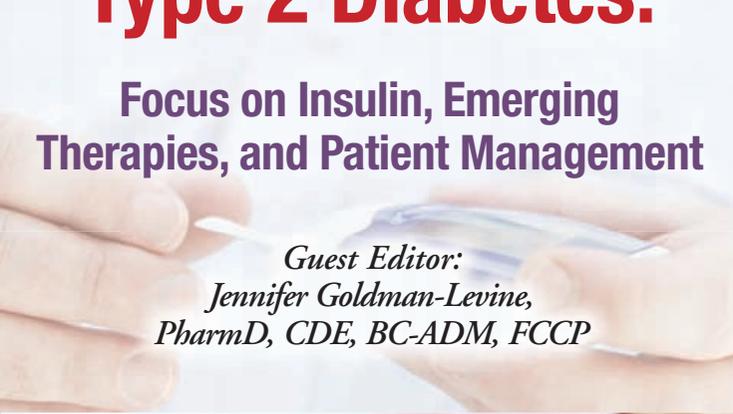
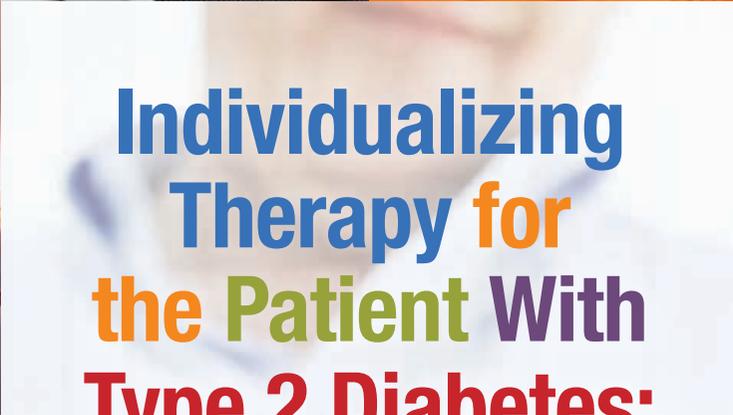




Pharmacist®



Individualizing Therapy for the Patient With Type 2 Diabetes:

Focus on Insulin, Emerging
Therapies, and Patient Management

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INTRODUCTION

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BASAL INSULIN: HISTORIC USE AND EMERGING THERAPIES

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UNCOVERING AND RESOLVING PATIENT ADHERENCE OBSTACLES

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UNCOVERING AND MANAGING HYPOGLYCEMIA: THE PHARMACIST'S ROLE

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Individualizing Therapy for the Patient With Type 2 Diabetes:

Focus on Insulin, Emerging Therapies, and Patient Management

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Individualizing Therapy for the Patient With Type 2 Diabetes: Focus on Insulin, Emerging Therapies, and Patient Management

Introduction

The development and progression of type 2 diabetes mellitus (T2DM) and its complications are characterized by complex heterogeneity of both a clinical and molecular nature.¹ T2DM is not a single disease, but rather a spectrum of metabolic disorders, each of which culminates in the common features of elevated fasting and postprandial blood glucose concentrations.¹ The heterogeneous nature of T2DM requires clinicians to consider patient-specific strategies for prevention and treatment that target the individual variability in pathogenic mechanisms, genetic risk factors, and clinical features of the disease. Although management strategies for patients with T2DM have traditionally not taken these patient-specific considerations into account sufficiently, improved understanding of the mechanisms underlying the diversity and complexity of T2DM is progressively leading to a more individualized approach to its management.^{1,2}

Clinicians may often be unsure as to optimal treatment strategies for specific patients with T2DM due to patient-level variability and complexities related to glycemic control. It can be challenging to effectively balance safety issues with the appropriate level of glycemic control to avoid microvascular complications in individual patients.² To address these concerns, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) convened a joint task force in 2012 to evaluate the evidence and develop recommendations for antihyperglycemic therapy for patients with T2DM.² The resulting statement emphasizes a patient-centered approach, but leaves that approach in the hands of the clinician.² According to the ADA-EASD statement, glycemic control is just one part of a multifactorial risk-reduction network (i.e., reduction

of macrovascular risk factors).²

In keeping with their framework of patient-centered therapy, the task force recommends that treatment strategies should consider the preferences and needs of individual patients.² The recommendations are less prescriptive than previous guidelines; rather, the intent is to persuade clinicians to consider the complex, progressive nature of T2DM in individual patients and the specific role of available therapies within those constraints. Clinicians should integrate currently available evidence within the context of identified patient- and disease-specific factors, such as limitations imposed by patient age and comorbidities.²

A defining component of individualized therapy is the direct involvement of patients in the decision-making process. Ultimately, it is patients who make the decisions regarding lifestyle modifications that they are willing to implement, and to some extent, medication treatment options that may be an acceptable part of their therapy.² Individual patients will have varying levels of desire for involvement in the process; this should be assessed and taken into account by the clinician during visits. Ideally, patients and clinicians should make decisions as a partnership, exchanging ideas and information and considering pros and cons of available treatments to determine the best course of action in each particular situation. Importantly, involvement of the patient in the decision-making process may improve adherence to therapy.²

Evidence-based therapy is dependent on the availability of primary source data from clinical trials. Currently, limited data exist to guide clinicians on how to individualize additional or alternative medication choices beyond the use of metformin.² Moreover, such data show median responses to therapy and do not necessarily indicate which *specific* patients would be likely to respond to particular treatments, or the reasons for underlying variations in treatment responses.² This is because clinical trials are structured to enroll highly selected and homogeneous patient groups and do not typically explore the full range

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of available treatment choices or their order of use.²

For many years, medication treatment options for patients with T2DM were limited to sulfonylureas and metformin.² Therapeutic advances during this period consisted of the introduction of a handful of new insulin formulations. However, several new treatment options have emerged during recent years, and new agents and treatment indications are on the horizon that will provide additional opportunities for the individualized treatment of patients with T2DM.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, both alone and in combination with insulin, have been evaluated in the treatment of T2DM. SGLT2 inhibition, unlike most currently-available therapies, is independent of increased insulin secretion or enhanced insulin action.³ SGLT2 inhibitors directly dispose of excess calories in the form of excreted glucose via the urine and have been shown to reduce measures of hyperglycemia, with a low propensity for causing hypoglycemia and a positive effect on blood pressure.³ Canagliflozin has recently been approved by the FDA for use in the United States.⁴ Dapagliflozin, a SGLT2 inhibitor, is currently available in Europe.^{3,5}

Long-acting glucagon-like peptide (GLP)-1 receptor agonist formulations, which target the incretin system, are currently available, with others in development. GLP-1 receptor agonists have been shown to improve glycemic control while reducing body weight and blood pressure in patients with T2DM.⁶ The once-daily GLP-1 receptor agonist liraglutide appears to provide better glycemic control compared with the twice-daily and the once-weekly long-acting release (LAR) formulations of exenatide.⁷ Taspoglutide, albiglutide, and dulaglutide are still under development.⁶ GLP-1 receptor agonists used concomitantly with insulin have demonstrated effectiveness in controlling both fasting and postprandial blood glucose levels and show positive effects on weight and a reduced rate of hypoglycemia in patients with T2DM.^{8,9} FDA approval of exenatide used concomitantly with insulin glargine, and liraglutide used concomitantly with insulin detemir, were granted in 2011 and 2012, respectively.⁸

The development of insulin has seen much advancement in recent years. The availability of recombinant human insulin (RHI) and neutral protamine Hagedorn (NPH) insulin and the introduction of pen delivery systems significantly improved the accuracy of insulin delivery and patient adherence. Unfortunately, however, the risk of hypoglycemia did not diminish with these products, due to the slow pharmacokinetic profile of RHI and variations in dosage and absorption of NPH.¹⁰ The devel-

opment of basal insulin analogs in the late 1990s and early 2000s were an improvement over NPH. Studies have shown that compared to NPH, both insulin glargine and insulin detemir effectively control blood glucose with less variability and lower risk of nocturnal hypoglycemia, in conjunction with a longer duration of action.¹¹

Several new formulations of insulin are currently being evaluated in patients with T2DM. Insulins in earlier stages of research include PEGylated insulin lispro (LY2605541) (ClinicalTrials.gov NCT01582451), an oral insulin formulation (ORMD0801) (ClinicalTrials.gov NCT00867594), and an inhalable insulin (Afrezza®; MannKind, Valencia, CA), which is composed of both a dry powder (Technosphere) insulin formulation and a breath-powered device.¹²⁻¹⁴ In addition, an ultra-fast-acting form of insulin aspart (FIAsp) is currently beginning phase III trials (ClinicalTrials.gov NCT01831765).¹⁵

Insulin degludec, a basal insulin with an ultra-long duration of action of more than 42 hours in adults, is currently approved in the European Union, Switzerland, Norway, Iceland, Japan, and Mexico.¹⁶ After initial review by the FDA, more data is being required for the agency to complete its review. Insulin degludec is associated with a lower incidence of hypoglycemia compared with other insulin formulations.¹⁶ It offers similar glycemic control and may allow patients more flexibility in the timing of their basal insulin dosage.^{17,18} The combination product of insulin degludec and liraglutide is being studied (ClinicalTrials.gov NCT01336023) as is degludec in a co-formulation with insulin aspart in a prefilled insulin auto-injector.^{19,20}

When evaluating new agents for T2DM, one should examine not only their effect on glycemic control, but the effect on cardiovascular risk factors and incidence of hypoglycemia as well. Many currently available treatments for T2DM are associated with eventual declines in glycemic control due to disease progression and declining β -cell function. The use of older, traditional therapies is associated with increased risk of hypoglycemia and weight gain. According to current guidelines, targets for T2DM therapy should include not only effective glycemic control, but also avoidance of weight gain, hypoglycemic events, and development or worsening of cardiovascular risk factors. Criteria to assess these goals should be built into clinical trial protocols of new agents to treat T2DM.⁶

The pharmacist is in an ideal role to positively impact patients' overall diabetes management. Hypoglycemia, which can have significant physiological and psychological effects, is feared by both patients and providers and is an important reason for the underutilization of insulin in

patients with T2DM.^{21,22} Pharmacists can identify potential risks for hypoglycemia as well as encourage patients to discuss their experiences with hypoglycemia. The pharmacist may work with the provider to suggest or modify therapy changes when appropriate and provide ongoing guidance and monitoring. Ultimately, this may empower the patient toward better disease self-management.

The purpose of this supplement is to describe how current and emerging strategies can be used to individualize therapy in patients with T2DM, with a focus on safety and efficacy in relation to hypoglycemia and adherence. A historical review of the development of basal insulin leading to the newest modalities available and on the horizon is examined in the first paper, **Basal Insulin: Historic Use and Emerging Therapies**. The second paper, **Uncovering and Resolving Patient Adherence Obstacles**, discusses how pharmacists have an established track record for improving patient adherence to therapy and are ideally positioned to identify and resolve barriers related to adherence and optimization of insulin therapy. Patient-centered and individualized strategies to improve adherence, such as motivational interviewing techniques, are discussed, with a focus on pharmacist-based assessment and monitoring. The final paper, **Uncovering and Managing Hypoglycemia: The Pharmacist's Role**,

focuses on how the pharmacist can leverage their access to patients to understand, manage, and prevent hypoglycemia. Short- and long-term effects of hypoglycemia are explored in detail. The physical and psychological impacts of hypoglycemia may lead to therapy nonadherence and suboptimal disease management; therefore, strategies for pharmacists to prevent, recognize, and treat hypoglycemia are a focus of this portion of the series.

