Efficacy, Tolerability, and Safety of a Novel Once-Daily Extended-Release Metformin in Patients With Type 2 Diabetes

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OBJECTIVE — The purpose of this study was to determine the efficacy and safety of a novel extended-release metformin in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Adults with type 2 diabetes (newly diagnosed, treated with diet and exercise only, or previously treated with oral diabetic medications) were randomly assigned to receive one of three extended-release metformin treatment regimens (1,500 mg/day q.d., 1,500 mg/day twice daily, or 2,000 mg/day q.d.) or immediate-release metformin (1,500 mg/day twice daily) in a double-blind 24-week trial.

RESULTS — Significant decreases ($P < 0.001$) in mean HbA_{1c} (A1C) levels were observed by week 12 in all treatment groups. The mean changes from baseline to end point in the two groups given 1,500 mg extended-release metformin (−0.73 and −0.74%) were not significantly different from the change in the immediate-release metformin group (−0.70%), whereas the 2,000-mg extended-release metformin group showed a greater decrease in A1C levels (−1.06%; mean difference [2,000 mg extended-release metformin − immediate-release metformin]: −0.36 [98.4% CI −0.65 to −0.06]). Rapid decreases in fasting plasma glucose levels were observed by week 1, which continued until week 8, and were maintained for the duration of the study. The overall incidence of adverse events was similar for all treatment groups, but fewer patients in the extended-release metformin groups discontinued treatment due to nausea during the initial dosing period than in the immediate-release metformin group.

CONCLUSIONS — Once- or twice-daily extended-release metformin was as safe and effective as twice-daily immediate-release metformin and provided continued glycemic control for up to 24 weeks of treatment.

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Metformin hydrochloride has been widely used as an effective and generally well-tolerated glucose-lowering agent for >40 years and is the most frequently prescribed first-line therapy for patients with type 2 diabetes (1). Metformin typically reduces basal and postprandial hyperglycemia by ~25% in >90% of patients when given alone or with other therapies during a program of managed care (2). In the U.K. Prospective Diabetes Study, intensive glucose control with metformin appeared to reduce the risk of diabetes-related end points in overweight patients and was associated with less weight gain and fewer hypoglycemic attacks than insulin (3).

The objective of this study was to evaluate the efficacy, tolerability, and safety of a novel extended-release oral formulation of metformin compared with conventional immediate-release metformin during 24 weeks of double-blind treatment. When administered with food, the extended-release metformin tablet gradually releases drug over 8 h into the upper gastrointestinal tract (4), where metformin is primarily absorbed (5). Prolonged release of metformin from extended-release metformin tablets has been demonstrated in pharmacokinetic studies (6,7). Extended-release metformin showed slightly lower maximum concentrations, longer times to maximum concentration (7–8 vs. 4–5 h), and similar bioavailability compared with immediate-release products (7). This extended release could potentially reduce dosing frequency to once daily compared with two or three times daily for immediate-release formulations.

RESEARCH DESIGN AND METHODS

— A randomized, double-blind, active-controlled, fixed-dose, phase III clinical trial was conducted at 85 centers in the U.S. between August 2001 and October 2003. The study protocol was approved by institutional review boards, and the study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice. Each patient provided written informed consent before undergoing any study procedures.

The trial enrolled male and female outpatients, 18–79 years of age, with type 2 diabetes. Patients were either drug naïve (with newly diagnosed diabetes or treated with diet and exercise only) or had received prior drug therapy (monotherapy with oral hypoglycemic agents other than metformin up to the maximum dose allowed, metformin monotherapy up to 2,000 mg/day, or metformin up to 1,500 mg/day with sulfonylurea up to one-half the maximum allowed dose). Patients underwent a full physical examination including an electrocardiogram before enrollment. Inclusion criteria (determined at the screening visit) included HbA_{1c} (A1C) levels 7.0–12.0% (drug-naïve patients) or 6.5–10.0% (prior drug therapy patients), fasting plasma glucose

