HHS Public Access

Author manuscript

Clin Geriatr Med. Author manuscript; available in PMC 2016 May 08.

Published in final edited form as:

Clin Geriatr Med. 2015 February ; 31(1): 17–vii. doi:10.1016/j.cger.2014.08.017.

Diabetic Medications and Polypharmacy

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Keywords

polypharmacy; adverse drug events; diabetic complications; prescribing cascade; geriatric syndromes

Introduction

Polypharmacy, defined as the use of multiple medications, increases with age.[1] Multiple medications are commonly prescribed for older adults, who may also contribute to complicated regimens by purchasing over-the-counter medications and dietary supplements with or without their providers' knowledge. Among community-dwelling older adults in the United States, 57% of women and 59% of men report using 5 or more medications (i.e., prescription medications, over-the-counter medications, and dietary supplements) on a weekly basis. Nearly 20% report taking 10 or more medications.[1] Older adults with diabetes are at greater risk of receiving polypharmacy than those without diabetes.[2]

Achieving a balance between overprescribing, underprescribing, and appropriate prescribing can be a challenge for providers, especially those involved in the care of complex older adults. In a hypothetical 79-year-old female with hypertension, diabetes, osteoporosis, osteoarthritis, and chronic obstructive pulmonary disease (COPD), applying clinical practice guidelines would yield 12 separate medications. Moreover, the regimen would require 19 doses per day taken at 5 different times of the day.[3] This example demonstrates need for additional guidance beyond guideline-based care.

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While the use of multiple medications is not always inappropriate, polypharmacy is associated with increased risks of medication nonadherence[4], drug-drug interactions[5], and adverse drug events[6]. As such, medication reconciliation and assessments of medication adherence and potential barriers to adherence are recommended at each patient appointment.[7] The presence of polypharmacy is also associated with prescribing cascades[8], in which adverse drug events are misinterpreted as new medical conditions and result in the prescription of new medications to treat those conditions.

Factors contributing to polypharmacy in older adults with diabetes

Management of hyperglycemia, microvascular complications (e.g., diabetic nephropathy, neuropathy, and retinopathy), and macrovascular complications (e.g., coronary artery disease, peripheral arterial disease, and stroke), geriatric syndromes associated with diabetes (e.g., cognitive impairment, falls, urinary incontinence), and medication side effects contribute to an increased number of medications among older adults with diabetes. Quality improvement measures and pay-for-performance initiatives aimed at management of diabetes and its complications may improve objective measures but also contribute to the addition of unnecessary medications to the drug regimen.[3] For example, adhering to non-age-specific clinical practice guidelines for A1c goals may result in the unsafe addition of antidiabetic agents, thus leading to tighter glycemic control and increased risk of hypoglycemia and other adverse drug events. In light of recent guidance documents from the American Geriatrics Society[7] and the American Diabetes Association[2], age- and patient-specific factors should be considered in order to accurately assess quality and performance.

Direct-to-consumer advertising may also contribute to polypharmacy in older adults with diabetes. In recent years, there has been a surge of new formulations of antidiabetic drugs and even new antidiabetic medication classes brought to market. (See Table 1 for a complete list of FDA-Approved Antidiabetic Agents.) In some cases, these agents deliver more convenient dosing and administration and lower risk of hypoglycemia than standard alternatives, like sulfonylureas and insulin. However, early adoption of new therapies for any medical condition can be of concern in older adults, as this patient population is at increased risk of experiencing adverse drug events and may experience different adverse drug events than their younger counterparts. Moreover, as a result of direct-to-consumer advertising, patients with diabetes may seek medication therapy for diseases other than diabetes, such as erectile dysfunction or restless legs syndrome, which can further contribute to the presence of polypharmacy.

Risks of antidiabetic medications in older adults

Although nonpharmacologic interventions are important in the management of diabetes, medications are a mainstay of therapy. It is particularly important when treating older adults with diabetes that the risks and benefits of pharmacologic interventions are weighed and discussed with patients and their caregivers to allow for shared decision making. What makes treating diabetes in older adults even more complex is that the risks versus benefits for an individual are rarely clear from the clinical data available. Medications used to treat diabetes and its complications may be associated with a host of negative outcomes that must

be considered, including falls, fractures, weight changes, cognitive changes, heart disease, and urinary incontinence.

