Polypharmacy as a Risk Factor in the Treatment of Type 2 Diabetes

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The desire to take medicine is perhaps the greatest feature which distinguishes man from animals.

—Sir William Osler (1849–1919)[1]

Polypharmacy is a term that has been used in health care for decades. In conventional use, it has meant the concurrent use of multiple medications in the same patient. However, this definition understates the potential for harm that polypharmacy may pose to the patient. Other definitions have appeared in the medical literature that put the problem of polypharmacy in a broader perspective. One defines polypharmacy as the "prescription, administration, or use of more medications than are clinically indicated, or when a medical regimen includes at least one unnecessary medication."[2–5]

However, polypharmacy may be unavoidable, given that multiple drug therapy has become the standard of care in most chronic conditions.[6] The comorbidities of diabetes commonly include hypertension, dyslipidemia, depression, and coagulopathies, each of which may require one or more drugs for adequate control. Add to this other conditions that often accompany diabetes, such as hypothyroidism, heart failure, and osteoporosis, and the total number of possible medications needed becomes significant.

Polypharmacy is inevitable when treating a common chronic condition such as diabetes, given the large number of treatment options now available. The potential for polypharmacy will continue to increase with time, as additional therapeutic options become available. Before the approval of metformin in the United States in 1995, only insulin and the sulfonylureas were available for the treatment of diabetes. Now, there are five classes of oral agents, three rapid-acting insulin analogs, and two long-acting analogs, as well as the "traditional" insulins. The emergence of other forms of insulin (inhaled, topical patches), the incretin gut hormones, newer mixed peroxisome proliferator–activated receptor-α and -γ agonists, a synthetic amylin analog, and still more agents to come will increase opportunities for success in treatment, as well as the potential for polypharmacy.

Causes of Polypharmacy

Predictors for polypharmacy include the number of drugs at start, patient age, the presence of conditions such as diabetes or coronary ischemic disease, and the use of medications without clear indications.[7] The most common causes of polypharmacy are listed in Table 1[2] and discussed in more detail below.

Multiple prescribers

Patients with a chronic disease such as diabetes often see specialists in addition to their primary care providers. Mid-level prescribers, such as physician assistants and nurse practitioners, may also see and treat these patients.

Table 1. Causes of Polypharmacy

- Multiple prescribers
- Aging population
- Complex drug therapies
- Psychosocial contributions
- Adverse drug reactions that may be interpreted as new medical conditions

Each of these providers may prescribe medications, adding to a growing list of drugs on a patient's profile. All too often, patients' drug lists are not regularly monitored for potential problems. There is a stronger tendency for drugs to be added to a patient's regimen than for drugs to be discontinued. Adding new treatments may make a previously used medication redundant.[8] The continuous addition of drugs over time, without periodic reevaluation of the drug regimen, is one of the major contributors to the development of polypharmacy.

Aging population

As the population ages, the incidence of chronic conditions increases.[5] With the availability of multiple medications and the variety of expert guidelines for the treatment of these conditions, additional drug therapy is often indicated. Debate has emerged about how many conditions need to be treated.[9,10]

The burden of polypharmacy falls especially hard on the elderly, who incur the highest incidence of chronic conditions coupled with reduced or fixed incomes and therefore inability to afford the cost of multiple medications. Treatment of elderly patients with diabetes requires special considerations, especially in how aggressively diabetes should be treated. Treatment decisions should consider age and life expectancy, comorbid conditions, cognitive status, living arrangements, and severity of vascular conditions.[11]

Complex drug therapies

The variety of expert panel recommendations, clinical practice guidelines, and other national standards for med-

ical treatment has grown exponentially in the last decade. The National Guideline Clearinghouse listed > 1,650 active clinical practice guidelines in July 2005, 386 of which were devoted to diabetes alone.[12] Many of these guidelines overlap, and sometimes they contradict each another.

Clinical practice guidelines rarely address the treatment of patients with three or more chronic diseases, and such patients make up half of the population > 65 years of age in the United States.[13] When other aspects of chronic disease management (e.g., dietary or other lifestyle modifications, attending regular office visits, and laboratory monitoring) are added, the burden on elderly patients and their caregivers becomes onerous and, in many cases, unsustainable over time. Guidelines and quality assurance initiatives largely ignore the issue of marginal benefits of multiple medications as recommended by various sets of treatment guidelines.[14]

Psychosocial contributions
Patients and their families often demand medications and frequently ignore explanations about why drug therapy may not be in their best interests.[5] The lay media frequently report outcomes of clinical trials, often before complete reports are available to physicians through the medical literature. Brief reports in the press may give false hopes or heightened expectations for the benefits of new therapies without adequate explanation of their inherent risks. This drives demand from patients or their families for additional treatment. Likewise, direct-to-consumer advertising of prescription drugs places additional pressure on providers to prescribe drugs that may not be warranted.

