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Insulin detemir: A new option for the treatment of diabetes

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Abstract

Purpose: To highlight the pharmacology, clinical data, and practical application for the use of insulin detemir, a new long-acting insulin analog in the treatment of type 2 diabetes.

Data sources: Published clinical, pharmacokinetic, and pharmacodynamic studies of insulin detemir, as well as contemporary studies and reviews about the management of patients with type 2 diabetes.

Conclusions: Insulin therapy, if titrated appropriately, is the most physiological and effective intervention for lowering blood glucose and may help preserve β-cell function in patients with type 2 diabetes. Insulin detemir, in comparative clinical trials, has been shown to provide effective glycemic control and a consistent blood glucose–lowering response for up to 24 h, a decreased incidence of nocturnal hypoglycemia, and less weight gain than other basal insulin formulations.

Implications for practice: Insulin therapy is often met with resistance from both patients and healthcare providers because of concerns about its effectiveness, hypoglycemia, injections, and weight gain. Insulin detemir, designed to closely mimic basal insulin secretion, may help overcome some of the barriers to effective diabetes management, i.e., hypoglycemia and weight gain, and lead to better outcomes.

Introduction

Diabetes is a major healthcare challenge for which patients require clinical care as well as self-management education and behavioral and emotional support. The needs of patients with diabetes are increasingly being met by nurse practitioners (NPs) who must remain knowledgeable not only about the broad range of available therapies but also about strategies to assist patients to integrate therapy into their lifestyles and cope with the demands of this challenging chronic disease.

The American Diabetes Association (ADA) estimated that in 2005, approximately 20.8 million people, about 7% of the U.S. population, had diabetes. Of these, 14.6 million people were diagnosed and 6.2 million remained undiagnosed (Centers for Disease Control, 2005). Type 1 diabetes, which results from β-cell destruction and usually leads to absolute insulin deficiency, accounts for approximately 5%–10% of diagnosed cases. Gestational diabetes includes varying levels of glucose intolerance that are initially recognized during pregnancy. Approximately 7% of all pregnancies are affected and treatment is required to avoid complications in the newborn. Type 2 diabetes, characterized by insulin resistance and relative insulin deficiency, accounts for the rest, comprising the vast majority of all diagnosed cases of diabetes in the United States (ADA, 2004). As a result of the increased incidence of type 2 diabetes, the responsibility for management of patients with diabetes is falling increasingly on the shoulders of primary healthcare providers, mainly primary care physicians, NPs, and certified diabetes educators.

Based on information collected in the Diabetes Prevention Program (Diabetes Prevention Program Research Group, 2002), the focus of education and care for

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individuals with prediabetes is on promoting physical activity and encouraging a healthy diet that will lead to weight loss or at least prevent weight gain (Franz et al., 2002). Therapeutic goals for diabetes are optimal blood glucose and A1C targets and medical nutrition therapy to achieve blood glucose, lipid, blood pressure, and weight targets (ADA, 2006). For practical purposes, however, patients are most successful when they develop their own specific, measurable, achievable, relevant, and time-specific behavioral goals during the course of treatment (Adiseshiah, 2005). An individual's self-selected behavioral goals and outcomes are more likely to be achieved if they receive ongoing support to deal with barriers to behavior change and the emotional aspects of having a chronic illness such as diabetes (Peyrot et al., 2005).

Changing the paradigm of type 2 diabetes therapy

Insulin therapy is required for the treatment of type 1 diabetes because of absolute insulin deficiency; however, the ability of people with type 2 diabetes to produce insulin varies from person to person and changes over time. Because of the progressive nature of type 2 diabetes, many patients who are initially able to achieve target A1C levels through lifestyle changes or with oral antidiabetic agents (OADs) will eventually require insulin therapy (Diabetes Control and Complications [DCCT] Trial Research Group, 1993; United Kingdom Prospective Diabetes Study [UKPDS] Group, 1998).

