Weight-Related Quality of Life, Health Utility, Psychological Well-Being, and Satisfaction With Exenatide Once Weekly Compared With Sitagliptin or Pioglitazone After 26 Weeks of Treatment

JENNIE H. BEST, PHD[1]
RICHARD R. RUBIN, PHD[2,3]
MARK PEYROT, PHD[2,4]
YAN LI, PHD[1]
PING YAN, PHD[1]
JARET MALLOY, PHD[1]
LOUIS P. GARRISON, PHD[4]

OBJECTIVE—To assess change in patient-reported outcomes in subjects with type 2 diabetes treated with exenatide once weekly compared with those treated with sitagliptin or pioglitazone.

RESEARCH DESIGN AND METHODS—In this 26-week randomized, multicenter, double-dummy study, 491 subjects received 2 mg of exenatide once weekly or maximum daily doses of sitagliptin (100 mg) or pioglitazone (45 mg) on a background of metformin. Weight-related quality of life, health utility, psychological well-being, and diabetes treatment satisfaction were assessed at baseline and week 26. Mean group changes from baseline to week 26 were estimated by ANCOVA.

RESULTS—Weight-related quality of life total scores improved significantly in the exenatide once weekly and sitagliptin arms only; the exenatide once weekly group experienced significantly greater improvement than the pioglitazone group in weight-related quality of life total scores and in several domain scores. Health utility scores improved significantly for exenatide once weekly and sitagliptin groups ($P < 0.05$) with no significant difference between the exenatide once weekly group and either comparison group. All groups experienced significant improvements on the psychological well-being global scale and all six domain scores, with no significant difference between the exenatide once weekly group and either comparator. All groups experienced significant improvements in total diabetes treatment satisfaction scores. The exenatide once weekly group experienced greater improvement than the sitagliptin group in treatment satisfaction total scores.

CONCLUSIONS—In combination with clinical outcomes from this study, these results indicate it is possible for patients treated with metformin to initiate exenatide therapy with potential benefits in both clinical and patient-reported outcomes.

Diabetes Care 34:314–319, 2011

In the past decade, several new classes of medication for type 2 diabetes have been introduced, including thiazolidinediones (TZD), glucagon-like peptide agonists (GLP-1 agonists), and dipeptidyl peptidase IV inhibitors (DPP-IV inhibitors). Each class of agents affects blood glucose control through different mechanisms, and each class has different effects on glucose profiles and on other important clinical outcomes such as weight (1). Weight is a critically important issue in patients with type 2 diabetes because over 50% of them are obese (2), and for these patients obesity exacerbates metabolic problems, leading to increased morbidity and mortality (3). Unfortunately, some medications that are effective in controlling glycemia may also contribute to weight gain (4).

Diabetes medications differ not only in their clinical effects, but also in their effects on patient-reported outcomes (PROs) such as general health utility, health-related quality of life (QOL), psychological well-being, and treatment satisfaction. Health utility, QOL, and emotional well-being are critical outcomes in their own right, and treatment satisfaction can influence clinical outcomes via its effect on treatment adherence (5). Measures specific to important potential intervention effects (e.g., a measure of weight-related QOL), and disease-specific measures (e.g., a measure of diabetes treatment satisfaction) are generally considered more sensitive than generic measures to the predicted effects of clinical trial interventions (6).

Assessment of PRO is increasingly recognized as important in determining the efficacy of new therapies (7,8), yet we could find few studies of TZD or GLP-1 receptor agonists that considered these outcomes (9–13), no such studies of DPP-IV inhibitors, and no studies that compared agents in these classes with each other. This study is the first to assess a broad range of PROs, including health utility, weight-related QOL, psychological well-being, and diabetes treatment satisfaction, in a fully blinded randomized clinical trial of patients treated with agents from three commonly used classes of oral diabetes medication (exenatide once weekly [exenatide QW], sitagliptin, and pioglitazone) who are also taking metformin.