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Abbreviations: FPG, fasting plasma glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

(FPG) levels 120–400 mg/dl (drug-naïve patients) or 120–250 mg/dl (prior drug therapy patients), C-peptide levels >1.0 ng/ml, BMI 22–50 kg/m^2, and a negative pregnancy test for female patients. Patients were excluded from the study if they were receiving insulin, systemic corticosteroids, nicotinic acid, or isoniazid; had a history of background retinopathy, symptomatic autonomic neuropathy, or unstable angina; had chronic gastroparesis or chronic severe gastrointestinal symptoms, a history of gastric or duodenal ulcers, abdominal surgery within 1 year, or active gastrointestinal disease within 2 years; had any uncontrolled or untreated cardiovascular, hepatic, pulmonary, renal, or neurological system conditions; or had serum creatinine >1.5 mg/dl (male patients) or >1.4 mg/dl (female patients) or proteinuria.

Eligible patients were randomly assigned in a 1:1:1:1 ratio within each of two stratification levels (metformin before enrollment: yes or no) to receive 1,500 mg extended-release metformin q.d. (Glumetza; Depomed, Menlo Park, CA), 1,500 mg extended-release metformin twice daily (500 mg in the morning and 1,000 mg in the evening), 2,000 mg extended-release metformin q.d., or 1,500 mg immediate-release metformin twice daily (Glucophage; Bristol-Myers Squibb, Princeton, NJ) (500 mg in the morning and 1,000 mg in the evening), together with appropriate placebo tablets to maintain the study blind. After a 6-week washout of current antihyperglycemic agents (for prior drug therapy patients), all patients began metformin dosing at 1,000 mg q.d., which was titrated to their assigned dose over 2–3 weeks and continued at that dose for a total treatment duration of 24 weeks. All study drugs and placebos were taken after a meal.

Patients were evaluated every 1–2 weeks during the screening and washout periods, weekly for the first 4 weeks of treatment and then every 4 weeks until the end of study. The primary efficacy end point was glycemic control as determined by the baseline-adjusted differences between treatment groups in the reduction in A1C levels from baseline to end point. Secondary efficacy parameters included changes in A1C, FPG, fructosamine, total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride concentrations from baseline to specified times during the study. The proportion of patients who discontinued treatment because of lack of efficacy (defined as fasting blood glucose >250 mg/dl for 1 week or >300 mg/dl for 3 days) was also determined. Adverse events were recorded throughout the study by direct questioning and observation of patients and from the results of physical examinations and clinical laboratory tests.

Statistical methods

Efficacy and safety analyses were performed using an intent-to-treat population, defined as all randomly assigned patients who received a study drug and had available efficacy data. The primary efficacy parameter, mean change in A1C concentration from baseline to end point, was analyzed using an ANCOVA parallel model that included treatment, center, and stratification factor as fixed factors and baseline A1C as a covariate. The least-squares estimate of the mean change from baseline for each treatment and its 95% CI were calculated. A two-sided 98.4% CI of the pairwise mean difference between each extended-release metformin treatment and immediate-release metformin (extended-release metformin − immediate-release metformin) in mean change from baseline to end point for A1C levels was constructed. The three extended-release metformin treatment groups were each considered noninferior to immediate-release metformin treatment if the upper boundary of this 98.4% CI was not >0.4%. Analyses of changes from baseline in A1C levels were also performed for subgroups of patients classified by prior hypoglycemic therapy, sex, age, race, and baseline BMI.

Continuous secondary efficacy parameters were analyzed using an ANCOVA model that included treatment, center, treatment-by-center interaction, and stratification factor as fixed factors and the baseline measurement as a covariate. Categorical secondary efficacy parameters were analyzed using a two-sided Fisher's exact test for overall comparison among treatment groups. In addition, a two-sample Z test on proportions was performed. The difference between a proportion and its 95% CI was determined.