Falls

The etiology of diabetes and falls is complex and multidimensional. Peripheral neuropathy, which is present in 50-70% of older patients with diabetes, can increase the risk of falls and functional impairment.[7] Polypharmacy can also contribute to falls.[7] Specific antidiabetic medications that cause hypoglycemia, like insulin, have also been associated with falls.[9,10] On the other hand, untreated or undertreated hyperglycemia can also contribute to falls.[7] Antihypertensive agents, which are commonly used in patients with diabetes, have also been associated with falls[9]; however, this section will focus mainly on antidiabetic agents.

Hypoglycemia is a risk factor for falls.[9] Insulin, insulin analogs, and insulin secretagogues (i.e., meglitinides and sulfonylureas) are the antidiabetic medications that predominantly cause hypoglycemia.[11] Insulin use has been shown to increase the risk of falls in older adults.[10] Insulin has a high risk of hypoglycemia; the risk of hypoglycemia may be less with insulin analogs.[11] For example, insulin glargine (Lantus) and insulin detemir (Levemir) may have a lower risk of hypoglycemia than NPH (Humulin N; Novolin N). Rapid-acting insulin analogs, such as lispro (Humalog), aspart (Novolog), and glulisine (Apidra), are also associated with a lower frequency of hypoglycemia than regular insulin (Humulin R; Novolin R).[11]

Sulfonylureas have a high risk of hypoglycemia, which may be an issue for older patients. Glyburide (Diabeta; Glynase), a sulfonylurea with a long duration of action, has a greater risk of severe, prolonged hypoglycemia in older adults as compared to glipizide (Glucotrol) and is a potentially inappropriate medication in this population.[12] The meglitinides are used to treat postprandial hyperglycemia. They have shorter half-lives and a lower risk of hypoglycemia than sulfonylureas.[7] Although hypoglycemia is a known risk factor for falls, there are no specific trials that link insulin secretagogues to falls to date.[13]

Dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 agonists target postprandial hyperglycemia and impart little risk for hypoglycemia.[7] Hypoglycemia is not common with metformin (Glucophage), thiazolidinediones (TZDs), or alpha-glucosidase inhibitors.[11] No direct link exists between metformin and falls; however, due to metformin-induced vitamin B_{12} deficiency resulting in neuropathy there may be an indirect association.[13] To date there are no studies linking other antidiabetic medications to falls.[13]

Older adults with diabetes are at an increased risk of having an injurious fall requiring hospitalization compared to those without diabetes.[10] In addition, certain risk factors, such as using insulin, a history of falls, poor standing balance score, and an A1c $\geq$ 8% can contribute to a fall requiring hospitalization.[10] Strategies that may help diabetic patients reduce their risk of falling include:

- Perform medication reviews on all prescription and over-the-counter medications to identify those at a high risk for falls[14]
- Limit the number of medications or doses[14]

- Avoid hypoglycemia and hyperglycemia[7]
- Counsel patients and caregivers on the signs and symptoms of hypoglycemia and how to manage it[9]

Fractures

Due to the higher risk of falls associated with diabetes noted above, possible injurious falls resulting in fractures may occur.[10] Thiazolidinediones, an oral antidiabetic class of medications, have been shown to reduce bone mineral density and are also associated with bone fractures.[15] A longitudinal, observational cohort study in older adults showed an increased risk of fractures in those taking a TZD compared with oral sulfonylureas or metformin.[15] Another longitudinal, observational cohort study looked to identify the time to fracture with TZDs as well as the risk of fracture in subgroups defined by sex and age.[16] The study suggests that in patients with diabetes, TZD use is associated with an increased risk of fractures in women, especially those over 65 years old, and after an exposure of approximately one year.[16] Weighing the risks versus benefits of TZD use in this population should be considered before initiating treatment.

Weight

Antidiabetic medications may cause weight loss or weight gain. As such, it may be prudent to evaluate if drug-induced weight loss may be detrimental to a patient's wellbeing, especially in cases of frail older adults and those experiencing unintentional weight loss. For example, in the Rancho Bernardo cohort study of 1,801 community-dwelling older adults with and without diabetes, weight loss of 10 pounds or more over a 10-year time period was associated with higher age-adjusted death rates over the next 12 years as compared to stable weight or weight gain.[17] [In this issue Rothberg et. al., "Obesity and Diabetes in an Aging Population: Time to rethink definitions and management?," provides a detailed discussion of weight change in older adults.]

