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Building Better Insulin Therapy to Improve Glycemic Control and Patient Adherence

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REVIEW ARTICLES

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Building Better Insulin Therapy to Improve Glycemic Control and Patient Adherence

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Target Audience

This educational activity is intended for endocrinologists, internists, and family physicians. Other healthcare professionals may also participate.

Learning Objectives

After completing this educational activity, learners should be better able to:

- Develop clinical strategies for the timely intensification of insulin therapy in order to achieve glycemic control
- Assess data to differentiate among insulin strategies and their potential hypoglycemic impact
- Incorporate practical techniques to address patient barriers to achieving treatment goals with insulin therapy
- Appraise emerging agents that will allow dosing flexibility with reduced side effects

Program Overview

This CME-certified educational supplement will examine the barriers presented by and limitations of current insulin strategies, as well as evaluate the data on emerging insulin agents to improve treatment success for patients with diabetes. It will also focus on how long-acting insulin analogs, novel short-acting insulin, and rapid-acting insulin analogs may be used to improve treatment success for patients with diabetes.

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review article

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REVIEW ARTICLE

The need for better insulin therapy

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Insulin replacement therapy corrects a core defect of diabetes pathophysiology. Since its introduction as a therapeutic modality almost 100 years ago, insulin therapy has undergone remarkable changes in purity and ability to provide more physiologic control of blood glucose levels. With glucose-lowering potential limited only by risks of hypoglycemia, which remains the major limitation in our ability to achieve glycemic goals, insulin replacement therapy remains a cornerstone of therapy. Major progress in reducing the risks of hypoglycemia has occurred with the development of insulin analogs. This review article briefly chronicles the evolution of insulin replacement strategies, highlighting both challenges in pharmaceutical development and patient acceptance, underscoring achievements, as well as denoting what improvements are still needed.
Keywords: analogues, basal, insulin, NPH, type 1 diabetes, type 2 diabetes

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Introduction

Prior to the discovery of insulin in the summer of 1921, type 1 diabetes mellitus (T1DM) was a universally fatal disease due to the inevitable development of diabetic ketoacidosis [1]. Nearly 92 years later, it is intriguing to review the rapid development of insulin as a therapeutic agent and the forms of its delivery, the changes and improvements that have occurred over time, and the durability of the native hormone as a core therapeutic modality for the treatment of both T1DM and type 2 diabetes mellitus (T2DM). By March 1922, the first clinical results were published in the Canadian Journal of Medicine where the authors reported that in February 1922, up to seven patients with T1DM had been treated, with only one, a 14-year-old boy named Leonard Thompson, described in detail [2]. Daily subcutaneous injections of the 'brown muck' reportedly resulted in reduced blood glucose levels, reductions in glycosuria, disappearance of acetone bodies, as well as improvements in subjective findings of well-being and vigour. By December of the next year (1923), the Nobel Prize had been awarded for this discovery and involvement of pharmaceutical companies had occurred. As such, the era of insulin therapy had begun.

Some of the reasons for this remarkable change in diabetes care can be attributed to the near universal efficacy of insulin in reducing hyperglycaemia and the lack of dose limits to its efficacy (Table 1) [3]. We later learned that the glucose-lowering achievable with insulin therapy reduces microvascular risk in patients with T1DM [4] and T2DM [5]. Notwithstanding these remarkable facts, there were disadvantages to insulin therapy, namely hypoglycaemia and weight gain [6]. In the early days, the idea of patients self-injecting medications was not widely acceptable to patients or their physicians and the methods available to do so were somewhat crude. Even to this day, some patients find injectable therapy difficult and fraught with some level of stigma [7]. For many years, among the medical community, there were also concerns about mitogenicity [8,9], which hopefully the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial [10,11], which showed no increase in cancer risk among insulin users, has put to rest (Table 1) [3].

Early insulin came from the purification of porcine or bovine pancreases. Common adverse effects of these preparations included abscesses, insulin-antibody-formation allergy and lipodystrophy, primarily related to impurities and to species-specific antibodies [1]. The early insulin products also did not mimic the physiologic release of insulin. Normal insulin release, as we know, is characterized by background basal insulin release throughout the day, with additional release of insulin in response to carbohydrate ingestion (prandial insulin release). The problems of lack of physiologic profiles of the early insulin preparations largely have been addressed by progressive improvements in formulations. After the move from animal to human insulin, rapid-acting insulin analogues were the first to be developed. These agents (aspart, lispro, and glulisine) provide more rapid onset of action than regular human insulin and can be administered at the time of food ingestion (rather than 30–45 min in anticipation of carbohydrate ingestion) and have a more rapid off-set of action, resulting in a lower risk of hypoglycaemia [12]. Their use also appears to be associated with moderately better metabolic control and treatment satisfaction than regular human insulin [13], and better postprandial glucose control [14]. It took many more years to develop effective long-acting basal insulin analogues (figure 1). This was a more challenging pharmaceutical development and a more important clinical need since ultralente, lente, and Neutral Protamine Hagedorn (NPH) all have/had variable

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Table 1. Characteristics of insulin. Adapted with permission from Ref. [3].

Class	Mechanism	Advantages	Disadvantages	Costs
Insulin	Activates insulin receptor ↑ peripheral glucose uptake	Universally effective Unlimited efficacy ↓ Microvascular risk	Hypoglycaemia Weight gain Injectable Training requirements 'Stigma'	Variable

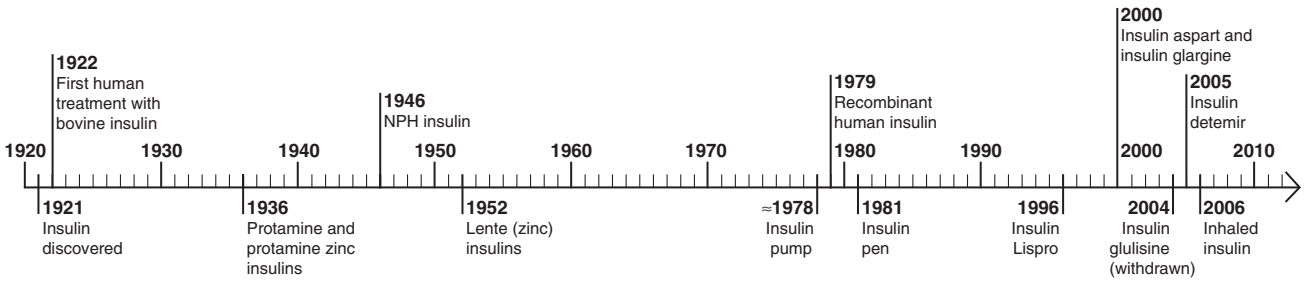

Figure 1. Milestones in insulin development.

pharmacokinetic and pharmacodynamic profiles. These have presented challenges for physicians and frustrations for patients with regard to consistency of action and risks of hypoglycaemia, particularly nocturnal hypoglycaemia. Most recently the analogue insulins have taken us to a modern age of being able to provide basal and bolus insulin replacement [12]. The analogue insulins, because of these more predictable physiologic profiles, are associated with lower rates of hypoglycaemia, particularly nocturnal hypoglycaemia, than NPH when compared to insulin detemir or insulin glargine [15–19]. These advances, coupled with improvement in both needle devices and insulin delivery systems such as pens, have also facilitated the use of insulin therapy [20]. Furthermore, in the case of insulin detemir, newer basal insulin appears to be associated with less weight gain than NPH [21] or glargine [22,23]. The balance of this article will focus on the challenges that still face physicians with regard to successful insulin therapy, both from a clinical perspective and a patient acceptance/adherence perspective.

Despite the well-documented benefits of timely glycaemic control and consensus guidelines encouraging earlier use of insulin [3,6], considerable clinical inertia exists with respect to initiating appropriate insulin therapy in patients with T2DM [24]. Physicians caring for patients with diabetes may fail to follow guidelines by not intensifying diabetes therapy when A1C levels are well above 8% [25,26]. Patients may have a substantial glycaemic burden for months to years before therapy is intensified or altered [27,28,29]. The use of insulin in the USA has been trending downwards over recent years [30]. Some of this is clearly related to the large number of drug approvals for patients with T2DM that have occurred in the past several years, offering physicians many more choices with which to address hyperglycaemia. However, at the end of the day, insulin is lifesaving and essential for patients with T1DM. In patients with T2DM, insulin corrects a core defect, and with the progressive decline in β-cell function and the inevitable decline in insulin secretion of T2DM, the use of insulin remains

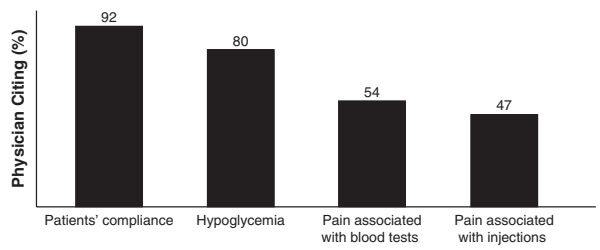

Figure 2. Physicians' main barriers to starting insulin. Adapted with permission from Ref. [32].

fundamental to our treatment approaches for this population as well. Many physicians, even specialists, prefer to delay insulin therapy until absolutely necessary [31]. Among the major reasons cited by physicians are concerns about patients' ability to comply with therapy as well as the risks of hypoglycaemia associated with insulin therapy (figure 2) [32]. While physicians are also worried for their patients about the pain of injections and glucose monitoring, patients themselves are not so worried about these aspects, but do show poor understanding of diabetes as a disease and the benefits of insulin therapy [32].