Adverse event analyses included all patients who received at least one dose of study drug. Fisher's exact test was used to compare the incidence of adverse events among treatment groups.

RESULTS — A total of 750 patients were enrolled and randomly assigned, 706 patients were included in the intent-to-treat population, and 529 patients completed the study per protocol. The most common reasons for discontinuation were withdrawal of consent (63 patients), lack of efficacy (40 patients), and loss to follow-up (21 patients). Reasons for discontinuation were similar among treatment groups, except that fewer patients discontinued treatment due to lack of efficacy in the 2,000-mg extended-release metformin group (1.8%) than in the immediate-release metformin group (8.0%) ($P = 0.007$). There were no significant differences among treatment groups for demographic and baseline characteristics (Table 1).

Efficacy results

Significant ($P < 0.001$) reductions in mean A1C concentrations were observed by week 12 in all treatment groups. A1C levels continued to decline until week 20 and were maintained for the duration of the study (Fig. 1). The mean changes in A1C concentrations from baseline to end point in all extended-release metformin groups were noninferior to those in the immediate-release metformin group (mean differences for change from baseline in A1C levels [extended-release metformin − immediate-release metformin]: −0.03 [98.4% CI −0.32 to 0.26], −0.04 [−0.33 to 0.25], and −0.36 [−0.65 to −0.06] for the 1,500-mg q.d., 1,500-mg morning and evening, and 2,000-mg q.d. extended-release metformin groups, respectively; $P = 0.013$ for overall comparison among groups).

Mean A1C concentrations decreased in all subgroups of patients analyzed, with the greatest decreases among drug-naïve patients. For patients at least 65 years of age, female patients, non-Caucasian patients, and patients with BMI ≥30 kg/m^2, each of the three extended-release metformin treatment groups had greater decreases from baseline than the immediate-release metformin group, with the greatest decreases observed in the 2,000-mg extended-release metformin group. At the end of treatment, mean A1C levels in the 2,000-mg extended-release metformin q.d. and immediate-release metformin groups, respectively, were 6.94 and 7.33% for drug-naïve patients, 6.76 and 7.23% for patients at least 65 years of age, 7.17 and 7.64% for female patients, 7.23 and 7.88% for non-Caucasian patients, and 7.05 and 7.62% for patients with BMI ≥30 kg/m^2.

Significant reductions ($P < 0.001$) in mean FPG concentrations were observed

Table 1—*Demographics and baseline characteristics: intent-to-treat population*

Parameter	Extended-release metformin			1,500 mg immediate-release metformin (AM/PM)	Total
	1,500 mg q.d.	1,500 mg (AM/PM)	2,000 mg q.d.		
n	178	182	172	174	706
Age (years)	54 ± 11.4	54 ± 11.8	55 ± 11.7	54 ± 12.5	54 ± 11.8
<65	138 (77.5)	142 (78.0)	129 (75.0)	135 (77.6)	544 (77.1)
≥65	40 (22.5)	40 (22.0)	43 (25.0)	39 (22.4)	162 (22.9)
Sex					
Male	83 (46.6)	111 (61.0)	91 (52.9)	95 (54.6)	380 (53.8)
Female	95 (53.4)	71 (39.0)	81 (47.1)	79 (45.4)	326 (46.2)
Race					
Caucasian	107 (60.1)	116 (63.7)	107 (62.2)	111 (63.8)	441 (62.5)
Black	30 (16.9)	18 (9.9)	23 (13.4)	22 (12.6)	93 (13.2)
Asian	5 (2.8)	5 (2.7)	3 (1.7)	3 (1.7)	16 (2.3)
Hispanic	32 (18.0)	38 (20.9)	36 (20.9)	37 (21.3)	143 (20.3)
Native American	1 (0.6)	3 (1.6)	1 (0.6)	0	5 (0.7)
Other	3 (1.7)	2 (1.1)	2 (1.2)	1 (0.6)	8 (1.1)
BMI (kg/m^2)	33.4 (6.6)	33.0 (6.3)	33.7 (6.6)	33.8 (6.8)	33.5 (6.6)
<30	60 (33.9)	67 (37.0)	53 (30.8)	58 (33.3)	238 (33.8)
≥30	117 (66.1)	114 (63.0)	119 (69.2)	116 (66.7)	466 (66.2)
Duration of diabetes (years)	3.9 ± 4.5	4.5 ± 4.9	3.9 ± 4.3	4.4 ± 5.4	4.2 ± 4.8
Diabetes treatment before entry*					
Drug naïve†	81 (45.5)	86 (47.3)	84 (48.8)	87 (50.0)	338 (47.9)
Metformin only	43 (24.2)	44 (24.2)	45 (26.2)	43 (24.7)	175 (24.8)
Sulfonylurea only	29 (16.3)	30 (16.5)	22 (12.8)	30 (17.2)	111 (15.7)
Metformin and sulfonylurea	20 (11.2)	12 (6.6)	17 (9.9)	10 (5.7)	59 (8.4)
Other‡	1 (0.6)	2 (1.0)	0 (0)	1 (0.6)	4 (0.5)

