Polypharmacy in Elderly Patients With Diabetes

Elderly patients with diabetes pose a particular challenge to clinicians with respect to managing medications. Not only are comorbidities common in elderly diabetic patients, but also careful management of these comorbidities is perhaps more important than in patients without diabetes. While nonpharmacological interventions for managing diabetes and the associated comorbidities are integral to the treatment plan, in reality, the cornerstone of management remains pharmacotherapy. As a consequence, there are strong factors that favor polypharmacy in patients with diabetes.

Rational medication prescribing dictates that the fewest medications be used to achieve the therapeutic goals as determined by clinician and patient. Multiple medications not only add to the cost and complexity of therapeutic regimens, but also place patients at greater risk for adverse drug reactions and drug-drug interactions. Studies evaluating appropriate prescribing in the elderly consistently find frequent polypharmacy and use of excessive or potentially harmful drugs. To address the problem of inappropriate polypharmacy, efforts have been studied in both inpatient and outpatient settings to decrease use of unnecessary medications, as well as the overall number of medications, both in inpatient and outpatient settings.

Thus, clinicians caring for people with diabetes face a therapeutic conundrum: balancing the needs of their patients and attempting to achieve optimum control of medical problems while trying to keep the medication profile as simple and small as possible.

CASE STUDY
Consider the following patient who is cared for in our clinic. He is a 70-year-old man with longstanding type 2 diabetes, dyslipidemia, hypertension for 8 years, chronic degenerative joint disease of the knees and back, gastroesophageal reflux disease (GERD), and angina pectoris status post myocardial infarction. As a result of his diabetes, he has elevated urinary microalbumin and painful neuropathy of the lower extremities. He is 25 kg above his ideal body weight.

On presentation to the clinic, he was complaining of worsening lower urinary tract symptoms related to prostatic hypertrophy, which we had been following with watchful waiting. His blood pressure in the clinic, repeated several times, was 144/84 mmHg. It has been borderline elevated for the past several visits, and he was attempting weight loss and low-level exercise in hopes of avoiding additional medications. These attempts have been hampered by his heart disease, arthritis, and neuropathy.
His blood pressure has been difficult to maintain, despite his being on optimal doses of lisinopril (Prinivil), hydrochlorothiazide (Hydrodiuril), atenolol (Tenormin), and felodipine (Plendil). To manage his diabetes, he takes glyburide (Micronase) and metformin (Glucophage). His glycated hemoglobin is 8.1%, similar to his usual level of control. His LDL cholesterol is well controlled (89 mg/dl) with simvastatin (Zocor), but his HDL cholesterol is low (28 mg/dl) and his triglycerides are modestly elevated (260 mg/dl). He takes acetaminophen (Tylenol) for his arthritis and uses topical capsaicin cream as an adjunct to this. He takes gabapentin (Neurontin) for his neuropathic pain, with some benefit. In addition to his hypertension medications, he takes aspirin as part of his cardiac regimen. He takes sublingual nitroglycerin (Nitrostat) as needed and wears a nitroglycerin patch (Nitrodot) for symptomatic angina. He uses ranitidine (Zantac) for his GERD.

While this patient may seem to be contrived, this scenario is not unusual in patients with diabetes, especially those who are elderly.

DEFINITION OF POLYPHARMACY

Although the term “polypharmacy” is frequently used, it is not clearly defined in the literature. Remarkably, this term is not addressed in several standard textbooks of pharmacology. One simple definition is based on the total number of different medications a patient takes concomitantly. This definition allows for easy identification of patients with polypharmacy issues for organizations that have a unified formulary with pharmacy benefits, such as health maintenance organizations or the Department of Veterans Affairs (VA). The number of medications constituting polypharmacy may be as high as 10,2 but most definitions use five or six medications.3–7

These definitions do not account for as-needed medications or over-the-counter (OTC) medications, including herbal products. It is also not clear how inhaled medications, ophthalmic drops, or topical medications are qualified in these definitions. Thus, while this definition is simple and easy to apply, it uses arbitrary numbers of medications and does not account for appropriate or inappropriate uses of medications.