In summary, personalized therapy for patients with T2DM refers to the incorporation of specific patient risk factors, disease characteristics, and preferences in designing diagnostic and treatment strategies that will optimize effectiveness, safety, and adherence to therapy for a given individual.¹ The patient-clinician partnership strategy requires that the clinician consider available evidence on various treatment options within the context of patient- and disease-specific characteristics. Importantly, this includes understanding individual patients' preferences and values relating to their own treatment, which may have an important impact on adherence to therapy. New and emerging therapies offer unique opportunities to individualize treatment based on patient- and disease-specific characteristics. Several of these novel therapies provide alternate choices to maximize patient outcomes and minimize risks. ■

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Individualizing Therapy for the Patient With Type 2 Diabetes: Focus on Insulin, Emerging Therapies, and Patient Management

Basal Insulin: Historic Use and Emerging Therapies

THE EARLY DEVELOPMENT OF INSULIN

In 1916, Nicolae Paulescu was the first individual to isolate insulin from an aqueous pancreatic extract which, when injected into a diabetic dog, normalized blood sugar levels.¹ The next great advancement in insulin occurred when Frederick Banting and Charles Best at the University of Toronto first isolated a glucose-reducing secretion from animal pancreas glands and, with John Macleod and James Collip, tested it on de-pancreatized dogs. The first successful in-human trial of insulin for the treatment of diabetes was performed in 1922 on a young boy in Toronto who was dying of type 1 diabetes mellitus (T1DM). Thus began the use of insulin to treat diabetes, a discovery that led to Banting and Macleod receiving a Nobel prize in 1923.² The earliest form of insulin was extracted from the pancreas of cows and pigs, and although mortality was improved in treated patients, adverse events (AEs) were significant and included allergic reactions, abscesses, lipodystrophy, and significant antibody formation. The development of an improved purification process by Collip in Toronto limited AEs, but resulted in a shorter-acting insulin formulation. The resulting need for multiple daily injections led to poor patient adherence and fluctuations between hyperglycemic and hypoglycemic states.³

In the 1930s, neutral protamine Hagedorn (NPH) insulin, a stabilized, slow-release insulin preparation, was developed. NPH insulin reduced hypoglycemic events and the number of injections needed per day. The combination of insulin with positively charged protamine gives NPH its prolonged duration (12-18 hours).³

With the advent of protein synthesis technology, human insulin was synthesized in the 1960s, and genetically engineered human insulin was produced in the late 1970s. In

August 1980, insulin dosing was standardized to U100 (100 units/mL), and other strengths were phased out in an effort to minimize dosing errors.⁴ Recombinant DNA technology was developed in the late 1970s and early 1980s, making large-scale synthesis of recombinant human insulin (RHI) possible.³ Hypoglycemia remained an issue due to the relatively slow pharmacokinetic (PK) profiles of RHI and the inconsistent dosing and absorption of NPH.³ The effective use of RHI and NPH was challenging for patients with diabetes because of the need for frequent dosing and precise timing in an attempt to achieve physiologic insulin levels; this negatively impacted patient adherence.³ Introduction of the first manufactured insulin pen in 1985, the NovoPen[®] (Novo Nordisk A/S, Bagsvaerd, Denmark), marked an advance in simplifying insulin dosing and delivery for patients with diabetes.⁵ Advantages of pens include improvements in accuracy, ease of use, patient satisfaction, quality of life, and adherence.⁵ In addition, continuous subcutaneous insulin infusion (CSII) offers some patients an option for good glucose control and improved lifestyle flexibility.⁶ The development of RHI and NPH and the introduction of pen delivery systems and CSII thus improved the accuracy of delivery and patient adherence, but the risk of hypoglycemia and need for multiple daily injections persists for many patients.

BASAL INSULIN ANALOGS

The development of basal insulin analogs in the late 1990s and early 2000s represented an advance over NPH in treating patients with diabetes and offered a once-daily option with relatively flat kinetics and a lower rate of hypoglycemia. These characteristics are particularly advantageous to those with type 2 diabetes mellitus (T2DM) who do not require postprandial bolus insulin injections. Basal insulin analogs are long-acting, injectable insulins that, compared with older preparations, more closely mimic the endogenous basal insulin levels normally maintained by the body between meals

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and at night. Their long-acting properties result from molecular modifications of the human insulin protein structure, leading to a more predictable pharmacodynamic (PD) and PK profile than the intermediate-acting human insulin, NPH.³

To best emulate physiologic insulin levels, the ideal basal insulin analog would have a true 24-hour duration of action from a single injection for all patients with diabetes as well as a flat PK profile. Compared with NPH, the basal insulin analogs insulin detemir and insulin glargine have relatively peak-free PK profiles, less within-patient variability of blood glucose, and a longer duration of action (TABLE 1).⁷⁻¹⁰ Although insulin glargine is soluble in acidic conditions, it precipitates into the neutral pH of subcutaneous tissues, resulting in prolonged absorption.⁹ Insulin detemir contains a molecular modification that facilitates both albumin binding and dihexameric complex formation, resulting in an injection depot.¹¹ In contrast to NPH, which is effective for 12-14 hours, insulin detemir and insulin glargine are effective for up to 24 hours.^{3,12} However, in some patients the duration of action (particularly of insulin detemir) is significantly shorter than 24 hours, thus requiring twice-daily injections.^{3,13} While insulin detemir and insulin glargine provide many benefits over NPH and allow once-daily injections for many patients, their initial use and titration still requires careful monitoring due to patient-specific variations in duration of action.

OTHER AVAILABLE INTERVENTIONS

Because many patients with T2DM still retain some insulin-producing and regulating activity, they are often able to achieve glycemic control with oral agents.¹⁴ Both the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) recommend metformin, which reduces hepatic glucose production, as the first choice oral agent in addition to lifestyle changes due to its mechanism of action and available data on safety and efficacy.^{15,16} Other oral antidiabetes drugs include, but are not limited to, sulfonylurea-insulin secretagogues, which stimulate insulin release; thiazolidinediones, which improve skeletal muscle insulin sensitivity and also reduce hepatic glucose production; dipeptidyl peptidase-4 (DPP-4) inhibitors, which increase glucose-dependent insulin secretion and decrease glucagon secretion; and sodium-glucose co-transporter 2 (SGLT2) inhibitors, which increase urinary glucose excretion. Pramlintide, a synthetic amylin analog, received United States FDA approval in 2005. Pramlintide complements insulin by targeting postprandial glucose, slowing gastric emptying and thus enhancing satiety, as well as inhibiting elevations in glucagon concentrations and increasing hepatic glycogen synthesis.^{17,18} Glucagon-like peptide-1 (GLP-1) receptor agonists are injectable non-insulin agents that stimulate endogenous pancreatic insulin secretion in a glucose-dependent manner.¹⁴ Despite lifestyle interventions and oral drug therapies, endogenous insulin mechanisms in patients with

Table 1. Time-Action Profiles of Insulin and Insulin Analogs

Insulin or Insulin Analog	Onset of Action	Time to Peak Action	Duration of Action
Rapid-acting, mealtime bolus insulins			
Aspart	5-15 min	30-90 min	4-6 h
Lispro	5-15 min	30-90 min	4-6 h
Glulisine	15 min	30-90 min	5.3 h
Short-acting human insulin			
Regular human insulin (RHI)	30-60 min	2-3 h	8-10 h
Intermediate-acting insulin			
Neutral protamine Hagedorn (NPH)	2-4 h	4-10 h	12-18 h
Long-acting insulins			
Detemir	0.8-2 h	Peakless	Up to 24 hr
Glargine	2-4 h	Peakless	20-24 h
Premixed insulins			
NPH/RHI 70/30 or 50/50	30 min	1.5-12 h	Up to 24 h
Biphasic insulin aspart 70/30	10-20 min	1-4 h	Up to 24 h
Insulin lispro 75/25	15-30 min	≤2 h	Approximately 22 h
Insulin lispro 50/50	15-30 min	30-90 min	Approximately 22 h

Source: Reference 10. Reprinted with permission.

T2DM progressively worsen over time with increasing insulin resistance and loss of β -cell activity, resulting in deteriorating glycemic control that cannot be treated effectively with oral agents alone.¹⁴ Many patients with T2DM will eventually require insulin to control their glucose levels, since insulin therapy, unlike various other antidiabetes agents, does not require endogenous insulin production.¹⁹

T2DM TREATMENT GOALS

In practice, gaps still remain in attempting to address the needs of certain populations of patients with diabetes. For some, the risk of nocturnal hypoglycemia is still a concern when using basal insulin analogs. In addition, currently available basal insulin analogs cannot be co-formulated with fast-acting insulin analogs to benefit those patients with high postprandial glucose levels. Ultimately, the aim of T2DM treatment is to obtain a patient-specific HbA_{1c} goal while avoiding adverse effects such as weight gain and hypoglycemia and preventing complications.

Uncontrolled diabetes may lead to cardiovascular (CV) disease, stroke, retinopathy, nephropathy, neuropathy, amputations, dental disease, and pregnancy complications.²⁰ The ADA recommends lowering HbA_{1c} to <7.0% in the majority of patients to reduce risk of microvascular disease.¹⁵ However, in selected patients (particularly those with short disease duration, long life expectancy, and no significant CV disease), more stringent goals (<6.5%) may be considered. Conversely, less stringent goals (<8.0%) may be employed in patients with a history of severe hypoglycemia, advanced complications, multiple comorbid conditions, or limited life expectancy.^{14,15} The AACE comprehensive diabetes management algorithm recommends an HbA_{1c} \leq 6.5% for patients who are healthy, who are at low risk for hypoglycemia, and who are without concurrent illness.¹⁶ Patients with concurrent illness and at risk for hypoglycemia should have individualized HbA_{1c} goals >6.5%.

Insulin is recommended as initial therapy for patients with very high plasma glucose levels (i.e., plasma glucose >300-350 mg/dL, HbA_{1c} levels \geq 10%-12%) or significant symptoms of hyperglycemia.¹⁴ If first-line therapy, usually with metformin, inadequately controls HbA_{1c}, two-drug combination therapy is warranted.^{14,16} Selection of the second drug should take into consideration patient-specific preferences and lifestyle patterns, disease status, cost issues, comorbid conditions, and susceptibilities to such AEs as weight gain and hypoglycemia. Individualization of optimal therapies should be ongoing throughout the course of the disease as endogenous glycemic control mechanisms progressively worsen.

Establishing the optimal time to introduce basal insulin therapy and treatment targets requires careful consideration of the previously mentioned patient characteristics.

