Efficacy of Pharmacotherapy for Weight Loss in Adults With Type 2 Diabetes Mellitus

A Meta-analysis

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Background: Obesity is closely related to type 2 diabetes mellitus, and weight reduction is an important part of the care delivered to obese persons with diabetes. The objective of this review was to assess the efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes.

Methods: A systematic review of the literature was performed, and studies were included if pharmacotherapy was used as the primary strategy for weight loss among adults with type 2 diabetes. Published and unpublished studies with any design were included. A random effects model was used to combine outcomes from randomized controlled trials.

Results: Sufficient data for the meta-analysis were available for fluoxetine, orlistat, and sibutramine. Fourteen randomized, placebo-controlled trials were included in the review, with a total of 2231 patients. Pharmacotherapy produced modest reductions in weight for fluoxetine (3.4 kg [95% confidence interval CI], 1.7–5.2 kg) at 8–16 weeks of follow-up; 5.1 kg [95% CI, 3.3–6.9 kg] at 24–30 weeks; and 5.8 kg [95% CI, 0.8–10.8 kg] at 52 weeks); orlistat (2.6 kg [95% CI, 2.1–3.2 kg] [2.6% loss] at 52 weeks); and sibutramine (4.5 kg [95% CI, 1.8–7.2 kg] [3.3% loss] at up to 26 weeks). Glycated hemoglobin was also modestly reduced: fluoxetine (1.0% [95% CI, 0.4%–1.5%]) at 8–16 weeks; 1.0% [95% CI, 0.6%–1.4%] at 24–30 weeks; and 1.8% [95% CI, –0.2%–3.8%] at 52 weeks); orlistat (0.4% [95% CI, 0.3%–0.5%]); and sibutramine (0.7% [95% CI, –0.3%–1.9%]). Gastrointestinal adverse effects were common with orlistat; tremor, somnolence, and sweating with fluoxetine; and palpitations with sibutramine.

Conclusions: Fluoxetine, orlistat, and sibutramine can achieve statistically significant weight loss over 26 to 52 weeks. However, the magnitude of weight loss was modest, and the long-term health benefits and safety remain unclear. Interventions that combine pharmacologic therapy with intensive behavioral interventions may be more effective but need additional research.

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Dietary and behavioral treatment for weight loss can produce an average loss of 8% of initial body weight over 3 to 12 months. It is difficult, however, to achieve long-term weight control in general populations, the majority of obese patients regain most of the weight they lose in successful interventions. Overweight or obese persons with diabetes face different issues than do non-diabetic persons in trying to lose weight; studies suggest that persons with diabetes lose less weight than do nondiabetic persons and may regain weight more rapidly. Physiologic abnormalities of diabetes may make weight loss more difficult and harder to maintain, although the mechanisms responsible are unclear and the validity of the observation has not been systematically examined. Treatment with insulin to achieve glycemic control may produce weight gain. Complex treatment regimens for diabetes, hypertension, and hyperlipidemia complicate behavioral change aimed at weight reduction.

Obesity is viewed as a chronic disease. Greenway suggests that it should be treated as such and that optimal management may require long-term pharmacotherapy. In patients in whom behavioral therapy has failed, adjunctive treatment with weight-management drugs may help reduce or maintain weight and improve other health parameters, including glycemic control and lipid levels. The objective of this systematic review was to assess the efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus.

**METHODS**

**DATA SOURCES**

A protocol was developed using methods of the Cochrane Collaboration. We developed search strategies using an iterative process that involved Medical Subject Headings (MeSH), text words, and drug names (generic and trade). We searched the following databases between the date indicated and September 2002: MEDLINE (1966), EMBASE (1974), CINAHL (1982), Web of Science (1981), BIOSIS (1970), International Pharmaceutical Abstracts (1970), Cochrane Library (2002, issue 3), and the Cochrane Register of Controlled Trials (2002, issue 3). We manually searched journals expected to have the highest relevance, from 1980 to the present: Diabetes Care, International Journal of Obesity and Related Metabolic Disorders, Obesity Research (commenced in 1993), American Journal of Clinical Nutrition, and Journal of the American Dietetic Association.

