

In Brief

This article provides a brief overview of the various insulin products currently available on the market and discusses considerations regarding insulin therapy in people with type 2 diabetes. Issues involving the initiation, titration, and optimization of insulin therapy to meet individual patient treatment goals are discussed.

Update on Insulin Management in Type 2 Diabetes

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Type 2 diabetes is a progressive disease characterized by insulin resistance and progressive β -cell dysfunction.¹ With the prevalence of type 2 diabetes increasing and with people being diagnosed at an early age, the use of insulin in type 2 diabetes will become increasingly important as patients develop severe insulin deficiency due to pancreatic β -cell loss over time. Although the decision to implement insulin therapy in patients who are on multiple oral agents and present with severe hyperglycemia, polyuria, and weight loss may be obviously warranted, the choice to initiate insulin therapy in many other patients with type 2 diabetes is less clear.

Factors to be considered when deciding whether to start insulin therapy for a given patient can be diverse and are often complex. Important considerations both in favor of and against the initiation of insulin therapy can include contraindications or intolerance to alternative therapies, cost, and physician and patient preferences, among others. Varying viewpoints also exist regarding whether insulin treatment should be considered early in type 2 diabetes or only as a last resort once oral and other alternative therapies have proven ineffective. The burden falls on the health care team to carefully weigh all of these and other pertinent factors against treatment guidelines and patient-specific treatment goals when determining the optimal therapeutic strategy for each patient.

Insulin Use in Type 2 Diabetes: Early or as a Last Resort?

Undoubtedly, one of the largest hurdles concerning the initiation of insulin is overcoming patients' fears and misconceptions regarding insulin use. Preconceived patient perceptions regarding injection pain, weight gain, regimen complexity and its impact on quality of life, and risks and consequences of hypoglycemia often hinder successful initiation of therapy.² Some patients even believe that their need for insulin reflects a personal failure and that they have somehow failed their family or health care providers.³

Given these common concerns, patient education is paramount when starting insulin. In fact, it may often prove beneficial for patients to receive education early regarding the progressive nature of type 2 diabetes so that they understand that, despite their best efforts, their disease will inevitably progress over time. Once patients develop an understanding that a need to add or transition to insulin therapy does not mean they have failed, they may be more likely to readily accept insulin therapy in the future.

Although few would argue against the importance of patient education, the overwhelming need and time commitment for intense education in people starting insulin is often itself a barrier for both patients and health care providers. So why initiate insulin early in type 2 diabetes when efficacious antidiabetic agents such as sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors,

GLP-1 receptor agonists, nonsulfonylurea secretagogues, and α -glucosidase inhibitors are available in our pharmacological armamentarium? Such therapies are often sought in lieu of insulin because of their increased acceptance by patients and less intense patient management and follow-up requirements. The important difference between the aforementioned agents and insulin, however, is that insulin possesses an unlimited ability to lower A1C.

Recent clinical treatment guidelines, such as those from the 2007 update to the American College of Endocrinology/American Association of Clinical Endocrinologists (ACE/AACE) treatment guidelines, suggest that these agents may be less

effective as add-on therapy for patients with an A1C $\geq 9.5\%$ and therefore recommend the initiation of insulin in all patients with an A1C $> 10\%$.⁴

Although most newly diagnosed patients with type 2 diabetes will not present with an A1C $> 10\%$, the early use of insulin is recommended in those patients experiencing limited benefit from oral therapies and in those at acute risk of glucotoxicity. Data show that intensive insulin therapy early in the course of type 2 diabetes can improve β -cell function by attenuating glucose toxicity.⁵⁻⁷

Some experts argue, however, that oral therapies such as sulfonylureas can effectively reduce glucose toxicity and improve subsequent insulin secretion, and thus insulin use early in type

2 diabetes is not absolutely necessary to realize such potential long-term benefits.⁸ Given these considerations, it is often argued that early initiation of insulin therapy imparts little to no benefit to patients when compared to treatment with alternative therapies. Ultimately, a case can be made that the time investment required from the physician and other health care providers both for adequate patient education at insulin initiation and for proper follow-up can be delayed until clinically necessary.