For some patients with diabetes, intensification of basal insulin treatment will be required due to continued hyperglycemia. Options for intensification include adding prandial bolus dosing of a rapid-acting insulin (i.e., “basal-bolus” dosing), using an insulin premix, or, most recently, adding a GLP-1 receptor agonist.¹⁴ Balancing the efficacy, cost, safety, and convenience of these options will guide how best to intensify treatment for the individual patient. Adding prandial bolus injections of a rapid-acting insulin analog provides the most effective way to individualize glycemic needs due to the flexibility of individually dosing the basal and rapid-acting insulin components. However, this option increases the complexity of the regimen and requires an increase in the number of daily injections as well as careful timing of injections in conjunction with meals. The rapid-acting insulin analogs insulin lispro, insulin aspart, and insulin glulisine all demonstrate PK profiles that more closely emulate endogenous prandial insulin levels than does RHI. Premix insulin formulations reduce the number of daily injections required, but this option is less flexible than basal-bolus therapy. Conventional premixes include human insulin (e.g., biphasic human insulin 70/30), whereas newer options include insulin analogs (e.g., biphasic insulin aspart 70/30 and insulin lispro mix 75/25).²¹

Recent evidence supports the addition of GLP-1 receptor agonists to basal insulin for intensification of therapy in patients with T2DM.²² GLP-1 receptor agonists stimulate glucose-dependent insulin secretion, suppress glucagon release, signal satiety, and slow gastric emptying. GLP-1 receptor agonists approved in the U.S. for the treatment of T2DM include exenatide, exenatide long-acting release (LAR), and liraglutide. Others in development include albiglutide, dulaglutide, and lixisenatide. A systemic review of the literature found that basal insulin in combination with GLP-1 receptor agonist therapy lowered HbA_{1c} without additional risk of hypoglycemia, reduced the need for basal insulin, decreased postprandial glucose levels, and resulted in either weight loss or less weight gain.²² The most common AEs associated with GLP-1 receptor agonists are gastrointestinal in nature, although these usually improve over time. The dose is typically initiated low and titrated upwards to help minimize these effects.²³

Despite the advantages of improved glycemic control, convenient daily dosing, and the reduced risk of hypoglycemia associated with the use of basal insulin analogs,

patients may still encounter challenges with insulin use. Because patient concerns and attitudes surrounding insulin can determine therapeutic success, frank discussions between health care professionals and patients regarding beliefs are important. A survey of 1,400 people with T2DM reported that an unwillingness or ambivalence to initiation of insulin therapy was significantly associated with negative beliefs about insulin.²³ A review by Meneghini and Reid lists the most prevalent patient concerns about insulin, including the risk of hypoglycemia, perceived failure and lack of self-efficacy, concerns about weight gain, repeated failure to achieve glycemic control, needle phobia, dissatisfaction with treatment or treatment complexity, perceived negative impact of insulin therapy on quality of life, and social stigma of injecting insulin around others.¹⁹

Health care providers may be hesitant to initiate insulin therapy due to fear of hypoglycemia and/or weight gain or the belief that insulin causes adverse metabolic effects. Practical concerns may include time constraints and complexity in training patients to use insulin.²⁴ Findings from the Diabetes Attitude, Wishes and Needs (DAWN) study indicate that providers worry about using insulin in elderly patients, are concerned about the costs of insulin therapy, and fear patient resistance.²⁵

The development of once-daily basal insulin analogs and the availability of insulin pen devices have addressed many of these issues. Insulin pen devices facilitate accurate dosing with discretion, in combination with shorter and painless needles which can help improve adherence and remove some of the social anxiety surrounding insulin use.^{26,27} The new 4 mm 32-gauge pen needles have been shown to provide equivalent glycemic control, less injection-related pain, improved patient satisfaction, and similar insulin leakage compared with 5 mm and 8 mm 31-gauge needles.²⁸

DEVELOPING NEW THERAPIES FOR T2DM: FDA GUIDANCE FOR EVALUATING CARDIOVASCULAR RISK

In December 2008, the FDA issued an industry guidance aimed at limiting the CV risk of treatments for T2DM currently in development.²⁹ Because diabetes is associated with an elevated CV risk, and CV disease is the leading cause of morbidity and mortality in patients with diabetes, the FDA has recognized data on CV risk as an important component of new diabetes drug applications.³⁰

Prescribers should be aware that the FDA has different criteria for evaluating CV risk, depending upon the drug's status in terms of drug development. Thus, therapies that

become available during this transition time as the guidance develops will not necessarily be assessed by the same standards that were applied previously. For drugs in the planning stages of clinical testing, FDA guidelines suggest including patients with diabetes who are at a higher risk for CV events in phase II and III studies, designing longer studies to capture CV events, and creating independent "CV endpoints" committees to independently adjudicate CV events that occur in trials. In addition, the FDA recommends the inclusion of data meta-analyses, including an examination of subgroups, when designing clinical studies and statistical protocols. For drugs already in clinical development, the FDA suggests conducting a meta-analysis showing that the upper bound of the estimated risk ratio for CV events occurring with the investigational drug is <1.8, and if this is true, then conducting a post-marketing trial to definitively show that the upper bound of the estimated risk ratio is <1.3. If the meta-analysis cannot show that the upper bound of the estimated risk ratio is <1.8, then a large safety study is required before a new drug application is approved by the FDA.³¹

BASAL INSULIN ANALOGS IN DEVELOPMENT

There are several new basal insulins in various stages of development. To date, degludec has been the most studied and has the most available data for review; it is currently approved in the European Union, Switzerland, Norway, Iceland, Japan and Mexico. Two other basal insulins under development are PEGylated insulin lispro (LY2605541; ClinicalTrials.gov NCT01582451) and a new insulin glargine formulation (LY2963016; ClinicalTrials.gov NCT01421147).^{32,33} These are currently in phase III trials and are not available in the U.S. or globally at this time. To date, no published data are available on LY2963016. In addition, an ultra-fast-acting form of insulin aspart (FIAsp) is currently beginning phase III trials (ClinicalTrials.gov NCT01831765).³⁴

Insulin Degludec: Insulin degludec, a novel basal insulin analog with an ultra-long-acting and relatively peak-free PK profile, is currently approved for patient use in several countries/regions outside of the U.S.³⁵ After initial review by the FDA, more data have been requested from the agency to complete its review for the U.S. market. Insulin degludec demonstrates a much longer duration of action than currently available basal insulin analogs. Molecular modifications that produce its PK properties include a dihexameric structure in solution that ultimately results in slow and gradual delivery from the SC injection site into the circulation.^{36,37} This novel protraction mechanism and PK profile allow for a long duration of

action (>42 hours) in adults.³⁸

Clinical data demonstrate that insulin degludec provides similar glycemic efficacy compared to insulin glargine but is effective for ≥ 24 hours across all study populations.^{39,40} Due to its longer duration of action, only one daily injection of insulin degludec is required, in contrast to other basal insulin analogs that may require more than one injection per day. This may improve acceptance and adherence among patients who require more than one injection of basal insulin and prefer less frequent dosing. In addition, insulin degludec also appears to lower the risk of hypoglycemia (particularly nocturnal hypoglycemia) and permits flexible timing of once-daily dosing (8–40 hour intervals).^{39–41} Garber et al found that after 1 year, insulin degludec was as effective as insulin glargine in decreasing HbA_{1c} levels in patients with T2DM who required basal-bolus dosing to control glucose levels between and after meals. When used with mealtime insulin aspart, overall rates of hypoglycemia and confirmed nocturnal hypoglycemia were significantly lower with insulin degludec than with insulin glargine.⁴² In a meta-analysis of phase III data, insulin degludec significantly reduced the risk of confirmed and nocturnal confirmed episodes of hypoglycemia compared with insulin glargine, most markedly during the maintenance period (from week 16 to the end of trial).⁴³

Two different dose concentrations are currently in use in countries where insulin degludec is approved: a 100 U/mL dose and a 200 U/mL dose. These provide additional options for individualization of treatment. Insulin degludec 200 U/mL is pharmacokinetically bioequivalent to the 100 U/mL formulation; and may be beneficial in patients requiring larger doses.⁴⁴ Because of the previously mentioned advantages of insulin pens, including ease of use, improved safety, and easier dosing, insulin degludec will only be available in pens.

A co-formulation of insulin degludec with insulin aspart (a rapid-acting insulin analog) is also in development. The unique molecular modification of insulin degludec renders it the first basal insulin analog that can be combined with a rapid-acting insulin analog while preserving the PK profile and efficacy of each individual insulin. Overall, studies suggest that insulin degludec/insulin aspart may improve glucose management with less risk for hypoglycemia than other basal-bolus or premix treatment regimens.^{45–48}

PEGylated Insulin Lispro: Another long-acting basal insulin analog, PEGylated insulin lispro (LY2605541; Eli Lilly, Indianapolis, IN), is currently in phase III clinical

studies, although it is too early to predict when it may become available. The molecular modification in LY2605541 is the novel addition of a 20-kDa polyethylene glycol (PEG) to insulin lispro. The attached PEG moiety delays absorption and reduces clearance, thus prolonging its duration of action. Theoretically, the larger size of LY2605541 may cause it to be preferentially sequestered in the liver, which may be related to its glucose-lowering effect and observed weight loss.^{49,50}

Of the two published trials of LY2605541, one evaluated treatment of T2DM.^{50,51} This was a 12-week, randomized, open-label, multinational, phase II, treat-to-target study that examined the effectiveness of LY2605541 compared with insulin glargine in lowering fasting plasma glucose (FPG). Study patients were transitioned from either insulin glargine or NPH to LY2605541 ($n = 195$) or insulin glargine ($n = 95$), and continued to take metformin and/or a sulfonylurea during the study. The findings revealed that LY2605541 and insulin glargine showed similar efficacy in lowering FPG, although intraday blood glucose variability was reduced with LY2605541. While body weight significantly decreased in the LY2605541 group (-0.6 ± 0.2 kg, $P = .007$), there was a nonsignificant increase in weight in the insulin glargine group for an overall significant treatment effect on weight when comparing insulin groups, respectively ($P = .001$). The incidence and rate of total and nocturnal hypoglycemia were not significantly different between the two groups; however, patients taking LY2605541 experienced a 48% reduction in nocturnal hypoglycemia after adjusting for baseline hypoglycemia ($P = .021$). Although still in the normal range, liver enzymes and triglyceride levels were elevated in the LY2605541 group. Triglyceride levels normalized by the 16-week follow-up period. It is unclear if these changes were transitory due to the novel mechanism of action of LY2605541. These issues are being further investigated in subsequent trials.⁵⁰

A recent study by Curtis et al reported that patients treated with LY2605541 demonstrated significantly less fear of hypoglycemia compared with patients treated with insulin glargine after 12 weeks ($P = .022$).⁵²

COMBINATIONS UNDER INVESTIGATION

In addition to the recently completed and ongoing trials designed to assess the efficacy and safety of novel insulin types, several studies have investigated combinations of insulin and other agents. A fixed-dose combination of insulin degludec and the GLP-1 receptor agonist liraglutide is in development.⁵³ There are currently multiple

phase III trials examining the use of this combination in patients with T2DM. The fixed combination of lixisenatide and insulin glargine is also currently under development, and the results from a study published in 2013 revealed this combination provided improved overall and postprandial hyperglycemia.^{54,55} Co-administration of detemir and liraglutide has been shown to provide an additive glucose-lowering effect with no impact on the PK profiles of either agent. Therefore the use of these two agents in combination can be accomplished using the same titration algorithms used when insulin is added to oral antidiabetes agents.⁵⁶

NOVEL DELIVERY DEVICES

Oral Products: There are multiple oral insulin formulations in various stages of development, although peer-reviewed, published trials are not yet available. Limited information on ORMD0801 (Oramed, Jerusalem, Israel), an oral insulin drug, has been presented in abstract form. In a phase II multicenter, placebo-controlled, double-blind, 6-week study of patients with T2DM (n = 29), ORMD0801 reduced HbA_{1c}, fructosamine, and FPG. Reductions were statistically significant for fasting plasma insulin and C-reactive protein (CRP).⁵⁷ Although this study was small in size and short in duration, it does suggest not only a positive effect on blood glucose, but also on chronic inflammation. Similar findings regarding CRP were found in another small study of patients with T2DM.⁵⁸ Larger and longer studies will be needed to not only demonstrate safety and efficacy, but also to determine if the unique effect on CRP may be linked to long-term benefits for CV disease risk. In addition, ORMD0901, an oral GLP-1 receptor agonist (exenatide), to be administered with oral insulin, is in development. In animal studies, the combined drugs were shown to better control postprandial glucose levels than each drug individually.⁵⁹