From the [1]Medical Development, Amylin Pharmaceuticals, San Diego, California; the [2]Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland; the [3]Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Maryland; and the [4]Department of Sociology, Loyola University Maryland, Baltimore, Maryland.
Corresponding author: Jennie H. Best, jennie.best@amylin.com.
Received 10 June 2010 and accepted 16 November 2010.
DOI: 10.2337/dc10-1119

In this study, we attempted to determine whether exenatide treatment affected patient-reported health utility, weight-related QOL, psychological well-being, and diabetes treatment satisfaction, and whether changes in these PROs were different for patients taking exenatide QW from those for patients taking sitagliptin or pioglitazone. Because all study subjects took injections of active drug or placebo, and given the known effects of these drugs on glycemic control and weight, we hypothesize that PRO changes during the study will be more favorable in patients taking exenatide than in those taking sitagliptin or pioglitazone.

RESEARCH DESIGN AND METHODS

—This randomized, double-blind, double-dummy, multicenter clinical trial was conducted at 72 sites with 514 patients in the U.S., India, and Mexico. The study was designed to assess the clinical outcomes, PROs, and safety of 26 weeks of treatment with exenatide QW compared with maximum approved doses of sitagliptin or pioglitazone in patients with type 2 diabetes treated with metformin. These medications address one or both of the clinical issues (hypoglycemia and weight) that have been raised as concerns during intensive management of patients with type 2 (14).

Eligible patients were male and nonpregnant female patients, at least 18 years of age, with type 2 diabetes, who were treated with a stable regimen of metformin monotherapy for a minimum of 2 months prior to screening. Additional inclusion criteria included A1C 7.1–11.0% and BMI 25–45 kg/m^2. Recruitment occurred between February and August of 2008.

Randomization and interventions

Patients were equally randomized to one of three treatment groups: exenatide QW (2 mg) subcutaneous injection once weekly (self-administered) plus placebo oral capsule each morning (QAM); sitagliptin (100 mg) QAM plus placebo subcutaneous injection self-administered once weekly; pioglitazone (45 mg) QAM plus placebo subcutaneous injection self-administered once weekly. Randomization was stratified according to country and screening A1C stratum (<9.0 or ≥9.0%). All patients, the study-site staff, the investigator, and the sponsor were blinded to the identity of study medication.

The appropriate ethical review board at each site approved a common clinical protocol. Patients provided written informed consent prior to participation. The study was conducted in accordance with the principles described in the Declaration of Helsinki, including all amendments through the South Africa revision (15).

Primary study outcomes

The primary results of this 26-week study for A1C, fasting plasma glucose, weight, and adverse events are reported elsewhere (16). Briefly, the exenatide QW group showed greater improvements in A1C (−1.55 vs. −0.92% for sitagliptin and −1.23% for pioglitazone; $P < 0.05$ for both) and fasting plasma glucose (−1.8 vs. −0.9 mmol/L for sitagliptin and –1.5 for pioglitazone; $P < 0.05$ for exenatide vs. sitagliptin). Patients who received exenatide QW experienced significantly greater reduction in weight (−2.3 kg) compared with those who received sitagliptin (−0.8 kg) and pioglitazone, who gained weight (+2.8 kg) ($P < 0.05$ for both). Nausea was transient and predominantly mild (24% exenatide QW; 10% sitagliptin; 5% pioglitazone); there was one withdrawal caused by nausea in each treatment arm. There was no major hypoglycemia. The incidence of minor hypoglycemia was low and similar among the treatment groups (1.3, 3.0, and 0.6% of patients who received exenatide QW, sitagliptin, and pioglitazone, respectively). The incidence of injection site-related events with exenatide QW was low (10%) and comparable to placebo microshere injection in the sitagliptin and pioglitazone groups (7%).

PRO instruments

At baseline and week 26, patients completed self-report measures of weight-related QOL, the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) (17); health utility, the EuroQol 5 Dimensions measure (EQ-5D) (18,19); psychological well-being, the Psychological General Well-Being Index (PGWB) (19,20); and diabetes treatment satisfaction, the Diabetes Treatment Satisfaction Questionnaire-status version (DTSQ-s) (21). Patients were asked to complete the PRO instruments at the beginning of their clinic visit, prior to any procedures. Patients who terminated their participation prior to week 26 were asked to complete the study questionnaires as part of their early termination assessment.