These concerns are supported by other surveys of T2DM patients [33]. Less than one-third of patients surveyed were unwilling to start insulin therapy. More recent surveys show that almost half of patients are willing to start insulin if it is offered [34]. The primary concern about insulin therapy appears to be fear of hypoglycaemia. In addition, patients feel that the need for insulin signals some failure on their part in the management of their disease, a signal that they did not appreciate the progressive nature of diabetes. Certainly the impact of insulin therapy on one's lifestyle remains a concern for patients. [33] Patients failing to initiate prescribed insulin commonly report misconceptions regarding insulin risk (in one study, 35% believed that insulin causes blindness, renal failure, amputations, heart attacks, strokes or early death), and

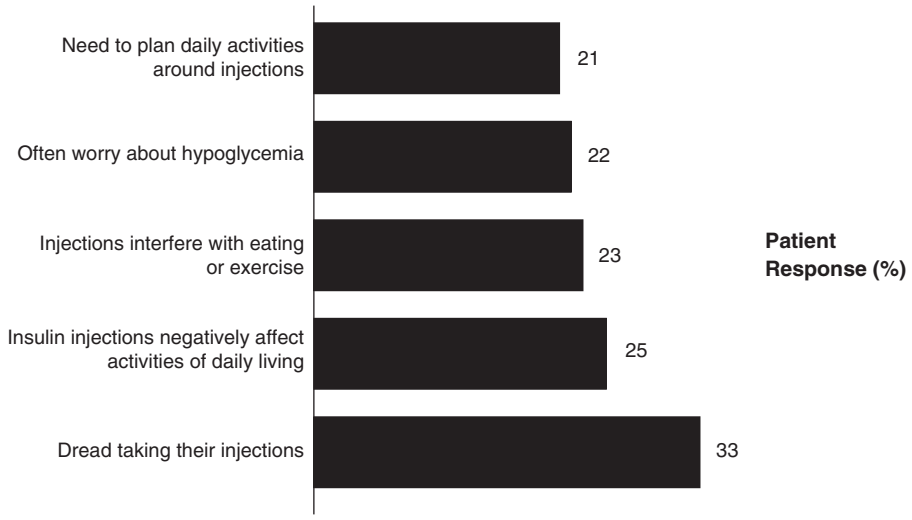

Figure 3. Patient reasons for omitting insulin injections. N = 502; 70% vial syringe users; 30% insulin pen users. Patients reported taking an average of 2.7 injections a day. Adapted with permission from Ref. [36].

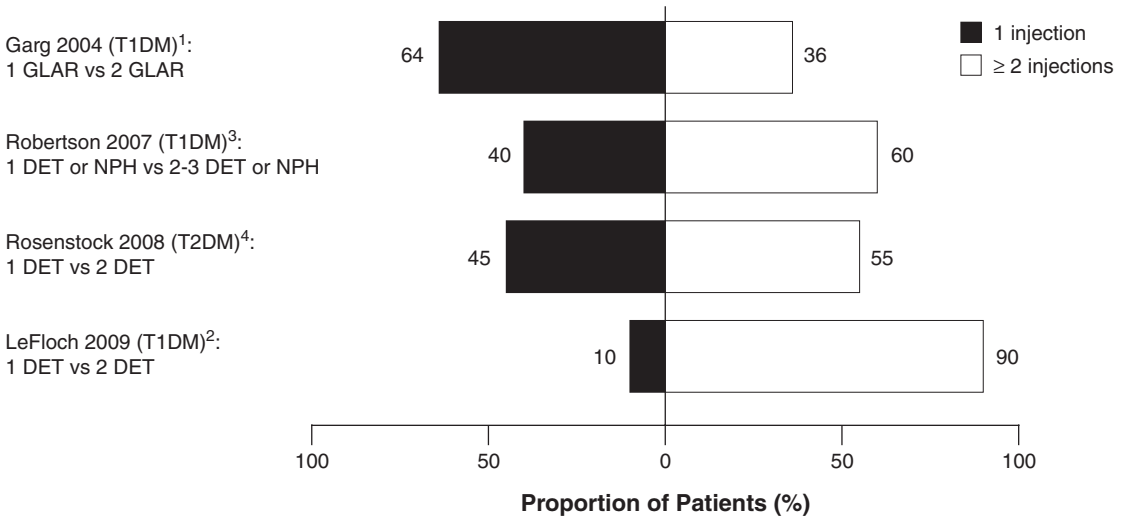

Figure 4. Multiple doses of basal insulin analogues may be needed to attain glycaemic goals. Adapted with permission from Refs. [22,42–44].

indicate the intention to instead work harder on lifestyle goals. They may indeed have some level of injection phobia, limited insulin self-management training, hypoglycaemia concerns, inadequate health literacy, which may in part reflect a health care provider inadequately explaining the risks/benefits [35] or failing to refer them to a diabetes educator. Many patients who are prescribed insulin and who do fill their prescriptions report skipping injections they know they should take. The reasons given in one survey are shown in figure 3 [36]. A patient survey of willingness to pay more for a long-acting insulin showed that features of an insulin that are attractive would be one that resulted in less weight gain, less delivery device trouble, more days with good glucose control, less dosing frequency, and less nighttime hypoglycaemia [37].

To further pursue the topic of less dosing frequency, let us explore the dosing frequency of the basal insulin analogues, putting aside meal-time insulin doses for the time being. When first introduced, NPH was considered a long-acting insulin, but as we now know, it is more of an intermediate insulin, exhibiting a peak (at 4–10 h) and having a duration of action of 12–18 h [12]. It was not until the introduction of insulin glargine in the year 2000 that we had the ability to deliver basal bolus insulin. Insulin glargine uses a crystalline precipitate to prolong the action of the synthetic insulin to create a flat insulin with a long duration of action [38]. The second long-acting insulin to be developed was insulin detemir, a long-acting human insulin analogue acylated with a 14-carbon fatty acid [39]. Both have a longer duration of action, less intrapatient variability, less pronounced peak in time-action profiles and decreased hypoglycaemic risks than NPH [40]. Insulins have dose-related duration of action, with a longer duration of action at higher doses (so a longer duration in patients with T2DM who typically require higher insulin doses because they are insulin resistant) [41]. Currently available

basal insulin analogues do not last 24 h in some patients and some patients may require up to two injections to maintain basal control (figure 4) [22,42–44]. These patients could benefit from insulin options with longer time-action profiles.

Conclusions

Although insulin products and treatment strategies have improved significantly, clinical challenges still exist. While there have been many advances in efficacy, safety, and now even patient flexibility and convenience based on pharmacokinetics and mechanisms of delivery since the first insulins became available, more improvements are needed. Among these is a need to provide more physiologic basal insulin coverage and to reduce hypoglycaemic risk in patients with diabetes as the disease progresses and treatment intensification is required.

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Disclosure

G. G. states that he is a member of the promotional speakers' bureau for Amylin Pharmaceuticals, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, Merck & Co., Inc., Novo Nordisk Inc., Sanofi, Santarus, Inc., and Takeda Pharmaceutical Company Limited. G. G. is a member of the advisory boards for scientific information for Amylin Pharmaceuticals, Inc. and Eli Lilly and Company. He has received grant/research support (paid to Grunberger Diabetes Institute) from Amylin Pharmaceuticals, Inc., GlaxoSmithKline, Johnson & Johnson Services, Inc., Eli Lilly and Company, and Novo Nordisk Inc. This supplement is based on a symposium held in conjunction with the American Diabetes Association's 72nd Scientific Sessions, which was supported by an educational grant from Novo Nordisk Inc. and jointly sponsored by the American Academy of CME, Inc. and E&S MedEd Group, Inc.

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REVIEW ARTICLE

review article

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Newer insulin analogs: advances in basal insulin replacement

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Basal insulin analog therapy is the most common method of introducing insulin replacement therapy for the majority of patients with type 2 diabetes mellitus. Long-acting insulin analogs provide relatively peakless and more physiologic insulin replacement therapy than neutral protaminated Hagedorn insulin. Recently 2 new basal insulin analogs have been developed with superior pharmacokinetic and pharmacodynamics properties; insulin degludec and a pegylated insulin lispro. These agents are generally well tolerated and have been evaluated in both type 1 and type 2 diabetes. In this article we review the results of clinical trials assessing the efficacy, safety and tolerability of these newer longer-acting insulin analogs. In general rates of hypoglycaemia in these trials were low, glucose control was comparable to currently available basal insulin analogs, and rates of nocturnal hypoglycaemia were significantly and substantially lower. While further study will be required, advances in basal insulin replacement may offer important advantages over existing options for starting insulin strategies.
Keywords: basal insulin, insulin degludec, investigational, nocturnal hypoglycaemia, PEGylated long-acting basal insulin, type 1 diabetes, type 2 diabetes

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Introduction

More than 20 years ago, in a NEJM article entitled 'The Physiologic Replacement of Insulin' that began with the sentiment, 'although insulin was discovered and first administered' . . . [many years ago] . . . 'The goal of physiologic replacement remains elusive, despite major advances in our understanding of insulin's physiologic effects, chemistry, kinetics and action' [1]—a statement that has remained largely unchanged.

