

# Exploring The Quality-Of-Life Benefits With Insulin Analog Use

S Cornell

---

## Citation

S Cornell. *Exploring The Quality-Of-Life Benefits With Insulin Analog Use*. The Internet Journal of Family Practice. 2009 Volume 9 Number 1.

## Abstract

**Purpose:** The need for early insulin treatment in patients with type 2 diabetes and the quality-of-life benefits provided by insulin analogs compared with human insulins are reviewed. **Summary:** Despite the proven efficacy of insulin therapy, patients with type 2 diabetes are often reluctant to start treatment with insulin. This can stem from the inconvenience of having to plan administration relative to meals, fears of self-injecting, and concerns about hypoglycemia and weight gain. Treatment dissatisfaction among insulin users can also hinder treatment adherence and negatively impact health-related quality of life (HRQoL). The development of new insulin therapies and delivery devices has focused on improving patient satisfaction and HRQoL in order to improve adherence and ultimately treatment outcomes. Insulin analogs allow more dosing flexibility and are associated with lower risks of hypoglycemia, and, in some cases, a reduced risk of weight gain compared with human insulin. The availability of pen devices has also facilitated easy and accurate subcutaneous injection. Numerous clinical trials have reported improved HRQoL and greater patient satisfaction with insulin analogs versus human insulin and pen devices over vial and syringe. Although analog insulins are associated with higher direct costs than human insulins, for most insurance plans, co-pays costs are equivalent for these different formulations. In addition, insulin analogs and pen devices represent a cost-effective insulin treatment due to improved adherence and dosing accuracy, reducing the number of diabetes-related complications and the need for hospitalization. Insulin analog preparations therefore provide a cost-effective treatment option that improves HRQoL and is associated with a high level of patient satisfaction compared with human insulins. **Conclusion:** Clinical studies have shown improved HRQoL and greater patient satisfaction with insulin analogs versus human insulin. Insulin analog preparations should be considered as an option for all patients using insulin therapy.

## INTRODUCTION

Diabetes is an increasingly important public health concern. Nearly 24 million people in the United States have the condition, corresponding to nearly 8% of the population, an increase of more than 3 million in approximately 2 years.<sup>1</sup> Moreover, recent projections of diabetes in the United States estimate that the total diabetes burden will be 13.5% (32.6 million) of the population in 2021 and 14.5% (37.7 million) of the population in 2031.<sup>2</sup>

Diabetes is known to have a detrimental impact on health outcomes, including health-related quality of life (HRQoL), and this has been demonstrated in a number of trials.<sup>3-8</sup> The Centers for Disease Control and Prevention (CDC) highlight that the concept of HRQoL refers to a person or group's perceived physical and mental health over time.<sup>9</sup> Today's definition of HRQoL is a direct descendent of the World Health Organization definition of health from over 50 years

ago—"a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"—and is thought to encompass three fundamental domains: (1) biological functioning, (2) psychological functioning, and (3) social functioning. The medical community's interest in HRQoL, rather than the mere presence or absence of disease, has been growing at a remarkable rate over the past few decades. An increasing number of studies incorporate assessments of HRQoL to measure the effects of chronic illness on the patient's day-to-day life.

The magnitude of the impact of diabetes on HRQoL has been reported to be comparable to that experienced by patients with cardiovascular conditions, cancer, and chronic respiratory disease.<sup>7</sup> Data from the CDC illustrate the far-reaching effects of diabetes on mental and physical well-being. In 2004, almost two-thirds (63.1%) of adults with diabetes reported having poor mental or physical health for at least 1 day in the past 30 days, and almost one-third

(32.8%) of the diabetes population were unable to perform a usual activity during this timeframe.<sup>10</sup> Similarly, data from 2007 showed that 58.4% of adults with diabetes reported limitations in their mobility, such as walking a quarter mile; climbing up 10 steps; standing for 2 hours; or stooping, bending, or kneeling.<sup>10</sup>

The negative impact of diabetes on quality of life is an important issue not only for the emotional and physical well-being of the patient, but also because it can interfere with treatment compliance and have a detrimental impact on treatment outcomes.<sup>11</sup> This review examines the need for early insulin treatment in patients with type 2 diabetes, and assesses the quality-of-life benefits provided by insulin analogs compared with human insulins.

### INSULIN THERAPY—THE MOST EFFECTIVE AGENT TO CONTROL GLYCEMIA

The benefits of intensive glycemic control on microvascular and macrovascular complications are well established for type 1 and type 2 diabetes.<sup>12–18</sup> Comprehensive interventions targeted at glycemic control are therefore essential for the long-term health of patients with diabetes.<sup>12,19</sup>

Because type 1 diabetes (T1DM) is associated with absolute insulin deficiency, all patients with this condition require intensive insulin therapy from initial diagnosis. In contrast, patients with type 2 diabetes (T2DM) may initially be treated with lifestyle changes, either alone or in combination with oral and/or injectable glucose-lowering drugs.<sup>20</sup> However, given the progressive nature of the disease and the limited glycemic control that can be achieved with non-insulin agents,<sup>21</sup> most patients with T2DM will eventually require insulin therapy.<sup>22</sup> It is estimated that by the time a patient is diagnosed with T2DM, they have actually had the disease for 9–12 years. It is also projected that 50–80% of  $\beta$ -cell function is lost by this time; therefore pharmacotherapy that preserves  $\beta$ -cell function is warranted.<sup>23</sup>

### NEED FOR EARLY INSULIN THERAPY

Despite the clear benefits of insulin therapy in achieving good glycemic control, patients do not always receive insulin early or in a timely manner.<sup>24,25</sup> The stepwise approach to therapy, which consists of lifestyle modifications and sequential addition of non-insulin glucose-lowering agents, followed by insulin as necessary, may result in delays in initiating insulin.<sup>26–28</sup> In other cases, psychological resistance on the part of both healthcare providers and patients can delay insulin therapy.<sup>29–31</sup>

Early utilization of insulin can help lower insulin resistance (physiological and psychological), reverse glucotoxicity, and preserve  $\beta$ -cell function for longer than is possible with most oral glucose-lowering drugs, alone or in combination.<sup>32–34</sup> Indeed, results from a number of recent trials suggest that aggressive lowering of hyperglycemia with insulin therapy in newly-diagnosed T2DM patients can result in extended normoglycemia without the need for glucose-lowering medications.<sup>32–34</sup> The most recent of these trials, in 382 patients with newly-diagnosed T2DM, showed that target glycemic control was attained more quickly with intensive insulin treatment (either continuous subcutaneous insulin infusion [CSII] or multiple daily insulin injections [MDI]) than with oral agents.<sup>34</sup> Treatment was stopped after normoglycemia was maintained for 2 weeks; patients were then followed up on diet and exercise alone. More patients achieved target glycemic control in the insulin groups (97.1% in CSII and 95.2% in MDI) in less time (4.0 days [SD 2.5] in CSII and 5.6 days [SD 3.8] in MDI) than those treated with oral hypoglycemic agents (83.5% and 9.3 days [SD 5.3]). After 1 year, remission rates were significantly higher among patients in the insulin groups compared with patients receiving oral glucose-lowering agents (51.5% vs. 26.7%;  $p = 0.0012$ ). In addition, the increase in acute insulin response was sustained in the insulin groups but declined significantly in the oral glucose-lowering drug group at 1 year.<sup>34</sup>