Strong arguments can certainly be made in favor of and in opposition to prescribing insulin therapy early in patients with type 2 diabetes in lieu of other therapeutic options. Such decisions ultimately depend on the patients

Table 1. Insulin Comparison Chart

Insulin Name	Onset	Peak	Duration	Notes for Use	Estimated Cost
Rapid-acting products					
Lispro	< 15 minutes	0.5–1.5 hours	3–5 hours	If mixing with NPH, rapid-acting insulin should be drawn into syringe first. Mixture should be given immediately to avoid effects on peak action.	\$103 (10-ml vial) \$198 (five 3-ml pen cartridges)
Aspart	< 15 minutes	1–3 hours	3–5 hours		\$112 (10-ml vial) \$219 (five 3-ml pen cartridges)
Glulisine	< 15 minutes	1 hour	3–5 hours		\$101 (10-ml vial) \$195 (five 3-ml pen cartridges)
Short-acting products					
Regular	0.5–1 hour	2–4 hours	4–8 hours	May be mixed with NPH in same syringe. Mixing order should be the clear regular drawn up first, then the cloudy NPH (i.e., “clear to cloudy”).	\$53 (10-ml vial) \$121 (five 3-ml pen cartridges) \$89 (five 3-ml Innolet cartridges)
Intermediate-acting products					
NPH	2–4 hours	4–10 hours	10–18 hours	Available as pen or in vial to be used with syringe.	\$52 (10-ml vial) \$121 (five 3-ml pen cartridges) \$91 (five 3-ml Innolet cartridges)
Long-acting products					
Glargine	2–4 hours	Same action throughout the day	24 hours	Do not mix with other insulins. Available as pen or in vial. Detemir duration (clinical trial data): 6 hours (0.1 units/kg), 12 hours (0.2 units/kg), 20 hours (0.4 units/kg), 23 hours (0.8 and 1.6 units/kg)	\$104 (10-ml vial) \$188 (five 3-ml Solostar pen cartridges)
Detemir	2–3 hours	6–8 hours	Dose-dependent 5.7–23.2 hours		\$103 (10-ml vial) \$191 (five 3-ml pen cartridges)

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Table 1. Insulin Comparison Chart *continued from p. 86*

Insulin Name	Onset	Peak	Duration	Notes for Use	Estimated Cost
Combination products					
Regular/ NPH 70/30	0.5–1 hour	2–10 hours	10–18 hours	70% NPH + 30% regular insulin. Insulin action includes two peaks (one from each formulation).	\$54 (10-ml vial) \$135 (five 3-ml pen cartridges) \$94 (five 3-ml Innolet cartridges)
Aspart protamine 70/30, lispro protamine 75/25, and lispro protamine 50/50	< 15 minutes	1–2 hours	10–18 hours	Aspart protamine 70% + aspart 30% Lispro protamine 75% + lispro 25% Lispro protamine 50% + lispro 50% Insulin action includes two peaks (one from each formulation).	Lispro protamine/lispro 75/25: \$110 (10-ml vial) \$188 (five 3-ml pen cartridges) Lispro protamine/lispro 50/50: \$198 (five pens) Aspart protamine/aspart 70/30: \$110 (10-ml vial) \$206 (five 3-ml pen cartridges)

Note: This chart indicates average insulin actions. Insulin action may vary within and between patients, so SMBG should be used to gauge actual effect.

and their specific circumstances. Professional organizations in the field of diabetes recognize insulin as a viable treatment choice for patients with type 2 diabetes at all levels of glycemic control. The April 2008 revision of the ACE/AACE roadmap even identifies prandial insulin as a viable treatment alternative for those with type 2 diabetes naïve to therapy with an A1C of 6–7% who are unable to take preferred initial therapies.⁹ Luckily, organizations such as the American Diabetes Association (ADA), ACE, and AACE provide consensus guidelines and recommendations to help guide clinicians in evidence-based decision making to select appropriate lifestyle and pharmacological interventions to meet patient-specific treatment goals.^{4,9,10}

Overview of Insulin Products

A wide range of insulin products are currently available, making it easy to design individualized insulin regimens to meet patients' lifestyle and blood glucose needs (Table 1). The standard human insulin products, regular and neutral protamine Hagedorn (NPH), are cost-effective and widely available on formularies and in pharmacies. Regular insulin is a short-acting insulin with onset in 30–60 minutes, peak action in 2–4 hours, and duration of up to 8 hours. NPH is an intermediate-acting insulin with onset in 2–4 hours, peak in 4–10 hours, and duration up

to 18 hours. However, the action of these products may vary widely both between patients and in individual patients at different times. Therefore, blood glucose monitoring should be used to guide an understanding of their effects in each patient.