IWQOL-Lite

The impact of weight-related QOL was assessed with the IWQOL-Lite. The five domains of the IWQOL-Lite are physical function, self-esteem, sexual life, public distress, and work. Normalized IQWOL-Lite scores (the total score and separate scores for each of the five domains) range from 0–100, with 0 representing the worst outcome and 100 representing the best. The IWQOL-Lite has demonstrated robust psychometric properties in obese persons with and without diabetes (17).

EQ-5D

Perceived health status was assessed with the EQ-5D, a generic measure that provides a single index value that can be used in clinical and economic evaluation of health outcomes (18). The EQ-5D has two parts. The first part is a descriptive system consisting of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (i.e., 1, 2, or 3), representing "no problems", "some problems", and "extreme problems", respectively. The second part is a visual analog scale that has end points labeled "best imaginable health state" and "worst imaginable health state" anchored at 100 and 0, respectively. The EQ-5D has demonstrated good reliability and validity in patients with type 2 diabetes (19).

PGWB

General psychological well-being was assessed with the PGWB (20). The six dimensions of the PGWB (and score ranges) are anxiety (0–25), depressed mood (0–15), positive well-being (0–20), self-control (0–15), general health (0–15), and vitality (0–20). A global score, computed as the sum of the six dimensions, ranges from 0 to 110. Normalized scores (the global score and each dimension score) range from 0 to 100. Higher scores for each dimension and the global score indicate higher well-being. The PGWB has demonstrated good reliability and validity in patients with type 2 diabetes (19).

DTSQ-s

Satisfaction with diabetes treatment was assessed with the DTSQ-s (21). The DTSQ-s contains eight items assessing overall treatment satisfaction, treatment convenience, treatment flexibility, satisfaction with understanding of diabetes, willingness to continue current treatment, willingness to recommend current treatment to others, frequency of unacceptably high blood glucose, and frequency of unacceptably low blood glucose. Response options for all items are on a 7-point

Likert scale ranging from 0 (i.e., very dissatisfied) to 6 (i.e., very satisfied). All items except perceived hypoglycemia and hyperglycemia items are summed to produce a total treatment satisfaction score. DTSQ-s total scores range from 0 to 36, with higher scores indicating higher satisfaction. The perceived frequency of hyperglycemia and hypoglycemia items are scored separately; lower scores on these two items represent better perceived blood glucose control. The DTSQ-s has demonstrated good reliability and validity in patients with type 2 diabetes (21).

Statistical analysis

The intent-to-treat population, defined as all randomized subjects who received at least one dose of randomized study medication, was used for all analyses. All tests of treatment effects were conducted at a two-sided significance level of 0.05. The prespecified primary analysis of PROs was to compare the treatment effects between groups (sitagliptin vs. exenatide QW, and pioglitazone vs. exenatide QW) at week 26.

The analysis was based on the ANCOVA model including factors for treatment group, country, and baseline A1C strata (<9 vs. ≥9%), and baseline PRO score as a covariate. Least squares means of changes from baseline to week 26 and the two-sided 95% CIs for changes at week 26 were derived from the model. To adjust for multiple comparisons, we first tested between-group differences for the overall measure from each instrument; tests for subscales were performed only if the overall score differed significantly between groups. Significance levels were adjusted for multiple comparisons using Holm's method for *1*) between-group differences in overall scores on each instrument, *2*) between-group differences in subscale scores within an instrument, and *3*) tests of changes from baseline values within each treatment arm.

Missing postbaseline PRO measures were imputed by the last observation carried forward method using values obtained at the time of each participant's termination. To check for potential interaction between completer status and treatment arm, changes in the overall PRO scores were treated as the response variables. Independent variables included treatment group main effect, completer status main effect, country, baseline A1C strata (<9 vs. ≥9%), baseline PRO scores, and the interaction term between completer status and treatment arms. The main effects by completer status and the interaction terms were explored.

Statistical analysis was performed using SAS (8·2; SAS Institute, Cary, NC).

RESULTS—A total of 491 patients comprised the intent-to-treat population (160 exenatide QW, 166 sitagliptin, and 165 pioglitazone). Demographic and baseline clinical variables were similar between treatment groups (Table 1). Mean age of study participants was 52–53 years, 48–56% were male, and 30–39% were white, with a mean BMI of 32–33 kg/m^2, a mean A1C of 8.2–8.3%, and a mean diabetes duration of 5–6 years. On entry to the study, participants were treated with metformin monotherapy.