Data are means ±SD or *n* (%). *P* values for statistical comparisons among the four treatment groups were >0.05 for all parameters. *Drug-naïve patients had newly diagnosed diabetes or were treated with diet and exercise only before enrollment. †Treatment within 30 days before enrollment. Patients received metformin up to 2,000 mg/day as monotherapy or up to 1,500 mg/day in combination with other therapy. ‡Other: metformin or sulfonylurea in combination with other oral antihyperglycemic therapy. AM/PM, morning and evening.

by the end of week 1 in all treatment groups. FPG concentrations continued to decline until week 8, and these reduced levels were maintained until the end of the study (Fig. 1). The mean changes from baseline to end point within each of the three extended-release metformin groups were comparable with or greater than that in the immediate-release metformin group.

Mean fructosamine levels also decreased from baseline within all treatment groups. There was a significant difference among treatment groups for fructosamine levels at the end point, with the lowest level in the 2,000-mg extended-release metformin group. Total, LDL, and HDL cholesterol levels were similar at baseline and end point in all treatment groups, except for significant differences among treatment groups for final LDL cholesterol ($P = 0.015$) and triglycerides ($P = 0.030$), with the lowest mean concentrations in the 2,000-mg extended-release metformin group for LDL cholesterol and in the immediate-release metformin group for triglycerides (Table 2).

Safety results

Even with a 1,000-mg q.d. starting dose, the overall incidence of gastrointestinal adverse events during the 1st week of dosing was low and comparable among treatment groups (Table 3). There was a higher incidence of nausea in the immediate-release metformin group than in the extended-release metformin groups ($P = 0.05$). In addition, there were more adverse events of nausea and diarrhea causing treatment discontinuation in the immediate-release metformin group than in the extended-release metformin groups. The overall incidence of adverse events considered possibly or probably related to the study drug was similar for all treatment groups; the only such events reported for >5% of patients in any treatment group were gastrointestinal events.

CONCLUSIONS — All extended-release metformin treatment regimens produced significant decreases in A1C levels that were similar to those with the comparator, immediate-release metformin, a widely used and highly effective oral hypoglycemic agent. The reductions in mean A1C levels were similar to those reported for patients with type 2 diabetes in comparable clinical trials with immediate-release metformin (8–11) and another extended-release metformin (Glucophage XR; Bristol-Myers Squibb) (12,13). Similarly, there were rapid decreases in FPG levels within the 1st week of treatment that were maintained for the duration of the study. Reductions in FPG with all extended-release metformin treatment regimens were comparable to that with immediate-release metformin treatment and similar to reductions observed in other controlled clinical studies (8–11). In an open-label extension of our study that included patients from all four treatment groups, the decreases in A1C and glucose levels were maintained for an additional 24 weeks of treatment with 2,000 mg extended-release metformin q.d. (mean A1C and FPG levels at end point were 7.15% and 146.8 mg/dl, respectively).