A more clinically useful definition is “the prescription, administration, or use of more than medications than are clinically indicated.”8 Inappropriate drug combinations, unnecessary medications, and inappropriate drugs for specific patients (such as the elderly) constitute the problems of polypharmacy. Thus, patients receiving only two medications could have polypharmacy.

While intellectually more satisfying, this definition is limited by several factors. Primarily, it generally requires review of patient-specific information and is labor intensive. Of some help are computer programs that review pharmacy profiles to identify inappropriate drug combinations, including those with serious potential interactions. Expert panels have developed consensus-based lists of medications considered to be inappropriate for use in the elderly.9

For the purposes of this article, polypharmacy will be defined using the simpler definition of use of multiple medications for a single patient.

FACTORS INFLUENCING POLYPHARMACY

Although in theory use of excess medications is recognized as problematic, many forces continue to promote addition of medications to therapeutic regimens for individual patients. Quality assurance monitors often focus on identification of unrecognizable comorbidities, such as depression. Additional efforts have been made to regularly assess and treat pain (the “fifth vital sign”). These efforts frequently lead to use of pharmacotherapy to address new diagnoses. In addition, quality assurance monitors often focus on appropriate pharmacotherapy for clinical diagnoses, as these monitors lend themselves to easy measurement and are backed by solid clinical evidence. Thus, programs to assess use of aspirin in coronary artery disease and angiotensin-converting enzyme (ACE) inhibitors for heart failure are common. While these efforts clearly are clinically sound, their influence on problems associated with polypharmacy is not known.

Another more recent influence on prescribing practices is pervasive direct-to-consumer advertising. In addition, advertising of OTC medications and alternative medications likely results in significant use of products. It is unclear how significantly direct-to-consumer advertising affects polypharmacy. Nevertheless, this practice has been cause for significant concern among both physicians and policy makers.

Unlike pharmaceutical industry promotions to health care providers, which cover brand-name drugs extensively, direct-to-consumer advertising focuses on relatively few products.10 Advertising for lifestyle medications (such as sildenafil [Viagra] for erectile dysfunction or finasteride [Propecia] for male baldness) or underrecognized conditions (such as depression, allergies, or dyslipidemia) is very common. Presumably, this strategy is based on marketing research that supports a greater impact on addition of new prescriptions.

Finally, remarkable improvements in drug therapy offer far greater options for treatment. Not only are new drug classes available for new indications, but also new medications within existing drug classes now offer improved efficacy, better side effect profiles and tolerability, and longer-acting preparations.

INCIDENCE OF POLYPHARMACY IN THE ELDERLY

Regardless of the definition of polypharmacy, it is prevalent, particularly in the elderly. In a study of patients randomly chosen from an
outpatient clinic at a VA Hospital (primarily a geriatric population), the mean number of medications was five, and 65% were taking more than four drugs. A VA study found that 42% of geriatric patients admitted to a facility were taking five or more medications. A study of Swedish elderly found that 39% were taking five or more drugs concomitantly.5

Although these studies did not separate out diabetes patients, it is likely that such patients will have an even greater incidence of polypharmacy than do elderly patients without diabetes. In a national survey in Finland, type 2 diabetic patients used significantly more medications, with significantly greater cost, than nondiabetic patients matched for sex, age, and area of residence.12 The presence of comorbidities associated with diabetes and advanced age is a strong factor favoring addition of multiple agents to an individual's medication regimen.

**CLINICAL RELEVANCE OF POLYPHARMACY**

Use of multiple medications increases in a variety of ways the likelihood of an unintended therapeutic outcome. This is especially true in the case of elderly patients, who are particularly susceptible to adverse drug events. Although not specifically studied, it is likely that diabetic elderly patients are even more susceptible to problems related to polypharmacy because of significantly greater underlying physical disability.13 Thus, polypharmacy adds expense for multiple drugs, increases the chance of an adverse reaction to a single agent, increases the incidence of drug interactions, decreases patient compliance, and plays a part in unwanted geriatric syndromes. Finally, polypharmacy increases the likelihood of prescribing and dispensing errors.

Drug interactions occur when two or more medications interact in a way not intended and with a nondesirable outcome. The addition of each medication increases the possibility of drug interactions.