Effects of exenatide QW treatment on weight-related QOL

At week 26, IWQOL-Lite total scores and all separate domain scores had increased significantly in both the exenatide QW and sitagliptin treatment arms (all $P < 0.05$). The exenatide QW group experienced significantly greater improvement than the pioglitazone group in total weight-related QOL; subsequent analysis revealed that the exenatide QW group experienced significantly greater improvement in public distress, physical function, and work. There were no statistically significant differences between the exenatide QW and sitagliptin groups in total weight-related QOL, and no additional between-group tests were conducted.

Effect of exenatide QW treatment on general health utility

At week 26, (Table 2) EQ-5D index scores and visual analog scores had increased significantly in the exenatide QW and sitagliptin treatment groups (all $P < 0.05$), but not in the pioglitazone group. There were no significant differences between groups for change in EQ-5D.

Effect of exenatide QW treatment on psychological well-being

At week 26, all three treatment groups experienced significant improvements in all six dimensions of the PGWB (anxiety, depressed mood, positive well-being, self-control, general health, and vitality) and on the PGWB global scale (all $P < 0.05$); there were no statistically significant differences between exenatide QW and the other groups for the global scale, and no additional between-group tests were conducted.

Effect of exenatide QW treatment on diabetes treatment satisfaction

At week 26, all three treatment groups experienced improvements in total DTSQ-s scores (all $P < 0.05$). Prior to adjustment for multiple comparisons, total DTSQ-s scores improved more in the exenatide QW group than in the sitagliptin group ($P = 0.041$); after adjustment this difference was not significant. All three groups experienced decreases in perceived frequency of hyperglycemia (all $P < 0.05$); there were no statistically significant differences between exenatide

Table 1—*Baseline demographic and clinical characteristics of intent-to-treat subjects with type 2 diabetes participating in a 26-week, randomized, multicenter, double-dummy study of patients treated with exenatide QW, sitagliptin, or pioglitazone*

	Exenatide QW	Sitagliptin	Pioglitazone
n	160	166	165
Age (years), mean (SD)	52 (10)	52 (11)	53 (10)
Sex, *n* (%)			
Male	89 (56%)	86 (52%)	79 (48%)
Female	71 (44%)	70 (48%)	86 (52%)
Race/Ethnicity, *n* (%)			
White	53 (33%)	50 (30%)	65 (39%)
Black	19 (12%)	20 (12%)	13 (8%)
Hispanic	50 (31%)	49 (30%)	44 (27%)
Asian	37 (23%)	42 (25%)	40 (24%)
Other	1 (1%)	5 (3%)	3 (2%)
Weight (kg), mean (SD)	89 (20)	87 (20)	88 (21)
BMI (kg/m^2), mean (SD)	32 (5)	32 (5)	33 (5.5)
A1C (%), mean (SD)	8.6 (1.2)	8.5 (1.2)	8.5 (1.1)
Duration of diabetes (years), mean (SD)	6 (5)	5 (4)	6 (5)

Table 2—*Baseline and change from baseline to week 26 in IWQOL-Lite, PGWB, DTSQ-s, and EQ-5D among subjects with type 2 diabetes participating in a randomized, multicenter, double-dummy study of treatment with exenatide QW, sitagliptin, or pioglitazone (intent-to-treat population)*