When initiating these agents, careful consideration should be given to their pharmacokinetic properties to ensure adequate timing of administration with regard to meals and activity and thus avoid hypoglycemia. In some patients, use of these agents may be limited by unanticipated hypoglycemia if dose administration does not adequately account for onset or peak action of the insulin. For example, a person starting regular insulin should understand the need to administer it at least 30 minutes before eating so that onset has occurred when meal absorption begins. Proper timing also helps to minimize any postprandial hypoglycemia caused when peak action is mismatched to meal-induced peak glucose levels.

The rapid-onset insulin analogs, made through genetic modification of human insulin, were introduced to the market in the mid-1990s. The three products currently available (lispro, aspart, and glulisine) are absorbed rapidly with general onset in 5–15 minutes, peak effects in 1–2 hours, and duration averaging 3–5 hours, although there may be slight differ-

ences among the products.^{11–14} The rapid onset of these insulin products allows for optimal mealtime flexibility, making them ideal for individuals with varying or unpredictable meal schedules.

Ideally, these agents should be administered with a lag time before eating that is proportional to the preprandial glucose level. The higher the glucose level, the greater amount of time before the meal the insulin should be administered to allow for onset of effect and a downward trend of pre-meal hyperglycemia before eating. In a randomized, crossover study of 12 subjects with type 1 diabetes, Rassam et al.¹⁵ demonstrated greater reduction in postprandial glucose elevation when lispro was administered 15 or 30 minutes before an 8.6 kcal/kg breakfast based on ADA nutrition guidelines (50% carbohydrate, 20% protein, 30% fat eaten over 15 minutes) than when lispro was administered at mealtime or 15 minutes after the meal.

A second consideration with lag time is the content of the meal and the effect of this on glucose absorption. Theoretically, rapid-acting insulin should be administered earlier (e.g., 10–15 minutes before the meal) for meals that contain primarily rapidly absorbed carbohydrates to ensure onset during carbohydrate absorption. Conversely, this insulin could be administered later (e.g., at the first bite

or 15 minutes after the meal) for meals with high fat content, which may slow carbohydrate absorption.

Another important concept when using insulin is to consider the amount of “insulin on board” (active insulin remaining in the body) so that correction doses take into consideration the lingering glucose-lowering effect of earlier doses, and ideally, the glucose trend. In an evaluation of the action profile of insulin aspart in 20 healthy subjects, Mudaliar et al.¹⁶ identified significant differences between regular insulin and insulin aspart in terms of peak action (180–300 minutes for regular vs. 90–160 minutes for aspart). However, it was noted that insulin aspart still had significant activity 300 minutes after injection. Based on the correlating insulin disappearance curve, one would expect to have 40% of dose activity remaining 3 hours after injection.¹¹ These insulin disappearance curves form the basis for the insulin-on-board feature used in insulin pumps, and this concept can also be incorporated into education and dosing instructions for individuals using subcutaneous injections to avoid insulin stacking and the related risk of hypoglycemia.

The long-acting insulin analogs currently available are glargine and detemir. The onset of insulin glargine occurs in 4–6 hours with no appreciable peak and a duration of 24 hours in most patients. For patients who experience dose waning toward the end of the dosing interval, twice-daily dosing may be considered or the administration time for single-dose regimens can be moved to earlier in the day during the period the patient will be using prandial coverage or periods of greater physical activity. Of note, administration of glargine at bedtime is not a requirement but rather a recommendation to minimize the risk of mixing this insulin with other insulin products. Ideally, the decision on administration time should be made with patients’ input to optimize convenience and promote adherence.