In one study of fatal adverse drug events in Norway, drug interactions were frequently suspected. During a 2-year period, 18% of deaths were thought to be related to adverse drug events directly or indirectly. Patients on greater numbers of medications were at greater risk of adverse events leading to death. Investigators found that nearly 24% of patients were on 12 or more medications at the time of their death.14

In another study of elderly patients presenting to an emergency room in Canada, adverse drug-related events accounted for more than 10% of visits. The average number of medications was 4.2. Of these patients, half had potential adverse drug interactions in their medication profile.15

While use of numerous medications is clearly a marker for greater burden of disease and likely increased susceptibility to adverse drug events, it is also likely that polypharmacy increases the probability of drug interactions or adverse events independently. In a nursing home study, number of medications administered was associated with greater risk of adverse drug events. The risk increased from an odds ratio of 2.0 for five to six medications, to 3.3 for nine or more medications.16

Elderly patients are susceptible to geriatric syndromes associated with inappropriate medications. Confusion or cognitive impairment, falls and fractures, and urinary retention are well recognized as potential causes of adverse drug reactions.17 Elderly patients are also more susceptible to orthostatic hypotension, insomnia, and constipation with commonly used medications, such as narcotics, anticholinergic medications, and α-blockers. Diabetic patients with long-standing disease are particularly susceptible to all of these adverse events because of neuropathy, dysautonomia, and vascular disease.

Because of the increased relevance of adverse drug interactions in the elderly, several consensus panels have developed lists of drugs or drug classes that should be avoided if possible.9 Medications considered to be potentially problematic in elderly patients include those with prolonged half-lives, significant anticholinergic actions, narrow therapeutic indices, and highly sedating properties, as well as medications with little evidence of efficacy in the elderly.

These lists have been widely employed in the assessment of appropriateness of drug therapy and suggest that inappropriate prescribing is common in the elderly. In a 1987 national survey of 6,171 community-dwelling elderly patients, 23.5% were receiving at least one of a list of 20 potentially contraindicated drugs. The authors interpreted their findings to indicate a strong need for broader educational and regulatory initiatives to improve drug prescribing in the elderly.18 More recently, respondents in an epidemiological study of elderly patients at Duke University Medical Center found inappropriate medication use in 22–27% of community-dwelling elderly patients.19

Hanlon et al.20 have developed the Medication Appropriateness Index (MAI) to identify inappropriate prescribing. This rating system evaluates 10 criteria (indication, effectiveness, dosage, appropriateness of directions, practicality of directions, drug-drug interactions, drug-disease interactions, duration, duplication, and cost) and has been validated in elderly inpatients and outpatients. Using this index, Schmader et al.21 found that polypharmacy (five or more medications) and MAI scores indicating less appropriate prescribing were associated with adverse health outcomes.21

Despite the concerns for polypharmacy in the elderly, paradoxically, some have suggested that patients with multiple chronic diseases are frequently undertreated with medications. In a study of elderly patients in Ontario, Canada, investigators found that medical problems unrelated to chronic medical disorders were less likely to be given appropriate medical therapy. For example, diabetic patients were significantly less likely to receive estrogen replacement therapy.22

For patients with diabetes, there are especially significant treatment goals and outcomes that are specifically tied to drug therapy. Thus, concerns for polypharmacy must be balanced against the need to adequately treat diabetes, as well as associated comorbidities.

**DIABETIC ISSUES THAT FAVOR POLYPHARMACY**

Several factors contribute to polypharmacy in diabetic patients. Not only is tight glycemic control important, but multiple comorbidities associated with diabetes also require drug therapy (Table 1).

**Importance of Glycemic Control in Diabetes**

There is an increasing understanding of the importance of good glycemic control in type 2 diabetes. The American Diabetes Association has set target A1C goals of <7%.23 Infor-
mation from the Third National Health and Nutrition Examination Survey (NHANES III) found that 18% of patients had poor glycemic control defined as glycated hemoglobin $>9.5\%$. Patients $>65$ years of age did slightly better, with 14.5% having a glycated hemoglobin $>9.5\%$.24

Some medical organizations have made an effort to track glycemic control among covered patients and have demonstrated improvement. The VA follows national trends in glycemic control among veteran patients. In 1998, for more than 200,000 patients with documented A1C results available, the median was 7.5%, with 60% of the patients having A1Cs of $<8.0\%$ and 16% having A1Cs $>9.5\%$. This information is provided to all facilities with comparisons to other facilities so that performance can be monitored. Underlying this initiative of providing feedback is the understanding that improved glycemic control will result in improved outcomes for patients.25

