U-100 glargine (100 units/mL) (41). The most recent basal insulin approved by the U.S. Food and Drug Administration (FDA), insulin degludec, may have advantages for people with cognitive impairment. It is an ultra-long-acting insulin with daily dosing, but because of its long half-life, exact timing of the daily dose may not be as crucial. Initial studies have shown lower rates of hypoglycemia with insulin degludec compared to glargine and detemir (42,43).

More important than the specific choice of basal insulin is careful attention to insulin dosing. The common practice of titrating basal insulin doses to a fasting morning blood glucose target should be performed with care. This is especially true in patients with cognitive impairment because this practice can result in a long-acting insulin dose that fails to account for late-evening and nighttime food intake and is therefore too high. The safest basal insulin dose is one that allows a patient to skip meals without resulting hypoglycemia (i.e., the insulin dose must be safe in the fasting state). This can be evaluated with overnight "basal testing," in which the patient is asked to eat an early dinner and not have an evening snack. Blood glucose tests are then performed 4–5 hours after dinner, at midnight, at around 2:00–3:00 a.m., and upon waking. If blood glucose decreases by >30 mg/dL overnight, the basal insulin dose is too high and should be reduced.

Metformin and DPP-4 inhibitors are associated with the least hypoglycemia and therefore are safest to combine with a basal insulin. A sulfonylurea or meglitinide can also be used to assist with mealtime coverage, but with a higher risk of hypoglycemia. If a patient has serious hyperglycemia despite combination therapy with a safe basal insulin dose, the patient has severe insulin deficiency and needs to be treated with basal-bolus therapy as described below for individuals with type 1 diabetes. When mealtime insulin is used, sulfonylurea and meglitinide drugs should be discontinued. In overweight or obese patients, continuing metformin might help reduce required insulin doses.

In patients with type 1 diabetes, current best practice emphasizes basal-bolus therapy using either a long-acting insulin combined with mealtime rapid-acting insulin or continuous subcutaneous insulin infusion (i.e., insulin pump) therapy. Many patients on basal-bolus regimens adjust mealtime insulin based on insulin-to-carbohydrate ratios and sensitivity (correction) factors to correct for hyperglycemia. This

type of regimen requires significant engagement and numerative processing skills that might be limited in patients with cognitive impairment. Such therapy can be successfully continued if a patient's partner or caretaker is engaged, comfortable, and skilled in this therapy and is willing and able to make insulin-dosing decisions. Alternatively, use of conservative fixed mealtime insulin doses may be needed. The involvement of a caregiver might be enhanced by the use of a CGM device. Especially helpful are CGM systems that transmit glucose values, alarms, and alerts to a smartphone or a remote monitor. These systems allow easier monitoring by caregivers but have not been studied in this population.

Simplification of insulin regimens can sometimes be achieved by using premixed insulin products that combine intermediate- and rapid- or short-acting insulins. This type of insulin regimen can be effective if a patient is eating regular meals. However, the peaks in insulin action inherent in such a regimen pose a significant risk of hypoglycemia if a patient is prone to irregular eating or skipping meals and can cause unrecognized nocturnal hypoglycemia.

In patients with more advanced cognitive dysfunction or dementia, it may be best to implement a regimen using a long-acting insulin at a dose that will not cause hypoglycemia combined with conservative fixed mealtime doses that are given immediately after a patient has eaten an adequate meal. Less insulin can be given based on the amount of food consumed (e.g., 50% of the rapid-acting insulin dose if 50% of the expected carbohydrate intake is actually eaten).

Treatment of Cardiovascular Risk Factors

Many studies have suggested that high blood pressure levels in midlife may have a detrimental effect on the risk of later development of cognitive dysfunction. Both low blood pressure and very high blood pressure later in life are associated with cognitive risk (44). This U-shaped relationship between blood pressure and cognitive performance has been described in a recent study examining patients with diabetes (45). Low and high 24-hour diastolic blood pressures were associated with worse performance on tests of information processing speed and verbal memory in people with diabetes. This association was not found in patients without diabetes.

Although some observational studies have shown that antihypertensive medications have a protective effect on cognitive function in older people, a recent study of elderly patients showed that, among patients treated with antihypertensive medications, low daytime systolic blood pressure was independently associated with a greater progression of cognitive decline in patients with dementia or mild cognitive impairment (46). This study did not report the diabetes status of the patients. In adults with longstanding type 2 diabetes in the ACCORD Memory in Diabetes study, intensive blood pressure control to a target systolic blood pressure of <120 mmHg did not prevent cognitive decline and, in fact, resulted in decreased total brain volume at 40 months (47).

In general, control of cardiovascular risk factors is an important goal in diabetes care to help prevent cardiovascular morbidity and mortality. This is a consideration in those with mild cognitive impairment but is less of a concern in those with advanced dementia, poor general health, poor quality of life, or limited life expectancy. The ADA recommends that blood pressure targets for healthy older patients and for those with only mild-to-moderate cognitive impairment should be the same as for healthy younger people (<140/90 mmHg). However, a higher target of <150/90 mmHg is recommended for those with moderate-to-severe cognitive impairment (2). The AGS guidelines (18) acknowledge the potential harm in lowering systolic blood pressure to <120 mmHg in older adults with type 2 diabetes. This is a reasonable consideration in patients with cognitive impairment, as well. In patients with cognitive impairment, simplification of dosing also should be considered. The use of once-daily combination medications is preferred to more complicated multi-dose, multi-pill regimens.

Although there is little evidence to guide the use of lipid-lowering medications in patients with cognitive dysfunction, there is no reason to limit statin use in physically healthy patients with mild-to-moderate cognitive impairment and good quality of life (unless contraindicated or not tolerated). However, when cognitive impairment coexists with very old age or physical frailty and poor quality of life, it is reasonable to use life expectancy as a guiding factor, as suggested by the ADA (2).

There has been controversy concerning the effects of statins on cognitive function. Some observational studies and case reports have suggested an association between statin use and transient cognitive decline, particularly in the elderly. Although more studies are needed to address this question, a systematic review using the FDA postmarketing surveillance databases did not support adverse effects of statins on cognition (48).

Conclusion

The management of diabetes in adults with cognitive dysfunction presents many challenges for patients, caregivers, and medical providers. It is important to be aware of the complexity of daily self-care tasks required of people living with diabetes and to recognize the ways in which cognitive impairment can interfere with these tasks. A team approach involving the patient, family, and caregivers and including the use of allied health professionals and assistive devices, as well as simplification of medication regimens with a focus on avoiding

hypoglycemia and symptomatic hyperglycemia, is needed for adults with moderate-to-severe cognitive impairment. More research is required to better understand optimal treatment approaches in this population.

Duality of Interest

Dr. Weinstock has participated in, and her institution has received funds for, multicenter clinical trials sponsored by Calibra Medical, Diasome Pharmaceuticals, Intarcia, Medtronic, Mylan, Novo Nordisk, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

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