We also searched systematically for reviews of pharmacotherapy for weight loss in persons with and without diabetes. Reference lists of all included studies and the identified reviews were examined, and experts in obesity research were consulted for additional citations. We contacted companies that produce the drugs we reviewed, requesting published and unpublished data on the efficacy of each drug. We attempted to contact authors if data were unclear or missing.

**STUDY SELECTION**

We searched for both published and unpublished studies in any language, in which pharmacologic treatment was used as a primary weight loss strategy in adults 18 years or older with type 2 diabetes, and weight was measured as an outcome. Our focus was drugs that are currently available in the United States, including off-label use and drugs available without a prescription (over-the-counter medications). Studies in which persons with diabetes were examined as a subgroup were included if they provided diabetic-specific weight outcomes. There were no restrictions on duration of the intervention, follow-up interval, or study design, and both full-text articles and abstracts were included. Drug therapy could be combined with any weight loss intervention, including dietary counseling and behavioral approaches.

We searched for efficacy, effectiveness, and adverse events data on the following drugs: centrally acting appetite suppressants (dexamphetamine, sibutramine, fluoxetine, phentermine, phendimetrazine or phendimetrazine, diethylpropion, yohimbine, methamphetamine or benzphetamine, amphetamine or dextroamphetamine, bupropion, and topiramate); drugs with a peripheral effect on appetite (benzocaine and ephedrine); drugs that affect nutrient partitioning (orlistat [known also as tetrahydrolipstatin] and threohydrochloric acid); and drugs that increase thermogenesis (ephedrine and caffeine). This review does not include drugs that have been withdrawn from the US market or are not available in the United States, specifically fenfluramine and dexfenfluramine, propranolol, and mazindol. Also excluded were investigational drugs and dietary supplements. Metformin and acarbose were excluded since their usual indication is glycemic control, although weight loss may result.

Two independent reviewers identified potentially relevant titles and abstracts from MEDLINE and CINAHL (S.L.N. and X.Z.) and the remaining databases were reviewed by 1 author (S.L.N.). One of the authors (S.L.N.) reviewed each full-text article to see if it fulfilled inclusion criteria. Where there was uncertainty about inclusion, a second person (A.A.) reviewed the article, and consensus was achieved.

**DATA EXTRACTION**

For studies that met inclusion criteria, 2 independent reviewers abstracted relevant data and consensus was achieved through discussion. Data abstracted from each study included participant characteristics, setting, intervention characteristics, and study design. We assessed internal validity based on assessment of individual components of quality according to Cochrane Collaboration methodology. We examined each study for potential selection, attrition, and detection bias. Studies were not excluded on the basis of poor quality, but, if data were sufficient, a sensitivity analysis was performed to compare results between studies with high vs low risk of bias.

**DATA ANALYSIS AND SYNTHESIS**

We performed a meta-analysis to combine continuous data when 2 or more randomized controlled trials (RCTs) reported outcomes of interest. We recorded the mean difference between baseline and follow-up measures for the control and intervention groups and the standard error of each difference. If the standard error of the difference for each group was not given, it was estimated assuming a correlation between baseline and follow-up of 0.75. If data were only presented in graphical form, point estimates were determined from enlargements of published graphs. If only the range was given as the measure of variation, then standard deviation was estimated as the range divided by 5.88 (99.7% confidence interval [CI] assuming a normal distribution). If the interquartile range was given, standard deviation was estimated. Pooled effects of the RCTs were determined with each study weighted by the inverse of the study variance, using a random effects model with the DerSimonian and Laird formula for calculating between-study variance. Meta-regression was performed to determine if various study-level intervention characteristics affect outcome. The meta-
regression was weighted by the inverse of the variance of the difference between each treatment group, and interaction terms were examined for all models. SAS statistical software was used for the meta-regression (version 8.02; SAS Institute Inc, Cary, NC). Cochrane Review Manager software (version 4.1.1) was used to combine data.