The benefits of early insulin introduction in preserving β-cell function are now being recognized; however, there is still significant patient and provider resistance to initiating insulin therapy (Meece, 2006; Polonsky & Jackson, 2004). The resistance can stem from a patient's apprehension about injections, a lack of understanding about the effectiveness and safety of insulin, fear of hypoglycemia, feelings of failure and guilt, and concern over weight gain, but importantly, also arises from "clinical inertia" and prescribing attitudes of healthcare providers about insulin therapy (Perlin & Pogach, 2006; Peyrot et al., 2005). The Diabetes Attitudes Wishes and Needs (DAWN) study, a large multinational survey examining patient and provider perceptions to insulin therapy, found that 51% of nurses, 60% of primary care physicians, and 52% of specialists admitted to always or often warning patients that they would have to start on insulin therapy if they did not follow lifestyle recommendations (Korytkowski, 2002). Rather than approaching insulin therapy as a threat or a "last resort," practitioners are beginning to see insulin in a new light because therapy with insulin is "physiological," effective, and beneficial for patients who are trying to achieve glycemic goals (Funnell & Kruger, 2004; Stoneking, 2005).

Treatment of diabetes, including helping patients successfully transition to insulin therapy, requires creating a partnership with patients where both the expertise of the nurse and the opinions and fears of the patient are equally valued (DCCT Research Group, 1993; Funnell, Kruger, & Spencer, 2004; UKPDS Group, 1998). To help ease the transition, new technological advances are now available, including more user-friendly blood glucose monitoring systems, comfortable and easy-to-use insulin pen devices, and an increasing number of insulin analogs.

There are more options than ever before to initiate insulin therapy. For example, premixed biphasic insulin analog formulations are one option for initiating insulin among patients with type 2 diabetes (Garber, 2006). These premixes, insulin lispro 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro) and biphasic insulin aspart 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart), offer patients the simplicity of once- or twice-daily dosing combined with rapid onset of action to cover prandial insulin needs, prolonged action to cover basal insulin needs, and the reduced variability of an analog compared with a human insulin premix (Garber).

Another common and simple regimen for initiating insulin in patients with type 2 diabetes involves the use of a basal or long-acting insulin analog alone or in combination with OADs. With a prolonged duration of action and relatively peakless action profile, basal insulin analogs offer once-daily dosing and a low risk of hypoglycemia. At present, there are two long-acting insulin analogs that have been developed for use as the basal component of insulin therapy: insulin glargine and insulin detemir. Insulin detemir, the newest of these, has been used in Europe for several years. Having received Food and Drug Administration approval in June 2005 for use in the United States, insulin detemir is highlighted in this review, with its usefulness placed into context for NPs, diabetes educators, and other practitioners who are the main sources of care and education for their patients with diabetes.

Pharmacology of insulin detemir

Insulin detemir is an analog of human insulin with a 14-carbon fatty acid chain attached to the lysine residue on position 29 of the insulin B chain (Vazquez-Carrera & Silvestre, 2004). The addition of the fatty acid chain on insulin detemir promotes increased self-association of insulin detemir molecules and allows for the reversible binding of insulin detemir to albumin at the injection site, contributing to its novel mechanism for protracted action

(Chapman & Perry, 2004; Novo Nordisk, 2005). Insulin detemir molecules can readily enter the circulation, where they again reversibly bind albumin, further delaying distribution to target tissues (Hordern & Russell-Jones, 2005).

Insulin detemir is soluble at neutral pH, which enables it to exist as a liquid following subcutaneous injection. This is different from neutral protamine hagedorn (NPH)—the traditional human intermediate acting formulation—which is a preformed crystalline/precipitate suspension, and insulin glargine, an acidic solution that precipitates at pH 7.0 in the subcutaneous tissue after injection (Chapman & Perry, 2004). Because precipitation and dissolution of a precipitate upon injection contribute to variability in absorption of insulin, the solubility of insulin detemir is likely a factor that reduces within-patient variability and provides more predictable glycemic control compared with NPH insulin or insulin glargine (see below) (Heise et al., 2004).