	Exenatide QW				Sitagliptin				Pioglitazone			
	n†	Baseline	Change‡	95% CI	*n*†	Baseline	Change‡	95% CI	*n*†	Baseline	Change‡	95% CI
IWQOL-Lite												
Total score	132	80.67	5.15* (1.04)	3.11–7.19	139	80.74	4.56* (1.02)	2.56–6.57	130	79.32	1.20§ (1.06)	−0.87–3.28
Physical function	133	73.37	6.78* (1.35)	4.11–9.44	141	73.75	5.81* (1.33)	3.20–8.42	131	73.00	2.00§ (1.38)	−0.71–4.71
Self-esteem	133	77.81	5.88* (1.39)	3.16–8.61	141	79.12	5.79* (1.36)	3.11–8.47	131	76.71	3.11 (1.41)	0.34–5.89
Sexual life	129	83.83	5.80* (1.61)	2.64–8.95	132	82.38	5.02* (1.61)	1.85–8.18	127	81.59	2.41 (1.63)	−0.79–5.60
Public distress	132	91.03	3.86* (1.17)	1.56–6.15	140	90.23	2.40* (1.14)	0.16–4.64	130	88.53	−0.63§ (1.18)	−2.96–1.70
Work	131	89.74	2.79* (1.28)	0.28–5.30	139	88.95	3.02* (1.25)	0.57–5.47	128	87.58	−1.28§ (1.29)	−3.82–1.26
EQ-5D												
Index score	129	0.77	0.04* (0.02)	0.01–0.08	139	0.78	0.05* (0.02)	0.02–0.08	130	0.82	0.02 (0.02)	−0.01–0.06
Visual analog score	132	74.25	4.46* (1.34)	1.82–7.10	139	73.10	6.04* (1.32)	3.45–8.64	130	74.85	2.54 (1.37)	−0.16–5.24
PGWB												
Global score	132	67.54	6.82* (1.00)	4.85–8.79	141	69.96	6.97* (0.98)	5.04–8.90	130	71.60	4.78* (1.02)	2.77–6.79
Anxiety	132	66.32	8.40* (1.31)	5.83–10.97	141	70.35	8.20* (1.28)	5.68–10.71	130	70.85	5.10* (1.33)	2.48–7.73
Depressed mood	133	80.23	3.84* (1.33)	1.22–6.45	141	81.98	3.80* (1.30)	1.24–6.37	130	84.00	3.73* (1.36)	1.06–6.40
Positive well-being	133	61.92	4.65* (1.42)	1.85–7.44	141	61.84	7.86* (1.39)	5.12–10.60	130	64.10	5.02* (1.45)	2.17–7.88
Self control	133	75.11	5.53* (1.37)	2.83–8.22	141	78.71	4.30* (1.34)	1.67–6.94	130	83.33	3.68* (1.40)	0.93–6.43
General health	133	65.39	9.46* (1.40)	6.72–12.21	141	67.84	6.95* (1.37)	4.26–9.65	130	67.56	6.37* (1.43)	3.56–9.17
Vitality	133	61.20	7.46* (1.37)	4.76–10.16	141	63.51	8.98* (1.35)	6.33–11.63	130	65.00	6.23* (1.41)	3.46–9.00
DTSQ												
Total score	121	27.99	3.96* (0.60)	2.78–5.15	127	28.13	2.35* (0.59)	1.19–3.51	123	26.78	2.50* (0.61)	1.31–3.69
Perceived frequency high blood glucose	121	3.84	−1.63* (0.17)	−1.96 to −1.30	127	3.94	−1.30* (0.17)	−1.63 to −0.97	123	3.56	−1.28* (0.17)	−1.62 to −0.94
Perceived frequency low blood glucose	120	0.94	0.22 (0.15)	−0.07 to 0.51	126	1.12	−0.05 (0.15)	−0.33 to 0.24	122	0.91	−0.12 (0.15)	−0.42 to 0.17

†Number of subjects with a baseline and postrandomization score. ‡Data are least squares mean changes (and SE). *$P \leq 0.05$ (change from baseline within treatment group). §$P \leq 0.05$ (difference compared with exenatide group at week 26).

QW and the other groups. There were no statistically significant decreases in perceived frequency of hypoglycemia in any of the groups and no statistically significant differences between exenatide QW and the other groups.

Effect of attrition on study outcomes

Attrition for the four PROs ranged from 10.74 to 14.39% in the exenatide QW arm, from 5.04 to 5.76% in the sitagliptin arm, and from 8.94 to 9.23% in the pioglitazone arm. The main effect by completion/attrition status was statistically significant for all overall PRO scores except IWQOL, with changes in PRO scores in the dropouts lower than those of the completers (IWQOL $P = 0.05$; all other P values < 0.01). However, the differences in PRO score change between completers and dropouts did not vary significantly across treatment arms. Thus, the last observation carried forward imputation did not affect the test for difference in PRO score change between treatment groups, which is the main interest of this article.