Even today, we are still attempting to maximize the therapeutic potential of insulin and achieve glycaemic goals, while minimizing both glucose variability and the risks of hypoglycaemia. However, we are now about to enter a new phase in the development of basal insulin analogs—from the first generation to the next generation of long-acting insulin analogs. This article will review the available data for two agents in development for the treatment of patients with type 1 (T1DM) and type 2 diabetes (T2DM). The published medical literature, as well as the meeting abstracts from recent diabetes meetings, was searched for information to support this review.

PEGylated Insulin Lispro

LY2605541 is a PEGylated basal insulin (hereafter called PEGylated insulin lispro) that, as of this writing, has completed Phase II clinical trials. This insulin molecule is embedded in a polyethylene glycol (PEG) chain; pegylation of other products has been used as a means of extending the duration of action in injectable drugs [3]. The molecule is quite large that its absorption from the subcutaneous space is slowed significantly, as is its clearance resulting in a prolonged duration of action [4,5]. For perspective, the functional size of the molecule exceeds that of albumin, which we know is a very large molecule (on the order of approximately 65 kD) [6]. While single-dose pharmacokinetic data begin to reveal the flat profile of the investigational agent (compared with insulin glargine) [5], steady-state profile data truly demonstrate the very flat profile and 24-h duration of action of PEGylated insulin lispro [7].

PEGylated insulin lispro is associated with comparable or better glycaemic control than insulin glargine as well as reduced weight in patients with T1DM and T2DM. In the study of patients with T1DM ($n = 137$), the improvements in glycated haemoglobin (HbA1c) with the novel insulin were significantly better than those seen with insulin glargine (−0.6% vs. −0.4%, $p < 0.05$; figure 1) [2]. Patients on the investigational agent lost a mean of 2.65 lb (1.19 kg), while those on insulin glargine gained a mean of 1.52 lb (0.68 kg, $p < 0.001$). Significantly more patients on the novel insulin lost 5% of their body weight (12% vs. 1%, $p < 0.001$). While patients receiving the novel insulin had higher rates of gastrointestinal adverse effects [e.g., nausea, abdominal distention, and dyspepsia (15% vs. 4% overall)], this did not appear to correlate with the patients who lost more weight, leaving the mechanism of weight loss unclear. Overall hypoglycaemia risk was greater with PEGylated lispro compared with insulin glargine (8.7 events vs. 7.4 events per month, $p = 0.04$); however, the risk of nocturnal hypoglycaemia was lower with the investigational agent (0.9 vs. 1.1 events, $p = 0.01$)

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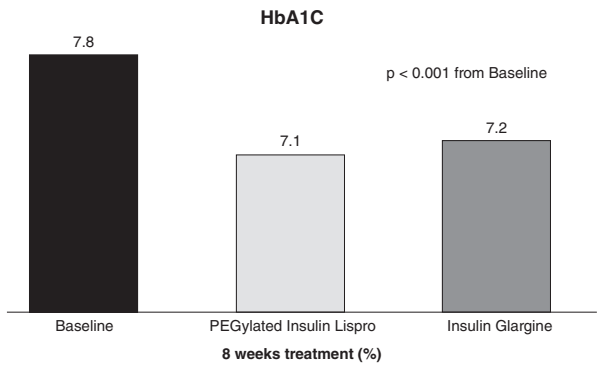

Figure 1. Glycaemic control with PEGylated insulin lispro compared with insulin glargine in patients with T1DM. Adapted from data in table 2, from poster, of Ref. [2].

[2]. The higher risk of overall hypoglycaemia may be explainable in part by the longer duration of action of the PEGylated insulin and perhaps a need for a slightly lower total insulin dose. In this context the mean prandial insulin doses were reduced during PEGylated insulin lispro treatment. Of note, with the PEGylated insulin there were some elevations in the liver function tests. For patients with T2DM, the novel drug provided similar improvements in glycaemic control as insulin glargine.

In patients with T2DM, PEGylated lispro resulted in a mean weight loss of 1.28 lb (0.68 kg), compared with a gain of 0.68 lb (0.31 kg) for those on insulin glargine ($p < 0.01$) and more patients on the investigational agent lost 5% of their body weight (5% vs. 0%, $p \leq 0.03$). The incidence and rate of both total hypoglycaemia and nocturnal hypoglycaemia were comparable between insulins, although patients treated with PEGylated insulin lispro had a 48% reduction in nocturnal hypoglycaemia after adjusting for baseline hypoglycaemia ($p = 0.021$). Liver function tests were significantly higher in patients treated with the investigational agent but remained within normal range ($p \leq 0.001$) [8].

A series of Phase III studies are underway with this novel basal insulin, and those of us who treat T1DM and T2DM look forward to reviewing additional data on PEGylated insulin as they become available.

Insulin Degludec

Another ultra long-acting insulin for which more data are currently available is insulin degludec. In November 2012, an advisory panel to the United States Food and Drug Administration recommend approval of insulin degludec. In January 2013, the European Commission granted marketing authorization to long-acting insulin degludec. The insulin degludec molecule retains the human insulin amino acid sequence with the exception of deleting threonine in the B30 position (ThrB30) and adding a 16-carbon fatty diacid side chain attached to lysine in position B29 (LysB29) of the insulin B-chain via a glutamic acid linker [9]. Upon injection, insulin degludec dihexamers begin to associate with each other inside the body like a 'string of pearls' forming long chains of multihexamers (figure 2) [9]. These long stable structures slowly dissociate into smaller units resulting in a slow release of active insulin monomers into the circulation. The process is remarkably smooth, without a significant peak, but rather with a very flat profile, producing a very stable glucose-lowering effect [10]. The terminal half-life of insulin degludec is approximately 25 h at steady state and is not dose-related (figure 3) [10]. With once-daily administration of insulin degludec, steady state is reached in approximately 3 days. When compared with insulin glargine, the day-to-day variability in glucose-lowering effect is four times lower with insulin degludec in patients with T1DM [11]. The duration of action is reportedly in the excess of 40 h [12].

Data from clinical trials of insulin degludec in patients with T1DM and T2DM have shown that this ultra long-acting insulin is able to lower blood glucose levels, with low rates of hypoglycaemia, especially nocturnal hypoglycaemia. The trials also suggest that insulin degludec can be administered once daily, at any time of the day, with little consequences from a change in injection timing that may result from an unexpected lifestyle event. In this regard, insulin degludec can be viewed as a more 'forgiving' insulin in that strict timing of insulin doses is not necessary for safety or efficacy. Short-term Phase II trials (16 weeks in duration) [13,14] have been followed by trials of 1 year in duration, providing more long-term clinical data, which will be reviewed here. Data for more flexible dosing of U-100 degludec and a more concentrated form of insulin degludec (U-200) will also be covered. In all of these studies, insulin glargine was the basal insulin comparator.

For patients with T1DM, insulin is life-saving and these patients require basal–bolus insulin therapy to approximate physiologic insulin replacement (or alternatively can be treated with continuous subcutaneous insulin infusions). In either case, hypoglycaemia is the rate-limiting factor in achieving glycaemic control. Intensive basal–bolus insulin therapy has been shown to improve glycaemic control and reduce the risk of long-term complications that are associated with T1DM [15–17]. Insulin degludec was compared to insulin glargine (both in conjunction with a prandial insulin analog as part of basal–bolus insulin therapy) in an open-label, treat-to-target, 52-week trial, in six countries. The trial was not double-blind because the pen delivery devices for the two insulin products are unique in design. Of 629 participants, 472 were randomly assigned to insulin degludec and 157 to insulin glargine. At 1 year, HbA1c had fallen by 0.40% points and 0.39% points, respectively, with insulin degludec and insulin glargine showing that these insulins were comparable in glucose-lowering effects. Similarly, rates of overall confirmed hypoglycaemia (<56 mg/dl) were similar in the insulin degludec and insulin glargine groups (42.54 vs. 40.18 episodes per patient-year of exposure). Notably, the rate of nocturnal confirmed hypoglycaemia was 25% lower with degludec than with glargine (4.41 vs. 5.86 episodes per patient-year of exposure; $p = 0.021$) [18].

Long-standing T2DM creates special challenges for the physician and patient. The progressive pathophysiologic nature of T2DM results in the need for numerous medications to address multiple metabolic defects [19], with an increasing likelihood of the need for insulin as β-cell function declines [20]. Most physicians are relatively comfortable with initiating insulin therapy with a single injection of basal insulin as add-on therapy to oral antidiabetic agents when HbA1c levels are no

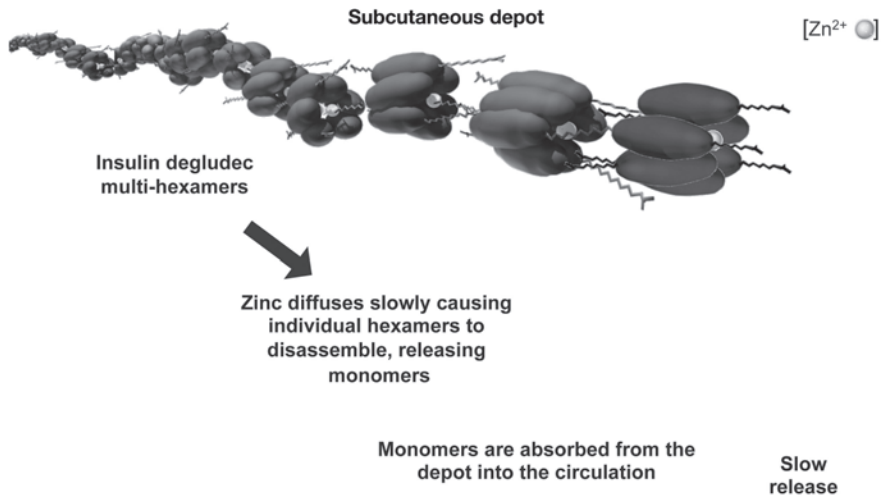

Figure 2. Schematic representation of insulin-zinc hexamer conformation used to create the prolonged action for insulin degludec. Zinc diffuses slowly after subcutaneous injection and the hexamer disassembles into dimers and insulin monomers and there is steady release of insulin of for more than 24 hours. Adapted with permission from Ref. [9].