Pharmacodynamics and pharmacokinetics of insulin detemir

Insulin detemir has a relatively flat time-action profile with a duration of action of up to 24 h (Klein et al., 2006; Novo Nordisk, 2005; Plank et al., 2005). With its fatty acid modification, insulin detemir is less susceptible to the variability in action that occurs with other basal insulin preparations. Several important factors contribute to its consistent activity: (a) insulin detemir is water soluble and resuspension is not required prior to injection, (b) insulin detemir remains in solution upon injection, and (c) reversible albumin binding buffers the effect of sudden changes in the depot absorption rate. In studies of the pharmacodynamics of insulin in patients with type 1 diabetes (measured by the rate that glucose must be infused to maintain stable glucose levels), insulin detemir was associated with significantly less within-patient variability than NPH insulin or insulin glargine (Heise et al., 2004; Klein et al.). Similarly, patients with type 2 diabetes treated with insulin detemir plus insulin aspart at mealtimes showed significantly lower within-patient variability of self-measured blood glucose compared with patients treated with NPH insulin (Haak, Tiengo, Draeger, Suntum, & Waldhausl, 2005). The shapes of the glucose infusion rate curves in patients with type 2 diabetes receiving either insulin detemir or insulin glargine are similar, with comparable durations of action up to 24 h at clinically relevant doses (Klein et al.).

When administered as a single dose to healthy volunteers, insulin detemir shows a linear and dose-dependent plasma concentration profile, with the maximum concentration (C_{max}) reached between 6 and 8 h (Novo Nordisk, 2005). The distribution of insulin detemir is dominated by a high percentage bound to albumin in the bloodstream. Despite this high level of albumin binding, insulin detemir is not likely to be involved in competitive drug interactions at the albumin-binding site (Chapman & Perry, 2004), as there is a vast excess of albumin-binding sites available to each drug molecule. The pharmacokinetics of insulin detemir are similar in children and adults (Danne, Lupke, Walte, Von, & Gall, 2003), and there are no differences in patients of different race or ethnicity (Chapman & Perry; Soran & Younis, 2006; Troupin et al., 2005). Dosing, administration, availability, and storage information about insulin detemir are summarized in Table 1. Insulin detemir is available in easy-to-use pen injection devices, which are discrete, convenient, and can increase a patient's confidence levels with regard to performing self-injections (Korytkowski, Niskanen, & Asakura, 2005). As with other injectable insulin formulations, minor local reactions around the injection site have occasionally been reported with insulin detemir (Hermansen et al., 2004; Raslova et al., 2004). Suggested management of injection site discomfort includes careful cleansing of the skin with a nonirritant solution, rotating injection sites within a given area, and the use of antihistamine creams to reduce discomfort (Jordan & Lake, 2005).

Overcoming barriers associated with insulin therapy

Despite evidence supporting the importance of glycemic control (Stevens et al., 2004; UKPDS Group, 1998), in practice, recommended glycemic targets are often not met. Data from a recent update of the National Health and Nutrition Examination Survey indicate that only 42% of adults had A1C values less than 7% (ADA goal) and one in five still have A1C levels of 9% or higher (Saaddine et al., 2006). Clinical inertia on the part of healthcare providers to change practice patterns, despite the known benefits of aggressive treatment, is now recognized as a part of the problem (Perlin & Pogach, 2006). In addition, glycemic targets are often considered too difficult for patients to attain and can result in poor motivation for providers and patients because of perceived failure (Hainsworth, 2005). NPs can help patients with diabetes to understand the natural progression of the disease and why different therapies are needed over the course of the disease (Funnell et al., 2004). They can also help patients to understand diabetes as an "insulin problem" rather than a "sugar problem," assess fears and barriers regarding insulin therapy, and assist patients to identify and address those issues (Meece, 2006).

Patient concerns that serve as barriers to initiation include perceived injection pain, lack of understanding about proper injection technique and timing, and fear of

Table 1 Insulin detemir dosing, administration, availability, and storage (Novo Nordisk, 2005)

Dose	The dosage of insulin detemir should be individualized according to the patient's needs, with the following suggestions to be used as a guide: • For insulin-naïve patients who are not achieving glycemic goals on OADs —Start with either 0.1 or 0.2 units/kg or 10 units once daily at the evening mealtime or bedtime[a] —Titrate gradually[b] (upward or downward) to achieve desired glycemic goals —For patients who require twice-daily insulin dosing for effective control, the evening dose can be administered with the evening meal, at bedtime, or 12 h after the morning dose • Patients already treated with a basal insulin can transition to insulin detemir on a unit-to-unit basis
Route of administration	• Subcutaneously in thigh, abdominal wall, or upper arm
Mixing	• Because of pH differences that could affect the action profile and efficacy of each, insulin detemir should not be mixed with other insulins
Availability	• 3 mL prefilled FlexPen® (100 units/mL) • 10 mL vials (100 units/mL)
Storage	• Unopened vials and FlexPen® can be stored at room temperature for 42 days or in the refrigerator until the expiration date • Once in use, vials can be used for 42 days and be kept at room temperature or refrigerated. Once in use, the FlexPen® should be kept at room temperature and can be used for 42 days • Never freeze preparations of insulin detemir; preparations that have been inadvertently frozen should be discarded • Refer to the manufacturer's instructions for further information about storage and handling