The landmark United Kingdom Prospective Diabetes Study (UKPDS)26 established that intensive blood glucose control reduced the risk of both microvascular and macrovascular complications in patients with type 2 diabetes. The modest 11% reduction in glycated hemoglobin over the 10-year study for the intensively treated patients resulted in reduction of clinically relevant endpoints. There were decreases in all diabetes-related endpoints (12%), diabetes-related death (10%), and all-cause mortality (6%).

This study included only patients with newly diagnosed diabetes and thus offered the opportunity to follow responses to therapy, including the need for multiple agents. Patients were started on monotherapy consisting of diet alone, insulin, or sulfonylurea (and metformin for obese patients). Patients not achieving or maintaining glycemic control were increased to maximum doses on monotherapy and then increased again to addition of other agents if glycemic control was not maintained.

Investigators found a progressive decline in glycemic control such that by 3 years, $<55\%$ of patients remained on monotherapy. At 9 years, $<25\%$ remained on monotherapy.27 In practice, it is likely that many patients will have diabetes of much longer duration, and thus it follows that most patients will require multiple antidiabetic agents to meet the glycemic goals that would be expected to derive the clinically relevant outcomes seen in clinical trials.28

Adding to the likelihood that good glycemic control will result in use of multiple antidiabetic agents is the fact that the therapeutic armamentarium continues to expand. In addition to the insulins, there are five different oral antidiabetic classes: sulfonylureas, biguanides, $\alpha$-glucosidase inhibitors, thiazolidinediones, and non-sulfonylurea secretagogues. Further confusing the issue is the expanding number of specific drugs or formulations in each class.

Different mechanisms of actions and complementary effects on glycemic control have led to use of diabetic drug combinations (Table 2). Multiple clinical trials focusing on combinations of two oral agents have demonstrated additional (albeit modest) improvements in glycemic control.29 Although limited, there are data supporting the effectiveness of adding a third drug in patients not meeting glycemic goals on two oral agents. For example, in patients on maximal doses of a sulfonylurea and metformin, the addition of troglitazone (Rezulin) resulted in improved glycemic control.30 Although troglitazone is no longer available, pioglitazone (Actos) and rosiglitazone (Avandia) have replaced it as safer alternatives and are being used in combination with multiple agents. Finally, the addition of insulin to oral agents is an option. Thus, although not approved by the Food and Drug Administration (FDA), three- and four-drug regimens are

### Table 1. Factors Contributing to Polypharmacy in Diabetic Patients

- Need for tight glycemic control, often requiring multi-drug regimen
- Frequent comorbidities requiring drug therapy:
  - Hypertension: Tight control often requires a multiple-drug regimen.
  - Dyslipidemia
  - Coronary artery disease: Multiple drugs are beneficial.
  - Renal disease: Drug therapy early in the disease prevents progression.
  - Congestive heart failure: Multiple-drug therapy is usually required.
  - Neuropathy: Pain management usually requires pharmacotherapy.
  - Glaucoma, peripheral vascular disease, lower-extremity ulcers, obesity, and gastrointestinal problems: Each occasionally requires therapy.

### Table 2. Therapeutic Options and Approved Combinations for Diabetes

<table>
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<tr>
<th>Drug</th>
<th>Approved Combinations</th>
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<tr>
<td>Sulfonylureas (SU)</td>
<td>Insulin, metformin, TZD, AG</td>
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<tr>
<td>• Glyburide</td>
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<td>• Glibizide</td>
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<td>• Glimepiride</td>
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<tr>
<td>Biguanides</td>
<td>Insulin, SU, non-SU, TZD</td>
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<tr>
<td>• M etformin</td>
<td>SU</td>
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<tr>
<td>$\alpha$-Glucosidase inhibitors (AG)</td>
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<td>• Acarbose</td>
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<tr>
<td>• M iglitol</td>
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<tr>
<td>Thiazolidinediones (TZD)</td>
<td>Insulin, SU, metformin</td>
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<tr>
<td>• Rosiglitazone</td>
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<tr>
<td>• Pioglitazone</td>
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<tr>
<td>Non-sulfonylurea secretagogues (non-SU)</td>
<td>M etformin</td>
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<tr>
<td>• Repaglinide</td>
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<tr>
<td>• Nateglinide</td>
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<tr>
<td>Insulins</td>
<td>SU, metformin, TZD</td>
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<tr>
<td>• Regular</td>
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<tr>
<td>• Lispro, aspart</td>
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<tr>
<td>• NPH</td>
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<td>• Lente</td>
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<td>• Glargine</td>
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not inconceivable, especially as patients progressively lose β-cell function.