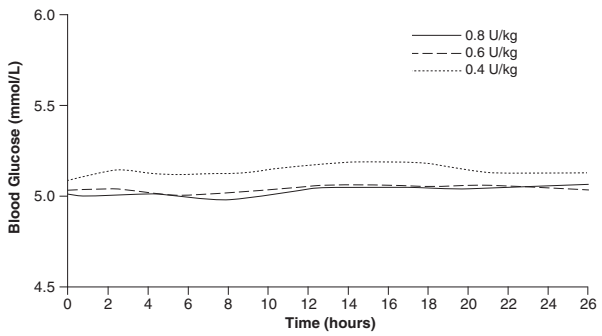

Figure 3. Insulin degludec has a flat pharmacodynamic profile at steady state that is not dose-related, with a glucose lowering profile that exceeds 24 h. Adapted with permission from Ref. [37].

longer controlled with combination therapy. However, some physicians and their patients may sometimes be reluctant to adopt or intensify insulin therapy to achieve treatment goals because of concerns about hypoglycaemia [21]. The incidence of hypoglycaemia with insulin therapy increases with duration of diabetes [22] and may become problematic in patients on basal–bolus insulin therapy [23]. Reducing the likelihood of hypoglycaemia, particularly nocturnal hypoglycaemia [24], may facilitate treatment acceptance and adherence. In a similarly designed study, patients with T2DM were randomized 3 : 1 to receive once-daily subcutaneous insulin degludec or glargine, titrated to a fasting plasma glucose (FPG) level of 70–90 mg/dl. Baseline characteristics of patients were as follows: mean age 59 years, diabetes duration 13.5 years, HbA1c 8.3%, and FPG 166 mg/dl. In patients with T2DM, use of insulin degludec and insulin glargine resulted in similar glucose lowering, but insulin degludec was associated with significantly less overall hypoglycaemia and significantly less nocturnal hypoglycaemia (figure 4) [25]. Rates of severe hypoglycaemia were low in both groups. The authors concluded that 'a policy of suboptimum diabetes control to reduce the risk of hypoglycaemia and its consequences in advanced T2DM might be unwarranted with newer basal insulins such as degludec, which are associated with lower risks of hypoglycaemia . . . [than available basal insulins]' [25].

Some patients who find insulin injections interfere with their lifestyle may omit injections [26], either because they find them inconvenient, fear hypoglycaemia, or forget to take the dose at the scheduled time [21,26]. Available basal insulin analogs last up to but sometimes not quite 24 h [27–30], and in theory require the patient to take their doses at the same time each day to maintain steady-state levels, with little room for 'life' to interrupt pharmacodynamics. An ultra long-acting insulin analog (one with a half-life in excess of 24 hours) might allow patients some flexibility in terms of lifestyle, without the need to rigidly adhere to administration times. This theory was tested in a controlled fashion in a 26-week study, wherein the dose of degludec was systematically changed so that it was either given 8 h from the last injection or 40 h from the last injection. Patients with T2DM received the same number of injections over the 7 days as they would have under normal prescribing conditions—that is, 7 days, seven injections of degludec. This was compared with degludec given at the same time every day, and insulin glargine given at the same time every day. The results demonstrated that insulin degludec, no matter how it was dosed, was still associated with similar improvements in glycaemic control and with less nocturnal hypoglycaemia. Recently, this concept of flexible dosing has been found to be feasible in a 1-year study of patients with T1DM [31]. These findings of less nocturnal hypoglycaemia have been observed across studies of insulin degludec, in addition to lower FPG levels in many of the studies compared to insulin glargine [32].

Obesity is a significant problem in patients with T2DM [33,34], especially in the USA [35] and contributes to the need for larger daily doses of insulin in many patients with T2DM. A 200 U/ml formulation of insulin degludec (IDeg U200) is also being developed to allow for delivery of larger insulin doses in a single injection. IDeg U200 will deliver twice

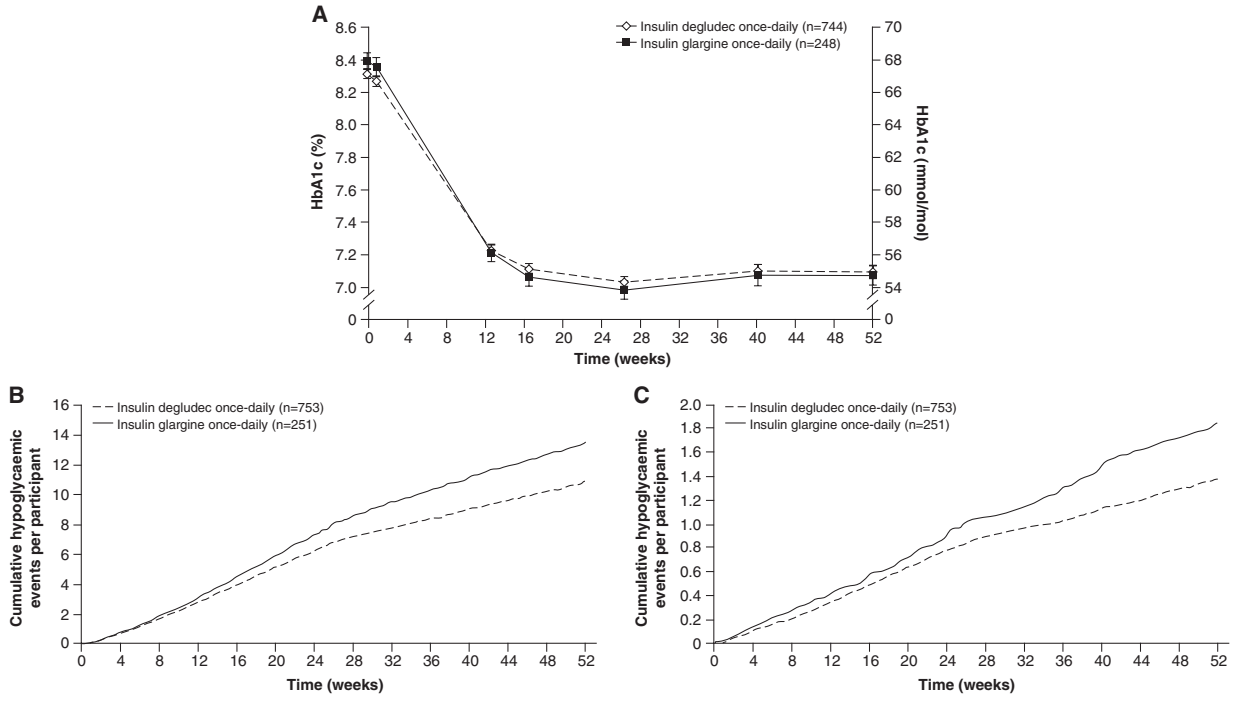

Figure 4. Insulin degludec versus insulin glargine plus prandial insulin analog in patients with T2DM: comparable glucose lowering, comparable overall rates of hypoglycaemia and much lower rates of nocturnal hypoglycaemia with insulin degludec. Adapted with permission from Ref. 25.

the amount of insulin—up to 160 U— in the same volume as the 100 U/ml formulation. To evaluate the safety of the concentrated formulation, Bergenstal et al. conducted a trial in insulin-naïve patients with T2DM comparing IDeg U200 with insulin glargine, in patients on background metformin therapy [36]. HbA1c lowering was similar for both agents; there were significantly greater FPG reductions and numerically less hypoglycaemia with insulin degludec. Insulin degludec 200 U/mL allowed patients who required larger daily doses of basal insulin and who used prefilled pen devices to administer up to 160 U in a single injection.

Summary

Emerging basal insulin analogs have better pharmacokinetics than currently available basal insulin analogs, which translates into flatter time-action profiles with less variability and less hypoglycaemia (particularly nocturnal hypoglycaemia). In addition, these agents appear to be associated with greater flexibility with time-of-day dosing, which may make it easier to compensate for missed doses and allow patients to stay on track with glycaemic control treatment strategies. It appears like we are coming closer to our goal of more physiologic insulin replacement. The availability of such agents and their use in clinical practice will hopefully continue to advance our efforts at improving diabetes care and reducing treatment-related adverse outcomes.