[a]In a treat-to-target trial (Hermansen et al., 2006), insulin (10 units/injection) was added to oral glucose-lowering drugs (metformin, insulin secretagogues, or α-glucosidase inhibitors).

[b]In the same treat-to-target trial, daily self-monitored plasma glucose values were averaged over three consecutive days. Corresponding to individualized elevated plasma glucose readings, insulin doses were adjusted upward in 2- to 10-unit increments in a sliding scale algorithm. For example, if average prebreakfast/predinner readings were 109–126 mg/dL, 145–162 mg/dL, or >180 mg/dL, insulin dose increases of +2, +4 to +6 units, or +10 units, respectively, were recommended (Hermansen et al., 2006). If plasma glucose readings were low after one reading, i.e., 56–72 mg/dL or <56 mg/dL, decreases in insulin doses by 2–4 units/injection were implemented, respectively.

hypoglycemia, weight gain, or disease progression (Korytkowski, 2002). Results from the DAWN study tell us that patients may not believe that insulin is effective, and self-blame among patients with type 2 diabetes is prevalent and associated with worry about starting insulin therapy. Individuals may express feelings of guilt and failure as they may consider insulin therapy to be the result of their inability to achieve their glycemic target through diet or exercise (Korytkowski). To prevent patient anxiety, it is recommended that NPs avoid the use of insulin as a threat or punishment in an effort to encourage better self-care (Peyrot et al., 2005). Instead, the focus should be placed on how insulin will help patients achieve their self-identified goals and targets and incorporate diabetes into their lives.

Teaching patients from the onset of diabetes about the use of insulin as a "next step" in therapy can help to prevent some feelings of guilt, as does avoiding phrases such as "you failed oral agents." Minimizing the number of injections, using insulin pens, discussing the relative risks of hypoglycemia, and asking patients to identify personal benefits associated with lower glucose levels (i.e., more energy) and how their goals may be achieved with insulin therapy are several recommended interventions to overcome patient concerns (Funnell & Kruger, 2004; Polonsky & Jackson, 2004).

Concerns surrounding insulin therapy are not limited to patients. Healthcare providers have reported fear of patients' anger, fear of patients' noncompliance, and irritation with OAD failure (Korytkowski, 2002). According to the DAWN study, general practitioners were more likely to delay insulin therapy than specialists, opinion leaders, and healthcare providers who treat many patients with type 2 diabetes. Prescribing insulin was more likely to be delayed when nurses and physicians viewed insulin as a less effective treatment (Peyrot et al., 2005). Thus, it is important to not only be aware of newer insulin therapies but also to create systems of care that support both the efforts of patients and the NPs to effectively use those therapies.

How insulin detemir can help overcome barriers to initiating insulin therapy

Insulin detemir has been shown to be as effective or more effective than NPH insulin and insulin glargine in maintaining glycemic control (Dornhorst, Merilainen, & Ratzmann, 2006b; Haak et al., 2005; Hermansen et al.,

2004, 2006; Home et al., 2004; Raslova et al., 2004; Rosenstock et al., 2006; Russell-Jones, Simpson, Hylleberg, Draeger, & Bolinder, 2004). In addition to efficacy, other clinically relevant characteristics of insulin detemir (i.e., low risk of hypoglycemia, less within-patient variability, and a reduced tendency to cause weight gain) make it a good option for practitioners and patients who are considering initiating insulin therapy (Chapman & Perry, 2004).

Clinical effectiveness

The clinical efficacy and tolerability of insulin detemir have been most commonly compared with NPH insulin. The major efficacy endpoint in these trials is glycemic control, typically monitored by A1C levels and fasting blood glucose (FBG), as well as the incidence of hypoglycemia.