Adverse drug reactions
Reactions to existing treatments may be misinterpreted as new medical conditions requiring treatment with additional medical or surgical intervention.[3] For example, edema caused by a thiazolidinedione might be mistaken as a sign of new-onset heart failure or as a worsening of preexisting heart failure. This may lead to the addition of a diuretic or the use of compression stockings if the root cause of the edema is not determined. Discerning the role that polypharmacy may play in such a problem may be difficult and requires meticulous and time-consuming review of a patient's medication history and medication-taking behaviors.

The prevalence of problems associated with multiple medications is probably underestimated. Increasing the number of medications prescribed increases the risk of adverse reactions.[14] The interaction of aging, concurrent comorbidities, pharmacokinetics, and polypharmacy places the elderly at increased risk of adverse drug reactions.[15]

Consequences of Polypharmacy

The major consequences of polypharmacy are listed in Table 2[3].

Duplication of therapy
The risk of duplication of therapy can be high; multiple agents in the same class are available, in addition to generic and brand name versions of the same medications. This potential is increased when patients see multiple prescribers without anyone conducting regular oversight of the drug regimen.

Decreased adherence
Medication adherence among patients with chronic conditions is disappointingly low. Providers may be inclined to overestimate the degree of medication adherence.[16] Adherence rates are diminished by complex drug regimens, incomplete explanation of benefits and side effects, lack of recognition of a patient's lifestyle, cost of medications, and communication style with patients.[17,18]

Adherence to a course of therapy is more likely when a patient understands the reasons for taking a medication and is involved in the decision to prescribe. Patients are more likely to have confidence in the prescriber if they are given basic knowledge of potential adverse effects and advice about what to do if such effects occur.[8] Increasingly, clinical practice guidelines are incorporating quality of life and patient preferences to increase adherence by both physicians and patients.[13]

Table 2. Consequences of Polypharmacy

- Adverse drug events
- Drug-drug interactions
- Potential duplication of therapy
- Increased costs
- Decreased adherence to the drug regimen
- Emergency department visits, hospitalizations, additional medical or surgical interventions
- Decreased quality of life

A Simple Method for Identifying Potential Polypharmacy
Review of a patient's drug therapy should begin with assessing the patient's adherence, asking about problems with side effects, and determining whether the provider's drug list in the patient's record matches the patient's own drug list. Asking patients to bring all of their medication containers to routinely scheduled office visits can facilitate this effort.
Providers can also help patients recall the need for each of their medications by adding the purpose to the directions for use in their written prescriptions (i.e., "once daily for blood pressure" or "two times a day for diabetes"). The medication list should include all prescription medications, including those taken routinely and those used on an as-needed basis; over-the-counter medications; herbal products; and vitamins or nutritional supplements. Medication lists constructed from memory or even from written lists are notoriously misleading and incomplete compared to examination of the actual medication containers.

Case Study

Presentation
A 70-year-old white man with diabetes for the past 15 years, atrial fibrillation, heart failure, hypertension, and dsylipidemia comes in for a routine office visit. His blood pressure is 140/82 mmHg, heart rate is 70 bpm, lungs are clear, and abdomen is soft and nontender. The patient is obese with 2+ pedal edema in both lower extremities; pedal pulses are decreased in both feet.

Recent lab data include: hemoglobin A_{1c} (A1C) 8.2%, LDL cholesterol 126 mg/dl, triglycerides 180 mg/dl, HDL cholesterol 45 mg/dl, potassium 5.3 mmol/l, albumin-to-creatinine

ratio 37.7 mg/g, serum creatinine 1.1 mg/dl, and estimated creatinine clearance 40 ml/min.