Insulin detemir is a newer long-acting insulin with onset similar to glargine at 3–4 hours. However, detemir has a potential peak at 3–4 hours and a duration that is dose-dependent ranging from 5.7 hours at lower doses to 23.2 hours at higher doses. A recent pharmacodynamic and pharmacokinetic study in 51 subjects with type 1 diabetes using a

glucose-infusion clamp on four dosing days demonstrated reduced within-subject variability for detemir (23% variability in glucose infusion rate [GIR_{max}] compared to glargine [36% GIR_{max}] or NPH [46% GIR_{max}]). However, mean glucose infusion rate was lower for glargine at each time point. Although extrapolation of these findings is difficult given the many other factors affecting glucose control, detemir may be an option for patients with unexplained day-to-day variability in glucose control.¹⁷

In addition to the short-, rapid-, and long-acting insulins, there are several premixed insulin products combining short- or rapid-acting insulin with intermediate-acting insulin. Human insulin combination products include 70/30 and 50/50 mixtures. In these combinations, the initial number in the ratio (e.g., 70 in the 70/30) refers to the percentage of the insulin that is the intermediate-acting insulin (NPH, in the case of human insulin combinations) and the latter number (e.g., 30 in the 70/30) refers to the short-acting (regular) insulin. Newer insulin mixes contain similar proportions of insulin lispro or aspart mixed with a protamine formulation of the same insulin to produce an extended duration beyond the rapid insulin action.

There are essentially two phases of absorption with the insulin combination and mix products. With the regular-NPH combinations, the initial phase of absorption and peak parallel that of regular insulin, whereas the second phase of absorption, peak, and overall duration reflect that of NPH. With the rapid insulin mixes, absorption is reported to occur over 30–240 minutes (lispro)^{18,19} and 60–240 minutes (aspart),²⁰ with the initial time to onset and peak similar to lispro or aspart alone. The second peak and duration are closer to that seen with NPH.

These combination and mix products are well suited for those with type 2 diabetes who need basal and prandial coverage yet are resistant to multiple daily injections. Using a combination product twice daily, it is possible to attain adequate basal coverage with prandial coverage for the meals nearest dose administration (e.g., breakfast and dinner). In addition, the peak action of the NPH insulin in the combination or delayed protamine formulation in the mix may provide coverage for meals a few hours

after the injection (e.g., lunch). The challenge can be to ensure that this secondary peak is matched to meal intake so that it does not produce daytime or nocturnal hypoglycemia.

Insulin Management Strategies in Type 2 Diabetes

Once a clinical decision has been made to initiate insulin therapy in a patient with type 2 diabetes, it then becomes necessary to decide on a regimen that best fits the needs of the individual. As discussed in the review of currently available insulin products, numerous individual and premixed combination products are available. The variety of insulin choices and pharmacokinetic profiles from which to choose allows health care practitioners to individualize regimens to meet the therapeutic needs of patients and complement their lifestyle. The following sections provide a discussion of insulin initiation strategies in type 2 diabetes, insulin titration to meet treatment goals, and recommendations for transitioning patients between various dosing paradigms to meet and maintain glycemic goals.

Insulin initiation strategies

Given the variety of patient-specific factors and needs present within the heterogeneous type 2 diabetic patient population, a variety of approaches can be taken. In general, patients are initiated on relatively less intensive insulin regimens to ease them into an appropriate routine. The insulin regimen can then be intensified as needed to meet glycemic goals. Some of the more common initial insulin regimens are included in Table 2.⁴

Basal insulin. Initiation of a once-daily long-acting insulin analog is often an excellent strategy to treat persistent hyperglycemia and introduce insulin in patients with type 2 diabetes. A once-daily dosing strategy is favorable to patients who are naïve to insulin therapy when compared to complex regimens requiring multiple injections. It is important to consider that the addition of insulin may lead to downstream lifestyle changes for the patient beyond the simple act of insulin injection. The initiation of insulin often requires careful coordination of insulin administration with eating habits and physical activity and requires patients to check their blood glucose more often than they may have when using oral agents.

Table 2. Common Initial Insulin Dosing Regimens in Patients With Type 2 Diabetes

- Long-acting insulin
- Long-acting insulin with rapid-acting insulin with the largest meal of the day
- Once-daily premixed insulin with the largest meal of the day
- Long-acting insulin with rapid-acting insulin twice daily
- Premixed insulin analog twice daily

Adapted from Ref. 4.