Several studies in patients with type 2 diabetes have demonstrated the efficacy of insulin detemir. The first to report comparative results to NPH was conducted in 505 individuals randomly assigned to NPH insulin or insulin detemir as part of a basal–bolus therapy. Rapid-acting insulin aspart was used at mealtimes. In this 6-month study, overall blood glucose control was not different between insulin detemir and NPH insulin (Haak et al., 2005). However, treatment with insulin detemir resulted in less within-participant variability in FBG compared with NPH insulin (Haak et al.). Studies of the pharmacodynamic properties of insulin detemir have shown reduced intra- and interpatient variability in FBG compared with NPH insulin (Heise et al., 2004; Hermansen et al., 2004; Pieber, Draeger, Kristensen, & Grill, 2005). Differences in within-patient variability were substantiated in patients with type 2 diabetes in a study comparing insulin detemir with NPH insulin (Raslova et al., 2004). In another study in which insulin detemir and NPH insulin were added to OAD therapy, more than 70% of patients in both groups achieved an A1C of 7% or lower. However, a significantly greater percentage of patients treated with insulin detemir reached this goal without any hypoglycemia compared with patients on NPH insulin (26% vs. 16%, $p < .01$) (Hermansen et al., 2006). Finally, in a study setting that reflects actual clinical practice with type 2 diabetes patients, adding basal insulin detemir to OADs reduced A1C by 1.29% and FBG by 58 mg/dL over 3 months and did so with an average reduction in weight of 0.9 kg and fourfold fewer hypoglycemic episodes than previous therapy (Dornhorst, Merilainen, & Ratzmann, 2006a).

Insulin detemir has also been extensively studied in patients with type 1 diabetes. Over 11 randomized trials using both once- and twice-daily regimens of insulin detemir have compared its efficacy to either NPH insulin or insulin glargine (Home & Kurtzhals, 2006). In one 4-month study, patients who received twice-daily insulin detemir (either at 12-h intervals or at morning and bedtime) or NPH insulin (morning and bedtime) with rapid-acting insulin aspart at mealtimes (Home et al., 2004) had significantly lower FBG when treated with insulin detemir compared with NPH. Within-participant variability in self-monitored FBG was also significantly lower in the insulin detemir treatment groups (Home et al., 2004). In a 6-month trial comparing once-daily insulin detemir or NPH insulin in combination with regular human insulin (Russell-Jones et al., 2004), analysis of self-monitored FBG readings showed significantly less variability during treatment with insulin detemir than with NPH insulin.

Hypoglycemia

Considerable risk of mild-to-severe hypoglycemia can be associated with any insulin therapy (Davis & Alonso, 2004), and the challenges of managing hyperglycemia must be balanced against the risk of hypoglycemia. Fear of hypoglycemia is often identified as a barrier (Cryer, Davis, & Shamoon, 2003), particularly among patients who worry that it will be a threat to their independence. Providers are concerned about hypoglycemia as well, explaining, at least in part, why glycemic targets are not achieved. For example, in one treat-to-target study, the most common reason that clinicians chose not to titrate insulin doses upward was related to concern over hypoglycemia (Fritsche, Haring, Togel, & Schweitzer, 2003).

If fear of hypoglycemia is identified as a barrier, the healthcare provider should first assess the source of the fear and then provide support as needed. Strategies for dealing with hypoglycemia include education about the usefulness and frequency of blood glucose monitoring and ensuring that patients are aware of warning signs, risk factors, and how to self-treat hypoglycemia (Jordan & Lake, 2005). It may be helpful to point out that hypoglycemia is more common in patients with type 1 than with type 2 diabetes (Cryer et al., 2003) and that the newer long-acting insulin analog preparations are less likely to cause hypoglycemia than the older, less predictable preparations.

The relatively flat time-action profile and consistent blood glucose–lowering response of insulin detemir results in reduced incidence of hypoglycemia when compared with NPH insulin (Heller & Kim, 2005; Hermansen et al., 2004, 2006; Home et al., 2004; Russell-Jones et al., 2004). In a 4-month trial of patients with type 1 diabetes randomly assigned to receive twice-daily insulin detemir or NPH insulin, insulin detemir was associated with a significant reduction in the risk of minor hypoglycemia (25%–32%) compared with NPH insulin (Home et al.). Observing patients with type 2 diabetes treated with or without OADs who switched to insulin detemir from previous therapy

with NPH or insulin glargine, the risk of hypoglycemia was reduced from 7.9 to 1.5 episodes and from 7.8 to 0.5 episodes per patient-year, respectively (Dornhorst et al., 2006b). A meta-analysis of four phase 3 trials with insulin detemir concluded that the reduction in intrapatient variability of FBG is a major contributor to the reduced risk of hypoglycemia with insulin detemir relative to NPH insulin (Heller & Kim, 2005).