The patient's medication list, obtained from his chart, included:

- lisinopril, 10 mg daily
- pioglitazone, 15 mg daily
- metformin, 1,000 mg twice daily
- warfarin (per international normalized ratio)
- simvastatin, 80 mg at bedtime
- rosiglitazone, 4 mg twice daily
- fenofibrate, 160 mg daily
- atenolol, 25 mg daily
- glyburide, 10 mg twice daily
- diltiazem, 240 mg once daily
- potassium chloride, 20 mEq once daily
- furosemide, 40 mg once daily
- digoxin, 0.25 mg once daily
- propoxyphene/acetaminophen, 10/650; 1 tablet every 8 hours as needed for pain

Organizing the drug regimen

Scanning the drug list above in its present arrangement does not facilitate detection of potential problems. Rearranging the list by the major therapeutic categories to which each drug belongs (or disease state being treated) presents a different perspective. Because many medications may be used for more than one indication, the same medication may be listed under different therapeutic categories or disease states. Thus, the drug list above can be rearranged as follows:

Diabetes
- pioglitazone, 15 mg once daily
- rosiglitazone, 4 mg twice daily
- metformin, 1,000 mg twice daily
- glyburide, 10 mg twice daily

Hypertension
- lisinopril, 10 mg once daily
- atenolol, 25 mg daily
- diltiazem, 240 mg once daily
- furosemide, 40 mg once daily

Heart failure
- digoxin, 0.25 mg once daily
- atenolol, 25 mg daily
- lisinopril, 10 mg once daily
- furosemide, 40 mg once daily

Dyslipidemia
- simvastatin, 80 mg at bedtime
- fenofibrate, 160 mg daily

Atrial fibrillation
- warfarin

Miscellaneous
- potassium chloride, 20 mEq once daily

Analysis of the drug regimen

Following are opportunities to improve this patient's drug therapy and avoid medication-related problems.

1. Two thiazolidinediones (TZDs) are being used concurrently (rosiglitazone and pioglitazone). This is duplicative therapy, and one agent should be stopped. Furthermore, the patient has a diagnosis of heart failure, although the stage of the heart failure is not provided. TZDs can cause edema and either precipitate or worsen heart failure and are contraindicated in advanced stages of heart failure. This patient's heart failure should be carefully evaluated and monitored. If the heart failure worsens or if edema continues, consideration should be given to stopping the TZD.
2. Three oral antihyperglycemic medications are being used (the thiazolidinediones, metformin, and glyburide), and yet the patient's A1C is still > 8%. The provider should discuss initiation of insulin with this patient. This may ultimately lead to the discontinuation of the glyburide, especially considering its high dose and the period of time this patient has had diabetes. It is possible that the glyburide is no longer effective, given the extent of β-cell loss. The continued use of metformin may be problematic given the patient's estimated creatinine clearance. Even though the serum creatinine is normal, it may overestimate the actual creatinine clearance in an elderly patient.[5]
3. The patient is on three antihypertensives (the ACE inhibitor lisinopril, the β-blocker atenolol, and the nondihydropyridine calcium channel blocker diltiazem), without achieving the goal blood pressure of < 130/80 mmHg. As noted above, adherence to the regimen should be discussed. The lisinopril dose may be titrated upward, which may also help to lower the patient's elevated albumin-to-creatinine ratio.
   a. If the blood pressure does not respond to maximum doses of the ACE inhibitor, the β-blocker dose could be increased. It should be noted that both lisinopril and atenolol have dual roles in treating the patient's blood pressure as well as his heart failure.
   b. The continuing need for diltiazem should also be evaluated as the ACE inhibitor and the β-blocker doses are increased, and the patient should be cautioned to be alert for orthostatic changes.
4. Stopping the potassium supplement should also be considered, given that the patient's serum potassium level is already elevated. ACE inhibitors cause potassium retention. Thus, the potassium supplement may be unnecessary.
5. Furosemide may have been prescribed for the patient's heart failure, or it may have been started to treat the edema caused by the TZDs. The reason why furosemide was started should be investigated.
6. The patient is also receiving both a statin (at maximum dose) and a fibrate for dyslipidemia. This combination has been associated with an increased risk of rhabdomyolysis. The addition of insulin to the regimen and the resulting improvement in glycemic control may help to lower the elevated triglycerides. Thus, the continuing need for the fibrate should be evaluated over time.
7. Propoxyphene has been associated with confusion and sedation and is not recommended for use in the elderly.[5,19] Another analgesic should be considered; acetaminophen alone may be sufficient, but this should be evaluated further. Other options for treating the patient's peripheral neuropathy should be considered, including gabapentin, duloxetine, or topical lidocaine patches.
8. The patient is taking warfarin for atrial fibrillation. Warfarin interacts with many different medications. The list should therefore be reviewed for drugs that could either increase the potential for bleeding or decrease anticoagulant effects.

Conclusion

Multiple drug therapy has become the standard of care in the treatment of most chronic diseases. However, patients' drug regimens need regular review and evaluation to ensure that unnecessary and redundant medications are discontinued. Patients and providers need to actively and regularly discuss the goals of therapy and address concerns about adherence, cost, side effects, and other matters of significance in achieving an individualized and realistic therapeutic plan.

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