Metformin is often considered first-line therapy in type 2 diabetes.[7] Most patients on metformin lose weight; other patients maintain weight on the drug.[18] About 88% of the weight loss associated with metformin is a result of losing body fat mass.[18] Glucagon-like peptide-1 agonists are also associated with weight loss.[7,19]

Dipeptidyl peptidase-4 inhibitors and alpha-glucosidase inhibitors are considered to be weight neutral.[19]

Sulfonylureas may contribute to weight gain. Upon initiation of sulfonylureas many patients experience more than a two-kilogram weight gain.[18] Meglitinides may also contribute to weight gain.[7] TZDs also are associated with weight gain, causing a redistribution of adipose tissue from visceral to subcutaneous depots.[18] Additionally, TZDs can cause edema, which may lead to an increase in weight. Insulin can cause significant weight gain.[7,19]

Cognition

Metformin, a biguanide, is associated with impaired cognitive performance in patients with diabetes.[20] Vitamin B_{12} deficiency in patients who take metformin is reported to be about

30%.[20] Vitamin B_{12} and calcium supplements may alleviate metformin-induced vitamin B_{12} deficiency and have been associated with better cognitive outcomes, suggesting that metformin-associated cognitive impairment is partially due to vitamin B_{12} deficiency.[20] In older adults with diabetes who take metformin, monitoring of cognitive function is warranted.[20] Adequately powered, prospective, controlled trials are needed to explore the association between diabetes, cognitive decline, and the effect of metformin as well as the possible advantageous effects of using vitamin B_{12} and/or calcium supplements to help improve cognition in this population.[20] Of note, vitamin B12 deficiency is also a potential cause of peripheral neuropathy and should be considered in patients reporting symptoms, especially those taking metformin for long periods of time.[2]

Heart disease

Thiazolidinediones increase the risk for heart failure.[21] They may cause or exacerbate existing heart failure.[22] In patients with signs and symptoms of New York Heart Association class III or IV congestive heart failure, initiation of these agents is contraindicated.[22] After initiation or dose increases of a TZD, patients should be observed for signs and symptoms of heart failure, including excessive, rapid weight gain, dyspnea, and edema.[22] If these signs or symptoms develop after heart failure is confirmed, appropriate management for heart failure should be initiated and a discontinuation or dose reduction of the TZD should be considered.[22]

Rosiglitazone (Avandia), a TZD, had been associated with an increased risk of myocardial infarction in short-term studies; however, the U.S. Food and Drug Administration (FDA) determined that data for rosiglitazone-containing drugs do not show an increased risk of myocardial infarction compared to metformin and sulfonylureas.[23] As a result, the FDA states that distribution of the medication should no longer be restricted.[23]

Urinary incontinence

A new antidiabetic medication class, sodium-glucose cotransporter-2 inhibitors, will need additional studies in older adults to assess if drug-associated urinary incontinence and urinary tract infections may be an issue in this population.[7,24]

Merging concepts with practice

Managing diabetes in an older adult requires careful consideration of comorbidities, medications, and physiologic changes. In practice, providers are often faced with pacifying measures that are disease-specific or guideline-based. Older adult patients are not easily grouped by presentation, health status, or a single disease, making attainment of generalized goals more challenging.[25] A variety of guidelines exist for the management of diabetes; however, their focus on a single disease limits their application in a population with high chronic disease burden and multiple medications.[3,26] In order to provide older adults with appropriate diabetes care, multidisciplinary strategies must be employed to ensure incorporation of geriatric-based principles.

Chronologic age vs. physiologic age

First and foremost, chronologic age may not equate with physiologic age. A 64-year-old patient with diabetes with serious comorbidity is very different from another 64-year-old who has diabetes in addition to heart failure, hypertension, and COPD. Management in the latter patient is more complex and will likely result in the clinician and patient shifting goals of care. Although age is important, an older adult's comorbidities as well as functional status should also be considered. Therefore, it is imperative that providers treat the patient rather than their specific age.

Determining life expectancy is one way in which providers can develop appropriate goals of care for a geriatric patient with diabetes.[2,27,28] Patients with life expectancy less than five years are unlikely to benefit from intensive therapy, whereas those with life-expectancy greater than 10 years may be appropriate candidates for intensive control.[7,29] Several tools for predicting mortality have been developed and can be used as initial guides for determining intensity of therapy; however, broad application in the clinical setting is limited.[30-32] Wells et al.[33] developed a mortality prediction model specific to diabetes. The tool takes into account 19 different variables, including disease-related medications, blood pressure, and renal function. Although the tool was validated in a population of over 33,000 and has a concordance index of 0.752 (correct predictability 75.2% of the time), the tool fails to take into account functional status and is limited to the population characteristics to which it was studied.[33] The study population was predominantly white and relatively young (age range 44 to 79) with low rates of renal impairment (31% with GFR < 60mL/min), highlighting the need for more data in the oldest old (those age 85 over) and in patient populations most affected by diabetes.