Nocturnal hypoglycemia often goes unrecognized because patients may not awake from symptoms, it is not readily self-treated, and it may be prolonged. Thus, nocturnal hypoglycemia poses special safety risks, including falls, adds to patient fears, and presents a barrier to insulin use. Reductions in the incidence of nocturnal hypoglycemia have also been demonstrated in patients who use detemir. For example, in trials comparing twice-daily insulin detemir to NPH insulin, in patients with type 1 or type 2 diabetes, the incidence of nocturnal hypoglycemic episodes was 53%–55% lower with insulin detemir than with NPH (Hermansen et al., 2004, 2006; Home et al., 2004). Once-daily insulin detemir also reduced the risk of nocturnal hypoglycemia by 26% compared with once-daily NPH insulin ($p = .003$), with comparable reductions in A1C (Russell-Jones et al., 2004). Compared with insulin glargine in patients with type 1 diabetes, insulin detemir resulted in a lower risk of major and nocturnal hypoglycemia at comparable levels of glycemic control (Pieber, Treichel, Robertson, Mordhorst, & Gall, 2005). A lower risk of hypoglycemic episodes with insulin detemir and therefore a reduction in the fear of such episodes may make patients less likely to skip injections.

Weight gain

Another barrier to insulin therapy commonly identified by patients with type 2 diabetes is weight gain. Although the cause of weight gain associated with insulin or other diabetes therapies is not completely understood, weight gain may result from better glucose control (Fritsche & Haring, 2004). As blood glucose levels fall, the amount of glucose excreted in the urine also falls, and patients may not adequately decrease caloric intake to compensate for the calories lost in the urine (Bode, 2004; DeWitt & Hirsch, 2003; Klingensmith, 2003; Sheehan, 2003). Some clinicians have speculated that weight gain may also be linked to the need to "feed the insulin" to prevent hypoglycemia, particularly when older preparations of insulin are used and/or patients' fear of hypoglycemia (Klingensmith; Sheehan).

To date, all studies conducted with insulin detemir in which weight was evaluated, in patients either with type 1 (Hermansen et al., 2004; Home et al., 2004; Pieber, Draeger, et al., 2005; Russell-Jones et al., 2004) or with type 2 diabetes (Haak et al., 2005; Hermansen et al., 2006; Raslova et al., 2004), have consistently shown less weight gain in comparison to NPH insulin. One study of once-daily insulin detemir in patients with type 1 diabetes found that patients lost a mean of 0.50 lb during the 6-month trial, whereas those treated with NPH insulin showed a mean weight gain of 0.70 lb (Russell-Jones et al.). Similarly, data from studies in patients with type 2 diabetes show that treatment with insulin detemir results in less weight gain compared with NPH insulin. A recent study comparing the addition of insulin detemir or insulin glargine to OADs also found significantly less weight gain with insulin detemir (Rosenstock et al., 2006). The lack of weight gain with insulin detemir may be, in part, because of decreased within-patient variability and a reduction in the perceived risk of hypoglycemia (Haak et al.; Russell-Jones et al.). However, the mechanisms behind the favorable weight effects of insulin detemir are not fully understood and are still being investigated (Hennige et al., 2006; Hordern & Russell-Jones, 2005).

Summary

The newer long-acting insulin analog, insulin detemir, is an excellent option for patients with diabetes who need a basal insulin replacement that closely mimics physiological basal insulin release. In comparative trials with other basal insulin preparations, insulin detemir has been shown to improve glycemic control with decreased within-patient variability, decreased incidence of hypoglycemia, including nocturnal hypoglycemia, and less weight gain. Given that the most difficult part of initiating insulin therapy often is overcoming patient and provider fears leading to clinical inertia, the availability of insulin detemir may help alleviate some of this difficulty and improve outcomes for patients with type 2 diabetes.

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