The potential advantages of early insulin therapy with a basal insulin analog before patients become unresponsive to oral therapy have also been demonstrated in the Canadian Implementing New Strategies with Insulin Glargine for Hyperglycemia Treatment (INSIGHT) trial.<sup>35</sup> Patients with T2DM and receiving no, one or two oral glucose-lowering agents were randomized to receive evening insulin glargine or conventional oral therapy. Patients receiving insulin glargine were 1.68 times more likely to achieve two consecutive A1C levels  $<6.5\%$  and had significantly lower mean A1C levels compared with those receiving conventional oral therapy ( $p = 0.0007$ ).<sup>35</sup>

### DEVELOPMENT OF INSULIN ANALOGS

The goal of insulin therapy is to mimic normal physiologic secretion of insulin as closely as possible in order to control both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG). Although human insulin formulations (short-, intermediate-acting, and premixed) have been used extensively for the treatment of diabetes, their ability to achieve tight glycemic control is limited by their

pharmacokinetic and pharmacodynamic profiles.<sup>36</sup> For example, human insulins have variable peaks in activity and unpredictable durations of action, and are also subject to considerable within-patient variations in blood glucose.<sup>37</sup> Insulin analogs (rapid, long-acting, and premixed) have been developed with the aim of more closely replicating physiologic insulin profiles. Insulin analogs have the added benefit of not requiring resuspension prior to injection—a step that can often be overlooked by patients, exacerbating the poor reproducibility with NPH (neutral protamine Hagedorn) insulin. Recognition of the benefits of insulin analogs versus human insulins are reflected in the recent guidelines published by the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE), which recommend the use of insulin analogs over human insulins.<sup>38</sup> Table 1 provides a summary of currently available insulin analog treatments. Use of both types of insulin analogs in a basal-bolus regimen is considered to be the ideal regimen that most closely mimics the physiological profile of endogenous insulin and achieves good glycemic control over 24 hours.

Figure 1

Table 1. Onset of action, peak action and duration of activity of available insulin analogs

Insulin analog	Onset of Action	Peak	Duration of Action (hours)
Rapid-acting			
Insulin aspart	10–20 min	40–50 min	3–5
Insulin lispro	15–30 min	30–150 min	3–6.5
Insulin glulisine	10–20 min	30–90 min	3–5
Long-acting			
Insulin detemir	0.8–2 h	No significant peak	≤4
Insulin glargine	1–2 h	No significant peak	≤4
Biphasic premixed			
70% APS/30% aspart, NovoLog Mix 70/30	10–20 min	Dual	≤4
75% NPL/25% lispro, Humalog Mix 75/25	15–30 min	Dual	≤4
50% NPL/50% lispro Humalog Mix 50/50	15–30 min	Dual	≤4

APS: Aspart protamine suspension; NPL: Neutral protamine lispro.

The time course of action of any insulin may vary in different individuals or at different times in the same individual. Because of this variation, periods indicated here should be considered general guidelines only.

Two long-acting basal insulin analog preparations are available: insulin glargine and insulin detemir. These analogs have been designed to provide consistent, relatively flat, and protracted basal insulin levels.<sup>46,47</sup> Rapid-acting insulin analogs—insulin lispro, aspart, and glulisine—are most appropriate at mealtimes to counter postprandial spikes in glucose levels. Compared with regular human insulin, rapid-acting insulin analogs show faster absorption, a more

rapid onset of activity, and a shorter duration of action.<sup>48,49</sup> These pharmacokinetic properties mean that rapid-acting analogs can be injected within 15 minutes of mealtimes, compared with the 30-minute timeframe required for regular human insulin.<sup>50,51</sup>

Three types of fixed-ratio insulin analog premixes are also available: a 75% insulin lispro protamine suspension with 25% insulin lispro, a 50% insulin lispro protamine suspension with 50% insulin lispro, and a 70% insulin aspart protamine suspension with 30% insulin aspart.<sup>49</sup> Premixed insulin analogs are derived from rapid-acting insulin analogs and consist of a mixture of a rapid-acting insulin analog and its intermediate-acting protaminated form. Accordingly, biphasic insulin regimens provide prandial and basal insulin requirements in a single insulin injection. These formulations have been developed to minimize the errors that can occur when patients self-mix insulin combinations. Premixed combinations may also simplify the insulin regimen and reduce the number of daily injections.

GLYCEMIC CONTROL

Results from a number of key clinical trials have shown that insulin analogs and human insulins have similar efficacy in terms of glycemic control.<sup>52–60</sup> This conclusion was reiterated in two Cochrane reviews that reported only minor benefits with regard to efficacy of short- and long-acting insulin analogs over human insulins.<sup>61,62</sup>

When assessing glycemic control, it is necessary to measure FPG and PPG levels in addition to measuring A1C levels. Increasing emphasis has been placed on integrating PPG levels into routine diabetes care, with evidence suggesting that PPG contributes as much as, or even more than, FPG to overall glycemic burden as A1C values approach near-normal levels <7%.<sup>63</sup> Rapid-acting analogs have resulted in greater reductions in PPG levels than human insulins in a number of trials carried out in patients with T1DM.<sup>54,64–73</sup> In addition, premixed insulin analogs have improved benefits in terms of PPG control compared with premixed human insulin.<sup>49,57,74–79</sup> For example, a recent 3-month trial of biphasic insulin aspart 70/30 and premixed human insulin 70/30 reported slightly better control of FPG (7.82 vs. 7.36 mmol/L) and PPG (decrease of 6.30 vs. 4.34 mmol/L) with biphasic insulin aspart 70/30 compared with the premixed human insulin.<sup>57</sup>

IMPROVEMENT OF QUALITY OF LIFE WITH

INSULIN ANALOGS VERSUS HUMAN INSULINS

The improvements in glycemic control observed with insulin treatments do not necessarily translate into comparable improvements in psychological outcomes. The evaluation of other endpoints, in particular HRQoL and treatment satisfaction, is therefore an important part of the assessment of insulin therapy. Determination of the impact of insulin therapy on HRQoL must take into account not only the impact of treatment on diabetes HRQoL, but also that the insulin therapy itself can impair HRQoL through fears of hypoglycemia, weight gain, and other potential adverse effects.