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review article

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REVIEW ARTICLE

Methods to enhance delivery of prandial insulin and basal-prandial insulin

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Most physicians are comfortable with initiating basal insulin replacement therapy in their patients with type 2 diabetes who are no longer meeting treatment goals with oral antidiabetic agents. What is more challenging is what to do when treatment goals are no longer being met despite adequate titration of basal insulin. Both fasting plasma glucose and postprandial glucose contribute to hemoglobin A1C levels. Addressing postprandial glucose levels can be accomplished by several approaches. Traditionally this has meant moving to basal bolus insulin, which is considered the gold standard. Premixed insulin may also be used. Data is also emerging for basal ''plus'' strategies, that is, incremental addition of prandial insulin injections. Newer approaches also reviewed in this article included premixed formulations containing ultra-long acting basal insulin with rapid-acting insulin analogs, inhaled insulin and insulin jet injectors, as well as the use of incretin-based therapies.
Keywords: basal insulin, insulin degludec, prandial insulin, premixed insulin, bolus plus, incretins, inhaled insulin, insulin jet injectors

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Introduction

The aim of insulin supplementation in patients with type 2 diabetes mellitus (T2DM) is glycaemic control and a reduction in microvascular disease and, if possible, macrovascular disease, without the induction of hypoglycaemia or weight gain. Patients with T2DM who progress to insulin therapy usually do so by starting with a single injection of a long-acting insulin analogue, added to oral antidiabetic drugs (OADs). The 4-T study supports the initiation of treatment with basal insulin [1,2], which is consistent with the concept that fasting hyperglycaemia contributes more than postprandial hyperglycaemia to glycated haemoglobin levels during periods of poor glycaemic control [3]. Long-acting insulin analogues provide basal insulin coverage and address elevated fasting plasma glucose (FPG) levels. They do so with a comparatively low risk of hypoglycaemia or weight gain [1,2]. Assuming adequate titration and treatment intensification, the use of basal insulin (along with background OADs) may be sufficient to achieve glycaemic targets. Typical titration strategies are to slowly increase insulin doses, typically by 2 units every 3 days until FPG levels are in the target range (70–130 mg/dl) (or more aggressively by 4 units every 3 days if BG > 180 mg/dl) [4,5].

The effect of increasing the basal insulin dose is about a 0.5% decrease in HbA1c for each 0.1 U/kg/day increment in insulin dose up to a threshold of 0.5 U/kg [6]. However, beyond this dose, the improvement in terms of HbA1c reductions is less substantial and the risk of hypoglycaemia increases. Increasing basal insulin in this situation may not improve glucose control, may increase weight and add to the risk of hypoglycaemia. In the 4-T study, most patients required and received insulin intensification by 3 years (figure 1) [2]. Insulin resistance and β-cell failure are common denominators in T2DM. However, the balance may tip towards increasing β-cell failure as the pathophysiology of T2DM progresses and FPG levels stop responding to basal insulin. Glycaemic goals can only be maintained when physicians are adroit in managing the complexities of both fasting and postprandial hyperglycaemia [7,8]. This review article examines current and emerging strategies for addressing postprandial glucose (PPG) control for basal insulin-treated patients (figure 2).

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Current Methods for Intensification

Premixed Insulin

Premixed insulin products provide both basal insulin and prandial insulin in a single injection, in a fixed dose ratio (70 : 30, 70 : 25, 50 : 50) to address both fasting and postprandial hyperglycaemia. Premixed insulin can be used as a starting insulin strategy as a single dose before the largest meal, which then has the flexibility to be intensified to two or three doses [9]. This regimen may be suitable for patients uncomfortable titrating basal and bolus insulin or for those who want to limit the number of injections, however, it requires the patient to have relatively standard meal types and sizes to be most successful and carries a slightly greater likelihood of weight gain and risk of hypoglycaemia. The success of premixed insulins in controlling glucose levels among patients with T2DM may reflect the greater importance of insulin resistance in this patient population. Thus, both prandial and basal doses are

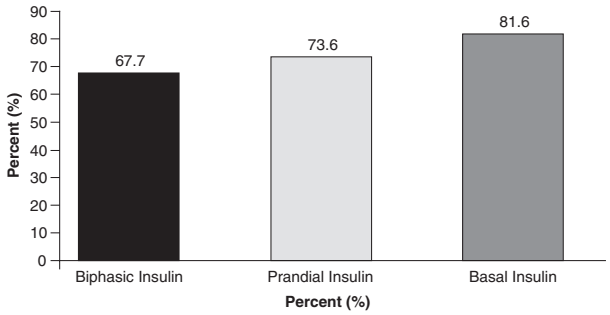

Figure 1. Patients requiring two types of insulin at 3 years [2].

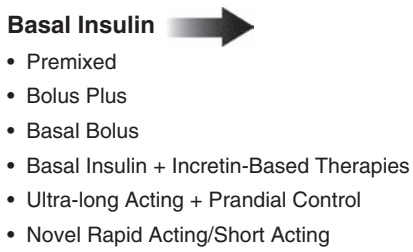

Figure 2. Current and emerging options for addressing postprandial glucose control for basal insulin-treated patients.

equally dependent upon overcoming the resistance to insulin action present in this patient population and the size and timing of meals is much less important than in patients with type 1 diabetes mellitus (T1DM). As a result in insulin naïve patients with T2DM, premixed and basal-bolus therapeutic arms were nearly equally effective in controlling hyperglycaemia in a randomized controlled trial [10]. Most endocrinologists tend not to use premixed insulin as it is less physiologic than basal plus prandial or basal-bolus insulin, but there are some patients who do well with it [1,10]. In the 4-T study, 40% of patients randomized to premixed insulin analogues achieved HbA1c levels less than 7% at 1 year, more than those receiving basal insulin alone, though not as many as on basal-bolus therapy [1]. The PREFER study was a randomized control study of patients with T2DM with inadequate control on OADs with or without basal insulin. OADs were discontinued and patients were randomized to analogue basal-bolus therapy (insulin detemir once daily and insulin aspart at mealtimes) or biphasic insulin aspart 30 (30% rapid-acting insulin aspart), twice daily. Insulin was titrated to targets for fasting, predinner and PPG, as appropriate. Both insulin-analogue regimens enabled patients to reach HbA1c < 7.0% (figure 3) [10]. Rates of hypoglycaemia were low and comparable between analogue regimens. Insulin-naïve patients achieved equal glycaemic control with a premixed analogue regimen or a basal-bolus regimen. However, patients not reaching target on NPH or insulin glargine (+OADs) benefited more from intensification to basal bolus than to premixed insulin [10]. Insulin-naïve individuals benefitted equally well from either regimen in this clinical trial and in clinical practice may be more amenable to a premixed regimen which involves fewer injections and less blood glucose testing.

Bolus Plus (Basal Plus Prandial Insulin)

Until relatively recently there was little published data bridging the gap between a single shot of basal insulin and full use of basal-bolus insulin therapy, that is multiple daily injections. In reality, many physicians in clinical practice were taking a stepwise approach and increasing the number of insulin injections by adding prandial insulin with little data to guide them as to the best way to do so. While multiple injection basal-bolus therapy is considered by many to be the gold standard; sequential addition of a single prandial dose added to basal-insulin therapy can bring many patients to goal in a simpler, and perhaps more patient-friendly manner. The Orals Plus Apidra and LANTUS (OPAL) study was one of the first large, randomized, albeit open-label, studies to address this issue in 393 patients who were suboptimally controlled on a basal-insulin analogue and OAD regimen [11]. The study evaluated the benefits of adding a single injection of a rapid-acting insulin analogue, in this case, insulin glulisine, either at breakfast or at main mealtime. Patients had a mean baseline HbA1c of 7.3%, not that far from the American Diabetes Association (ADA) HbA1c goal of < 7%. With the addition of a prandial insulin before meals, HbA1c levels were reduced to < 7% (6.99%) (figure 4) [11], in clear support of the 'classic' Monnier data that describes the need to focus on PPG levels in patients close to, but not at HbA1c levels of < 7% [3]. The effects of doing this were comparable regardless of whether the prandial insulin was given before breakfast or before the main meal (figure 4) [11], offering physicians and patients flexibility in when to add a second insulin injection to the therapeutic regimen [11].

Delving into this a bit further, one may ask the question, should we be basing prandial insulin doses on preprandial or postprandial glucose levels? Does it make a difference? The STEPWISE randomized trial sought to compare two intensification regimens using rapid-acting insulin analogues in patients with T2DM not at goal on basal insulin + OADs [12]. One strategy involved the sequential addition of insulin aspart to meal(s) perceived by the patient as being the largest of the day, with titrations based on the premeal plasma glucose concentration (the SimpleSTEP strategy). The other strategy involved the sequential addition of insulin aspart to meal(s) with the highest measured PPG increase, with titrations based on the PPG level (the ExtraSTEP strategy). The study design is shown in figure 5 [12] and the titration schedule used is shown in Table 1 [12]. Notice that there are slightly different titration schedules based on whether you are titrating against preprandial or postprandial glucose levels. In these patients with relatively long-standing T2DM (~12–13 years), use of the two titration regimens achieved similar HbA1c reductions (1.2%) (figure 6) [12] which was achieved with the addition of prandial insulin and brought a similar percentage of patients to HbA1c levels < 7%. Although many patients reported an episode of symptoms-only hypoglycaemia, the overall rate of episodes per year was low for both regimens, with most episodes occurring during the daytime. Addition of prandial insulin resulted in some weight gain (2–2.7 kg; no statistical difference between intensification arms).