Sensitivity analyses were performed on the effect of attrition on weight change by altering assumptions about weight loss of participants who dropped out of the study. We also compared pooled estimates derived from abstracts combined with full-text articles with estimates from full-text articles alone.

### RESULTS

The study flow diagram is presented in Figure 1. No studies were identified that fit inclusion criteria for pseudoephedrine, ephedrine, sertaline, yohimbine, amphetamine and its derivatives, bupropion, topiramate, benzocaine, threchlorocitic acid, sertaline, and bromocriptine. There were sufficient data for analysis of fluoxetine, orlistat, and sibutramine, and the quantitative synthesis therefore focuses on RCTs of these 3 drugs.

Characteristics of the 14 eligible RCTs are given in Table 1, and these studies included 2231 participants. The follow-up intervals ranged between 8 and 52 weeks for fluoxetine, 52 and 57 weeks for orlistat, and 12 and 26 weeks for sibutramine. Most studies used a run-in period between 1 and 5 weeks, in which a placebo was given and dietary counseling started. Generally, drug treatment duration was the same as follow-up interval, although in 2 studies weight change was recorded from the beginning of the lead-in period. Only 1 study examined weight maintenance after discontinuation of the study drug. Study participants’ mean age was between 44 and 66 years across studies, and most were female. Body mass index was presented in only 4 of the studies (mean, 34 [range, 31-37]). Participants generally had poor glycemic control by current treatment standards. Most studies included subjects who were taking insulin, although 2 studies examined insulin-users exclusively. Drug dosages were very consistent among studies, except for 1 study of sibutramine that used a twice-daily dosage regimen. All studies examined continuous therapy. All studies except 1 involved a dietary intervention for both the treatment and control groups, and all the comparison groups received a placebo. The average number of contacts was 1.1 per month (range, 2-18 per month). Attrition during the run-in period ranged from 1.5% to 18% in the studies in which it was reported. In 2 studies, participants were randomized only if they had high rates of compliance for visits or pill consumption during the run-in period.

Sampling frame and subject recruitment methods were rarely described. Only 1 study described the randomization process, and no studies discussed allocation concealment. In 11 of the 14 trials, the drug manufacturer supported the study. Attrition varied considerably; the intervention group ranged from 0% to 49%, and the control group from 9% to 52%. In 4 of 13 studies in which attrition rates were reported, the control group had a higher rate than did the intervention group. Most studies were described as double-blinded (11/14), but none examined weight maintenance after discontinuation of the study drug. Study participants’ mean age was between 44 and 66 years across studies, and most were female. Body mass index was presented in only 4 of the studies (mean, 34 [range, 31-37]). Participants generally had poor glycemic control by current treatment standards. Most studies included subjects who were taking insulin, although 2 studies examined insulin-users exclusively. Drug dosages were very consistent among studies, except for 1 study of sibutramine that used a twice-daily dosage regimen. All studies examined continuous therapy. All studies except 1 involved a dietary intervention for both the treatment and control groups, and all the comparison groups received a placebo. The average number of contacts was 1.1 per month (range, 2-18 per month). Attrition during the run-in period ranged from 1.5% to 18% in the studies in which it was reported. In 2 studies, participants were randomized only if they had high rates of compliance for visits or pill consumption during the run-in period.

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Change in weight (kilograms) and glycated hemoglobin (GHB) (%) for full-text studies are shown in Figure 2 and Figure 3, and the meta-analysis results are given in Table 2. Pooled estimates for weight reduction ranged from 4.5 kg for sibutramine (3.3%) to 2.6 kg for orlistat (2.6%). Reduction of GHB ranged from 1.0% for fluoxetine to 0.4% for orlistat. Results for fluoxetine are stratified in Table 2 and Figures 2 and 3 because of the broad range of follow-up intervals and several studies examined more than 1 follow-up interval. Weight loss was slightly greater with longer follow-up intervals, but differences were small, and only 1 study examined fluoxetine for longer than 30 weeks of treatment.