Another oral insulin, IN-105 (Biocon, Bangalore, India), showed good safety and tolerability in clinical studies but failed to show efficacy based on the primary efficacy endpoint of lowering HbA_{1c} levels by 0.7% as compared to placebo.^{60,61} Further studies are planned in partnership with Bristol-Myers Squibb.⁶² Most recently, a successful phase I trial (NCT01597713) was announced for oral insulin NN1954 (Novo Nordisk A/S, Bagsvaerd, Denmark), which uses medium-chain fatty acids to achieve bioavailability (gastrointestinal permeation enhancement technology, or GIPET).^{63,64}

Inhaled Insulin: The failure of dry powder inhaled insu-

lin (Exubera[®]; Pfizer Labs, New York, NY) to gain traction in the medical marketplace ended many of the contemporaneous clinical programs focusing on inhaled insulin. A recent observational follow-up of patients with diabetes enrolled in Exubera clinical studies examined the incidence of lung cancer mortality. Preliminary results show a 3.2-fold increased risk of developing lung cancer and a 2.3-fold increased risk of lung cancer mortality among patients with diabetes in the Exubera treatment arms compared to those in the comparator arms.⁶⁵ One remaining inhalable insulin, Afrezza[®] (MannKind, Valencia, CA), is a fast-acting insulin compound that is still in development. This product is composed of both a dry powder (Technosphere) insulin formulation and a breath-powered device; the efficacy of the treatment is dependent upon both components.⁶⁶ In a report of 677 subjects with T2DM, prandial use of Afrezza plus basal use of insulin glargine showed significantly lower weight gain and fewer hypoglycemic events than patients with T2DM administered twice-daily premixed biphasic insulin (70% insulin aspart protamine suspension and 30% insulin aspart). Tolerability was reported to be similar, although there were increased reports of cough in the Afrezza treatment arm.⁶⁷

Transdermal Insulin: While different technologies for transdermal insulin delivery are in various stages of technological development, one product, the U-Strip[™] transdermal patch (Transdermal Specialties, Norwalk, CT), is scheduled for a phase II trial according to its manufacturer, although there have been no published studies on the product as of yet. Introduced at the ADA 2012 conference, the U-Strip patch utilizes ultrasound to expand skin pores enough to permit large molecular drugs to pass through the skin. The patch is being studied in four doses of insulin lispro (25, 50, 100, and 150 Units) and works with glucose monitoring-enabled smartphones. The patch is designed to deliver insulin in similar fashion to a pump, with basal dosing in the 25-, 50-, and 100-Unit patches and both basal and bolus dosing in the 150-Unit patch. According to information released by the company, the scheduled phase II trial will examine efficacy and safety of the patch for 4 months in 500 subjects with T2DM.⁶⁸

Insulin Patch Pumps: Research has shown that use of insulin pumps reduces the incidence of hypoglycemic events compared with multiple daily insulin injections.⁶⁹ Closed-loop systems utilize continuous glucose monitors, insulin pumps, and algorithms for pump control and are

superior to open-loop control in reducing hyperglycemia and hypoglycemia episodes and in achieving greater time in therapeutic target range. Insulin patch pumps may be optimal components of closed-loop systems because they involve no tubing that can detach or kink, they are small and discreet, and they adhere easily to the body. One patch pump, the V-Go[®] system (Valeritas, Inc, Bridgewater, NJ), is currently available in the U.S., and a number of other patch pumps are under development.

V-Go is a basal-bolus pump which utilizes a transdermal hydraulic patch. The pump does not have batteries or electronics and does not require programming. The original product received FDA premarket approval in 2005 and recently received FDA 510(k) approval. It is designed to simplify basal-bolus insulin therapy in adults with T2DM. It delivers insulin at a continuous basal rate with on-demand bolus dosing; preset basal rates can deliver 20, 30, or 40 Units of insulin per 24-hour period, as well as bolus dosing in 2 Unit increments up to 36 Units per 24-hour period.⁶⁹

Other patch pumps in development include the PaQ (CeQur[®]; CeQur, Ltd) and Finesse[®] (developed by Calibra Medical, Inc; acquired by Johnson and Johnson, Inc). CeQur is a 3-day pump which is currently approved in Europe and is a disposable basal-bolus patch pump to treat patients with T2DM. Finesse is a three-day bolus-

only disposable pump which is approximately one-fourth inch thick and the length of a paper clip. FDA approval to market this pump was recently received.⁶⁹

CONCLUSIONS

The initial discovery and development of insulin in the early 1900s revolutionized the treatment of diabetes and our ability to save patients' lives. The majority of progress with technology and improved insulins has occurred in the latter half of the century and continues to progress. The role of insulin in treating T2DM remains underutilized despite being an essential component in our options for better glycemic control. During the course of disease, patients with T2DM will require different methods of disease management and individualized therapy due to the progressive deterioration of endogenous insulin production, which often culminates in the need for insulin. The projected availability of new types of insulin agents in the future with benefits beyond those presently available presents a greater opportunity to tailor therapy to patient-specific needs and lifestyle patterns; however, the diversity of choices may also complicate therapeutic choices. It will be up to the entire health care team to educate and support patients in managing T2DM, determining which products are most appropriate and how to use them most effectively and safely. ■

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Individualizing Therapy for the Patient With Type 2 Diabetes: Focus on Insulin, Emerging Therapies, and Patient Management

Uncovering and Resolving Patient Adherence Obstacles

Pharmacists are ideally positioned to identify and resolve barriers related to medication adherence and the optimization of insulin therapy. They have an established track record for improving patient adherence to therapy, particularly through the use of patient-centered and individualized strategies such as motivational interviewing techniques and comprehensive medication review. Pharmacist-based assessment and monitoring can result in improved adherence to insulin therapy for patients with type 2 diabetes (T2DM), leading to better patient outcomes, fewer adverse events, and reduced utilization of health care resources and costs.

CONSEQUENCES OF MEDICATION NONADHERENCE

Health care costs related to diabetes and its complications are substantial. According to the American Diabetes Association (ADA), patients with diabetes utilize more health care resources than non-diabetic patients, including additional hospital inpatient care, outpatient clinic visits, emergency room visits, nursing facility stays, and prescription drug and medical supply use.¹ The ADA estimates that total national health care expenditures related to diabetes in 2007 were \$174 billion, with \$116 billion resulting from diabetes-related medical expenditures and \$58 billion from reduced national productivity. Diabetes-related medical costs included \$27 billion to directly treat diabetes, \$58 billion to treat diabetes-related complications, and \$31 billion in excess general medical costs.¹ This staggering financial burden is disproportionately endured by patients with diabetes and their families. Ultimately, however, the burden is passed on to society in the form of higher insurance premiums and reduced earnings and standards of living. Diabetes and its complications affect almost everyone in society either directly or indirectly.¹

Medication nonadherence, or failure to take medications as prescribed, is a widespread phenomenon that is

associated with lower treatment success rates, increased adverse events, increased overall mortality, and increased utilization of health care resources across many different chronic conditions.²⁻⁹ TABLE 1 describes several examples of these relationships from published research studies focusing on patients with chronic conditions such as diabetes and cardiovascular disease.^{2,4-9} Clearly, medication nonadherence is a critical problem leading to increased morbidity and mortality and increased health care resource use. Many opportunities exist for pharmacists to improve patient adherence to prescribed treatments, particularly in patients with chronic diseases such as T2DM.

Medication persistence, which differs from adherence, is another important measure of medication-taking behavior. *Adherence* is defined as the proportion of medication taken within a given time interval; it refers to the extent of conformity to day-to-day treatment recommendations with respect to timing, dosage, and frequency. By contrast, *persistence* refers to the act of continuing treatment for the prescribed duration and is measured from time of initiation of treatment to discontinuation.^{10,11} The proportion of patients who are persistent with treatment at one year is a commonly-used measure of persistence.¹¹ A Medicare database study evaluated persistence with antidiabetes medication (as well as with ACE inhibitors, angiotensin II receptor blockers, and lipid-lowering agents) and reported that each additional prescription fill was associated with significantly lower risk of hospitalization, fewer days in the hospital, and lower Medicare spending.¹² Patients must demonstrate persistence with therapy to derive its full benefit. The pharmacist can monitor this parameter and develop disease management plans for its improvement.

BARRIERS TO MEDICATION ADHERENCE

Much research has been conducted with the aim of identifying barriers to medication adherence and persistence. Many variables are important for optimal treatment adherence; these are frequently categorized as being specific to the patient, the provider, or the treatment itself.¹³ Patient-

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specific variables include sociodemographic factors, comorbidities, cognitive function, adverse effects associated with treatment, and the level of the patient's knowledge about the disease. In addition, health beliefs and perceptions of the disease and its treatments, such as the patient's perceived efficacy of treatment, may impact adherence.^{13,14} Provider-specific variables include gaps in knowledge about the disease and its treatments, as well as characteristics of the patient-provider relationship.^{13,14} Treatment-specific variables such as efficacy and adverse events, as well as the complexity of the regimen, also have an effect on adherence.¹³⁻¹⁵ Pharmacists have the potential to impact adherence to therapy by identifying these barriers and addressing them in ways that are specific to each patient.

EFFECT OF PHARMACIST INTERVENTIONS ON TREATMENT OUTCOMES AND ADHERENCE

Pharmacist Effect on Diabetes-Related Outcomes

Numerous recent studies have established the ability of pharmacists to positively impact disease outcomes. One

randomized, controlled trial compared pharmacist-physician collaborative management of poorly controlled diabetes to usual medical care in a community-based primary care group.¹⁶ Median decreases in glycosylated hemoglobin (HbA1c) levels of 1.5% and 0.4% were seen in the intervention and control groups, respectively ($P = 0.06$). Furthermore, significantly more intervention patients showed improvements in HbA1c levels of at least 1% compared with control patients (67.3% vs. 41.2%; $P = 0.02$).

In another study conducted in Jordan, patients with T2DM attending an outpatient diabetes clinic of a large teaching hospital were randomly assigned to usual care or intervention consisting of face-to-face directed education from a clinical pharmacist about T2DM, medications, and lifestyle changes, followed by 8 weekly telephone follow-up calls to resolve concerns.¹⁷ Patients in the intervention group experienced a significant reduction in HbA1c levels at 6 months compared with the control group (0.8% reduction vs 0.1% increase, $P = 0.019$). Six of eight secondary biomarkers were also significantly improved (fasting blood

Table 1. Relationship Between Medication Adherence and Clinical Outcomes

Study	Medical Condition	Study Design	Outcome
Mashitani et al (2013) ⁴	T2DM	Registry-based cohort (N=1,441 patients on insulin)	Patients with higher self-reported adherence to insulin had significantly better glycemic control.
Aikens & Piette (2013) ⁵	T2DM	Prospective (N=287 adult T2DM outpatients; 40% on insulin)	Patients with higher self-reported medication adherence had significantly better glycemic control.
Mazzaglia et al (2009) ⁶	Hypertension	Prospective (N=18,806 newly treated hypertensive patients)	Newly-treated antihypertensive patients free of cardiovascular disease at baseline and adherent to medications had significantly reduced risk of cardiovascular disease (4.6±1.2 years follow-up).
Jackevicius et al (2008) ⁷	Myocardial infarction	Registry-based cohort (N=4,591 post-myocardial infarction patients ≥65 years of age)	One-year mortality after acute myocardial infarction was significantly higher for patients who did not fill all of their discharge medication within 120 days post-discharge.
Roebuck et al (2011) ⁸	Chronic vascular disease	Claims database analysis (N=135,008 patients with congestive heart failure, diabetes, hypertension, and/or dyslipidemia)	Although improved medication adherence increased pharmacy costs, substantial overall savings were realized (largely due to reductions in hospitalizations and emergency department use).
Sokol et al (2005) ⁹	Diabetes, hypercholesterolemia, congestive heart failure, hypertension	Claims database analysis (N=137,277 patients)	High medication adherence was associated with significantly lower disease-related medical costs in patients with diabetes and hypercholesterolemia; higher medication costs were more than offset by reductions in overall medical expenditures. Hospitalization rates were significantly lower for patients with better adherence across all four medical conditions.
Nasseh et al (2012) ²	Diabetes, hypertension, and/or dyslipidemia	Economic cost model (per-person cost estimates of non-adherence from published studies applied to estimated proportions of patients who were adherent to medications)	Total health care cost (to insurers, patients, and society) of nonadherence per adult diagnosed with at least one of the three conditions was \$453 in 2010; the total overall health care cost of nonadherence across all adults was \$105.8 billion.