Although drug combinations have been shown to be effective at lowering blood glucose in type 2 diabetic patients, they have not been well studied in randomized, controlled trials with regard to clinically relevant outcomes. Indeed, in a substudy of the UKPDS, addition of metformin to sulfonylurea was associated with a significant increase in diabetes-related death as well as overall death. This unexpected finding has not yet been replicated but perhaps should be considered when setting target glycemic goals for fragile elderly diabetic patients.

Prevalence of Comorbidities With Diabetes

Complicating the management of diabetes is the remarkable number of organ systems potentially affected by the disease process. Cardiovascular disease, including hypertension, myocardial infarction, congestive heart failure, cerebrovascular disease, and peripheral vascular disease, is particularly prevalent in patients with diabetes. Likewise, dyslipidemia, obesity, renal disease, erectile dysfunction, retinopathy, neuropathy, and gastrointestinal problems such as gastroparesis are prevalent in patients with type 2 diabetes.

In reviewing the presence of comorbidities in elderly diabetic patients from NHANES III, there was significantly greater presence of concomitant myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, and vision problems in diabetic subjects compared to those without diabetes. In another population-based study, hypertension, congestive heart failure, coronary artery disease, dyslipidemia, renal disease, and glaucoma were all significantly more prevalent in patients with type 2 diabetes than in matched control subjects. The presence of diabetes with these diagnoses may dramatically increase morbidity and mortality in affected patients. Clinical trials have demonstrated the benefits of aggressive management of disease comorbidities in patients with type 2 diabetes. Because treatment of hypertension, coronary artery disease, and renal disease in diabetic patients has been shown to result in clinically relevant beneficial outcomes, aggressive control of blood pressure and dyslipidemia have special importance.

Although nonpharmacological interventions are an important part of all diabetes care, adequate treatment of these comorbidities relies on aggressive pharmacotherapy. Thus, the presence of comorbidities significantly adds to the likelihood that multiple medications will be utilized in the appropriate care of these patients.

Hypertension in diabetes

Hypertension is approximately twice as common in type 2 diabetic patients as in those without diabetes and is found in up to 85% of patients with nephropathy. Although the incidence of hypertension increases with duration of type 2 diabetes, a substantial number of patients have hypertension present at the time of diabetes diagnosis.

Studies suggest that hypertension is frequently less-than-adequately controlled in diabetic patients. In the UKPDS, 38% of all subjects had blood pressure >160/90 mmHg and 62% required combination therapy to achieve tight blood pressure control, which averaged 144/82 mmHg. In a VA study of hypertension, 34% of patients with hypertension also had diagnosed diabetes, 40% of patients had blood pressure >160/90 mmHg, and <25% had blood pressure <140/90 mmHg. The presence of diabetes did not predict more aggressive blood pressure therapy.

Multiple studies have conclusively demonstrated that even modestly lowering blood pressure in type 2 diabetic patients results in significant clinical outcomes. Observational studies have shown that the risk of diabetes complications significantly decreases with lower blood pressure, with the lowest risk in patients with a systolic blood pressure <120 mmHg.

Intervention trials have also confirmed that aggressive lowering of blood pressure is important. The UKPDS evaluated tight (<150/85 mmHg) or less tight (<180/105 mmHg) blood pressure control in diabetic patients and demonstrated a 32% decrease in diabetes-related mortality. Indeed, tight control of blood pressure had greater benefits than tight glycemic control.