Potential mediators of effects on treatment satisfaction

There was no significant difference in total treatment satisfaction in the 40 subjects who experienced nausea and/or vomiting versus the 190 who did not ($P = 0.80$), and the effect did not differ across treatment arms ($P = 0.51$) (results not shown).

We conducted analyses to assess the correlation between weight change and changes in weight-related QOL in the entire study population and in each treatment group. Reduction in body weight was correlated with improvement in overall IWQOL scores in the entire study population ($r = -0.26$, $P < 0.0001$).

CONCLUSIONS—Because there are many treatment options for patients with type 2 diabetes, data comparing the effects of treatments can inform choices among these options. This study compared three treatment options for patients whose blood glucose levels are not adequately controlled on metformin monotherapy. These treatment options address one or both of the clinical issues (hypoglycemia and weight) that were raised as concerns during intensive management of patients with type 2 diabetes (14). The primary outcomes of this study, reported elsewhere (16), indicated that participants in the exenatide QW arm experienced

greater A1C reductions and greater reductions in weight than participants in the sitagliptin or pioglitazone arms, that there was no major hypoglycemia in the exenatide QW arm, and that the incidence of minor hypoglycemia was low and similar in all treatment groups. This suggests that exenatide QW treatment provides clinically relevant benefits to patients early in the disease process. The findings of the current study suggest that exenatide QW treatment also provides benefits across a broad range of PRO, including general health utility, weight-related QOL, psychological well-being, and diabetes treatment satisfaction. For some of these PROs, the benefits of exenatide QW therapy were significantly greater than the benefits of sitagliptin or pioglitazone therapy.

We hypothesized that there would be PRO advantages for exenatide QW, especially for PROs likely to be most sensitive to the known benefits of this agent—the IWQOL (weight control) and the DTSQ-s (glycemic control). The PRO advantages of exenatide QW over the other study treatments were most notable for the measure of weight-related QOL. Patients in the exenatide QW arm experienced greater improvements than patients in the pioglitazone arm on most IWQOL measures. These findings are consistent with the large and statistically significant difference in weight change during the study in the two arms (−2.3 vs. 2.8 kg). The association of clinical benefits such as weight loss with cognate PRO has been demonstrated in other studies (22). In this study, the smaller difference in weight change between the exenatide QW and sitagliptin arms (−2.3 vs. −0.8 kg) was not associated with a difference between arms in weight-related QOL.

The more generic QOL measures assessed in the current study—general health utility and psychological well-being—showed fewer differences among treatment arms. Health utility improved in the exenatide QW arm and the sitagliptin arm but not in the pioglitazone arm, and psychological well-being improved in all three arms, with no significant differences among arms on any of these measures. As might be expected (6), these generic measures were less sensitive than the more specific measures to differences in the clinical effects of the study interventions (glucose control and weight changes).

The PRO advantages of exenatide QW were also apparent for diabetes treatment satisfaction, for which improvement in DTSQ-s total scores was greater for the exenatide QW arm than for the sitagliptin arm. These advantages for exenatide QW may reflect the medication's greater benefits for both glucose control and weight control. Earlier studies have demonstrated the associations of clinical benefits with treatment satisfaction and treatment preference (22). However, this study did not demonstrate differences in patients' perceptions of the actual group differences in improved glucose (reduction of hyperglycemia), and there was no measure of the perceived benefit of weight control.

This study is consistent with findings that improvements in clinical outcomes (e.g., glycemic control) in patients with diabetes are associated with increases in overall diabetes treatment satisfaction (23). This study is also consistent with our earlier report of improved treatment satisfaction and QOL in patients treated with exenatide QW and exenatide BID (9), and with the finding from that study that the potential adverse effects of exenatide treatment (nausea/vomiting), which were more common in the exenatide QW group, did not affect patients' treatment satisfaction. This suggests that these adverse effects were not severe enough to affect patients' perceptions of the study medication.

Although the association between treatment satisfaction and treatment adherence—a sine qua non for realizing the potential benefits of a therapy—have not been demonstrated conclusively, several studies suggest that greater treatment satisfaction is associated with greater treatment adherence (5,24,25).