The clinical utility of adding insulin in this manner was first shown in the Treat-to-Target trial.²¹ In this trial, people with type 2 diabetes not meeting treatment goals with oral agents were randomized to receive either a single evening dose of insulin glargine or NPH. Patients were provided with an algorithm for weekly dose titrations in increments of 0–8 units and were asked to titrate their insulin to achieve a fasting glucose of 100 mg/dl. At the end of the 26-week study, an A1C reduction of ~1.6% was achieved in both treatment groups, with ~58% of all study participants (both insulin glargine and NPH groups) reaching an A1C of <7.0%. Of note in this trial, nearly 25% more subjects receiving insulin glargine reached target glycemic goals without any documented occurrences of nocturnal hypoglycemia. Subsequent studies have demonstrated the benefit of insulin glargine in type 2 diabetic patients with similar results.^{22–27}

Similar to data with insulin glargine, insulin detemir use in clinical trials has yielded beneficial reductions in A1C when administered as add-on therapy to preexisting oral antidiabetic regimens. In the first Treat-to-Target trial comparing insulin detemir with NPH, both agents were administered twice daily as add-on therapy to baseline oral therapies.²⁸ A1C reduction with insulin detemir was ~1.8% after 26 weeks of therapy, and 70% of all subjects (both insulin detemir and NPH groups) reached an A1C of <7.0%. In addition to less nocturnal and overall hypoglycemia compared to NPH, insulin detemir treatment resulted in significantly less weight gain compared to patients receiving NPH insulin (1.2 vs. 2.8 kg; $P < 0.001$). A similar trial comparing once-daily insulin detemir to evening NPH reported similar reductions in A1C between groups, with insulin detemir again associated with fewer hypoglycemic events and less weight

gain compared to patients receiving NPH insulin.²⁹

In conclusion, current data indicate that long-acting insulin analogs such as insulin glargine and insulin detemir provide benefit in regard to A1C reduction when used as add-on therapy to preexisting oral regimens in patients with poorly controlled type 2 diabetes. Long-acting analogs may also possess added benefit when compared to NPH insulin in regard to rates of hypoglycemia and, in the case of insulin detemir, decreased weight gain. That being said, patients have varying needs and many patients do quite well on NPH insulin.

A common strategy for implementing basal insulin in patients with type 2 diabetes is beginning with a dose of 10 units once daily for insulin glargine and insulin detemir. An alternative strategy for the initiation of insulin detemir is to begin with a dose of 0.1–0.2 units per kg of body weight once daily followed by appropriate dose titration to reach glycemic targets.³⁰

Premixed insulin. Premixed insulin can be initiated once or twice daily. One strategy for deciding between once- and twice-daily administration suggests initiating a once-daily regimen in patients for whom hypoglycemia is not severe and a twice-daily regimen in patients with an A1C > 8.5%.³⁰ For once-daily regimens, the mix is often added before the evening meal in clinical trials and in practice.^{31,32} In one study, the addition of once-daily biphasic insulin aspart 70/30 before the evening meal in patients failing to meet glycemic goals on metformin resulted in A1C reductions of 1.1–1.3%.³¹

Twice-daily premixed insulin regimens, however, certainly have the potential for greater A1C reductions for those patients requiring a more pronounced A1C reduction. Lingvay et al.³³ recently demonstrated a 100% success rate in achieving a goal A1C

of <7.0% in patients with newly diagnosed type 2 diabetes by initiating twice-daily biphasic insulin aspart 70/30 insulin in combination with metformin.

Premixed insulin products are a viable option when initiating insulin therapy in patients with type 2 diabetes, particularly in those with an obvious need for both basal and prandial insulin coverage who wish to minimize regimen complexity and their number of daily injections.

Basal/bolus insulin regimens. The basal/bolus insulin dosing strategy is the closest paradigm available to mimic normal physiological insulin secretion. However, many patients are reluctant to start insulin therapy with such an aggressive approach.³⁴ Patients with type 2 diabetes will often transition into a basal/bolus regimen since less complex once- or twice-daily regimens no longer allow them to meet their individual glycemic goals.

Insulin titration to meet therapeutic goals

On initiation of insulin therapy, the AACE/ACE 2007 guidelines recommend that patients be encouraged to practice self-monitoring of blood glucose (SMBG) a minimum of twice daily and report SMBG data to their clinician weekly to mediate adjustments to their insulin regimen.⁴ Similarly, the ADA recommends SMBG three or more times daily for patients on multiple daily insulin injections.¹⁰

Ultimately, SMBG is a necessary component in achieving patient success when implementing an insulin regimen. Without SMBG, timely and appropriate stepwise adjustments cannot be made in response to glucose values. This in turn can lead to suboptimal therapeutic outcomes and place patients at undue risk for hypoglycemic events.