In the Hypertension Optimal Treatment study, blood pressure targets were diastolic blood pressure ≤90, 85, or 80 mmHg. Although the difference between the highest and lowest group in actual blood pressure control achieved was relatively modest (144/85 vs. 140/81 mmHg), there was a 51% reduction of major cardiovascular events in the lowest group. In light of these studies, the National Kidney Foundation recommends a target blood pressure of 130/80 mmHg for all diabetic patients, with more aggressive blood pressure targets in the presence of renal disease.

Multiple antihypertensive medications are required to achieve the aggressive blood pressure goals recommended for diabetic patients. In their observational hypertension study in the VA, Berlowitz et al. found that despite less-than-adequate blood pressure control, nearly 60% of subjects were taking two or more blood pressure medications. In five randomized clinical trials of blood pressure treatment including diabetic patients, subjects took an average of 3.2 antihypertension medications (range 2.8–4.2) to achieve an average blood pressure of ~140/90 mmHg. Despite this, it should be noted that no randomized controlled trial has yet achieved a blood pressure of <130/80 mmHg. Thus, it is clear that efforts to achieve target blood pressure levels associated with beneficial clinical outcomes will require multiple antihypertensive agents.

Dyslipidemia in diabetes

Lipid abnormalities are very prevalent in patients with diabetes. Not only does poor glycemic control contribute to elevations in triglycerides, low HDL cholesterol, and, to a lesser extent, elevated LDL cholesterol, but obesity also complicates dyslipidemia. Recent cholesterol treatment guidelines suggest treating diabetic patients with dyslipidemia similarly to patients with established coronary artery disease regardless of whether you are treating for primary or secondary prevention. These recommendations are based on the high incidence of myocardial infarction and death from vascular disease in patients with diabetes.

One widely referenced study compared 7-year incidence rates for myocardial infarction in diabetic patients without prior events to those of patients with established coronary artery disease but without diabetes. Investigators found no difference in rates for death from coronary artery disease between the two groups even after adjusting for age, sex, cholest-
terol, hypertension, and smoking.\textsuperscript{38} This study has been interpreted to indicate that type 2 diabetes is a coronary artery disease equivalent in terms of risk for future cardiovascular events.

Subgroup analysis of several trials supports aggressive treatment of dyslipidemia in diabetic patients with documented cardiovascular disease. The Scandinavian Simvastatin Survival Study\textsuperscript{39} demonstrated that simvastatin therapy was associated with significant reductions in coronary events and mortality compared to placebo both for patients with established diabetes and for those with impaired fasting plasma glucose levels but no history of diabetes. Subgroup analysis of the Cholesterol and Recurrent Events trial\textsuperscript{40} also demonstrated significant reduction of absolute risk of coronary events compared to placebo using pravastatin as the lipid-lowering agent.

The recent Heart Protection Study (HPS) is the first randomized trial to demonstrate the benefit of lipid lowering with simvastatin in diabetic patients for primary prevention.\textsuperscript{41} There are no trials demonstrating reductions in adverse clinical outcomes in the treatment of elevated triglycerides, the most common lipid abnormality in diabetic patients. Nonetheless, based on the HPS and epidemiological evidence, it is prudent to extend treatment of dyslipidemia for both primary and secondary prevention in diabetic patients.

Treatment of dyslipidemia in diabetes is thus important, with focus on lowering LDL cholesterol. However, because triglycerides are frequently elevated, therapy may not always be straightforward. Initial efforts at lowering triglycerides should focus on optimal glycemic control. Both simvastatin and atorvastatin (Lipitor) are potent cholesterol-lowering agents that also have FDA indications for lowering triglycerides. However, the triglyceride-lowering efficacy is modest in many patients, and these drugs may not lower triglycerides to desired levels. Niacin (Niaspan) is more potent at lowering triglycerides, but may worsen glycemic control. Thus, a fibrate could be added to a statin, but this increases the possibility of muscle myopathy and rhabdomyolysis. Theoretically, pravastatin (Pravachol) might be safer because it is not metabolized by the cytochrome P450 system, but this is not proven. In any event, appropriate treatment of lipid abnormalities in diabetic patients offers clear benefit but adds to polypharmacy in these patients.