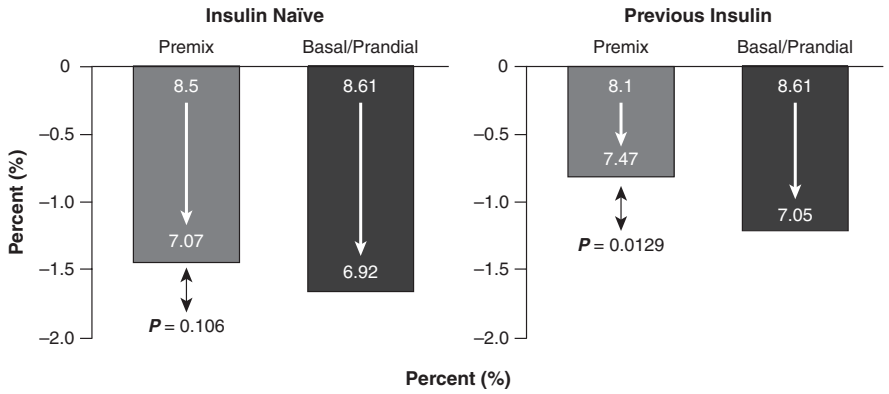

Figure 3. PREFER: HbA1c reduction in insulin-naïve versus insulin-treated patients: comparison of premixed versus basal-bolus insulin regimens [10].

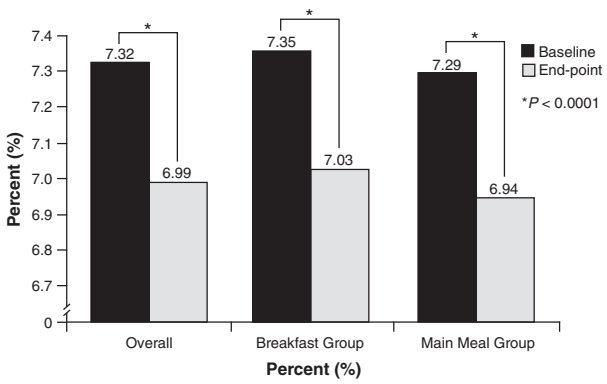

Figure 4. Orals Plus Apidra and LANTUS (OPAL): sequential addition of prandial insulin analogue at mealtime: change in HbA1c; overall and by meal. Adapted with permission from Ref. [11].

Carbohydrate counting is an effective approach to mealtime insulin adjustment usually used in patients with T1DM. In some adult patients with T2DM, it can also lead to improved diabetes control and weight loss. Bergenstal et al. [13] compared an insulin-to-carbohydrate ratio ('Fix') with a simple pattern control-based algorithm ('Flex') for adjusting the dose of prandial rapid-acting insulin analogues along with a standard algorithm for titrating a long-acting basal insulin in T2DM patients. Patients may also have been on metformin. The regimens are described in Table 2 [13]. Basically, the 'fix' regimen was a constant carbohydrate office-centred approach where the patient brought their glucose profiles in, and the physician adjusted their bolus insulin dosages based on what the patient reported to the physician or the diabetes educator; no carbohydrate counting was involved. The 'flex' regimen basically adopted a Diabetes Control and Complications Trial (DCCT) [14] approach for a patient with T2DM: carbohydrate counting and education on how to adjust the premeal insulin dose based on premeal blood glucose levels, and the potential need for correction bolus dosing. This approach required approximately five more hours of patient education, which may only be feasible if a diabetes educator is available to the physician. Both approaches resulted in similar levels of glucose control; there were modest but statistically significant differences in weight gain between regimens (figure 7) [13], which may be clinically significant to patients. Taken together, these data suggest that having more than one effective approach to adjusting mealtime insulin may increase patient and physician willingness to advance therapy from a basal-only regimen.

Recently Approved Strategies

Other new ways to augment basal insulin therapy in patients no longer achieving adequate control despite appropriate titration of basal insulin doses are to add incretin-based agents. Currently, the dipeptidyl peptidase-4 (DPP-4) inhibitors, as well as both liraglutide and short-acting exenatide, which are glucagon-like peptide receptor agonists (GLP-1 RAs), are approved for use with long-acting basal insulin analogues for patients with T2DM who are not achieving glycaemic goals. The incretin-based therapies primarily target postprandial hyperglycaemia (although longer-acting GLP-1 RAs also have effects on FPG levels) and have advantages over prandial-insulin analogues in that they lower postprandial-glucose levels with a low risk of hypoglycaemia and without weight gain.

In a study of relatively straightforward design, Barnett et al. [15] showed that addition of sitagliptin to patients with T2DM and inadequate control on basal insulin and metformin was better than placebo, and was generally well tolerated. HbA1c improvements were primarily due to decreases in PPG levels (−27 mg/dl in sitagliptin-treated patients versus −4 mg/dl in placebo-treated patients); FPG reductions were −10 mg/dl and −6 mg/dl, respectively for sitagliptin and placebo [15]. Recently, Hong et al. [16] reported in this journal a study comparing the efficacy and tolerability of adding sitagliptin, an oral DPP-4 inhibitor, utilizing an up to 20% increase in insulin dosing in patients with uncontrolled T2DM on primarily basal-insulin therapy (<25% of patients were on basal and prandial insulin). Average baseline HbA1c was 9.2% in both groups and mean insulin dose was 35–40 units/day. In this randomized parallel group study (N = 114), the complementary effects of DPP-4 inhibitors and insulin on FPG and PPG control resulted in better HbA1c control than a 25% increase in insulin dose with less weight gain and less hypoglycaemia.

Even before the recent approvals, there was information in the literature about the use of GLP-1 RA with insulin from

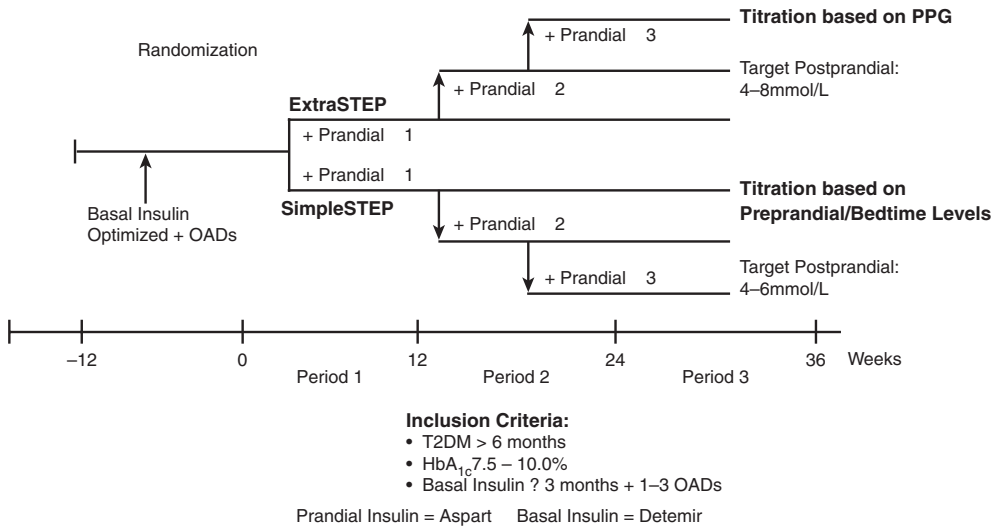

Figure 5. Comparison of two intensification regimens: study design of the STEP-wise randomized study [12].

Table 1. Titration schedule used in 2 prandial intensification strategies. Adapted with permission from Ref. [12].

IDet titration		Simple STEP*			Extra STEP†	
Prebreakfast plasma glucose levels (mg/dl)	IDet dose adjustment	Premeal plasma glucose levels (mg/dl)	Bedtime plasma glucose levels (mg/dl)	IAsp dose adjustment	Two-hour postmeal plasma glucose levels (mg/dl)	IAsp dose adjustment
<56‡	−4 U					
56–71‡	−2 U	<72‡	<72‡	−2 U	<72‡	−2 U
72–108	0	72–108	72–144	0	72–144	0
109–144	+2 U	109–162	145–180	+2 U	145–180	+2 U
145–162	+4 U	>162	>180	+4 U	>180	+4 U
>162	+6 U					
IDet titrated based on average of three plasma glucose measurements before breakfast		IAsp added to largest self-reported meal. Titration based on premeal and bedtime plasma glucose concentrationsfrom four daily plasma glucose measurements			IAsp added to meal with largest plasma glucose increment. Titration based on postmeal plasma glucose concentrations from six daily plasma glucose measurements	

IAsp, insulin aspart; IDet, insulin detemir; U, unit.
*SimpleSTEP = Sequential addition of insulin aspart to meal(s) perceived by the patient as being the largest of the day, with titrations based on the premeal plasma glucose concentration.
†ExtraSTEP = Sequential addition of insulin aspart to meal(s) with the highest measured postprandial plasma glucose increase, with titrations based on the postprandial plasma glucose level.
‡One or more plasma glucose values less than 72 mg/dl without obvious explanation.