QUALITY OF LIFE AND TREATMENT SATISFACTION

A limited number of studies have assessed quality of life as an endpoint in comparative studies of insulin analogs and human insulins. Quality of life and treatment satisfaction were compared in a 6-month, open-label trial of 424 patients with T1DM receiving basal-bolus treatment with either insulin aspart or human insulin as the prandial insulin component. Insulin aspart was associated with significantly greater improvement in treatment satisfaction than human insulin ( $p < 0.01$ ). The improvement in patient satisfaction was mainly due to increased flexibility regarding diet and leisure time ( $p < 0.0001$ ). Small, but significant, improvements in total HRQoL were achieved in 23% of patients in the insulin aspart group versus 14% in the human insulin group.<sup>80</sup> The benefits in HRQoL with insulin aspart compared with human insulin are summarized in Figure 1.

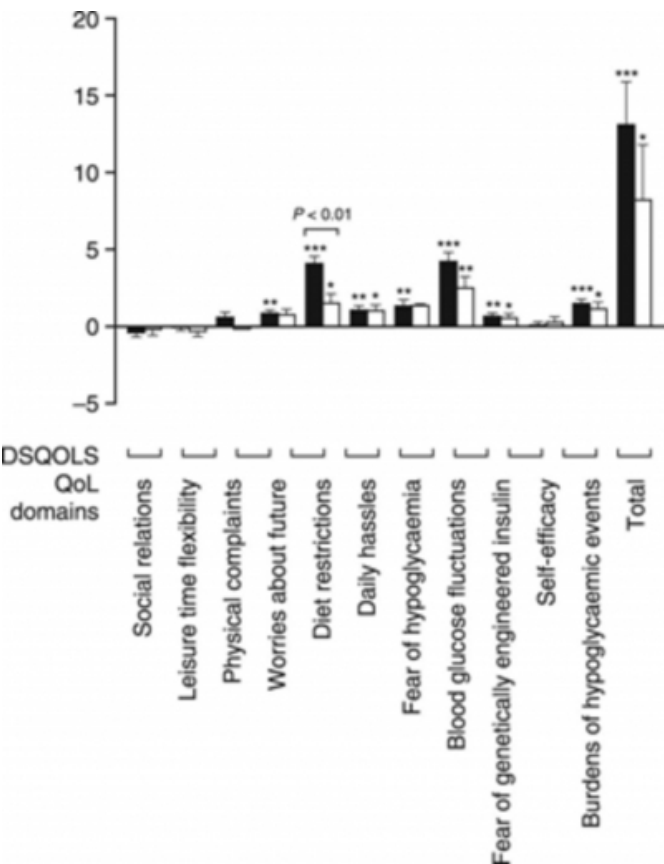
A limited number of studies have assessed quality of life as an endpoint in comparative studies of insulin analogs and human insulins. Quality of life and treatment satisfaction were compared in a 6-month, open-label trial of 424 patients with T1DM receiving basal-bolus treatment with either insulin aspart or human insulin as the prandial insulin component. Insulin aspart was associated with significantly greater improvement in treatment satisfaction than human insulin ( $p < 0.01$ ). The improvement in patient satisfaction was mainly due to increased flexibility regarding diet and leisure time ( $p < 0.0001$ ). Small, but significant, improvements in total HRQoL were achieved in 23% of patients in the insulin aspart group versus 14% in the human insulin group.<sup>80</sup> The benefits in HRQoL with insulin aspart compared with human insulin are summarized in Figure 1.

In a study of teenagers with T1DM, those not meeting glucose control goals through multiple daily insulin

injections of regular human insulin were given the option of switching to insulin lispro.<sup>81</sup> After 12 months, subjects who received insulin lispro experienced a similar degree of metabolic control compared with controls, as assessed by measurement of A1C levels. However, they found that coping with diabetes was less difficult, there was a reduced negative impact of diabetes on HRQoL, and fewer diabetes-related worries were reported compared with those using regular insulin.<sup>81</sup> Similarly, a questionnaire survey regarding the use of insulin lispro and insulin aspart in children and adolescents revealed that the majority of patients (305/389; 78%) experienced an improvement in HRQoL after switching to a rapid-acting insulin analog.<sup>82</sup> Quality of life in this study was estimated based on the opinions of the attending physician rather than on assessment by the patients.

Figure 2

Effects of treatment with insulin aspart or human insulin on health-related quality of life (HRQoL). Changes from baseline in DSQOL scores after 6 months of treatment with insulin aspart or human insulin. â–, Insulin aspart; â–i, human insulin. Reproduced with permission from , 2003;20(8):626-34.



A separate switching study has examined the effects of glargine on disease-specific HRQoL in T1DM patients.<sup>83</sup>

Forty-seven patients with suboptimal glucose control under intensive insulin treatment (IIT) were switched from NPH to glargine. Forty patients maintained on IIT were used as controls. Diabetes-related HRQoL was assessed using the Well-being Enquiry for Diabetics (WED), before and after a 6- to 8-month switch to glargine. Results showed that patients treated with glargine showed several improvements in WED scores (discomfort,  $p = 0.020$ ; impact,  $p = 0.0002$ ; total score,  $p = 0.0005$ ). WED changes were associated with a lower perceived risk of hypoglycemia and fewer problems in daily life with glargine.<sup>83</sup> Patients also showed improved glycemic control following treatment with insulin glargine (A1C decreased by 0.7%, treatment vs. baseline,  $p < 0.001$ ).

HRQoL effects of basal-bolus therapy using an all-analog insulin regimen have also been compared with an all-human insulin regimen. Fifty-six T1DM patients were randomized to a regimen of glargine plus lispro or NPH insulin plus unmodified human insulin for 32 weeks. At study endpoint, insulin glargine plus insulin lispro both reduced the negative impact of diabetes on HRQoL and improved HRQoL, compared with the human insulin regimen. Treatment satisfaction, assessed using the WHO Diabetes Treatment Satisfaction Questionnaire (DTSQ), was also markedly greater with glargine plus lispro compared with NPH plus human insulin ( $32.2 \pm 3.4$  vs.  $23.9 \pm 7.2$ , 86. [6.5–10.6];  $p < 0.001$ ), with notable improvements in flexibility and convenience.<sup>84</sup>

Additional studies have also reported a higher level of treatment satisfaction among patients receiving an insulin analog compared with those using regular human insulin regimens, the findings of which are summarized in Table 2. All trials evaluated treatment satisfaction using the DTSQ assessment. Significantly greater treatment satisfaction was reported for mealtime intensification with insulin aspart and once-daily insulin glargine than for the corresponding treatment with human insulin, despite small differences in A1C with the insulin analogs.<sup>11,54,85-88</sup> An open-label study of 481 patients with T2DM in which insulin treatments were used in combination with once-daily glimepiride also showed a pronounced treatment satisfaction improvement with glargine versus NPH ( $p < 0.02$ ; full analysis).<sup>89</sup> Crossover trials, in which either insulin lispro or human insulin were used for bolus treatment, also reported significantly greater treatment satisfaction with the rapid-acting insulin analog than with human insulin (Table 2).<sup>11,86</sup> Interestingly, one trial also assessed patient treatment preference at baseline and study end for human insulin or

insulin lispro. At baseline, the majority of patients did not have a preference for either treatment; however, by the end of the trial there was a significant shift in preference towards insulin lispro ( $p = 0.001$ ).<sup>86</sup> Among the insulin analogs, improvements in the DTSQ flexibility and convenience items were most notable.