Prevention of end-stage renal disease in diabetes

End-stage renal disease in diabetes can be delayed or prevented with appropriate screening and aggressive medical therapy in higher-risk patients. Controlling blood pressure is of paramount importance to the prevention of renal disease. Screening diabetic patients for microalbuminuria identifies those patients at the earliest stage of diabetic nephropathy. The National Kidney Foundation and others recommend that these patients receive even more intensive blood pressure therapy, as well as tight glycemic control, to preserve renal function.\textsuperscript{32} ACE inhibitors, angiotensin receptor blockers, \(\beta\)-blockers (including carvedilol [Coreg]), diuretics, and calcium-channel blockers have all been shown to reduce proteinuria in high-risk diabetic patients.\textsuperscript{32} However, ACE inhibitors and angiotensin receptor blockers are preferred in these patients because they have shown the most consistent benefit. Indeed, angiotensin blockade provides renoprotective effects that are independent of blood pressure lowering.

Other common comorbidities in diabetes

In addition to hypertension, dyslipidemia, and renal disease, other common comorbidities contribute to polypharmacy in diabetes. Congestive heart failure is more common in diabetes, and evidence is compelling for use of multiple drugs to prevent its morbidity and mortality. Indeed, the standard of care in treating congestive heart failure is polypharmacy including ACE inhibitors, angiotensin receptor blockers, \(\beta\)-blockers, and hydralazine/isosorbide dinitrate.\textsuperscript{42} Symptoms may also dictate the use of diuretics, digoxin, or dihydroxypyrindine calcium-channel blockers.

Diabetic neuropathy is also prevalent in diabetes. Clinical trials have demonstrated benefit of tricyclic antidepressants, as well as gabapentin, in relieving symptoms. Other analgesics are frequently required. For example, in a review of patients taking gabapentin for chronic pain at my facility, 40% required additional pain medications.
priateness of prescribing for the elderly or to decrease polypharmacy would be beneficial. However, caution must be taken to obtain careful, rational clinical input from the clinicians caring for such patients. Elderly patients are more susceptible not only to adverse outcomes from medications, but also to the absence of clinically beneficial medications. This may be particularly true in the case of elderly type 2 diabetic patients, who are prone to requiring multiple medications for their multiple medical problems.

RATIONAL DRUG PRESCRIBING FOR ELDERLY DIABETIC PATIENTS
As I have noted, many forces tend to add to the drug regimens of type 2 diabetic patients. Given the frequency of comorbidities and compelling evidence for treatment of each condition, it is likely that the average patient will require multiple medications to achieve therapeutic goals. Thus, the goal of therapy is to treat all pertinent medical problems using the most appropriate drug regimen, including issues of efficacy, dose frequency, side effect profile, drug interaction potential, and, finally, cost.

Various recommendations have been made to improve prescribing for the elderly (Table 3).

In fragile elderly patients, nonpharmacological means should be attempted before adding a new drug when feasible. For example, use of assistive devices or physical therapy for pain or behavior modification for insomnia should be considered before resorting to oral medications. In addition, when assessing patient complaints, clinicians should consider whether symptoms are related to an adverse drug reaction. Simply discontinuing a medication or changing to a different drug may be effective.

When starting a new drug, patients should receive education about the medication: indications for use, instructions for taking it, common side effects, and potential serious adverse events. In doing so, compliance can be enhanced when side effects are transient, temporary, or easily controlled with simple measures. For instance, some drugs initially may cause changes in bowel habits, which can be managed by nonpharmacological measures. On the other hand, patients should know when to stop a medication immediately if they are experiencing a potentially serious adverse outcome, such as recognizing that muscle pain may indicate early rhabdomyolysis when taking a statin.

Simple measures can have a significant impact on managing complex medication profiles. Clinicians should regularly review all of the medications their patients take. Patients being cared for with a unified pharmacy benefit plan are at an advantage because providers have access to complete lists of medications. However, even in such a system, patients may not be taking their medications as prescribed.

Patients should be encouraged to maintain a list of all active medications they are taking. Alternatively, they can be asked to bring in all medications (clinic “brown bag” day). Physicians frequently neglect to ask about OTC medications and nutritional supplements. This can help identify important potential interactions with prescription drugs, such as patients with severe heart failure or poorly controlled hypertension taking nonsteroidal anti-inflammatory drugs (NSAIDs). In these situations, NSAIDs can decrease the effect of medications on the kidney, leading to fluid retention or elevated blood pressure. Because patients may see multiple providers, it is necessary to try to coordinate medications, to avoid duplication of medications, and to avoid drug interactions.