We identified studies published only as abstracts that fulfilled inclusion criteria: 6 for fluoxetine, 20 for orlistat, and 7 for sibutramine. Combining data from abstracts and full-text articles did not produce significant changes in the direction or significance of results.

Using the net change in the intervention groups minus the control group, we performed a meta-regression to investigate potential interactions of weight loss, GHB, and fasting blood glucose with study level variables including follow-up interval, number of contacts between care provider and participant, and percentage attrition in the intervention group. Only follow-up interval and weight loss approached significance (P = .07).
We performed a sensitivity analysis, making 2 different assumptions about the behavior of intervention group dropouts. After excluding studies that used last-outcome-carried-forward data-reporting techniques, we had 3 sibutramine, 2 orlistat, and 5 fluoxetine studies remaining. We therefore performed the sensitivity analysis only for fluoxetine. When we assumed that none of the dropouts had a weight change, the pooled reduction was 3.0 kg (95% CI, 1.4-4.6 kg), and when we assumed that none of the dropouts had a weight change equivalent to those of the control group, the pooled reduction was also 3.0 kg (95% CI, 1.5-4.6 kg). These differed little from the pooled estimate of 4.0 kg (95% CI, 2.0-5.9 kg) for the 5 studies eligible for this analysis.35-37,39,40 We also performed a sensitivity analysis of our estimate of correlation between baseline and follow-up measures, using values of 0.25, 0.5, and 1.0. In no case was there a significant change in the result.

Sibutramine studies showed significant heterogeneity for both weight (P<.001) and GHb (P<.001). The study by Gokcel and colleagues46 used twice-daily dosing for sibutramine and had more marked improvements in both weight and GHb. The pooled effect excluding this study was a reduction in weight of 2.5 kg (93% CI, 1.8-3.2 kg) and in GHb of 0.2% (95% CI, -0.1%-0.4%).

Adverse events are summarized in Table 3, which includes information from both full-text articles and abstracts, and from RCTs as well as other study designs. Adverse events were common in all 3 drugs, both in the intervention and control groups. Rates of gastrointestinal adverse effects with orlistat were noted to be about 30% higher in the treatment group than in control groups. Tremor, somnolence, and sweating were common with sibutramine. There were no significant differences in the rates of depression, suicide attempts, or hospitalization for any of the 3 drugs. Adverse events are summarized in Table 3.

This meta-analysis provides evidence that fluoxetine, orlistat, and sibutramine can achieve modest but statistically significant short-term weight loss when used as a primary weight loss strategy. This weight loss ranged from 2.6 to 4.5 kg, or approximately 2% to 3% of initial body weight. Although the weight loss demonstrated in this review is small, evidence in general populations suggests that modest loss may have health benefits. There are positive associations between weight loss and health.
blood pressure, blood glucose, and serum lipid levels over a range of weight loss, including the magnitudes noted here.

Since treatment duration was up to 52 weeks for fluoxetine and orlistat and 26 weeks for sibutramine, the long-term effects of these drugs on weight and health outcomes in persons with type 2 diabetes remain uncertain. Across studies, participants were middle-aged, were for the most part not using insulin, and had moderately poor glycemic control. Body mass index was infrequently reported, making it difficult to characterize the degree to which participants were overweight. Since study populations might be highly selected and run-in periods eliminated noncompliant participants in some studies, our findings should be considered generalizable only to similar populations and not, for example, to the elderly.

Weight loss from pharmacotherapy in nondiabetic populations is generally also modest, ranging from 2 kg to 10 kg; weight is usually regained after discontinuation of the drug; and generally there is no difference between treatment and placebo groups several months after treatment ends. The rather small reductions in weight noted in the present review may reflect the difficulty persons with diabetes have in losing weight, including when pharmacotherapy is used.

Fluoxetine and orlistat had statistically significant effects on GHb. The reduction of 1.0% noted for fluoxetine at 8 to 16 weeks was sustained at 52 weeks in 1 study (1.8%). This reduction in GHb is encouraging given that the magnitude achieved was similar to that achieved in several large trials, in which rates of diabetes microvascular complications were reduced. However, the pharmacokinetics of fluoxetine differ from those of hypoglycemic agents, and therefore the benefits of a decrease in hemoglobin A1c level may not be identical.