### CONVENIENCE

As highlighted above, the increased flexibility of dosing afforded by insulin analogs has been one of the major reasons cited for greater patient satisfaction with insulin analogs compared with human insulins. Because of the faster absorption, more rapid onset of activity, and shorter duration of action of rapid-acting insulin analogs,<sup>48,49</sup> treatments can be administered closer to meals rather than the typical 30 minutes prior to eating required with regular human insulin.<sup>50,51</sup> This ability to adjust insulin regimens to accommodate individual differences in eating and activity patterns is both flexible and convenient for the patient.

Aside from the insulin preparation, the method of delivery has also been a barrier to patient acceptance of insulin therapy. The inconvenience associated with vial and syringe administration has long represented a challenge for the uptake of insulin treatment. Attempts to address these issues have led to the development of insulin administration using pen devices. Pens offer the advantages of being discreet, portable, and accurate, and their ease of use makes them attractive to both patients and healthcare providers.<sup>90,91</sup> Comparative clinical trials have demonstrated that patients not only prefer pen devices over syringe/vial delivery<sup>90,92</sup> but also experience an improvement in HRQoL compared with the traditional syringe/vial delivery method.<sup>93-95</sup> The dimensions that contributed most to a preference for the pen device were ease of use, activity interference, and social acceptability ( $p \leq 0.001$ ).<sup>9</sup>

**Figure 3**

Table 2. Summary of clinical trials assessing treatment satisfaction with insulin analogs compared with human insulin

Patient Population	Trial Design	Insulin Analog	Human Insulin	Treatment Satisfaction	Reference
Type 1 diabetes, n = 424	Parallel group, 6 months of basal-bolus treatment	Insulin aspart	Unmodified human insulin	Greater with insulin aspart $p < 0.01$	Bott et al. 2003 <sup>10</sup>
Type 1 diabetes, n = 368	Parallel group, 64 weeks of basal-bolus treatment	Insulin aspart	Unmodified human insulin	Greater with insulin aspart Difference in DTSQ score 1.57 [95% CI, 0.49–2.64] $p = 0.004$	DeVries et al. 2003 <sup>12</sup>
Type 1 diabetes, n = 1070	Parallel group, 6 months of basal-bolus treatment	Insulin aspart	Unmodified human insulin	Greater with insulin aspart Difference in DTSQ score 2.3 $p < 0.001$	Hosse et al. 2000 <sup>14</sup>
Type 1 diabetes, n = 517	Parallel group, 28 weeks basal therapy	Insulin glargine once-daily	NPH insulin	Greater with insulin glargine Difference in DTSQ score 1.83 $p = 0.001$ Treatment satisfaction with insulin glargine increased at each visit, but decreased with NPH insulin	Wirtz et al. 2001 <sup>17</sup>
Types 1 and 2 diabetes, n = 52	Crossover, 2 x 12 weeks basal-bolus treatment	Insulin lispro	Unmodified human insulin	Greater with insulin lispro, $p = 0.001$	Howorka et al. 2000 <sup>18</sup>
Type 1 diabetes, n = 468	Crossover, 2 x 3 months	Insulin lispro	Unmodified human insulin	Greater with insulin lispro, $p = 0.001$	Kotamos et al. 1997 <sup>11</sup>
Type 1 diabetes, n = 56	2-way crossover, 2 x 16 weeks basal-bolus treatment	Insulin glargine plus insulin lispro	Unmodified human insulin plus NPH insulin	Greater with insulin analogs Difference 8.6 [95% CI, 6.3–10.6] $p < 0.001$ Treatment satisfaction with insulin analog regimen increased by 3.2 points, but decreased by 4.9 points with human insulin	Ashwell et al. 2008 <sup>16</sup>
Type 1 diabetes, n = 423	3-month, prospective, multicenter, randomized, open-label, parallel-group study	Insulin aspart	Unmodified human insulin	DTSQ for perceived hyperglycemia was lower with insulin aspart ( $p = 0.005$ ); patients found insulin aspart treatment more flexible ( $p = 0.022$ )	Tamas et al. 2001 <sup>15</sup>
Type 2 diabetes, n = 481	Open-label, 24-week, randomized trial	Insulin glargine plus glimepiride	NPH insulin plus glimepiride	Greater treatment satisfaction improvement with insulin glargine vs NPH insulin ( $p < 0.02$ , full analysis). The proportion of patients who lost time from work or normal activities due to diabetes was lower with insulin glargine vs NPH (1.8 vs. 3.3%, full analysis)	Korytkowski et al. 2003 <sup>19</sup>

CI, Confidence interval; DTSQ, Diabetes Treatment Satisfaction Questionnaire

## WEIGHT GAIN

Weight gain is a concern for many patients taking insulin therapy, particularly considering that many T2DM patients are already overweight.<sup>96</sup> However, the introduction of the long-acting insulin analog, insulin detemir, means that weight gain is no longer an inevitable side effect of insulin therapy.

Data from a number of clinical trials in T1DM and T2DM patients have shown that insulin detemir is associated with significantly less weight gain compared with NPH insulin.<sup>53,97–100</sup> In a multinational, open-label, prospective, observational study (n = 20,531) assessing the safety and efficacy of insulin detemir in clinical practice, there was a reduction in mean body weight (–0.7 kg;  $p < 0.0001$ ), which was most apparent in patients with a higher body mass index (BMI) at baseline.<sup>97</sup> The weight-sparing effects seem to be unique to insulin detemir, as data with insulin glargine have shown less consistent effects on weight gain, with two recent comparative studies showing significantly less weight gain in patients treated with insulin detemir compared with those treated with insulin glargine.<sup>101,102</sup>

Although the changes in weight are often small, knowing that a treatment will not cause significant weight gain can make a big difference psychologically to a patient's

acceptance of treatment. Furthermore, evidence clearly shows that even modest amounts of weight loss can have an important clinical impact in T2DM patients.<sup>103</sup>

## HYPOGLYCEMIA

Fear of hypoglycemia is a major barrier to effective insulin therapy and intensive glycemic control, and can impact on patient quality of life and adherence to treatment. Insulin analog treatments are associated with a reduced risk of hypoglycemia compared with human insulins.<sup>53,99,104–107</sup>