Patients or their caretakers should know and understand the indications for each medication. This can avoid confusion about when a medication should be used, particularly for “p.r.n.,” or “as needed” medications. Providers should regularly review with patients the therapeutic responses to each medication. Medications without a clear indication for use and those that are not effective should be discontinued with careful observation for clinical deterioration.

Clinicians should be familiar with lists of medications to be avoided in vulnerable elderly patients and should try to use alternative drugs when possible. Studies have documented frequent continued use of these medications in elderly patients. Clinicians should seek new treatment strategies or even use nonpharmacological measures when possible to avoid them.

Whenever possible, use of a single drug to treat multiple conditions should be attempted. For this reason, ACE inhibitors or angiotensin receptor blockers are particularly appealing for diabetic patients because they treat hypertension and heart failure and are renoprotective or even cardioprotective. Likewise, -blockers can be used to treat symptoms of lower urinary tract symptoms, as well as hypertension.

Because the elderly frequently have decreased renal and hepatic function and a lower volume of distribution, they are at greater risk for drug accu-

<table>
<thead>
<tr>
<th>Table 3. Suggestions for Appropriate Prescribing for the Elderly</th>
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<tbody>
<tr>
<td>• Attempt nonpharmacological measures when feasible.</td>
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<tr>
<td>• Before starting a new drug, consider the possibility that the patient’s symptoms are related to an adverse drug reaction.</td>
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<tr>
<td>• When prescribing a new drug, provide education about indications for use, instructions for taking the medication, common side effects, and potential serious adverse effects, as well as what to do when these side effects occur.</td>
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<tr>
<td>• Regularly review all medications. Include OTCs, herbal products, and vitamin and mineral supplements. Encourage patients to maintain an active medication list.</td>
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<td>• Coordinate care with all providers to eliminate duplication of prescriptions.</td>
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<td>• Identify indications for each medication.</td>
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<td>• Regularly assess therapeutic responses to medication.</td>
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<td>• Discontinue drugs without a clear indication for use.</td>
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<td>• Discontinue drugs that have not achieved the therapeutic goal.</td>
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<td>• Avoid medications with high incidence of adverse outcomes in the elderly (Beers list).</td>
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<td>• When possible, combine indications with a single drug.</td>
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<td>• Regularly assess patient compliance, especially before changing doses of a drug or adding a new drug.</td>
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<td>• Choose drugs with wide therapeutic windows when possible.</td>
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<tr>
<td>• Check for potential drug interactions; use available software programs.</td>
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<tr>
<td>• When considering pharmacotherapy for preventive purposes, consider the likelihood that a patient will benefit from treatment given his or her age and comorbidities.</td>
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mulation. Use of drugs with a wide therapeutic window should be preferred because they are associated with less drug toxicity.

Potential drug interactions must be considered. Fortunately, software programs are increasingly available and offer some assistance in identifying potentially serious interactions. Additionally, free software offering drug interaction information is widely available for handheld personal devices.

Finally, when contemplating pharmacotherapy for preventive purposes, consider the likelihood that a patient will benefit from the treatment being offered. For example, the benefits of tight glycemic control in the UKPDS required years to be of significance, and many of the benefits were for microvascular complications, such as the need for laser therapy for retinopathy. Thus, when contemplating the addition of medications to achieve tight glycemic control or for microalbumuria, one must consider the patient’s life expectancy and adjust goals accordingly. Although an A1C of <7% is certainly justified in younger type 2 diabetic patients with longer life expectancies, it cannot be justified in elderly diabetic patients with severe inoperable coronary heart disease or congestive heart failure. Indeed, some have suggested that tight control in these patients is associated with worse outcomes.47

In summary, elderly type 2 diabetic patients will frequently require multiple medications to adequately and appropriately treat their diabetes and associated comorbidities. The challenge to clinicians is to carefully evaluate the medication profile and to work with patients individually to provide the safest, most efficacious, and simplest medication regimen feasible.

References
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Diabetes Spectrum Volume 15, Number 4, 2002

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