Source: References 2,4-9.

glucose, systolic and diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol [LDL-C], and serum triglycerides), but high-density lipoprotein cholesterol (HDL-C) or body mass index (BMI) were not improved. In addition, multiple self-care activities (diet, exercise, and self-monitoring of blood glucose) were significantly improved.¹⁷

Heisler et al randomized 16 primary care teams at five medical centers to the “Adherence and Intensification of Medications” intervention or usual care.¹⁸ The primary outcome measured in this prospective, multisite, randomized trial was change in systolic blood pressure for 1,797 patients receiving the intervention and 2,303 patients receiving usual care. The intervention consisted of patient-centered motivational interviewing delivered by the pharmacist to identify barriers to adherence and resolve medication issues, and was aimed at improving blood pressure control in patients with diabetes. Patients receiving the intervention achieved more rapid blood pressure reduction, although patients receiving usual care achieved equally low systolic blood pressure levels by 6 months after the intervention period.¹⁸

Pharmacist Effect on Medication Adherence

A great deal of research has focused on the ability of pharmacists to improve adherence to prescribed treatments in patients with chronic conditions, including T2DM. Odegard et al evaluated adherence in 265 patients with T2DM from four community chain pharmacies who were taking oral diabetes medications and who were late for refills by at least 6 days.¹⁹ Adherence was measured by calculating elapsed days between medication refills. Patients who received telephone-initiated support were significantly more adherent to medications at 12 months.

Sarangarm et al evaluated pharmacist medication therapy counseling and disease-state interventions in 279 patients discharged from an internal medicine unit.²⁰ The intervention consisted of discharge counseling and a follow-up telephone call. Patients were considered adherent to medication therapy if they picked up their prescription within 30 days of discharge or if they had an adequate amount of medication at home based on prescription refill histories prior to hospitalization. Patients who received the intervention demonstrated significantly improved medication adherence and significantly higher patient satisfaction.²⁰

A prospective, randomized trial assessed the effect of pharmacist interventions on medication adherence and quality of life in 52 patients with hypertension.²¹ Pharmacist interventions included patient counseling, patient printed information, and frequent telephone

reminders. Adherence was measured via the Morisky Medication Adherence Scale (MMAS) and the Medication Adherence Report Scale (MARS). The intervention was associated with significantly improved medication adherence and quality of life scores.²¹

Pharmacist Effect on Medication Regimen Complexity

Pharmacists can successfully reduce the complexity of patients’ medication regimens. A before-and-after study of 391 patients at least 60 years of age was conducted in two acute general medicine wards and two subacute aged care wards.²² Patients received usual care in the pre-intervention period. During the intervention period, pharmacists reviewed the medication regimen for complexity prior to patient discharge and made recommendations to simplify regimens when appropriate. Medication complexity was measured using the Medication Regimen Complexity Index, a validated measure of regimen complexity. The improvement seen in medication regimen complexity during the intervention period was equivalent to reducing the regimen by one to two medications.²²

STRATEGIES FOR PHARMACIST-BASED IMPROVEMENTS IN ADHERENCE

Medication Therapy Management

The pharmacist is typically considered the most accessible health care provider and as such can support frequent monitoring and communication between the physician and patient.²³ Medication therapy management (MTM) is a service designed to improve collaboration among pharmacists, physicians, and other health care professionals and enhance communication between patients and their health care team.²⁴ The ultimate goal of MTM is to optimize medication use for improved patient outcomes. MTM services are distinct from medication dispensing and instead focus on patient-centered (rather than product-centered) care. These services encompass the evaluation of the patient’s complete medication therapeutic regimen and empower patients to take an active role in managing their medications. The success of this model is dependent on pharmacists working collaboratively with physicians and other health care providers to optimize medication use in accordance with evidence-based guidelines. MTM services have demonstrated positive clinical, economic, and humanistic outcomes across diverse medical conditions and patient populations and in a variety of care settings.²⁴ In fact, some state Medicaid and Medicare Part D programs use pharmacist-based comprehensive medication review as a

foundation on which to build MTM programs. Private-sector organizations are beginning to follow suit, and pharmacist-based MTM programs are becoming increasingly common.

Motivational Interviewing and Insulin Management

Pharmacists are ideally suited to work closely with individual patients to optimally manage the use of insulin to treat T2DM. They can successfully use strategies such as motivational interviewing (MI) to identify and resolve patient-specific barriers to optimal adherence to insulin therapy. In addition, pharmacists can work closely with physicians and other clinicians to alleviate misconceptions they may have regarding optimal use of insulin.

MI is a well-known, scientifically tested method for interacting with patients, and is considered a useful strategy of intervention to resolve issues related to treatment of disease and other lifestyle problems.²⁵ A systematic review and meta-analysis concluded that motivational interviewing in a scientific setting outperforms traditional advice given in the treatment of diseases and behavioral problems.²⁵ MI is a patient-centered approach with a main focus of facilitating behavior change by resolving patient ambivalence about the change.²⁶ It differs from other patient-centered approaches in that it is directive; systematic strategies are used to explore ambivalence in such a manner that patients are likely to choose to change their behavior in the desired direction.²⁶ Through MI, pharmacists can establish individualized relationships with patients that are respectful, trusting, and collaborative.²⁷

MI, as it applies to optimizing medication adherence, is guided by four principles represented by the acronym “RULE.”²⁸ The first of these principles, “Resisting righting reflex,” is based on the concept that the desire of the clinician (in this case, the pharmacist) to correct problems may be counterproductive to patients, as ambivalent patients may be likely to present a counter-argument. Rather, the patient should be the one who presents the argument for medication adherence. The second principle, “Understand patient’s motivation,” states that patients’ motivations for treatment adherence (as opposed to motivations of the pharmacist) are most likely to result in improvements. Instead of telling patients why they should be adherent, the pharmacist should learn about patients’ specific concerns and motivations by asking them why they would want to be more adherent and how they would attempt to achieve that goal. The premise of the third principle, “Listen to patient,” is that the patient typically has the “right” answers to their own issues with adherence and which behavior changes will improve it; the pharmacist should listen to the patient and identify those

issues through two-way dialogue. The last principle, “Empower patient,” affirms that the patient, when empowered, becomes the pharmacist’s consultant on the patient’s life and can best effect positive change.

In MI, these four principles are implemented by the pharmacist by the use of three different skills. The first skill, “Asking,” is based on the tendency of pharmacists and other clinicians to ask closed questions which cut off conversation and erect barriers to adherence. Successful MI incorporates open-ended questions which encourage discussion about change, and allows patients to talk things through. For example, rather than asking, “When was the last time you took your insulin?” the pharmacist should instead ask, “How do you fit your insulin into your daily routine?” The latter provides a base for a two-way discussion focusing on barriers to using insulin as prescribed and how these barriers might be successfully addressed in specific patients.²⁸ The second skill, “Listening,” is considered a key skill in MI, because only by listening to the patient can the pharmacist identify the specific behavior change desired. The pharmacist should avoid the creation of emotional roadblocks caused by interrupting the patient and interfering with their train of thought. Even statements that seem to be positive can generate resistance if they are implicitly judgmental. Examples include sympathizing (rather than empathizing) and agreeing (rather than affirming). Avoiding judgmental statements and concentrating on listening to the patient is vital to the success of MI.²⁸ The third skill, “Informing,” is necessary when adherence is a concern and the pharmacist needs to provide information to the patient. Two methods for providing information include the “chunk-check” method and the “learning opportunities” method. In the former method, digestible chunks of information are provided to the patient, with time allotted after each chunk to ensure that the patient has comprehended the information. The latter method relies on open-ended questions to elicit specifically what the patient needs to know (e.g., “What would you most like to know about taking your insulin?” and “What do you know about taking your insulin?”). This allows the pharmacist to draw the patient into a conversation about adherence and correct any specific misperceptions that the patient may hold.²⁸ In summary, the goal of MI is to allow the pharmacist to identify patient-specific barriers to adherence and to implement individualized solutions to resolve each challenge.

Challenges to Optimal Use of Insulin

Many patient- and clinician-specific challenges related specifically to insulin use have been identified. These may result in resistance of the clinician to prescribe insulin, as well as suboptimal patient adherence to insulin therapy.

Adherence to insulin therapy in patients with T2DM has been reported to range from 71%-77%.^{29,30} A survey conducted by Polonsky et al documented that patient unwillingness to use insulin therapy was common; 28.2% said they would be unwilling to take insulin if prescribed, and another 24.0% and 23.3% said they would be slightly willing and moderately willing, respectively.³¹ This unwillingness, termed “psychological insulin resistance,” may be due to patient fears of injections (“needle phobia”), feelings of personal failure, hesitation to use insulin in public or in front of family and friends, and fear of hypoglycemia or weight gain related to insulin use.³²⁻³⁵ Alleviating patient as well as clinician concerns about the pain and discomfort patients may experience from injections is a key area for potential improvement in adherence and attitude toward insulin therapy.³⁵ Patients’ sense of personal failure represents one of the strongest reasons for resistance to insulin therapy, as it is perceived as the inability to adequately control T2DM by lifestyle modification, use of oral medications, or weight loss.³² Pharmacists can avert these beliefs by explaining to the patient that insulin is part of the normal continuum of care as the disease progresses and that insulin therapy will make the patient feel better. They can also alleviate fear of injections by explaining to the patient that improvements in insulin delivery techniques have resulted in insulin needles that are short and very small in diameter, and by showing the patient devices for insulin injection or providing an in-office demonstration for the patient that includes the first injection.³²

Clinicians may be hesitant to prescribe insulin therapy due to apprehension about hypoglycemia or other adverse events, or due to perceived complexity of insulin regimens.³²⁻³⁴ In some cases they may also use insulin therapy as a “threat” to compel better adherence to initial interventional strategies.^{32,33,36} Clinician hesitance to initiate insulin therapy may be due to physiologic concerns for their patients, such as the belief that insulin causes adverse metabolic effects, or fear of hypoglycemia or weight gain. Practical concerns can also play a role; these may include clinician awareness of patient anxiety, complexity in training patients to properly use insulin, and time demands related to managing insulin therapy.³² In addition, findings from the Diabetes Attitude, Wishes and Needs (DAWN) study indicate that providers are concerned about the costs of insulin therapy for patients, patient resistance to insulin therapy, and using insulin in elderly patients.³⁷

Pharmacist-Led Optimization of Insulin Use

In reality, insulin is actually associated with positive effects on cardiovascular status.^{32,36} Furthermore, patient anxieties

about insulin frequently disappear after therapy has begun.³² New and emerging insulin formulations and options have the potential to alleviate the syringe/vial issue and can simplify insulin treatment regimens. These formulations are frequently associated with fewer adverse events such as hypoglycemia.^{32,38,39} Insulin regimens can also be simplified as much as possible, by reducing the number of doses in favor of two-agent regimens (e.g., basal insulin plus metformin or metformin plus an insulin premix), by using insulin pen devices, or by using the latest addition to insulin delivery, a disposable patch pump. Pharmacists can and should educate prescribers of these options as they become increasingly available.