In a 26-week, treat-to-target trial comparing twice-daily insulin detemir with NPH insulin, the risk for all hypoglycemia and nocturnal hypoglycemia with insulin detemir was reduced by 47% ( $p < 0.001$ ) and 55% ( $p < 0.001$ ), respectively.<sup>53</sup> Similarly, in a meta-analysis comparing once-daily insulin glargine with NPH insulin, there was a significant reduction in hypoglycemia risk associated with insulin glargine, in terms of overall symptomatic hypoglycemia (11%;  $p = 0.0006$ ) and nocturnal hypoglycemia (26%;  $p < 0.0001$ ).<sup>106</sup> The Cochrane review of rapid-acting insulin analogs also found a lower median incidence of severe hypoglycemic episodes per 100 patient-years compared with regular insulin (21.8 vs. 46.1).<sup>62</sup> Similarly, the Cochrane review of basal insulin analog trials showed significantly lower risks of symptomatic and nocturnal hypoglycemia with insulin glargine and insulin detemir compared with NPH insulin.<sup>61</sup> A recent observational and non-interventional study of 2923 patients with T1DM and T2DM reported that switching from an all-human to an all-analog insulin regimen significantly reduced the incidence of both overall (mean difference –22.10;  $p < 0.0001$ ) and nocturnal (mean difference –9.88;  $p < 0.0001$ ) hypoglycemia.<sup>107</sup>

## COST-EFFECTIVENESS OF INSULIN ANALOGS VERSUS HUMAN INSULINS

In terms of direct prescription costs, insulin analogs and pen devices are more expensive than human insulins and syringes; although for insured patients, co-pays are typically the same regardless of the type of insulin or device used. Pharmacoeconomic modeling studies have consistently shown that insulin analogs provide gains in quality-adjusted life-years at costs well below accepted cost-effectiveness limits. The additional acquisition costs were offset by reductions in complications.<sup>108–114</sup> Retrospective analyses of healthcare databases have also shown cost-effectiveness for analogs versus human insulins, primarily because of lower inpatient care costs as a result of decreased length of stay in

hospital.<sup>108</sup> For example, one insulin and glargine-treated group had higher 12-month drug costs (mean, \$374 more per patient) and outpatient care costs (mean, \$279 more), but these were more than offset by decreased inpatient costs (\$820 less), giving a net saving of \$166 per patient.<sup>115</sup>

Emerging data also indicate that the improved adherence made possible through the administration of insulin using a pen device has the potential to reduce diabetes care costs (not including cost of insulin) when compared with delivery by syringe/vials, despite higher prescriptions costs for pen delivery.<sup>116-118</sup> It has also been demonstrated that patients find insulin administration easier using a pen device, and that the dose delivered is more accurate than equivalent administration using a vial and syringe.<sup>94,119-121</sup>

## CONCLUSIONS

Assessment of glycemic control is a key means for determining the effect of diabetes treatment. However, it is now becoming apparent that the success of diabetes treatment is affected not only by the clinical efficacy of the treatment but also by a range of additional factors. In order to obtain a comprehensive understanding of the potential value of a diabetes intervention, it is therefore important to evaluate treatment outcomes in a broader context of treatment-related factors and adherence issues, particularly those that may impact on patient satisfaction and quality of life.

Relative to human insulins, analogs provide a better balance between glycemic control and tolerability. They can alleviate patient fears of hypoglycemia and concerns about weight gain. In addition, the greater flexibility and convenience afforded by their pharmacokinetic characteristics and associated pen devices can contribute to improved HRQoL. Such benefits do not need to come at an increased cost; it has been shown that the overall cost of insulin analog treatment and pen devices can be lower than that for human insulins and syringes due to reductions in complications. In addition, the ability of analogs to achieve improved HRQoL may result in improved adherence to therapy and consequently lower expenses related to poor compliance with or delayed adoption of insulin therapy.

In conclusion, insulin analog preparations should be considered as an option for all patients using insulin therapy. However, there is a need for ongoing education and reassurance to enable patients to accept their condition and gain the skills, self-confidence, and motivation necessary to achieve optimum control with insulin therapy.

## References

1. Centers for Disease Control. Prevention. National Diabetes Fact Sheet. Atlanta, GA: DHHS CDC, 2007.
2. Mainous AG, 3rd, Baker R, Koopman RJ et al. Impact of the population at risk of diabetes on projections of diabetes burden in the United States: an epidemic on the way. *Diabetologia*. 2007;50(5):934-40.
3. Alonso J, Ferrer M, Gandek B et al. Health-related quality of life associated with chronic conditions in eight countries: results from the International Quality of Life Assessment (IQOLA) Project. *Qual Life Res*. 2004;13(2):283-98.
4. Harris MI. Health care and health status and outcomes for patients with type 2 diabetes. *Diabetes Care*. 2000;23(6):754-8.
5. Hornquist JO, Wikby A, Stenstrom U, Andersson PO. Change in quality of life along with type 1 diabetes. *Diabetes Res Clin Pract*. 1995;28(1):63-72.
6. Hornquist JO, Wikby A, Stenstrom U et al. Type II diabetes and quality of life: a review of the literature. *Pharmacoeconomics*. 1995;8(suppl):112-6.
7. Sprangers MA, de Regt EB, Andries F et al. Which chronic conditions are associated with better or poorer quality of life? *J Clin Epidemiol*. 2000;53(9):895-907.
8. Stewart AL, Greenfield S, Hays RD et al. Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study. *JAMA*. 1989;262(7):907-13.
9. Centers for Disease Control. Health-related quality of life. [www.cdc.gov/hrqol/](http://www.cdc.gov/hrqol/) (accessed 2010 Jan 14).
10. Centers for Disease Control and Prevention. Diabetes complications. [www.cdc.gov/diabetes/statistics/complications\\_national.htm](http://www.cdc.gov/diabetes/statistics/complications_national.htm) (accessed 2009 Aug 12).
11. Kotsanos JG, Vignati L, Huster W et al. Health-related quality-of-life results from multinational clinical trials of insulin lispro. Assessing benefits of a new diabetes therapy. *Diabetes Care*. 1997;20(6):948-58.
12. American Diabetes Association. Standards of medical care in diabetes – 2009. *Diabetes Care*. 2009;32 (suppl 1):S13-61.
13. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977-86.
14. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352(9131):837-53.
15. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352(9131):854-65.
16. Ohkubo Y, Kishikawa H, Araki E et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract*. 1995;28(2):103-17.
17. Stratton IM, Adler AI, Neil HA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405-12.
18. Stratton IM, Kohner EM, Aldington SJ et al. UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. *Diabetologia*. 2001;44(2):156-63.

19. AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocr Pract.* 2007;13(suppl):11-68.
20. Nathan DM, Buse JB, Davidson MB et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2009;32(1):193-203.
21. Nathan DM. Finding new treatments for diabetes—how many, how fast... how good? *N Engl J Med.* 2007;356(5):437-40.
22. Logtenberg SJ, Kleefstra N, Ubink-Veltmaat LJ et al. Intensification of therapy and no increase in body mass index with longer disease duration in type 2 diabetes mellitus (ZODIAC-5). *Fam Pract.* 2007;24(6):529-31.
23. UK Prospective Diabetes Study Group. UK prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes.* 1995;44(11):1249-58.
24. Ford ES, Li C, Little RR, Mokdad AH. Trends in A1C concentrations among U.S. adults with diagnosed diabetes from 1999 to 2004. *Diabetes Care.* 2008;31(1):102-4.
25. Hoerger TJ, Segel JE, Gregg EW, Saadine JB. Is glycemic control improving in U.S. adults? *Diabetes Care.* 2008;31(1):81-6.
26. Brown JB, Nichols GA. Slow response to loss of glycemic control in type 2 diabetes mellitus. *Am J Manag Care.* 2003;9(3):213-7.
27. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. *Diabetes Care.* 2004;27(7):1535-40.
28. Nichols GA, Koo YH, Shah SN. Delay of insulin addition to oral combination therapy despite inadequate glycemic control: delay of insulin therapy. *J Gen Intern Med.* 2007;22(4):453-8.
29. Funnell MM. The Diabetes Attitudes, Wishes, and Needs (DAWN) study. *Clin Diabetes.* 2006;24(4):154-5.
30. Peyrot M, Rubin RR, Lauritzen T et al. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. *Diabetes Care.* 2005;28(11):2673-9.
31. Peyrot M, Rubin RR, Lauritzen T et al. Patient and provider perceptions of care for diabetes: results of the cross-national DAWN Study. *Diabetologia.* 2006;49(2):279-88.
32. Ilkova H, Glaser B, Tunckale A et al. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. *Diabetes Care.* 1997;20(9):1353-6.
33. Li Y, Xu W, Liao Z et al. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of beta-cell function. *Diabetes Care.* 2004;27(11):2597-602.
34. Weng J, Li Y, Xu W et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet.* 2008;371(9626):1753-60.
35. Gerstein HC, Yale JF, Harris SB et al. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with Type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) Study. *Diabet Med.* 2006;23(7):736-42.
36. Home PD, Thow JC, Tunbridge FK. Insulin treatment: a decade of change. *Br Med Bull.* 1989;45(1):92-110.
37. Haak T, Tiengo A, Draeger E et al. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obes Metab.* 2005;7(1):56-64.
38. Rodbard HW, Jellinger PS, Davidson JA et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract.* 2009;15(6):540-59.
39. Hirsch IB. Insulin analogues. *N Engl J Med.* 2005;352(2):174-83.
40. Plank J, Bodenlenz M, Sinner F et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. *Diabetes Care.* 2005;28(5):1107-12.
41. Roach P, Woodworth JR. Clinical pharmacokinetics and pharmacodynamics of insulin lispro mixtures. *Clin Pharmacokinet.* 2002;41(13):1043-57.
42. Owens D, Vora J. Insulin aspart: a review. *Expert Opin Drug Metab Toxicol.* 2006 Oct;2(5):793-804.
43. Heise T, Heinemann L, Hövelmann U et al. Biphasic insulin aspart 30/70: pharmacokinetics and pharmacodynamics compared with once-daily biphasic human insulin and Basal-bolus therapy. *Diabetes Care.* 2009;Aug;32(8):1431-3.
44. Helms KL, Kelley KW. Insulin glulisine: an evaluation of its pharmacodynamic properties and clinical application. *Ann Pharmacother.* 2009;Apr;43(4):658-68.
45. Hompesch M, Ocheltree SM, Wondmagegnehu ET et al. Pharmacokinetics and pharmacodynamics of insulin lispro protamine suspension compared with insulin glargine and insulin detemir in type 2 diabetes. *Curr Med Res Opin.* 2009;Nov;25(11):2679-87.
46. Home P, Kurtzhals P. Insulin detemir: from concept to clinical experience. *Expert Opin Pharmacother.* 2006;7(3):325-43.
47. Owens DR, Bolli GB. Beyond the era of NPH insulin; long-acting insulin analogs: chemistry, comparative pharmacology, and clinical application. *Diabetes Technol Ther.* 2008;10(5):333-49.
48. Oiknine R, Bernbaum M, Mooradian AD. A critical appraisal of the role of insulin analogues in the management of diabetes mellitus. *Drugs.* 2005;65(3):325-40.
49. Rolla A. Pharmacokinetic and pharmacodynamic advantages of insulin analogues and premixed insulin analogues over human insulins: impact on efficacy and safety. *Am J Med.* 2008;121(6 suppl):S9-S19.
50. Gredal C, Rosenfalck A, Dejgaard A, Hilsted J. Optimal dose and timing of insulin Aspart to mimic first phase insulin response in patients with recently onset type 2 diabetes. *Diabetes Res Clin Pract.* 2008;80(2):293-8.
51. Home PD, Hallgren P, Usadel KH et al. Pre-meal insulin aspart compared with pre-meal soluble human insulin in type 1 diabetes. *Diabetes Res Clin Pract.* 2006;71(2):131-9.
52. Fonseca V, Bell DS, Berger S et al. A comparison of bedtime insulin glargine with bedtime neutral protamine hagedorn insulin in patients with type 2 diabetes: subgroup analysis of patients taking once-daily insulin in a multicenter, randomized, parallel group study. *Am J Med Sci.* 2004;328(5):274-80.
53. Hermansen K, Davies M, Derezinski T et al. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetes Care.* 2006;29(6):1269-74.