This type of prediction model can be useful as a starting point; however, the results require translation to life expectancy for an older adult. Furthermore, clinicians should be mindful of variables not captured by available tools that could easily influence diabetes management. These variables include functional status, drug-disease interactions, and geriatric syndromes. Providers can estimate an older adult's approximate life expectancy compared with the median for like individuals by considering the presence or absence of unusually good or poor health and function, which will in turn determine trajectory of care.

Microvascular and macrovascular complications

The primary goal of diabetes management is to prevent and control hyperglycemia without predisposing patients to adverse events. Untreated hyperglycemia can lead to both macrovascular and microvascular complications. Prior to therapeutic intervention, clinicians should consider the magnitude of risk associated with each classification.

The risk of macrovascular complications, as it relates to morbidity and mortality, far exceeds the risk associated with microvascular complications in older adults with diabetes.[29] Although The United Kingdom Prospective Diabetes Study (UKPDS) excluded patients over 65 years of age at the time of enrollment, researchers observed microvascular complications in 9% of type 2 diabetics after nine years of follow-up, compared to rates of 20% for macrovascular complications.[29,34,35] It can be postulated that this difference between

endpoints would have been even larger if more older adults were included during enrollment. Vijan et al.[36] evaluated the incidence of microvascular disease with increasing age and demonstrated a decline in microvascular risk as the age of type 2 diabetes onset increases [Table 2]. In addition, the authors found the greatest improvement in microvascular complications when improving A1c from poor to moderate (A1c 11% to 9%) as compared to moderate to *goal* (A1c 9% to 7%).[37] Both studies demonstrate the importance of understanding risk associated with diabetes in the geriatric population and altering goals of care to receive the best patient outcomes. Additional studies with emphasis on risks versus benefits of differing therapeutic goals and treatment approaches in older adults should be completed to better understand disease progression and in-turn help guide management, drug therapy, and monitoring. Ultimately, the provider's care plan should be based on age of onset, function, life expectancy, and most importantly goals of care agreed upon by the patient and provider.

Macrovascular complications, such as coronary artery disease and stroke, pose the greatest risk to older adults with diabetes. There are 10.9 million Americans 65 years of age or older with diabetes, representing nearly 30% of this population segment. In the United States, diabetes is the seventh leading cause of mortality with 69,071 deaths in 2010 alone. Among people 64 years of age or older, cardiovascular disease accounts for 68% of diabetes-related deaths.[38]

In an effort to understand the role of glycemic intervention on cardiovascular endpoints three pivotal randomized control trials (the Action to Control Cardiovascular Risk in Diabetes [ACCORD] trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE] trial, and the Veterans Affairs Diabetes Trial [VADT]) were completed. All three trials incorporated an intensive therapy arm with a goal A1c of less than 6.0% or less than 6.5%. The ACCORD trial ended early (after three years) due to excessive deaths in the intensive glucose control arm.[38,39] Post-hoc analysis of the VADT trial also suggests that mortality risk increases with increasing duration of diabetes. Those with diabetes for less than 15 years received benefit while those with diabetes for 20 years or more had a higher mortality in the intensive therapy arm.[40,41] To the contrary, the ADVANCE trial did not observe an increase risk of mortality in the intensive glucose control arm over a median follow-up of five years.[42]

While the results for two of the three trials favor more lenient glycemic control for older adults with diabetes, uncertainty remains. Treating older adults with diabetes requires deliberate and thoughtful interventions. More studies focusing on the oldest old must be conducted to challenge our assumptions, particularly as we prepare to care for an increasingly aged population. Until more data is available, clinicians must weigh the potential risks and benefits of therapy on reducing the excess morbidity and mortality associated with diabetes.

Patient-centered care and quality of life

Given the intricacy and variability of diabetes management in the geriatric population, patient involvement and shared decision making is essential. Positive outcomes in this

patient population rely heavily on the patient's and/or caregiver's ability to manage multiple chronic diseases and medications on a daily basis. Patient-centered care is defined as an approach to "providing care that is respectful of and responsive to individual preferences, needs, and values and ensuring the patient values guide all clinical decisions."[43,44] Clinicians should actively engage patients in clinical decisions by helping patients prioritize treatment options consistent with their goals and preferences while also accounting for the magnitude and time to benefit in the context of the patient's overall health.[45] Oftentimes when this shared decision-making model is implemented, providers are given a greater perspective on patient's needs and ability to manage their diabetes in the setting of other chronic conditions. Ultimately, it is the patient's decision to implement or forgo therapy based on their needs and wishes in order to maintain the patient's definition of quality of life.