Orlistat was associated with statistically significant improvements in total cholesterol, low-density lipoprotein, and triglyceride levels, which were sustained at 52 weeks follow-up. These changes in lipid levels have been noted by others, and although modest improvements, they correspond to changes associated with a decrease in the incidence of ischemic heart disease. It remains unclear whether the improved glycemic control and lipid levels noted in this review could be maintained over the long-term to influence the risk of complications as demonstrated in large trials.

Publication bias is possible in weight loss intervention studies and pharmacotherapy trials, which are often sponsored and financed by drug manufacturers. We attempted to obtain unpublished studies from the manufacturers of each of the included drugs, as well as from researchers in this field, but received no data. We tried to minimize language bias by not excluding studies based on language of publication.

The quality of individual studies in this review was fairly consistent, and common deficiencies were noted. Methods for concealing allocation were not described in any study, and randomization method was described...
in only 1. Sampling frame and the method of recruitment and selection of participants were rarely described, making it difficult to conclude from individual and pooled studies to whom the interventions can be applied.

Attrition is an important issue in weight loss studies because selective loss to follow-up has been demonstrated; higher attrition occurs among those who do not achieve a weight loss goal.\textsuperscript{63} Attrition was often very significant in the control group, particularly for orlistat, perhaps because control participants became unblinded due to fewer gastrointestinal adverse events and had weight loss expectations that were not being fulfilled. Last-outcome-carried-forward data were presented in 5 studies, which could have variable effects on measured outcomes depending on when the participant dropped out, as other researchers have noted that weight loss with pharmacotherapy tends to plateau at 6 months.\textsuperscript{58,64} Ideally, researchers would provide complete data on all subjects, including last measured weight and time and reason for attrition, particularly in studies of longer duration. The sensitivity analysis for fluoxetine demonstrates that with conservative assumptions for weight loss in the intervention dropouts, weight loss is smaller but remains statistically significant.

Orlistat, sibutramine, and fluoxetine were generally well tolerated and produced a low incidence of serious adverse events. The use of orlistat has been associated with lower levels of fat soluble vitamins and supplementation,\textsuperscript{65} although this was only evident in 1 study in this review.\textsuperscript{51} Sibutramine produced palpitations and a nonsignificant increase in pulse rate consistent with its mechanism as a reuptake inhibitor of serotonin, norepinephrine, and dopamine.\textsuperscript{66} Palpitations led to withdrawal from 1 study in 2 of 69 patients.\textsuperscript{48} Major adverse cardiovascular events were not noted, and rates of rhythm disturbances were similar in the intervention and control groups.\textsuperscript{45} We found no significant blood pressure increase with sibutramine; however, only 3 studies reported this outcome.\textsuperscript{45,46,48} Concerns have been raised about the safety of sibutramine after review of postmarketing data.\textsuperscript{67} Health Canada and a number of European countries are reviewing the safety of sibutramine, and Italy temporarily suspended marketing of the drug in March 2002 after adverse events (tachycardia, hypertension, and arrhythmias) and 2 deaths were associated with use of the drug.\textsuperscript{68} Statistically significant increases in both systolic (0.1 mm Hg) and diastolic blood pressure (2.3 mm Hg) and pulse rate (4.1 beats/min) have been noted in general obese populations after 24 months of sibutramine use.\textsuperscript{69}

In nondiabetic populations, comprehensive, intensive group behavioral programs without pharmacotherapy produce mean losses of 8 kg to 10 kg at 6 months, with a regain of 30% to 35% of weight loss at 1 year; 50% of participants have returned to baseline weight at 3 to 5 years.\textsuperscript{70,71} Brown and colleagues\textsuperscript{72} noted that dietary interventions in persons with diabetes produced a weight loss of 9 kg and behavioral programs, 3 kg, but few stud-
Fluoxetine, 24-30−wk Follow-up
Fluoxetine, 52-wk Follow-up
Sibutramine

caused moderate physical activity76 and improved lipid lev-

els61 can reduce the risk of cardiovascular disease inde-

pendent of weight change, combined interventions can

likely achieve improved health outcomes.