Study strengths and limitations

This is the first study comparing PRO for three treatment options that address one or both of the clinical issues (hypoglycemia and weight) that have been raised as concerns during intensive management of patients with type 2 diabetes (14). In addition, we assessed a broad range of PROs using validated questionnaires likely to be sensitive to the established clinical effects of the study medication. The study included a substantial number of participants in three countries, and the participation of ethnic minorities was reasonably large, so the findings of this study are more broadly generalizable than is often the case. Finally, we were able to assess the effects of the more commonly reported medication side effects on treatment satisfaction and other PRO.

The double-dummy design of the current study had advantages and disadvantages. An advantage is that it permits a head-to-head comparison of effects on PRO that is not confounded with mode of medication administration, thereby overcoming one of the problems of studying PRO in open-label designs comparing injectable and oral medications. On the other hand, it makes the comparison of treatment satisfaction problematic, because it may have masked any negative effects on treatment satisfaction associated with injection therapy (exenatide QW) compared with oral therapy (sitagliptin and pioglitazone).

The lack of a control group with no change in medication prevents us from making definitive interpretations of study findings. For example, the fact that patients in all arms reported improvements in total treatment satisfaction scores despite adding an injection to their treatment regimen could reflect the benefits of improved glucose control seen in all arms, or it could reflect a placebo effect resulting from receiving a change in medication; the lack of a control group with no change in medication prevents us from distinguishing these alternative explanations. In addition, the generalizability of the study findings is limited by features of all randomized clinical trial, including intensified efforts to promote adherence and retention, the artificiality of providing free intervention and medication (especially in developing nations), exclusion criteria, and influences upon self-selection such as socioeconomic status and willingness to be in a clinical trial.

Implications for future research

Although the results suggest that exenatide QW has PRO advantages over sitagliptin and pioglitazone, it remains to be seen whether the different medications are preferred by different patient subgroups. Systematic evaluation of patient differences that account for alternative preferences should be pursued. A comparison of exenatide QW with other potential treatment options is also warranted. Research to assess potential mediators of the association between exenatide use and PRO, including the possibility that exenatide use reduces C-reactive protein and nitrous oxide levels, is also warranted.

Clinical implications

In this study exenatide QW treatment was associated with important clinical benefits,

including improved glucose control and weight loss (16), and patients previously treated with metformin monotherapy reported improved weight-related QOL and higher satisfaction with their study medication regimen than their previous therapy. Moreover, nausea/vomiting—a side effect associated with exenatide—did not affect treatment satisfaction in this study, suggesting that these effects might not be a barrier to patients' accepting treatment with these medications.

In combination with earlier findings from this study (16), our results indicate it is possible for patients treated with metformin monotherapy to initiate exenatide therapy with potential benefits in both clinical outcomes and PROs.

Acknowledgments—J.H.B., Y.L., P.Y., and J.M. are employees and stockholders of Amylin Pharmaceuticals. M.P. has received research and consultation funding from Amylin, Animas, Eli Lilly, Genentech, MannKind Corporation, Medtronic MiniMed, Novo Nordisk, and Patton Medical Devices. R.R.R. has received research and consultation funding from Amylin, Animas, Eli Lilly, Genentech, LifeScan, MannKind, Medingo, Medtronic MiniMed, Novo Nordisk, Patton Medical Devices, and sanofi-aventis. L.P.G. has received consulting fees from Amylin, Eli Lilly, and Roche and research grant support from Roche. No other potential conflicts of interest relevant to this article were reported.

J.H.B., Y.L., and P.Y. researched data for the manuscript. J.H.B., R.R.R., M.P., and L.P.G. wrote the manuscript and contributed to discussion. J.H.B., R.R.R., M.P., Y.L., P.Y., J.M., and L.P.G. reviewed and edited the manuscript.

Parts of this study were presented in abstract form at the 45th Annual Meeting of the European Association for the Study of Diabetes, Vienna, Austria, 27 September–1 October 2009.

The Diabetes Treatment Satisfaction Questionnaire is available from Dr. Clare Bradley, University of London, Egham, Surrey.