54. Home PD, Lindholm A, Riis A. Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: a randomized controlled trial. *Diabet Med*. 2000;17(11):762-70.
55. Rosenstock J, Park G, Zimmerman J. Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. U.S. Insulin Glargine (HOE 901) Type 1 Diabetes Investigator Group. *Diabetes Care*. 2000;23(8):1137-42.
56. Ross SA, Zinman B, Campos RV et al. A comparative study of insulin lispro and human regular insulin in patients with type 2 diabetes mellitus and secondary failure of oral hypoglycemic agents. *Clin Invest Med*. 2001;24(6):292-8.
57. Velojic-Golubovic M, Mikic D, Pesic M et al. Biphasic insulin aspart 30: better glycemic control than with premixed human insulin 30 in obese patients with Type 2 diabetes. *J Endocrinol Invest*. 2009;32(1):23-7.
58. Ashwell SG, Amiel SA, Bilous RW et al. Improved glycaemic control with insulin glargine plus insulin lispro: a multicentre, randomized, cross-over trial in people with Type 1 diabetes. *Diabet Med*. 2006;23(3):285-92.
59. Hermansen K, Fontaine P, Kukolja KK et al. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia*. 2004;47(4):622-9.
60. Murphy NP, Keane SM, Ong KK et al. Randomized cross-over trial of insulin glargine plus lispro or NPH insulin plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens. *Diabetes Care*. 2003;26(3):799-804.
61. Horvath K, Jeitler K, Berghold A et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2007(2):CD005613.
62. Siebenhofer A, Plank J, Berghold A et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *Cochrane Database Syst Rev*. 2006(2):CD003287.
63. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care*. 2003;26(3):881-5.
64. Gough SC. A review of human and analogue insulin trials. *Diabetes Res Clin Pract*. 2007;77(1):1-15.
65. Anderson JH, Jr., Brunelle RL, Koivisto VA et al. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Multicenter Insulin Lispro Study Group. *Diabetes*. 1997;46(2):265-70.
66. Anderson JH, Jr., Brunelle RL, Koivisto VA et al. Improved mealtime treatment of diabetes mellitus using an insulin analogue. Multicenter Insulin Lispro Study Group. *Clin Ther*. 1997;19(1):62-72.
67. Garg SK, Rosenstock J, Ways K. Optimized Basal-bolus insulin regimens in type 1 diabetes: insulin glulisine versus regular human insulin in combination with Basal insulin glargine. *Endocr Pract*. 2005;11(1):11-7.
68. Heller SR, Amiel SA, Mansell P. Effect of the fast-acting insulin analog lispro on the risk of nocturnal hypoglycemia during intensified insulin therapy. UK Lispro Study Group. *Diabetes Care*. 1999;22(10):1607-11.
69. Holcombe JH, Zalani S, Arora VK et al. Comparison of insulin lispro with regular human insulin for the treatment of type 1 diabetes in adolescents. *Clin Ther*. 2002;24(4):629-38.
70. Holleman F, Schmitt H, Rottiers R et al. Reduced frequency of severe hypoglycemia and coma in well-controlled IDDM patients treated with insulin lispro. The Benelux-UK Insulin Lispro Study Group. *Diabetes Care*. 1997;20(12):1827-32.
71. Pfutzner A, Kustner E, Forst T et al. Intensive insulin therapy with insulin lispro in patients with type 1 diabetes reduces the frequency of hypoglycemic episodes. *Exp Clin Endocrinol Diabetes*. 1996;104(1):25-30.
72. Raskin P, Guthrie RA, Leiter L et al. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care*. 2000;23(5):583-8.
73. Valle D, Santoro D, Bates P et al. Italian multicentre study of intensive therapy with insulin lispro in 1184 patients with Type 1 diabetes. *Diabetes Nutr Metab*. 2001;14(3):126-32.
74. Christiansen JS, Vaz JA, Metelko Z et al. Twice daily biphasic insulin aspart improves postprandial glycaemic control more effectively than twice daily NPH insulin, with low risk of hypoglycaemia, in patients with type 2 diabetes. *Diabetes Obes Metab*. 2003;5(6):446-54.
75. Hermansen K, Vaaler S, Madsbad S et al. Postprandial glycemic control with biphasic insulin aspart in patients with type 1 diabetes. *Metabolism*. 2002;51(7):896-900.
76. Malone JK, Woodworth JR, Arora V et al. Improved postprandial glycemic control with Humalog Mix75/25 after a standard test meal in patients with type 2 diabetes mellitus. *Clin Ther*. 2000;22(2):222-30.
77. Roach P, Trautmann M, Arora V et al. Improved postprandial blood glucose control and reduced nocturnal hypoglycemia during treatment with two novel insulin lispro-protamine formulations, insulin lispro mix25 and insulin lispro mix50. Mix50 Study Group. *Clin Ther*. 1999;21(3):523-34.
78. Velasquez-Mieyer PA, Neira CP. Biphasic insulin aspart 30 for the treatment of type 1 diabetes mellitus. *Expert Opin Pharmacother*. 2008;9(13):2377-82.
79. Qayyum R, Bolen S, Maruthur N et al. Systematic review: comparative effectiveness and safety of premixed insulin analogues in type 2 diabetes. *Ann Intern Med*. 2008;149(8):549-59.
80. Bott U, Ebrahim S, Hirschberger S, Skovlund SE. Effect of the rapid-acting insulin analogue insulin aspart on quality of life and treatment satisfaction in patients with Type 1 diabetes. *Diabet Med*. 2003;20(8):626-34.
81. Grey M, Boland EA, Tamborlane WV. Use of lispro insulin and quality of life in adolescents on intensive therapy. *Diabetes Educ*. 1999;25(6):934-41.
82. Urakami T, Kawamura T, Sugihara S et al. A questionnaire survey on the use of quick-acting insulin analog in Japanese children and adolescents with type 1 diabetes. *Pediatr Int*. 2004;46(3):285-90.
83. Manini R, Forlani G, Moscatiello S et al. Insulin glargine improves glycemic control and health-related quality of life in type 1 diabetes. *Nutr Metab Cardiovasc Dis*. 2007;17(7):493-8.
84. Ashwell SG, Bradley C, Stephens JW et al. Treatment satisfaction and quality of life with insulin glargine plus insulin lispro compared with NPH insulin plus unmodified human insulin in individuals with type 1 diabetes. *Diabetes Care*. 2008;31(6):1112-7.
85. DeVries JH, Lindholm A, Jacobsen JL et al. A randomized trial of insulin aspart with intensified basal NPH insulin supplementation in people with Type 1 diabetes. *Diabet Med*. 2003;20(4):312-8.
86. Howorka K, Pumprla J, Schlusche C et al. Dealing with ceiling baseline treatment satisfaction level in patients with diabetes under flexible, functional insulin treatment:

- assessment of improvements in treatment satisfaction with a new insulin analogue. *Qual Life Res.* 2000;9(8):915-30.
87. Witthaus E, Stewart J, Bradley C. Treatment satisfaction and psychological well-being with insulin glargine compared with NPH in patients with Type 1 diabetes. *Diabet Med.* 2001;18(8):619-25.
88. Tamas G, Marre M, Astorga R et al. Glycaemic control in type 1 diabetic patients using optimised insulin aspart or human insulin in a randomised multinational study. *Diabetes Res Clin Pract.* 2001;54(2):105-14.
89. Eliasschewitz FG, Calvo C, Valbuena H et al. Therapy in type 2 diabetes: insulin glargine vs. NPH insulin both in combination with glimepiride. *Arch Med Res.* 2006;37(4):495-501.
90. Korytkowski M, Bell D, Jacobsen C et al. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. *Clin Ther.* 2003;25(11):2836-48.
91. Rex J, Jensen KH, Lawton SA. A review of 20 years' experience with the NovoPen family of insulin injection devices. *Clin Drug Investig.* 2006;26(7):367-401.
92. Summers KH, Szeinbach SL, Lenox SM. Preference for insulin delivery systems among current insulin users and nonusers. *Clin Ther.* 2004;26(9):1498-505.
93. Hornquist JO, Wikby A, Andersson PO, Dulva AM. Insulin-pen treatment, quality of life and metabolic control: retrospective intra-group evaluations. *Diabetes Res Clin Pract.* 1990;10(3):221-30.
94. Graff MR, McClanahan MA. Assessment by patients with diabetes mellitus of two insulin pen delivery systems versus a vial and syringe. *Clin Ther.* 1998;20(3):486-96.
95. Lee IT, Liu HC, Liao YJ et al. Improvement in health-related quality of life, independent of fasting glucose concentration, via insulin pen device in diabetic patients. *J Eval Clin Pract.* 2009;15(4):699-703.
96. Hermansen K, Davies M. Does insulin detemir have a role in reducing risk of insulin-associated weight gain? *Diabetes Obes Metab.* 2007;9(3):209-17.
97. Dornhorst A, Luddeke HJ, Sreenan S et al. Insulin detemir improves glycaemic control without weight gain in insulin-naïve patients with type 2 diabetes: subgroup analysis from the PREDICTIVE study. *Int J Clin Pract.* 2008;62(4):659-65.
98. Meneghini L, Koenen C, Weng W, Selam JL. The usage of a simplified self-titration dosing guideline (303 Algorithm) for insulin detemir in patients with type 2 diabetes--results of the randomized, controlled PREDICTIVE 303 study. *Diabetes Obes Metab.* 2007;9(6):902-13.
99. Dornhorst A, Luddeke HJ, Koenen C et al. Transferring to insulin detemir from NPH insulin or insulin glargine in type 2 diabetes patients on basal-only therapy with oral antidiabetic drugs improves glycaemic control and reduces weight gain and risk of hypoglycaemia: 14-week follow-up data from PREDICTIVE. *Diabetes Obes Metab.* 2008;10(1):75-81.
100. Rosenstock J, Davies M, Home PD et al. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetologia.* 2008;51(3):408-16.
101. Hollander P, Cooper J, Bregnhøj J, Pedersen CB. A 52-week, multinational, open-label, parallel-group, noninferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes. *Clin Ther.* 2008;30(11):1976-87.
102. Raskin P, Gylvin T, Weng W et al. Comparison of insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes. *Diabetes Metab Res Rev.* 2009;25(6):542-8.
103. Wing RR, Marquez B. Behavioral aspects of weight loss in type 2 diabetes. *Curr Diab Rep.* 2008;8(2):126-31.
104. Bretzel RG, Arnolds S, Medding J, Linn T. A direct efficacy and safety comparison of insulin aspart, human soluble insulin, and human premix insulin (70/30) in patients with type 2 diabetes. *Diabetes Care.* 2004;27(5):1023-7.
105. Raslova K, Bogoev M, Raz I et al. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes Res Clin Pract.* 2004;66(2):193-201.
106. Rosenstock J, Dailey G, Massi-Benedetti M et al. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care.* 2005;28(4):950-5.
107. Hermansen K, Dornhorst A, Sreenan S. Observational, open-label study of type 1 and type 2 diabetes patients switching from human insulin to insulin analogue basal-bolus regimens: insights from the PREDICTIVE study. *Curr Med Res Opin.* 2009;25(11):2601-8.
108. Brixner DI, McAdam-Marx C. Cost-effectiveness of insulin analogs. *Am J Manag Care.* 2008;14(11):766-75.
109. Chen K, Chang EY, Summers KH et al. Comparison of costs and utilization between users of insulin lispro versus users of regular insulin in a managed care setting. *J Manag Care Pharm.* 2005;11(5):376-82.
110. Hall JA, Summers KH, Obenchain RL. Cost and utilization comparisons among propensity score-matched insulin lispro and regular insulin users. *J Manag Care Pharm.* 2003;9(3):263-8.
111. Valentine WJ, Palmer AJ, Erny-Albrecht KM et al. Cost-effectiveness of basal insulin from a US health system perspective: comparative analyses of detemir, glargine, and NPH. *Adv Ther.* 2006;23(2):191-207.
112. Zhang Q, Menditto L. Incremental cost savings 6 months following initiation of insulin glargine in a Medicaid fee-for-service sample. *Am J Ther.* 2005;12(4):337-43.
113. Tunis SL, Minshall ME, Conner C et al. Cost-effectiveness of insulin detemir compared to NPH insulin for type 1 and type 2 diabetes mellitus in the Canadian payer setting: modeling analysis. *Curr Med Res Opin.* 2009;25(5):1273-84.
114. Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. *CMAJ.* 2009;180(4):400-7.
115. Miller DR, Gardner JA, Hendricks AM et al. Health care resource utilization and expenditures associated with the use of insulin glargine. *Clin Ther.* 2007;29(3):478-87.
116. Davis EM, Christensen CM, Nystrom KK et al. Patient satisfaction and costs associated with insulin administered by pen device or syringe during hospitalization. *Am J Health Syst Pharm.* 2008;65(14):1347-57.
117. Lee WC, Balu S, Cobden D et al. Medication adherence and the associated health-economic impact among patients with type 2 diabetes mellitus converting to insulin pen therapy: an analysis of third-party managed care claims data. *Clin Ther.* 2006;28(10):1712-25; discussion 10-11.
118. Pawaskar MD, Camacho FT, Anderson RT et al. Health care costs and medication adherence associated with initiation of insulin pen therapy in medicaid-enrolled patients with type 2 diabetes: a retrospective database analysis. *Clin Ther.* 2007;29 Spec No:1294-305.
119. Hermans N, Kulzer B, Haak T. Dosing accuracy with a novel pen device (SoloSTAR) as performed by patients

with diabetes in a clinical setting. Diabetes Technol Ther. 2008;10(4):322-7.

120. Kadiri A, Chraïbi A, Marouan F et al. Comparison of NovoPen 3 and syringes/vials in the acceptance of insulin therapy in NIDDM patients with secondary failure to oral

hypoglycaemic agents. Diabetes Res Clin Pract. 1998;41(1):15-23.

121. Lteif AN, Schwenk WF. Accuracy of pen injectors versus insulin syringes in children with type 1 diabetes. Diabetes Care. 1999;22(1):137-40.

**Author Information**

**Susan Cornell, BS, PharmD, CDE, FAPhA, FAADE**

Assistant Director of Experiential Education and Assistant Professor of Pharmacy Practice, Midwestern University Chicago  
College of Pharmacy