In all measures of glycemic control, including short-term FPG, medium-term

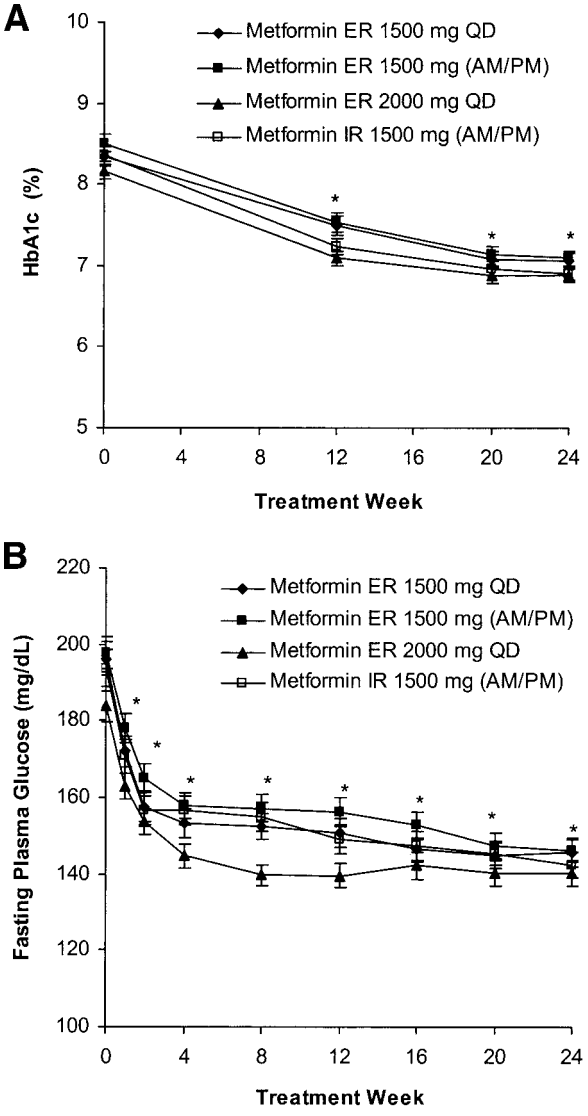

Figure 1—*Means ± SE of A1C* (upper panel) *and FPG* (lower panel) *concentrations over time for the intent-to-treat population.* ♦*, 1,500 mg extended-release (ER) metformin q.d. (QD);* ■*, 1,500 mg extended-release metformin morning and evening (AM/PM);* ▲*, 2,000 mg extended-release metformin q.d.;* □*, 1,500 mg immediate-release (IR) metformin morning and evening. Each time point includes patients who had data for that visit. *Significant change from baseline within each treatment group* ($P < 0.001$).

fructosamine, and long-term A1C levels, large and consistent reductions were observed in all extended-release metformin treatment groups after 24 weeks of treatment. In contrast with other extended-release metformin formulations, for which once-daily treatment is slightly less effective than twice-daily treatment (13), once-daily treatment with the extended-release metformin used in this study was at least as effective as twice-daily treatment at the same total daily dose.