Pharmacists can also empower patients to self-monitor their blood glucose and adjust insulin treatment accordingly, which may help patients avoid hyperglycemia and hypoglycemia.³² In the PREDICTIVE 303 trial, patient-directed adjustment of insulin detemir following a titration algorithm was associated with similar glycemic control compared to investigator-adjusted insulin. A higher rate of hypoglycemia was observed in the patient-directed adjustment group, possibly because of more aggressive insulin dose adjustments, but the investigators concluded that the vast majority of patients in both groups were effectively treated with insulin therapy with minimal risk of hypoglycemia and no weight gain.^{40,41} In another prospective, multicenter, randomized trial, Davies and colleagues reported that glycemic control was improved in patients with T2DM using a self-titration algorithm to adjust insulin glargine compared to patients with investigator-led insulin initiation and titration.⁴² These studies suggest that a patient-driven approach for blood glucose monitoring and insulin adjustment is safe and effective, and may empower patients to take greater responsibility in their own care.

Importantly, pharmacists are ideally situated to encourage and support communication between the patient and physician for monitoring of insulin. Pharmacists should always follow up with the patient and communicate progress clearly with the physician on a regular basis. This relationship between the pharmacist and physician can be a formal collaborative practice agreement, with detailed and specific processes for communication and patient interventions. The collaborative practice agreement may include patient training by the pharmacist on insulin titration and use of devices, procedures for injection, and measuring doses. It may also include discussion and coordination with the patient about treatment goals and education on potential adverse events (e.g., identification and management of hypoglycemia). Such a relationship requires flexibility, trust, and ongoing two-way communi-

cation between the pharmacist and physician. It also requires that the pharmacist stay in touch with the patient every few days to allow for monitoring of outcomes and adverse events across time.

The pharmacist is typically considered the most accessible health care provider and, as such, can effectively

serve as the intermediary in frequent monitoring and communication between the physician and patients with T2DM. An important goal for pharmacists should be to spread a positive message to both patients and other clinicians regarding the use of insulin as part of the optimal and appropriate treatment for patients with T2DM. ■

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Individualizing Therapy for the Patient With Type 2 Diabetes: Focus on Insulin, Emerging Therapies, and Patient Management

Uncovering and Managing Hypoglycemia: The Pharmacist's Role

UNDERSTANDING THE MAGNITUDE AND CONSEQUENCES OF HYPOGLYCEMIA

Hypoglycemia can present significant physical and psychological challenges to achieving glycemic goals, for both patients with diabetes and health care providers.¹ The symptoms of hypoglycemia range from minor discomfort (e.g., palpitations, sweating, and tremor) to more severe manifestations, including cognitive impairment, coma, seizure, and rarely, death.^{1,2} The American Diabetes Association (ADA) defines hypoglycemia as a blood glucose level ≤ 70 mg/dL.² Hypoglycemia can be further classified based on the presence or absence of blood glucose readings and/or symptoms. Relative symptomatic hypoglycemia, in particular, occurs when the patient with diabetes reports symptoms of hypoglycemia accompanied by a blood glucose concentration >70 mg/dL, which can be a sign of poorly controlled blood glucose or that the patient is not taking their medications, including insulin, correctly. In fact, errors with use of medication are among the most common causes of hypoglycemia among patients with type 2 diabetes mellitus (T2DM).³ A 2013 publication from the Workgroup of the ADA and The Endocrine Society classified hypoglycemia according to specific criteria (TABLE 1).⁴ Nocturnal hypoglycemic events are the most feared and potentially harmful.^{5,6} Severe nocturnal episodes may contribute to “dead-in-bed” syndrome, defined as sudden death among young patients with dia-

betes who have no history of long-term complications, which is responsible for approximately 6% of deaths in patients with type 1 diabetes mellitus (T1DM).⁷

Recurrent hypoglycemia has been shown to reduce the threshold for a counterregulatory response necessary to restore euglycemia during a subsequent episode of hypoglycemia. This phenomenon may contribute to the development of hypoglycemic unawareness.^{8,9} Hypoglycemic unawareness is extremely dangerous, as the number of severe episodes can be up to nine-fold higher than in patients with normal awareness, due to the lack of autonomic symptoms warning the patient that hypoglycemia is taking place.^{8,9} Evidence (mostly in T1DM studies) suggests that nocturnal hypoglycemia can contribute to impaired glucose counterregulation and hypoglycemic unawareness.^{2,10} The psychosocial impact of hypoglycemia adds to the disease morbidity and can induce behavioral changes that negatively affect treatment and glycemic outcomes, thus placing patients at further risk for long-term diabetes complications.^{11,12}

A recent survey of 813 patients with T2DM, identified from a large United States health plan, found that 31% of patients with self-reported confirmed hypoglycemia (symptoms, accompanied by blood sugar levels <70 mg/dL) admitted adjusting their antidiabetes medications, and 88% reported adjusting their eating habits in response to hypoglycemia.¹² A Canadian-based survey conducted by Leiter et al. including patients with T1DM ($n = 202$) and T2DM ($n = 133$), reported that 63.2% of T2DM patients reported consuming additional food following a severe episode of hypoglycemia and 57.9% reported modifying their insulin dose.¹¹ Mild or moderate hypoglycemia may also lead to lifestyle modifications, with 62.9% of T2DM patients from this same survey reporting consuming additional food, and 43.3% reporting modifying their insulin dose.¹¹

Fear of hypoglycemia is another psychosocial chal-

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Table 1. American Diabetes Association and Endocrine Society Classification of Hypoglycemia

Classification	Definition
Severe hypoglycemia	<ul style="list-style-type: none"> An event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration
Documented symptomatic hypoglycemia	<ul style="list-style-type: none"> An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 70 mg/dL
Asymptomatic hypoglycemia	<ul style="list-style-type: none"> An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 70 mg/dL
Probable symptomatic hypoglycemia	<ul style="list-style-type: none"> An event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dL
Pseudo-hypoglycemia	<ul style="list-style-type: none"> An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured plasma glucose concentration >70 mg/dL but approaching that level

Source: Reference 4.

lence that can significantly affect both T1DM and T2DM patients, regardless of treatment regimen. A study by Marrett in T2DM patients found that patients with any history of mild, moderate, or severe hypoglycemia reported significantly greater fear of experiencing future episodes than patients who did not report hypoglycemia, with the magnitude of fear increasing with the severity of the hypoglycemic episode.¹³ It is not surprising then that hypoglycemia is also associated with a negative impact on health-related quality of life (QoL), with QoL declining in parallel with both the frequency and severity of hypoglycemic episodes.^{13,14} These findings emphasize the importance of educating patients about hypoglycemia, with the ultimate goal of preventing hypoglycemic episodes from occurring in the first place.

The economic burden of hypoglycemia must be considered. Costs to both an individual and society (health care resources, loss of work productivity) can be substantial.¹⁴ A recent U.S. study conducted between 2004 and 2008 revealed that the average costs attributed to a hypoglycemia-related event for patients with T2DM were \$17,564 for an inpatient admission; \$1,387 for an emergency department visit; and \$394 for an outpatient visit.¹⁵ A multinational survey published in 2011 con-

ducted in the U.S., France, United Kingdom, and Germany assessed the impact of nonsevere hypoglycemic events (those that do not require assistance from another individual) on productivity and costs.⁶ Nonsevere hypoglycemic events, which occur much more frequently than severe events, accounted for an average of 9.9 hours of work time lost per event and were associated with lost productivity costs ranging from approximately \$15 to \$93 per event.⁶ Interestingly, the highest costs reported in this analysis were associated with a nonsevere nighttime (nocturnal) event, with 22.7% of respondents who experienced a nocturnal event reporting that they were either late for

work or missed a whole day of work.⁶ Additional costs related to increased blood glucose monitoring (e.g., additional lancets, test strips, alcohol swabs) in response to a hypoglycemic event should also be taken into consideration.¹⁴

While the incidence of medication-induced hypoglycemia in T2DM patients is generally less than T1DM patients, T2DM hypoglycemia rates increase over time and approach those of T1DM patients.¹ Taking into account the greater prevalence of T2DM versus T1DM and the fact that insulin can be utilized both early and late in the course of the disease, health practitioners should not underestimate the overall burden of hypoglycemia in the T2DM population.¹

Long-term effects of hypoglycemia in patients with T2DM have been linked to cognitive decline and cardiovascular (CV) complications.¹⁶⁻¹⁹ Prior episodes of severe hypoglycemia may increase the risk for cognitive impairment, particularly among elderly patients.^{16,17} An analysis of elderly T2DM patients found an increased risk of dementia among patients with a history of severe hypoglycemia compared with those with no hypoglycemia, and this risk increased with the number of episodes of severe hypoglycemia.¹⁶ Another analysis found that elderly patients with T2DM who reported at least one

severe hypoglycemic episode in their lifetime had lower late-life general cognitive ability than those who never reported an episode of severe hypoglycemia.¹⁷ These results, in part, have led to the ADA recommending a more relaxed glycemic goal for some patients in order to avoid acute complications since older adults with T2DM may be at greater risk of hypoglycemia that is associated with dementia.²⁰

The potential link between hypoglycemia and cardiac events gained attention after results were published from three pivotal randomized trials, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, Veterans Affairs Diabetes Trial (VADT), and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial that included patients with an average duration of T2DM of 8.0-11.5 years.^{4,18,19,21-23} These trials demonstrated the negative results of strict blood glucose control on cardiovascular outcomes in some patients with T2DM. Collectively, these trials enrolled almost 24,000 patients with T2DM at high risk for cardiovascular outcomes and randomized patients to receive up to 5 years of intensive blood glucose control therapy or standard therapy.²¹ Glycosylated hemoglobin (HbA_{1c}) goals in the intensive arms were <6.0% for ACCORD, <6.0% for VADT, and <6.5% for ADVANCE.^{18,22,23} The ADVANCE and VADT trials reported no significant decrease in CV events and all-cause mortality among the intensive blood glucose control arms, although VADT was underpowered to explore this relationship, and the ACCORD trial revealed a significant increase in mortality, leading to early termination of intensive therapy.^{18,19} Several explanations of the findings of ACCORD have been offered, including chance, greater weight gain, and specific medication effects, but perhaps the most convincing explanation was hypoglycemia, which was three-fold higher in the intensive arm of ACCORD.^{4,19} The rate of death from CV events for patients receiving intensive blood glucose control in ACCORD was 2.6% compared with 1.8% for patients receiving standard blood glucose control (hazard ratio [HR] 1.35, confidence interval [CI] 1.04-1.76, $P = .02$).^{19,22} Death from any cause was 5.0% compared with 4.0% for those receiving intensive therapy and standard therapy, respectively (HR 1.22, CI 1.01-1.46, $P = .04$).¹⁹ On the other hand, patients receiving intensive blood glucose control in the ADVANCE trial experienced no significant reductions in all-cause mortality and CV disease.²³ In the ACCORD and VADT trials, the percentage of severe hypoglycemic events (defined as requiring assis-

tance and impaired consciousness, respectively), were significantly higher in the intensive blood glucose treatment arms compared with the standard arms (16.2% vs. 5.1%, $P < .001$, respectively, in the ACCORD trial; 21.2% vs. 9.9%, $P < .001$ in the VADT trial).^{18,19,21} In the ADVANCE trial, the percentage of patients with at least 1 severe hypoglycemic event (defined as requiring assistance) was also higher in the intensive blood glucose control arm than in the standard arm (2.7% vs. 1.5%, $P < .001$).²³