It is clear that obesity in persons with diabetes must be
treated aggressively in the long-term, as one would treat
any other cardiovascular disease risk factor. Various po-
tential approaches need to be examined in the future. Al-

though pharmacotherapy has been used in nondiabetic

populations for treatment lasting longer than 1 year,72 fur-

ther research is needed with long-term follow-up of large
diabetic populations. More data are needed on health out-

comes such as cardiovascular events. Populations with

broad ranges of BMI, age, and ethnicity need to be stud-

ied. Research is needed on the efficacy and safety of over-

the-counter drugs that persons with diabetes are using for

weight loss, and additional research is also needed on other
drugs that appear promising in nondiabetic populations.
Goldstein and Potvin64 have suggested that a targeted ap-

proach may be useful and that further research is needed
to identify subsets of patients who can safely achieve and
maintain long-term weight loss with initial pharmaco-

therapy. Several years ago, Blackburn and Kanders78 sug-
gested an incremental approach with repeated goal set-
tings for small amounts of weight loss; perhaps intermittent
pharmacotherapy could be used with this approach.

Further work is needed to examine whether the com-
bination of lifestyle modification and pharmacotherapy
improves the efficacy of drug therapy,79 whether such

ies examined outcomes beyond 6 months. Pharmacot-

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combinations are synergistic or additive, and what dosage schedules and sequencing of the 2 interventions are optimal. The incidence of adverse events must be carefully monitored over the long term in diabetic populations, which already have multiple risk factors for major cardiovascular and neurologic events. The advancement of research in these areas will help reduce cardiovascular disease risk factors and events for persons with type 2 diabetes.