Decreases in total cholesterol, LDL cholesterol, and triglycerides and increases in HDL cholesterol have been observed in some metformin studies in patients with type 2 diabetes but not in others (11,14–16). In our study, mean lipid levels showed only minor changes from baseline in all treatment groups. Triglyceride levels tended to increase slightly with extended-release metformin, similar to a trend previously reported with other extended-release metformin formulations (12,13), although this increase has not been observed with immediate-release metformin formulations. The mechanism underlying this rise is unclear. One possibility is that immediate-release metformin taken with meals may affect postprandial triglyceride and fatty acid flux, and this effect is not seen with slow-release formulations. The clinical significance of these findings is unclear. Although triglycerides are a risk factor for cardiovascular disease, changes in triglycerides may not always lead to significant changes in cardiovascular events and mortality (17). It is important to recognize that the primary aim of oral hypoglycemic therapy is to improve glycemia, which is likely to improve glucose-related complications in the long term.

The highest dose of extended-release metformin used in our study, 2,000 mg/day, is the maximum recommended daily dose for other extended-release metformin formulations and is the dose at which glycemic response appears to plateau with immediate-release formulations (9). This dose provided consistently greater efficacy than the other three treatments, with mean A1C levels decreasing to <7.0% for some subgroups of patients and a lower rate of discontinuation due to lack of efficacy. In particular, the 2,000-mg/day dose resulted in greater decreases in A1C among female, non-Caucasian, older, and overweight patients. Although the effect of metformin monotherapy has been shown to be independent of age, body weight, and ethnicity (14), our results indicate that the 2,000-mg/day dose may be more effective in some patient populations. This potentially improved efficacy may be related to the nearly linear increase in the area under the curve with extended-release metformin at doses up to 2,500 mg/day (7) and is in contrast to the plateau in efficacy at doses >1,500 mg/day with other extended-release metformin formulations (13).

It is not possible to realistically measure patient adherence to therapy in controlled clinical trials, since adherence is enhanced by the rigorous study environment. In particular, the possible benefit of once-daily dosing cannot be measured in a double-blind study. However, patient adherence to once-daily extended-release metformin therapy in the open-label extension study mentioned was 97.2%. This low-intervention study had only three study visits after enrollment, similar to the frequency of doctor visits that patients might normally experience.

Metformin therapy is associated with gastrointestinal effects, including abdominal discomfort, nausea, and diarrhea, although these can be minimized by slow titration and administration with food (15). The titration regimen used in this study was intended to provide rapid and effective glycemic control, a convenient

Table 2—*A1C, FPG, fructosamine, and lipid levels at baseline and end point*

	n	Extended-release metformin			1,500 mg intermediate-release metformin (AM/PM)	*P* value
		1,500 mg q.d.	1,500 mg (AM/PM)	2,000 mg q.d.		
A1C (%)	673					
Baseline		8.22 ± 0.25	8.50 ± 0.24	8.26 ± 0.24	8.70 ± 0.25	0.483
End point		7.62 ± 0.12	7.60 ± 0.12	7.29 ± 0.12	7.65 ± 0.12	0.013
FPG (mg/dl)	686					
Baseline		190.0 ± 9.9	192.5 ± 9.9	183.9 ± 9.9	196.5 ± 11.2	0.855
End point		154.4 ± 4.4	161.1 ± 4.4	151.0 ± 4.5	160.9 ± 4.5	0.051
Fructosamine (μmol/l)	624					
Baseline		338.4 ± 13.8	344.8 ± 13.0	344.6 ± 13.0	356.4 ± 15.8	0.860
End point		310.3 ± 5.7	312.0 ± 5.6	295.1 ± 5.7	312.2 ± 5.8	0.026
Total cholesterol (mg/dl)	645					
Baseline		207.6 ± 7.3	204.7 ± 6.9	207.8 ± 7.2	202.7 ± 7.3	0.951
End point		210.2 ± 4.6	196.8 ± 4.3	187.1 ± 4.5	197.0 ± 4.5	0.005
HDL cholesterol (mg/dl)	642					
Baseline		45.5 ± 1.9	45.5 ± 1.8	44.6 ± 1.9	44.1 ± 1.9	0.927
End point		47.6 ± 0.7	46.8 ± 0.7	47.4 ± 0.7	46.8 ± 0.7	0.506
LDL cholesterol (mg/dl)	594					
Baseline		123.3 ± 6.3	122.5 ± 5.9	124.6 ± 5.9	122.4 ± 5.9	0.993
End point		112.3 ± 2.5	112.2 ± 2.5	110.4 ± 2.5	117.9 ± 2.5	0.015
Triglycerides (mg/dl)	642					
Baseline		198.8 ± 29.3	199.0 ± 27.7	216.2 ± 29.3	186.0 ± 29.3	0.909
End point		203.0 ± 12.2	201.2 ± 12.1	206.8 ± 12.3	181.7 ± 12.2	0.030