References

1. Nathan DM, Buse JB, Davidson MB, et al.; American Diabetes Association; European Association for Study of Diabetes. 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;32:193–203
2. Bays HE, Chapman RH, Grandy S; SHIELD Investigators' Group. The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys. Int J Clin Pract 2007;61:737–747
3. Maggio CA, Pi-Sunyer FX. The prevention and treatment of obesity. Application to type 2 diabetes. Diabetes Care 1997;20:1744–1766
4. 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;352:837–853
5. Charpentier G, Fleury F, Dubroca I, Vaur L, Clerson P. Electronic pill-boxes in the evaluation of oral hypoglycemic agent compliance. Diabetes Metab 2005;31:189–195
6. Leidy NK, Revicki DA, Genesté B. Recommendations for evaluating the validity of quality of life claims for labeling and promotion. Value Health 1999;2:113–127
7. Food and Drug Administration. Guidance for industry. Patient-reported outcome measures: Use in medical product development and labeling claims. Available from www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf. Accessed 21 March 2010
8. Marra G; DIAB. & TE.S Project Study Group. The DIAB.&TE.S Project: how patients perceive diabetes and diabetes therapy. Acta Biomed 2004;75:164–170
9. Best JH, Boye KS, Rubin RR, Cao D, Kim TH, Peyrot M. Improved treatment satisfaction and weight-related quality of life with exenatide once weekly or twice daily. Diabet Med 2009;26:722–728
10. Lingvay I, Legendre JL, Kaloyanova PF, Zhang S, Adams-Huet B, Raskin P. Insulin-based versus triple oral therapy for newly diagnosed type 2 diabetes: which is better? Diabetes Care 2009;32:1789–1795
11. Aljabri K, Kozak SE, Thompson DM. Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial. Am J Med 2004;116:230–235
12. Rosenstock J, Goldstein BJ, Vinik AI, et al.; RESULT Study Group. Effect of early addition of rosiglitazone to sulphonylurea therapy in older type 2 diabetes patients (>60 years): the Rosiglitazone Early vs. SULphonylurea Titration (RESULT) study. Diabetes Obes Metab 2006;8:49–57
13. Bailey CJ, Bagdonas A, Rubes J, et al. Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24-week, multicenter, randomized, double-blind, parallel-group study. Clin Ther 2005;27:1548–1561
14. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
15. World Medical Association Declaration of Helsinki. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997;277:925–926
16. Bergenstal RM. Wysham, MacConell L, Malloy J, Yan P, Wilhelm K, Malone J, Porter LE, for the DURATION-2 Study Group: A comparison of the efficacy and safety of exenatide once weekly, sitagliptin, and pioglitazone when added to metformin in the treatment of type 2 diabetes. DURATION-2: a randomized trial. Lancet 2010;376:431–439
17. Kolotkin RL, Crosby RD, Williams GR. Assessing weight-related quality of life in obese persons with type 2 diabetes. Diabetes Res Clin Pract 2003;61:125–132
18. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Med Decis Making 2002;22:340–349
19. Matza LS, Boye KS, Yurgin N. Validation of two generic patient-reported outcome measures in patients with type 2 diabetes. Health Qual Life Outcomes 2007;5:47
20. Dupuy HJ. The psychological general well-being (PGWB) Index. In *Assessment of Quality of Life in Clinal Trials of Cardiovascular Therapies*. Wenger NK, Ed. New York, LeJacq Publications, 1984, p. 170–183
21. Bradley C. The Diabetes Treatment Satisfaction Questionnaire: DTSQ. In *Handbook of Psychology and Diabetes: a Guide to Psychological Measurement in Diabetes Research and Practice*. Chur BC, Ed. Switzerland, Harwood Academic Publishers, 1994, p. 111–132
22. Peyrot M, Rubin RR. How does treatment satisfaction work? Modeling determinants of treatment satisfaction and preference. Diabetes Care 2009;32:1411–1417
23. Hermansen K, Kolotkin RL, Hammer M, Zdravkovic M, Matthews D. Patient-reported outcomes in patients with type 2 diabetes treated with liraglutide or glimepiride, both as add-on to metformin. Prim Care Diabetes 2010;4:113–117
24. Pollack MF, Purayidathil FW, Bolge SC, Williams SA. Patient-reported tolerability issues with oral antidiabetic agents: Associations with adherence; treatment satisfaction and health-related quality of life. Diabetes Res Clin Pract 2010;87:204–210
25. Bharmal M, Payne K, Atkinson MJ, Desrosiers M-P, Morisky DE, Gemmen E. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes 2009;7:36