Table 3. Adverse Events

<table>
<thead>
<tr>
<th>AE</th>
<th>Orlistat*</th>
<th>Sibutramine</th>
<th>Fluoxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Minor AEs</td>
<td>Minor AEs</td>
<td>Minor AEs</td>
</tr>
<tr>
<td>GI: events</td>
<td>65%-80% I, 37%-62% C (most mild to moderate, transient)</td>
<td>Constipation: 9%-55% I, 6%-8% C</td>
<td>Various: NSD between I and C</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Major AEs</td>
<td>Major AEs</td>
<td>Major AEs</td>
</tr>
<tr>
<td>Rhythm disturbances: NSD between groups</td>
<td>Palpitations (moderate to severe): 41% I, 29% C</td>
<td>Palpitations: 7.4% I</td>
<td>Palpitations: 3% I, 0% C</td>
</tr>
<tr>
<td>Chest pain not suggestive of angina: 7% (2/27)</td>
<td>Increase pulse rate: mean 2.4 beats/min-1 (P &lt; .05)</td>
<td>Palpitations: 22% I, 40% C</td>
<td>Hypertension: 3% (1 patient)</td>
</tr>
<tr>
<td>Palpitations (moderate to severe): 41% I, 29% C</td>
<td>Various: NSD between groups</td>
<td>Palpitations: 7% I</td>
<td>Nausea, lethargy, or excessive sweating: 20%</td>
</tr>
<tr>
<td>Minor AEs</td>
<td>Minor AEs</td>
<td>Minor AEs</td>
<td>Minor AEs</td>
</tr>
<tr>
<td>Increase pulse rate: mean 2.4 beats/min-1 (P &lt; .05)</td>
<td>Palpitations: 7.4% I</td>
<td>Palpitations: 7% I</td>
<td>Unspecified: 1%-9% I, 1%-2% C</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Minor AEs</td>
<td>Minor AEs</td>
<td>Minor AEs</td>
</tr>
<tr>
<td>Headache: 22%-32% I, 40% C</td>
<td>Dizziness, insulin, or diarrhea: 7%</td>
<td>Dizziness, hyperglycemia, nausea: 3%</td>
<td></td>
</tr>
<tr>
<td>Dizziness: 9%-14% I, 5%-13% C</td>
<td>Chest pain not suggestive of angina: 4%</td>
<td>Dizziness, hyperglycemia, nausea: 3%</td>
<td></td>
</tr>
<tr>
<td>Anxiety: 9% I, 0% C</td>
<td>Dizziness: 9%-14% I, 5%-13% C</td>
<td>Dizziness, hyperglycemia, nausea: 3%</td>
<td></td>
</tr>
<tr>
<td>Withdrawal due to AE</td>
<td>Minor AEs</td>
<td>Minor AEs</td>
<td>Minor AEs</td>
</tr>
<tr>
<td>Various: 13% I, 8% C; 10% I, 5% C (P &lt; .05)</td>
<td>Palpitations: 3% I, 0% C</td>
<td>Palpitations: 3% I, 0% C</td>
<td></td>
</tr>
<tr>
<td>Deterioration in glycemic control: 15% I, 28% C</td>
<td>Hypertension: 3% (1 patient)</td>
<td>Hypertension: 3% (1 patient)</td>
<td></td>
</tr>
<tr>
<td>GI: 4.3% I, 1.2% C; 2.6% I, 0.5% C; 0.3%</td>
<td>Palpitations: 3% I, 0% C</td>
<td>Palpitations: 3% I, 0% C</td>
<td></td>
</tr>
<tr>
<td>Minor AEs</td>
<td>Minor AEs</td>
<td>Minor AEs</td>
<td>Minor AEs</td>
</tr>
<tr>
<td>Palpitations: 3% I, 0% C</td>
<td>Hypertension: 3% (1 patient)</td>
<td>Hypertension: 3% (1 patient)</td>
<td></td>
</tr>
<tr>
<td>Dizziness: 9%-14% I, 5%-13% C</td>
<td>Palpitations: 3% I, 0% C</td>
<td>Palpitations: 3% I, 0% C</td>
<td></td>
</tr>
<tr>
<td>Anxiety: 9% I, 0% C</td>
<td>Dizziness, hyperglycemia, nausea: 3%</td>
<td>Dizziness, hyperglycemia, nausea: 3%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Minor AEs</td>
<td>Minor AEs</td>
<td>Minor AEs</td>
</tr>
<tr>
<td>Hypoglycemia: 10%-17% I, 4%-10% C</td>
<td>Serious AE: 6% I, 1% C (1/5 in I possibly drug related [somnolence, dizziness, confusion])</td>
<td>Serious AE: 6% I, 1% C</td>
<td></td>
</tr>
<tr>
<td>Decrease in vitamin E and beta carotene levels in I vs C (P &lt; .001)</td>
<td>Minor AEs</td>
<td>Serious AE: 6% I, 1% C</td>
<td></td>
</tr>
<tr>
<td>NSD in AEs between I and C (P = .75)</td>
<td>Minor AEs</td>
<td>Serious AE: 6% I, 1% C</td>
<td></td>
</tr>
<tr>
<td>Minor AEs</td>
<td>Minor AEs</td>
<td>Minor AEs</td>
<td></td>
</tr>
<tr>
<td>Drying mouth: 38% I, NR C</td>
<td>Infections (not specified): 18%-26%</td>
<td>Infections (not specified): 18%-26%</td>
<td></td>
</tr>
<tr>
<td>Increased platelet count, serum sodium: 1% (within normal range)</td>
<td>Increased platelet count, serum sodium: 1% (within normal range)</td>
<td>Increased platelet count, serum sodium: 1% (within normal range)</td>
<td></td>
</tr>
<tr>
<td>AE unspecified: 61% I, 52% C</td>
<td>AE unspecified: 61% I, 52% C</td>
<td>AE unspecified: 61% I, 52% C</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: C, control group; AE, adverse event; GI, gastrointestinal; I, intervention group; NR, not reported; NSD, no significant difference.

*There were no gallstones or renal stones and plasma levels of vitamins A, D, E, and beta carotene were normal.

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