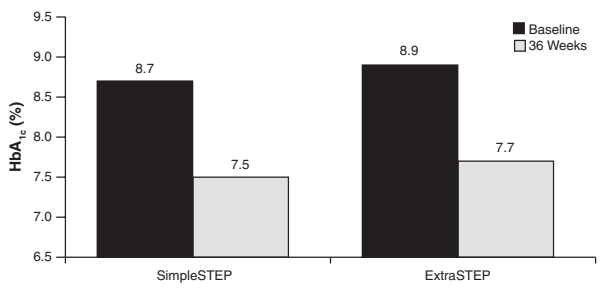

Figure 6. Comparison of two insulin intensification regimens in patients with long-standing diabetes [12].

retrospective reviews of clinical practice showing reductions in mean HbA1c, weight, and prandial insulin requirements, and in total insulin requirements [17–19], along with a lower risk of hypoglycaemia [19,20]. Other data support the use of basal insulin analogues along with DPP-4 inhibitors [21]. While DeVries et al. [22] recently published their data on the addition of insulin detemir to patients receiving liraglutide and metformin, which may be indicative of future treatment trends where GLP-1 RAs are used earlier in the treatment paradigm [23], what is more germane to the discussion herein, are data on the addition of GLP-1 RAs to background insulin therapy. A recent randomized, controlled trial showed that adding twice-daily exenatide injections improved glycaemic control without increased hypoglycaemia or weight gain in patients with uncontrolled T2DM who were receiving basal-insulin analogue treatment with weight loss, rather than weight gain (figure 8) [24].

Adverse events of exenatide in this study included nausea, diarrhoea, vomiting, headache and constipation.

Table 2. Basal insulin and mealtime insulin dose adjustment based on pattern of mealtime blood glucose values for the last week. Adapted with permission from Ref. [13].

Insulin glargine adjustments: both groups		
Mean of last 3-day fasting SMBG mg/dl	Adjustment	
<180 mg/dl	Increase 8 units	
140–180 mg/dl	Increase 6 units	
120–139 mg/dl	Increase 4 units	
95–119 mg/dl	Increase 2 units	
70–94 mg/dl	No change	
<70 mg/dl	Decrease by the same number of units as insulin glulisine increase that titration week or up to 10% of total insulin glargine dose	
Insulin glulisine adjustments: simple algorithm group		
Mealtime dose	Pattern of mealtime blood glucose values below target*	Pattern of mealtime blood glucose values above target†
≤ 10 units	Decrease by 1 unit	Increase by 1 unit
>11–19 units	Decrease by 2 units	Increase by 2 units
≥20 units	Decrease by 3 units	Increase by 3 units
Insulin glulisine adjustments: carbohydrate counting (insulin-to-carbohydrate ratio) group‡		
Mealtime dose	Pattern of mealtime blood glucose values below target*	Pattern of mealtime blood glucose values above target†
1 unit/20 g	Decrease to 1 unit/25 g	Increase to 1 unit/15 g
1 unit/15 g	Decrease to 1 unit/20 g	Increase to 1 unit/10 g
1 unit/10 g	Decrease to 1 unit/15 g	Increase to 2 units/15 g
2 units/15 g	Decrease to 1 unit/10 g	Increase to 3 units/15 g
3 units/15 g§	Decrease to 2 units/15 g	Increase to 4 units/15 g

*If more than one-half of the mealtime blood glucose values for the week were below target.
†If more than one-half of the mealtime blood glucose values for the week were above target.
‡Each patient in the carbohydrate count group was also given a schedule for a mealtime insulin glulisine correction dose to add a few units if high or subtract a few units if low.
§Increase mealtime insulin as needed following this pattern.

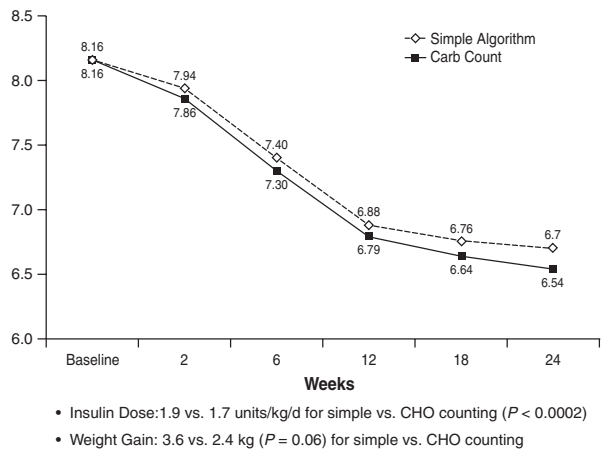

Figure 7. Fixed versus flexible prandial insulin dosing: comparison of a simple pattern control-based (no carbohydrate counting) and a more complex carbohydrate counting regimen [13].

Emerging Strategies

As discussed in the article by Zinman [25], evolving research efforts are focusing on improving our options for the pharmacokinetics and pharmacodynamics of long-acting insulin analogues to make them even less variable and even longer acting – truly once daily – as well as more forgiving of our patient's busy schedules so that there is little to no impact on glucose levels in case of some variation in the time of administration. Extending this research is the evaluation of a product that is a soluble combination of ultra-long-acting insulin degludec and insulin aspart. This is a fixed-dose combination of basal and mealtime insulin (70% degludec and 30% aspart). Data are available for this combination agent in patients with T1DM [26]. Proof of concept studies show that including some element of prandial control improves HbA1c better than basal insulin alone, primarily because of effects on postprandial hyperglycaemia (figure 9) [27]. More recently, and more relevant to clinical practice, this formulation has been compared to premixed insulin aspart in patients with T2DM in a randomized trial, where it provided comparable glycaemic control with less hypoglycaemia [28]. As such, it may provide the convenience of a premixed formulation without the disadvantage of hypoglycaemia.

Other research is focusing on improving options for rapid-acting insulin for PPG control. Acknowledging the need for different delivery options for patients, especially those who are extremely needle-phobic, efforts are still being made to develop an inhaled insulin that is quickly absorbed in the alveoli [29]. Technosphere insulin is a ultra-rapid-acting inhaled insulin reaching maximum blood concentration within 15 min and resulting in rapid glucose lowering with a short duration of action (~2–3 h [30]). In a comparison of safety and efficacy of technosphere insulin versus insulin lispro as prandial insulin in patients with T1DM, technosphere insulin use was comparable to insulin lispro in HbA1c reduction and was associated with significantly lower 1- and 2-h PPG and FPG as well as

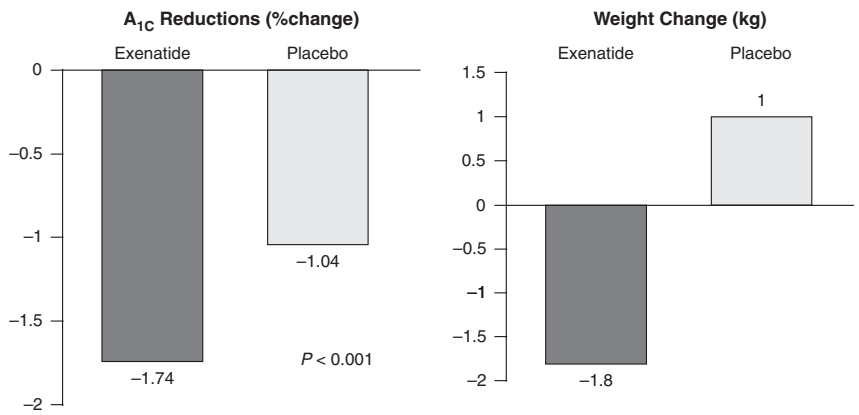

Figure 8. Twice-daily exenatide in basal insulin-treated patients: adults with T2DM and an HbA1c level of 7.1% and 10.5%, respectively, who were receiving insulin glargine alone or in combination with metformin or pioglitazone (or both agents) [24].

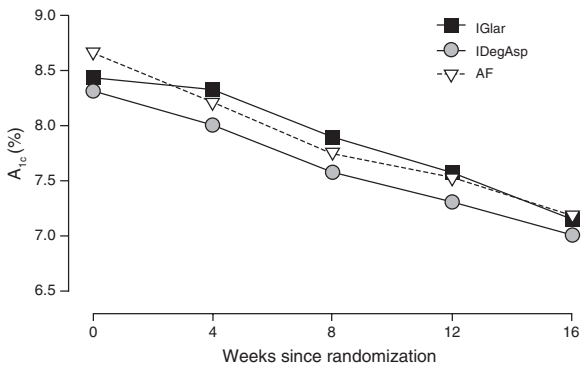

Figure 9. Insulin degludec/insulin aspart (IDegAsp) is a soluble coformulation of the novel basal analogue insulin degludec (IDeg: 70%) and insulin aspart (IAsp: 30%). This figure shows a comparison of the glucose efficacy of IDegAsp, an alternative formulation (AF) (55%IDeg and 45% IAsp), and insulin glargine (IGlar) in insulin-naïve subjects with type 2 diabetes mellitus (T2DM) inadequately controlled with oral antidiabetic drugs. Adapted with permission from Ref. [27].

significantly fewer hypoglycaemia events per patient-month. In a multicenter, randomized, open-label, parallel-group study, patients were randomly allocated in a 1 : 1 ratio to receive 52 weeks of treatment with prandial technosphere inhaled insulin powder plus bedtime insulin glargine or twice-daily premixed biaspart insulin (70% insulin aspart protamine suspension and 30% insulin aspart of rDNA origin). The results showed similar HbA1c reduction, less weight gain, and fewer mild-to-moderate and severe hypoglycaemic events on inhaled insulin plus insulin glargine than on biaspart insulin [31]. There was an increased occurrence of cough and change in pulmonary function in the group receiving inhaled insulin plus insulin glargine [32].