Summary

Polypharmacy, or the use of multiple medications, is a common concern in older adults with diabetes. Age, comorbidities, and microvascular and macrovascular complications of diabetes may further complicate diabetes management in older adults. Moreover, older adults may be more sensitive to potentially serious adverse effects of antidiabetic medications, including cognitive changes. Diabetic care in the elderly should not focus on any one of these aspects alone; instead a comprehensive approach should be used with the patient's goals of care in mind.

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Key Points

1. Polypharmacy, or the use of multiple medications, is common in older adults and more prevalent in older adults with diabetes.
2. Medications used to treat diabetes and its complications may be associated with falls, fractures, weight changes, cognitive changes, heart disease, and urinary incontinence.
3. Shared decision making should be implemented to ensure appropriate goals of care for older adults with diabetes.

Synopsis

Polypharmacy, or the use of multiple medications, is a serious concern for providers who care for older adults, as polypharmacy is associated with medication non-adherence, drug-drug interactions, drug-disease interactions, and adverse drug events. Multiple medications, high chronic disease burden, and age related changes make management of older adults with diabetes increasingly difficult. Given high medication burden and potential for increased medication sensitivity in this patient population, it is prudent that providers are aware of potential risks and benefits of antidiabetic medications and implement shared decision making practices to ensure appropriate care for older adults with diabetes.

Table 1

FDA-Approved Antidiabetic Medications

Drug Class	Generic Drug Name
Alpha-glucosidase inhibitor	Acarbose (Precose) Miglitol (Glyset)
Amylin analog	Pramlintide (Symlin)
Biguanide	Metformin* (Glucophage)
Dipeptidyl peptidase-4 (DPP-4) inhibitor	Alogliptin* (Nesina) Linagliptin* (Tradjenta) Saxagliptin* (Onglyza) Sitagliptin* (Januvia)
Glucagon-like peptide-1 (GLP-1) agonist	Exenatide (Byetta) Liraglutide (Victoza)
Insulin	NPH* (Humulin N; Novolin N) Regular* (Humulin R; Novolin R)
Insulin analog	Aspart* (Novolog) Detemir (Levemir) Glargine (Lantus) Glulisine (Apidra) Lispro* (Humalog)
Meglitinide	Nateglinide (Starlix) Repaglinide* (Prandin)
Sodium-glucose co-transporter 2 (SGLT2) inhibitor	Canagliflozin (Invokana) Dapagliflozin (Farxiga)
Sulfonylurea – first generation	Chlorpropamide (Diabinese) Tolazamide (Tolinase) Tolbutamide (Orinase)
Sulfonylurea – second generation	Glyburide* (Diabeta; Glynase) Glipizide* (Glucotrol) Glimepiride* (Amaryl)
Thiazolidinedione (TZD)	Pioglitazone* (Actos) Rosiglitazone* (Avandia)
Bile acid sequestrant	Colesevelam (Welchol)
Dopamine agonist	Bromocriptine (Cycloset)

*Also available in combination formulations with other antidiabetic agents Data from:

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Table 2

Lifetime Risk of Diabetes-related Microvascular Complications (Blindness and End-stage renal disease)

Lifetime Risk of End-Stage Renal Disease / Lifetime Risk of Blindness from Diabetic Retinopathy				
Hemoglobin	**Age at Onset of Diabetes**			
A_{1c} Level	**45 years**	**55 years**	**65 years**	**75 years**
←		%	→	
7	2.0 / 0.3	0.9 / 0.1	0.3 / <0.1	0.1 / <0.1
8	2.7 / 1.1	1.3 / 0.5	0.5 / 0.2	0.1 / <0.1
9	3.5 / 2.6	1.6 / 1.2	0.6 / 0.5	0.1 / 0.1
10	4.3 / 5.0	2.1 / 2.5	0.8 / 1.0	0.2 / 0.3
11	5.0 / 7.9	2.5 / 4.4	0.9 / 1.9	0.2 / 0.5

Data from: Vijan S, Hofer TP, Hayward RA. Estimated benefits of glycemic control in microvascular complications in type 2 diabetes. Ann Intern Med. 1997; 127(9): 788-795. doi:10.7326/0003-4819-127-9-199711010-00003