Occurrence of hypoglycemic events was explored in order to determine the possible factors contributing to CV and mortality results. Post-hoc analysis of the ACCORD data revealed that severe hypoglycemia was associated with an increased risk of death regardless of the study arm.²¹ In addition, analysis of results obtained during a median of 3.4 years of follow-up revealed that patients did not reach their treatment goals, and therefore had higher average A1C and a greater risk of death.²⁴ The VADT trial also found that a recent severe hypoglycemic event was associated with an increased risk for CV death (HR 3.72, 95% CI 1.34-10.4, $P < .01$) and all-cause mortality (HR 6.37, 95% CI 2.57-15.8, $P = .0001$).²¹ Analysis of the ADVANCE trial found that patients reporting severe hypoglycemic events had significantly higher adjusted rates at 6 months after the episode for negative outcomes compared with those reporting no severe hypoglycemic events; negative outcomes included major macrovascular events (HR 2.75, 95% CI 1.22-6.19, $P = .01$), major microvascular events (HR 2.41, 95% CI 1.07-5.43, $P = .03$), death from any cause (HR 4.28, 95% CI 2.36-7.75, $P < .001$), death from CV cause (HR 3.57, 95% CI 1.43-8.90, $P = .01$), and death from non-CV-related cause (HR 4.95, 95% CI 2.26-10.80, $P < .001$).²⁵ Major macrovascular events included CV death, nonfatal myocardial infarction, or nonfatal stroke; major microvascular events included new or worsening retinopathy or nephropathy.²⁵

The current ADA Standards of Medical Care in Diabetes now recommend flexible HbA_{1c} targets based on patient-specific factors.²⁰ While most adults will still benefit from a target HbA_{1c} <7.0%, less stringent goals (<8.0%) may be more appropriate for patients with significant comorbidities, severe hypoglycemia, shorter life expectancy, or advanced micro- or macrovascular complications, as well as older individuals as mentioned above.²⁰ Likewise, patients in good health with a shorter duration of diabetes may benefit from a more stringent HbA_{1c} goal (<6.5%), if it can be achieved without precipitating hypoglycemia or other adverse events. In con-

trast, less stringent goals may be considered for elderly individuals who have gait imbalance and frailty that can result in risk of life-changing injury if they fall during a hypoglycemic event.⁴

CONSULTING WITH PATIENTS TO UNCOVER MASKED HYPOGLYCEMIA

Hypoglycemia in patients with T2DM may often be masked when episodes are asymptomatic and only captured in patients who closely monitor their blood glucose. Furthermore, episodes of hypoglycemia may go unrecognized because the symptoms are nonspecific. Evidence also suggests that patients with mild-to-moderate symptomatic hypoglycemia may not recount such episodes when discussing their diabetes with their health care providers.^{1,26} Ultimately, as T2DM progresses, the body's mechanisms that defend against falling blood glucose (e.g., from prior hypoglycemic episodes, exercise, or sleep) become attenuated, leading to impaired counter-regulatory responses, hypoglycemia unawareness, and a recurrent cycle of hypoglycemia.¹⁰

Because the prevention of hypoglycemia is clearly preferable, experts from The Endocrine Society recommend that all patients taking antidiabetes medications, especially those receiving insulin or insulin secretagogues, be asked about hypoglycemia at every contact.²⁶ Pharmacists should take the opportunity to review the signs and symptoms of hypoglycemia, assess patient risk for hypoglycemia (TABLE 2),²⁷ and ask patients about the frequency and types of hypoglycemic events they are experiencing. Once hypoglycemia is unmasked, the goal

should be to educate and empower the patient, as well as work with the patient to individualize treatment regimens and glycemic goals.^{26,28} To this end, blood glucose monitoring can be extremely useful in uncovering hypoglycemia, particularly among insulin-treated patients.²⁰ The data from frequent blood glucose self-monitoring can be used by the patient and health care providers to make specific modifications to therapy regimens. Continuous glucose monitoring (CGM) may also be beneficial for certain individuals, particularly those with a history of hypoglycemia unawareness or nocturnal hypoglycemia.²⁰

HYPOGLYCEMIA TREATMENT RECOMMENDATIONS FOR PATIENTS

For an individual experiencing hypoglycemia who is conscious, the "rule of 15" can be used as a general guide for treatment of hypoglycemia (TABLE 3).²⁹ This includes the consumption of 15-20 g of glucose (preferred), or any simple carbohydrate.²⁰ Examples of foods containing 15 g of carbohydrate include: 4 oz (1/2 cup) of juice or regular soda, 2 tablespoons of raisins, 4 or 5 saltine crackers, 4 teaspoons of sugar, and 1 tablespoon of honey or corn syrup. Repeat monitoring after 15 minutes and retreat if blood glucose continues to be <70 mg/dL. Once blood glucose returns to normal, the patient should consume a meal or complex carbohydrate or protein snack to prevent hypoglycemia recurrence.

Glucagon should be prescribed to any individual who is at risk for severe hypoglycemia and patients' caregivers or family members should be instructed on its use (See Glucagon below). People with diabetes should wear diabetes identification to prevent delayed diagnosis and treatment in the event of loss of consciousness due to hypoglycemia. Patients with hypoglycemia unawareness or ≥ 1 episode of severe hypoglycemia should also be advised to raise glycemic targets for at least several weeks in order to avoid hypoglycemia and reduce the risk of future episodes.²⁰

Glucose-Containing Products

Glucose is recommended for the treatment of mild or moderate hypoglycemia. Commercially available glucose products come in a variety of formulations, including tablets, gels, powders, and liquids. The pharmacist can help make sure the patient is well informed when selecting the most appropriate product and how much of it will be required in order to receive the correct dose. For example, many patients only chew one glucose tablet when they actually need four tablets. Additional patient counseling points to consider include: 1) whether a product is a single-use versus

Table 2. Conventional Risk Factors for Hypoglycemia

- Doses of insulin, insulin secretagogue, or combined antidiabetes medications are excessive, ill-timed, or the inappropriate type
- Exogenous glucose delivery is decreased (e.g., after missed meals and during the overnight fast)
- Endogenous glucose production is decreased (e.g., after alcohol ingestion)
- Glucose utilization is increased (e.g., during and after exercise)
- Insulin sensitivity is increased (e.g., after weight loss or improved glycemic control, in the middle of the night)
- Insulin clearance is decreased (e.g., with renal failure)

Source: Adapted from Reference 27. Used with permission.

multi-use container, 2) ease of use when experiencing hypoglycemia (e.g., gels and liquids do not require chewing; unscrewing bottle versus tearing a pouch), 3) convenience (e.g., travel sizes), and 4) cost.

Glucagon Injections: What the Pharmacist Should Teach

Glucagon, the counter-regulatory hormone to insulin, is the first-line treatment for severe hypoglycemia in insulin-treated patients. Glucagon has also been given in small doses to children as a treatment for mild hypoglycemia.³⁰ Glucagon delivery devices available by prescription include Glucagon for Injection (Eli Lilly) and GlucaGen[®] HypoKit (Novo Nordisk) for intramuscular and subcutaneous administration.^{31,32} The kits consist of a vial of recombinant glucagon powder and a prefilled syringe containing solvent. Patient directions for glucagon injection vary slightly by product, but in general, should cover how to reconstitute the glucagon powder and draw up the reconstituted solution, as well as the proper dosage and administration. After a severe hypoglycemic episode, the patient's physician should be contacted.

Verbal instructions and demonstration alone in regard

to glucagon injections is likely not as effective as hands-on training, which pharmacists can help administer. A study designed to simulate glucagon administration among parents of children with diabetes found that 69% of them demonstrated handling difficulties when administering glucagon, including opening the container and drawing the correct dose into the syringe.³³ In addition, 20.6% of respondents were not aware if the glucagon kit was within its use-by date, and 54.9% stored the kit in the refrigerator, despite recommended storage at controlled room temperature. An auto-injecting glucagon pen device called GlucaPen[®] (Enject Inc.) is currently under development, and, if approved by the FDA, may help simplify glucagon delivery.³⁴ This device contains a dual chamber cartridge for easy mixing and a pre-attached needle which activates at the time of use. Regardless of the type of kit or pen used, caregivers should be reminded to properly store products, always know the location of the kit, and periodically check expiration dates.³⁵

α -Glucosidase Inhibitors

The α -glucosidase inhibitors, acarbose and miglitol, delay postprandial glucose absorption through inhibition of the pancreatic enzymes that convert complex carbohydrates into glucose.^{36,37} Evidence from several small randomized and non-randomized trials suggests that both α -glucosidase inhibitors may be effective in preventing postprandial reactive hypoglycemia, but they are also associated with slight decreases in fasting glucose blood concentrations.³⁷⁻⁴¹ However, patients taking α -glucosidase inhibitors should be advised to treat episodes of hypoglycemia with glucose products rather than foods or juice, since α -glucosidase inhibitors will slow the digestion of carbohydrates and delay recovery.

PATIENT EDUCATION TO PREVENT HYPOGLYCEMIA

Although episodes of hypoglycemia may be caused by conventional factors such as alterations in meals, exercise, or consumption of alcohol, they often are caused by excessive doses of diabetes medications.⁴ Medication adjustments to current antidiabetes regimens, such as substitution of rapid-acting insulin (lispro, aspart, glulisine) for regular insulin or basal insulin glargine or insulin detemir for NPH insulin, may help to prevent those episodes.⁴ As a trusted health care professional with a high degree of patient accessibility, the pharmacist can play an important front-line role in preventing hypoglycemia by educating and empowering the patient. Patient education on hypoglycemia allows the pharmacist to

Table 3. American Diabetes Association Recommendations for Patients Addressing Hypoglycemia—The Rule of 15

- If you feel low, check your blood glucose.
- If blood glucose level is low, follow the rule of 15
 - Eat or drink something with 15 grams of carbs (fast-acting carb like glucose gel or juice).
 - Wait 15 minutes, then check your blood glucose.
 - If your blood glucose is still too low, eat another 15 grams of carbs and check your blood glucose again after 15 minutes. Once your blood glucose level starts to get back in your target range, you should start to feel better.
- Lots of people overtreat themselves when they feel low because they treat the symptoms and not the glucose level. You may not feel better instantly after eating your 15 grams of carbs, but remember the rule of 15.
- You may want to keep eating until you feel better but that might make your blood glucose shoot way up. Be patient with your body and give it the full 15 minutes!
- If you feel low, but cannot check your blood glucose, go ahead and treat it. When in doubt, it is always safer to get some food. If you go too low, you can faint, have a seizure, or go into a coma.

Source: Reference 29.

help increase awareness about the risks of hypoglycemia, empower patients to employ preventative and treatment measures, and mitigate patient fear and other psychosocial challenges. A variety of lifestyle factors can also impact blood glucose levels. Missed or irregular meals have been identified as one of the most common behavioral factors associated with individual episodes of severe hypoglycemia.⁴² Thus, one example of an intervention a pharmacist can perform is educating patients about the importance of bringing meals and snacks when away from home, as well as anticipating the effects that illness (e.g., gastroenteritis, vomiting) and fasting have on blood glucose, so that patients can adjust their medications accordingly.