A variety of published titration schemes are available for practitioners and patients to choose from depending on their individual preferences and level of experience. Table 3 provides one example of a titration schedule available to aid in the adjustment of basal and preprandial insulin.³⁴

Intensifying insulin therapy over time

Even with appropriate titration of insulin therapy, insulin needs for patients with type 2 diabetes will inevitably change over time. Although patients

Table 3. Sample Titration Schedule for Patients Using Basal and/or Prandial Insulin Therapy

Fasting Blood Glucose Levels for 3 Consecutive Days (mg/dl)	Adjustment of Basal Insulin Dose (units)	Premeal Glucose Levels for 3 Consecutive Days (mg/dl)	Adjustment of Rapid-Acting Insulin Dose (units per injection)*
> 180	8	> 180	3
160–180	6	160–180	2
140–159	4	140–159	2
120–139	2	120–139	1
100–119	1	100–119	Maintain dose
80–99	Maintain dose	80–99	–1
60–79	–2	60–79	–2
< 60	–4 (or more as appropriate)	< 60	–4

*If the patient has an elevated blood glucose level at lunchtime, the breakfast rapid-acting dose should be adjusted; if the preprandial blood glucose level is elevated at dinnertime, the lunchtime rapid-acting insulin dose should be adjusted; if the patient has an elevated bedtime blood glucose, the dinnertime rapid-acting insulin dose should be adjusted. Adapted from Ref. 34.

Table 4. Guidelines for Transitioning Patients From Less Intensive to More Intensive Insulin Regimens**Once-daily long-acting insulin analog → Premixed insulin analog twice daily**

- Divide total daily dose of long-acting insulin analog in half. Give half the dose as premixed insulin analog 0.5 hour before breakfast and the other half before the evening meal. Start new regimen 18–24 hours after the last basal dose was given.
- Titrate to goal based on SMBG and diet history. The largest meal will require a larger portion of insulin.
- Reduce the total daily dose by 20% if recurrent hypoglycemia occurs.

Once-daily long-acting insulin analog → Once-daily long-acting insulin analog + rapid-acting insulin analog with the largest meal

- Reduce long-acting insulin analog by 10%.
- Administer 10% of the total daily dose as rapid-acting insulin analog with the largest meal.

Once-daily premixed insulin analog → Twice-daily premixed insulin analog

- Divide total daily dose of premixed insulin analog in half. Give half the dose as premixed insulin analog 0.5 hour before breakfast and the other half before the evening meal.
- Titrate to goal based on SMBG and diet history. The largest meal will require a larger portion of insulin.
- Reduce the total daily dose by 20% if recurrent hypoglycemia occurs.

Twice-daily premixed insulin analog → Multiple daily injections

- Divide the total daily dose in half.
- Initiate basal insulin dose as: $(\text{total daily dose}/2) \times 80\%$.
- Initiate prandial insulin dose as: $(\text{total daily dose}/2) \times \text{percentage of estimated daily carbohydrate for each meal}$.

Adapted from Ref. 35.

may do quite well initially with the simple addition of a long-acting insulin analog to their preexisting oral antidiabetic regimen, they often require more intensive insulin regimens as their response or β -cell function declines over time. Table 4 provides guidelines for transitioning patients from less intensive to more intensive insulin regimens as patient-specific insulin needs change over time.³⁵

Conclusion

Type 2 diabetes is a progressive disease characterized by insulin resistance

and progressive β -cell dysfunction. As more patients are diagnosed with type 2 diabetes earlier in life, many patients will require insulin therapy as they receive less benefit from alternative therapies over time. Many insulin products and dosing strategies are available to patients and health care providers. Luckily, consensus guidelines exist to guide prescribers and patients as they initiate and titrate insulin therapies to meet individual therapeutic goals.

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Note of disclosure: Dr. Wysham has received honoraria for speaking engagements from Sanofi-Aventis, Novo Nordisk, and Eli Lilly and Co., all of which are manufacturers of insulin products for the treatment of diabetes.