Insulin jet injectors are also being evaluated as a way to deliver insulin into the subcutaneous region without penetrating the skin with a needle. Preliminary data show that this approach, which uses a high-velocity jet injector, results in more rapid absorption of insulin, faster onset of glucose-lowering action, shorter duration of hyperinsulinemia and a shorter duration of glucose-lowering action [33].

Summary

What is clear from the available data is that the number of options available to clinicians, once basal insulin therapy ± traditional OADs are no longer sufficient to maintain the glucose control desired and in fact needed to continue to protect patients from the ravages of persistence of uncontrolled hyperglycaemia, is rapidly increasing. For this we should all be grateful, as the proportion of patients at desired HbA1c goals is still below Healthy People 2020 diabetes indicators. Whether clinicians choose to add available or future prandial-insulin analogues to basal-insulin analogues, use available or future combination insulin regimens, or add incretin-based therapies (DPP-4 inhibitors or GLP-1 RAs) to long-acting basal insulin analogues, the imperative to continue to modify diabetes therapy exists and with it, the 'art of endocrinology' cannot be underestimated.

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Disclosure

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Building Better Insulin Therapy to Improve Glycemic Control and Patient Adherence

Posttest

1. Which of the following statements is TRUE about early insulin replacement therapy?
   A. Early insulin came from the purification of equine pancreases.
   B. Common adverse effects included ketoacidosis, glycosuria, and abscesses.
   C. Limitations of early preparations were hypoglycemia and weight gain.
   D. From the beginning, physiologic insulin replacement was possible.

2. Which of the following was the FIRST insulin analog to be developed?
   A. Aspart
   B. Detemir
   C. Glulisine
   D. Lispro

3. Which of the following is an advantage of long-acting insulin analogs compared to neutral protamine Hagedorn (NPH) insulin?
   A. Lower risks of hypoglycemic-unawareness
   B. Lower risks of nocturnal hypoglycemia
   C. Lower risks of severe hypoglycemia
   D. All of the above are advantages.

4. Patients with type 2 diabetes who progress to insulin therapy usually do so by starting with which of the following?
   A. Basal insulin added to oral antidiabetic drugs
   B. Basal "plus" some bolus (mealtime) insulin ± oral antidiabetic drugs
   C. Multiple daily injections of insulin
   D. Premixed insulin added to oral diabetic drugs

5. What is the recommended increase in insulin dose for patients receiving long-acting basal insulin analogs along with background oral antidiabetic drugs who have blood glucose levels above 180 mg/dL?
   A. 0.5 units every 3 days
   B. 1 unit every 3 days
   C. 2 units every 3 days
   D. 4 units every 3 days

6. What is the expected decrease in HbA1c for each 0.1 U/kg/day increment in insulin dose?
   A. 0.25%
   B. 0.5%
   C. 0.75%
   D. 1.0%

7. Which of the following statements is CORRECT about the results of the Oral Plus Apidra and LANTUS (OPAL) study?
   A. Adding prandial insulin to basal insulin therapy is most effective when prandial insulin is given before breakfast.
   B. Adding prandial insulin to basal insulin therapy is most effective when prandial insulin is given before the main meal.
   C. It does not matter which meal prandial insulin is administered before in patients not at goal on basal insulin therapy.
   D. Sequential addition of giving basal insulin plus a single prandial insulin injection is not effective in achieving glycemic goals.

8. Which of the following is/are effective means of improving glycemic control in patients on basal insulin analogs?
   A. Addition of a DPP-4 inhibitor
   B. Addition of a short-acting GLP-1 receptor agonist
   C. Addition of a long-acting GLP-1 receptor agonist
   D. All of the above

9. Which of the following statements is CORRECT about the available clinical trial data for pegylated insulin lispro?
   A. The most common adverse effects are influenza-like reactions and increases in serum potassium.
   B. Pegylated insulin lispro appears to be associated with less nocturnal hypoglycemia and some weight loss, as compared with insulin glargine.
   C. Pegylated insulin lispro was associated with superior HbA1c reductions, as compared with insulin detemir.
   D. All of the above are correct.

10. Which of the following is CORRECT about the available clinical trial data for insulin degludec, as compared to insulin glargine?
   A. The day-to-day variability is two times less.
   B. It can be dosed once daily, but should be given at about the same time each day.
   C. Nocturnal hypoglycemia rates were 25% lower.
   D. All of the above are correct.

Building Better Insulin Therapy to Improve Glycemic Control and Patient Adherence

Instructions for Posttest and Evaluation

Two ways to claim credit:

1. Go online to **http://tinyurl.com/ENDOCRINOLOGYBL**, click on the blue "Assessment" button and register or log in (if you previously registered on the site).
   - o You *must* type http:// when entering this URL into the address bar at the top of your Internet browser (do not enter this url into your browser search box)**.**
   - o Upon successfully completing the activity posttest and evaluation, your certificate will be made available immediately to print online.
2. Complete the paper-based activity posttest and evaluation included at the end of the monograph and fax it to 609-921-6428. Your certificate will be sent to you via email within 6 weeks of receipt of your materials.

Please print clearly.

Name: _____

Address: _____

City: _____ State: _____ ZIP: _____

E-mail address: _____

Reenter E-mail address: _____

PHYSICIANS: please indicate number of credits claimed

☐ 1.25 ☐ 0.5

☐ 1.0 ☐ 0.25

☐ 0.75 ☐ I am not a physician.

Signature

_____

Professional title ☐ Physician ☐ Nurse ☐ Pharmacist ☐ Scientist/Researcher
☐ Physician Assistant ☐ Nurse Practitioner ☐ Other: _____

Specialty ☐ Endocrinologist ☐ Internal Medicine
☐ Family Medicine ☐ Other _____

POSTTEST ANSWER FORM

Please refer to the posttest on pages 18 for questions. Indicate your answers below, selecting one answer choice per question. A score of ≥70% is required to receive credit**.**

Posttest Question Number	A	B	C	D
1.	☐	☐	☐	☐
2.	☐	☐	☐	☐
3.	☐	☐	☐	☐
4.	☐	☐	☐	☐
5.	☐	☐	☐	☐

Posttest Question Number	A	B	C	D
6.	☐	☐	☐	☐
7.	☐	☐	☐	☐
8.	☐	☐	☐	☐
9.	☐	☐	☐	☐
10.	☐	☐	☐	☐

EVALUATION

I certify that I have participated in this activity. ☐

Approximately how many patients with diabetes do you see per week who may be impacted by this education?
☐ 1-25 ☐ 26-50 ☐ 51-75 ☐ 76-100 ☐ >100 ☐ Not applicable. I have no patient contact

Number of years in practice? ☐ 5 or less ☐ 6-10 ☐ 11-15 ☐ 16-20 ☐ 21-25 ☐ >25

This activity has or will improve my: (check all that apply) ☐ Competence ☐ Performance ☐ Patient Outcomes

Please list one new concept you learned in this activity. _____

_____

Please indicate your agreement with the following statements about this activity.	**Strongly Agree**				**Strongly Disagree**
The content covered was useful and relevant to my practice.	5	4	3	2	1
The activity was fair, balanced, and free of commercial bias.	5	4	3	2	1
The information learned during this activity will help improve my skills or judgment within the next 6 months.	5	4	3	2	1
I am better able to develop clinical strategies for the timely intensification of insulin therapy in order to achieve glycemic control.	5	4	3	2	1
I am better able to assess data to differentiate among insulin strategies and their potential hypoglycemic impact.	5	4	3	2	1
I am better able to incorporate practical techniques to address patient barriers to achieving treatment goals with insulin therapy.	5	4	3	2	1
I am better able to appraise emerging agents that will allow dosing flexibility with reduced side effects.	5	4	3	2	1
Instructional effectiveness and expertise of faculty was excellent.	5	4	3	2	1
The learning method was excellent.	5	4	3	2	1

If you selected 1 or 2 for any of above, please explain. _____

Based on the educational content of the activity, what will you do differently in the care of your patients?* (check all that apply)

☐ Implement new information or skill in my practice

☐ Seek additional information

☐ Do nothing differently—Current practice reflects activity recommendations

☐ Do nothing differently—The content was not convincing

☐ Do nothing differently—System barriers prevent me from changing my practice

☐ Not applicable. I have no patient contact.

Please list one change you anticipate making in your practice (if no changes anticipated, please write "N/A").

_____

What barrier(s) have an impact on your ability to make the practice change(s) indicated above? (check all that apply)

☐ Institutional

☐ Insurance/financial

☐ Lack of practice guidelines

☐ Time

☐ Lack of patient compliance/adherence

☐ Adverse side-effects of treatment

☐ Patient lack of knowledge regarding disease/treatment

☐ Other

☐ No barriers

What information would you like to see in future activities that may help you address those barriers?

_____

Suggestions to improve this activity? _____

_____

Suggestions for future educational activities? _____

_____

Thank you for participating. Please return this completed form upon exiting. As an added bonus we will inform you of upcoming opportunities for future CME certified activities.