Physical activity is an important lifestyle recommendation for patients with T2DM, although hypoglycemia can often occur during or after exercise in insulin-treated patients.

Individuals should assess their blood glucose before engaging in physical activity and properly prepare as needed by ingesting carbohydrates, and/or reducing insulin doses.^{20,26} Pharmacists should counsel patients that “physical activity” is not limited to intensive exercise like aerobic or strength-training exercise at the gym, but can also include performing daily household chores, yard work, etc.

Patients should also be made aware that alcohol consumption can lower blood glucose by blocking the liver from releasing glucagon, particularly in a fasting state, as well as the fact that hypoglycemia can develop as long as ≥ 6 hours after intake of alcohol. Additionally, alcohol consumption may be detrimental for patients because it acts by modifying the kinetic parameters of glucose, delays the symptoms of hypoglycemia, and impairs judgment, making patients more susceptible to hypoglycemia.⁴³ ADA recommends that patients with T2DM limit the intake of alcohol and eat when drinking. Pharmacists should review daily recommended limits for men and women: 2 or fewer drinks per day for men, and 1 drink or less per day for women (1 drink is equivalent to 12 oz of beer, 5-oz glass of wine, 1½ oz of distilled spirits). Additional counseling points for alcohol consumption include testing blood glucose before drinking, wearing diabetes identification, and choosing non-caloric drink mixers such as club soda or diet soda. Also, intoxication may decrease awareness of hypoglycemic symptoms.

An effective way for pharmacists to engage patients in meaningful dialogue about hypoglycemia and diabetes is to utilize open-ended questioning and active listening, as is promoted by the American Society of Health-System Pharmacists (ASHP) guidelines for pharmacist-led patient education and counseling.⁴⁴ Simply offering patient education as a “one-size-fits-all” approach is not enough. According to the ASHP guidelines published in 1997, which are still relevant today, all pharmacists should be able to tailor information to meet the specific needs of the patient, taking into account cognitive ability, lifestyle, language, and cultural considerations as well as assessing the patient’s willingness to receive educational instruction.⁴⁴ Pharmacists should also attempt to understand the patient’s underlying attitude toward their diabetes management. For example, a pharmacist converses with a patient and discovers that he reports hypoglycemia only when he is playing golf with his friends. Upon questioning, the pharmacist identifies the several issues that are occurring: 1) increased physical activity and 2) skipping meals. This demonstration of

understanding allows the pharmacist to better direct patient education; for instance, by explaining how specific types of physical activity may lower blood sugar levels and recommending something as simple as bringing a snack or lunch to the golf course. This unobtrusive solution improves quality of life by empowering the patient to be proactive with his diabetes management.

Self-monitoring of blood glucose is an important tool that can empower patients to minimize progression to a hypoglycemic event. Pharmacists not only assist with selecting and providing hands-on training for glucometers, but also serve to facilitate communication between the patient and the physician, which can lead to more effective treatment management.

THE HYPOGLYCEMIC RISK OF ANTIDIABETES AGENTS

Among the available antidiabetes medications, insulin use is associated with the highest risk of hypoglycemia, although this risk varies among agents due to differences in their pharmacokinetic (PK) profiles. According to a Cochrane Review, the newer, rapid-acting insulin analogs (insulin aspart, insulin glulisine, and insulin lispro) are associated with lower rates of hypoglycemia compared

An effective way for pharmacists to engage patients in meaningful dialogue about hypoglycemia and diabetes is to utilize open-ended questioning and active listening, as promoted by ASHP guidelines.

with regular human insulin, which has a slower onset, delayed peak, and longer duration of action.⁴⁵ A meta-analysis also showed a decreased incidence of symptomatic and nocturnal hypoglycemia with the long-acting basal insulin analogs, insulin detemir and insulin glargine, compared with neutral protamine Hagedorn (NPH) insulin.⁴⁶ Insulin premixes contain a rapid-acting insulin component and an intermediate basal component, either NPH and regular human insulin or an insulin analog combined with a protamine suspension of the analog.⁴⁷ The hypoglycemic risk among insulin analog premixes compared with human insulin premixes is somewhat variable. A meta-analysis consisting of 9 randomized controlled trials found biphasic insulin aspart was associated with significantly less nocturnal and major hypoglycemia compared with biphasic human insulin.⁴⁸ On the other hand, the rate of daytime hypoglycemia was significantly lower with biphasic human insulin with no difference between the two treatments in overall hypoglycemia. A more recent 2011 systematic review of randomized trials comparing analog premixes with human premixes in patients with T2DM also found comparable overall levels of hypoglycemia between biphasic insulin analogs and biphasic human insulins, but several studies noted a safety benefit with insulin analog premixes in certain subsets of patients, including those who had progressed to later stages of disease or those who exercised post-injection.⁴⁷

A variety of studies have demonstrated greater patient preference, ease of use, and improved dosing accuracy of insulin pen devices compared with vials and syringes. Pen devices, in some instances, help reduce hypoglycemia by providing more accurate dosing than vials and syringes, as well as alleviate some of the psychosocial resistance and challenges to insulin use and treatment adherence.⁴⁹ An analysis from a large U.S. claims database of T2DM patients initiating insulin glargine therapy with either a pen or vial and syringe found that patients who initiated insulin therapy with a pen device were significantly less likely to experience a hypoglycemic event compared with those using vial and syringe (6.35% vs. 8.47%, respectively; $P = .012$).⁵⁰ In contrast, a U.S. claims database analysis comparing T2DM patients initiating a rapid-acting insulin analog using pen devices versus needle and syringe found no significant difference in the incidence of hypoglycemia between the two treatment cohorts (change in 6-month pre- and post-insulin initiation index period of episodes per patient was +0.004 pen vs. -0.003 vial and syringe, $P = .707$).⁵¹ These studies are limited in that they only captured hypoglycemic

events requiring clinical interventions associated with a recorded claims code (ICD-9-CM)⁵¹ and the retrospective data were not able to account for covariates. With a variety of options available, the selection of insulin delivery method is another excellent opportunity for the pharmacist to play a direct role in individualizing insulin therapy by taking into account patient-specific factors, including financial constraints or insurance, lifestyle needs, and physical traits, including manual dexterity and eyesight.

Non-Insulin Therapies

Among non-insulin therapies, the use of sulfonylureas (SUs) is most commonly associated with hypoglycemia.³⁷ Within the second-generation sulfonylurea class, glyburide, which is metabolized by the liver to active metabolites, is most commonly associated with hypoglycemia, while glimepiride is associated with the lowest risk of hypoglycemia as reported in the literature.⁵² In fact, among that class, glipizide is the preferred agent because it does not have active metabolites and does not increase the risk of hypoglycemia among individuals with chronic kidney disease.⁵³ Meglitinides (e.g., repaglinide and nateglinide) are another class of insulin secretagogues that are associated with a lower risk of hypoglycemia than the sulfonylureas, due in part to their shorter duration of action.⁵² Other agents lower blood glucose in either a glucose-dependent manner or through a mechanism other than increasing insulin, and as a result, carry a lower risk of hypoglycemia.^{37,52} These agents include the biguanide, metformin, thiazolidinediones (e.g., pioglitazone and rosiglitazone), dipeptidyl peptidase-4 inhibitors (e.g., sitagliptin, saxagliptin, linagliptin, vildagliptin [UK only], alogliptin, dapagliflozin), the amylin analog, pramlintide, glucagon-like peptide-1 receptor agonists (e.g., exenatide, liraglutide), the α -glucosidase inhibitors (acarbose and miglitol), and the newly approved sodium-glucose cotransporter 2 (SGLT2) inhibitor, canagliflozin. It is important to note that the risk of hypoglycemia is lower for these newer agents when used as monotherapy, but as with all medications, the risk increases when they are used in combination with other agents, especially with a sulfonylurea or insulin.^{37,52}

Investigational Insulin Agents

Risk of hypoglycemia has always been a great concern among patients. As novel insulin products have developed over time, from human insulin, to rapid-acting insulin analogs, and then basal insulin analogs, reduction in the risk of hypoglycemia has remained the primary goal.

LY2605541 is a novel long-acting basal insulin currently in development that consists of lispro that has been pegylated to produce a large hydrodynamic molecule; this modification, which slows absorption and reduces clearance, results in a prolonged duration of action.⁵⁴ A 12-week phase II clinical trial in patients with T2DM found the adjusted rate of nocturnal hypoglycemia in patients treated with LY2605541 was reduced by 48% compared with those treated with insulin glargine ($P = .021$); in both treatment arms, insulin was administered in combination with oral antidiabetes medications. There was no difference in overall hypoglycemia between agents.⁵⁴

Co-injections of recombinant human hyaluronidase (rHuPH20) with rapid-acting insulin to accelerate insulin absorption has also been investigated.⁵⁵ A phase II crossover analysis of 21 T2DM patients receiving insulin lispro+rHuPH20, lispro alone, and regular human insulin+rHuPH20, reported that fewer patients treated with lispro+rHuPH20 (19%) required glucose to treat hypoglycemia (at the discretion of the investigator) compared with lispro alone (48%) ($P = .0023$).⁵⁵ Additionally, 29% of patients receiving lispro+rHuPH20 experienced overall hypoglycemia (defined as blood glucose <70 mg/dL \pm symptoms) compared with lispro alone (57%).

Insulin degludec is an ultra-long-acting insulin that produces a flat and consistent blood glucose-lowering effect.⁵⁶ A prospectively-planned, pre-specified meta-analysis of 7 pooled phase III trials of basal-bolus or basal only found significantly lower rates of overall confirmed hypoglycemia (relative risk [RR] 0.83, CI 0.74-0.94) and nocturnal confirmed hypoglycemia (RR 0.68, CI 0.57-0.82) with insulin degludec compared with insulin glargine in the overall T2DM patient population across the entire treatment period reporting comparable glycemic reductions.⁵⁷ These differences were more apparent during the maintenance phase.⁵⁷

A co-formulation consisting of insulin degludec 70% and insulin aspart 30% has been evaluated in phase II and III trials in patients with T2DM and T1DM. The phase II data in T2DM patients reported significantly lower rates of confirmed hypoglycemia for the insulin degludec/insulin aspart co-formulation compared with biphasic insulin aspart, both in combination with metformin (2.9 vs. 7.3 events/patient year, respectively; RR 0.42; 95% CI 0.23-0.75; $P < .05$).⁵⁸ Another phase II trial found that 16 weeks of insulin degludec/insulin aspart and insulin glargine (both in combination with metformin) were associated with similar rates of confirmed hypoglycemic events.⁵⁹ In this trial, there was only one nocturnal hypoglycemic event among the 59 patients receiving insulin degludec/insulin aspart and three events among the 60 patients treated with insulin glargine.⁵⁹

Conclusion

Hypoglycemia, whether symptomatic or asymptomatic, can have profound physiological and psychological effects on individuals, which can impact their glycemic control. While some of the counseling points reviewed in this article may seem intuitive, a hypoglycemic episode (especially if severe) can be a terrifying experience and may persist in the minds of both patients and their families. Therefore, it is understandable when patients react by “overtreating” hypoglycemia or engaging in avoidance behaviors (i.e., missing doses, avoiding physical activity). In these situations good glycemic control may be difficult to attain, which emphasizes the importance of diligent blood glucose monitoring to prevent hypoglycemic episodes from occurring initially. Pharmacists can have a positive impact on patients' diabetes management by engaging patients to discuss their experiences with hypoglycemia, identifying potential risks, uncovering masked hypoglycemia, suggesting therapy changes, directly modifying drug therapy, and ultimately empowering the patient toward better disease self-management. ■

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