Data are least-squares means ± SE estimated from the ANOVA or ANCOVA model described in RESEARCH DESIGN AND METHODS and include patients who had baseline and end point data. *P* values are overall comparisons among treatment groups from the ANOVA or ANCOVA model. AM/PM, morning and evening.

dosing schedule, and comparable efficacy to twice-daily immediate-release metformin. Even with this rapid titration, the dropout rate and incidence of gastrointestinal events during the titration period were very low for all extended-release metformin treatment regimens. Many patients who would otherwise benefit from metformin therapy discontinue treatment because of gastrointestinal symptoms, typically during the first few weeks of treatment. The lower incidence of nausea in the extended-release metformin groups during the 1st week of treatment may help improve patient adherence to metformin therapy.

The overall incidence of adverse events was comparable among all extended-release metformin dosage regimens (up to 2,000 mg/day) and immediate-release metformin. Importantly, there was no increase in adverse events with the 2,000-mg/day dose, even with the improved efficacy at this dose. The good tol-

Table 3—*Gastrointestinal adverse events*

	Extended-release metformin			1,500 mg immediate-release metformin (AM/PM)
	1,500 mg q.d.	1,500 mg (AM/PM)	2,000 mg q.d.	
Gastrointestinal events during dosing at 1,000 mg q.d.				
Any gastrointestinal event	33 (18.9)	28 (15.5)	35 (20.7)	33 (19.3)
Diarrhea	12 (6.9)	15 (8.3)	15 (8.9)	18 (10.5)
Nausea	5 (2.9)	7 (3.9)	4 (2.4)	14 (8.2)*
Discontinuations due to gastrointestinal events during the 1st week of treatment				
Diarrhea	1 (0.6)	0 (0)	0 (0)	2 (1.2)
Nausea	0 (0)	0 (0)	0 (0)	3 (1.7)
Other gastrointestinal event	1 (0.6)	1 (0.6)	0 (0)	2 (1.2)
Adverse events during entire study†				
Diarrhea	25 (14.2)	33 (18.2)	27 (15.8)	25 (14.4)
Nausea	17 (9.7)	14 (7.7)	14 (8.2)	19 (10.9)
Dyspepsia	9 (5.1)	5 (2.8)	8 (4.7)	10 (5.7)
Upper abdominal pain	9 (5.1)	6 (3.3)	4 (2.3)	4 (2.3)

Data are *n* (%). *Significant difference among treatment groups ($P = 0.050$). †Events reported for at least 5% of patients in any treatment group and considered possibly or probably related to study drug. AM/PM, morning and evening.

erability of immediate-release metformin in this study was probably related to its dosing regimen, i.e., 1,500 mg/day, given twice daily with meals and the larger dose segment with the evening meal. The incidence of events considered related to the study drug (33.1% for the combined extended-release metformin groups and 34.5% for immediate-release metformin) is comparable to a 28% incidence reported in a similar study, which included patients who received lower metformin doses (500 or 1,000 mg/day) than used in our study (9).

In summary, extended-release metformin was highly effective, safe, and well tolerated for up to 24 weeks of treatment. Once-daily extended-release metformin was as effective as twice-daily immediate-release metformin, and this reduced dosing frequency could improve the rapidity of initial titration, patient convenience, and potentially treatment adherence.

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