Effect of Noninsulin Antidiabetic Drugs Added to Metformin Therapy on Glycemic Control, Weight Gain, and Hypoglycemia in Type 2 Diabetes

Olivia J. Phung, PharmD
Jennifer M. Scholle, PharmD
Mehak Talwar, BS
Craig I. Coleman, PharmD

The American Diabetes Association (ADA) recommends metformin and lifestyle modifications for initial pharmacological therapy of type 2 diabetes mellitus (DM). However, due to the progressive nature of the disease, most patients will require the use of combination pharmacological therapy to reach therapeutic goals. The ADA recommends adding a sulfonylurea or insulin when metformin monotherapy is insufficient to reach or maintain target goals. The thiazolidinedione pioglitazone may be recommended when the risk of hypoglycemia is especially undesirable, and the glucagon-like peptide-1 (GLP-1) analog exenatide may be recommended if weight loss is a major goal of therapy. Remaining drugs (glinides, α-glucosidase inhibitors [AGIs], and dipeptidyl peptidase-4 [DPP-4] inhibitors) get only cursory mention in the ADA guidelines due to limited data supporting their relative efficacy.

Much of the available literature in type 2 DM evaluates antidiabetic drugs as monotherapy or in combination with metformin. The optimal second-line drug when metformin monotherapy fails is unclear. The objective of this study was to determine the comparative efficacy, risk of weight gain, and hypoglycemia associated with noninsulin antidiabetic drugs in patients with type 2 DM not controlled by metformin alone.

The study included 27 randomized controlled trials (RCTs) with at least 3 months' duration, evaluating noninsulin antidiabetic drugs added to metformin in patients experiencing an inadequate response to maximized and stable (≥4 weeks at ≥1500 mg or maximally tolerated dose) metformin therapy. The different classes of drugs were associated with similar HbA1c reductions compared with placebo. Although use of thiazolidinediones, sulfonylureas, and glinides was associated with weight gain, glucagon-like peptide-1 analogs, α-glucosidase inhibitors, and dipeptidyl peptidase-4 inhibitors were associated with weight loss or no weight change. Sulfonylureas and glinides were associated with higher rates of hypoglycemia than placebo.

When added to maximal metformin therapy, all noninsulin antidiabetic drugs were associated with similar HbA1c reductions but differed in their associations with weight gain and risk of hypoglycemia. JAMA. 2010;303(14):1410-1418 www.jama.com

Author Affiliations: University of Connecticut School of Pharmacy, Storrs, and Drug Information Center, Hartford Hospital, Hartford, Connecticut.

Corresponding Author: Craig I. Coleman, PharmD, University of Connecticut School of Pharmacy, 80 Seymour St, Hartford, CT 06102-5037 (ccolema@harthosp.org).

Clinical Review Section Editor: Mary McGrae McDermott, MD, Contributing Editor. We encourage authors to submit papers for consideration as a Clinical Review. Please contact Mary McGrae McDermott, MD, at mmd608@northwestern.edu.

©2010 American Medical Association. All rights reserved.
drugs other than metformin. However, the efficacy of an agent may be smaller when combined with another drug compared with the agent as monotherapy. Furthermore, patients with uncontrolled disease while receiving metformin monotherapy may differ from those with uncontrolled DM while receiving other types of monotherapies either in individual patient characteristics or their disease progression, thereby affecting their response to different classes of drugs. Because the current recommendations from the ADA do not address these concerns, our goal was to evaluate the efficacy of antidiabetic drugs for second-line therapy in addition to stable doses of metformin in a mixed-treatment comparison meta-analysis. A mixed-treatment comparison method was selected specifically to allow the use of direct comparisons and the indirect estimates via a network of trials.

**METHODS**

**Study Selection**

A systematic literature search for all relevant articles through January 2010 was conducted in MEDLINE (beginning January 1950) and Cochrane CENTRAL. The search strategy combined the Medical Subject Headings and keywords metformin with terms for type 2 DM (type 2 diabetes mellitus, T2DM, noninsulin dependent diabetes, NIDDM) and for glycated hemoglobin A\(_1c\) (glycosylated hemoglobin, hemoglobin A\(_1c\), HbA\(_1c\), A\(_1c\)). No language restrictions were imposed. For our MEDLINE search, we used the Cochrane Collaboration’s Highly Sensitive Search Strategy sensitivity maximizing version for randomized controlled trials (RCTs). A manual search of references from reports of clinical trials or review articles was performed to identify additional relevant studies. When applicable, efforts were made to contact investigators for clarification or additional data. Two investigators (O.J.P. and C.I.C.) reviewed all potentially relevant articles independently.

Trials were included in the analysis if they (1) were parallel-design RCTs; (2) compared noninsulin antidiabetic drugs with either placebo or another noninsulin antidiabetic drug in addition to metformin in all treatment groups; (3) treated patients for at least 12 weeks but no more than 52 weeks after randomization; (4) included only patients who showed inadequate response to stable metformin monotherapy at randomization; and (5) reported outcomes of glycated hemoglobin A\(_1c\) (HbA\(_1c\)). For the purposes of our meta-analysis, the criterion of stable metformin monotherapy was considered met if a study included patients who received a total metformin dose of at least 1500 mg/d maintained for at least the preceding 4 weeks before randomization or if the total dose was at least 1000 mg/d for at least the preceding 4 weeks before randomization (allowing a patient to have a lower dose only if specified as the maximally tolerated dose), as long as the mean metformin dose of enrolled patients was at least 1500 mg/d during the study.

Trials that included patients not previously taking metformin monotherapy (including those receiving sulfonylureas, thiazolidinediones, or other noninsulin therapies) were eligible if they assigned patients to a metformin monotherapy titration and dose-stable period of at least 4 weeks before randomization. Trials were excluded if they evaluated the addition of more than 1 drug to metformin, participants were not considered to have inadequate response to a stable metformin monotherapy, participants were taking background therapies other than metformin, or they evaluated insulin. Although insulin is generally considered the most effective antidiabetic treatment in patients with type 2 DM, it was not evaluated in this mixed-treatment comparison because unlike other medications, it is conceivable that any degree of hyperglycemia can be corrected by insulin treatment, provided adequate doses are administered (because the therapeutic effect of insulin maintains a dose-response relationship in virtually any dose range).

**Validity Assessment**

Validity assessment was performed by using the Jadad scale. The Jadad scale assesses inherent controllers of bias by assessing randomization, double-blinding, and patient withdrawals. These individual components were assessed and an aggregate score was calculated for each included trial (0=weakest, 5=strongest). Trials scoring less than 3 were deemed to have lower methodological quality. All trials were reviewed and graded by 2 investigators (O.J.P. and J.M.S.) independently. Disagreement was resolved through discussion.

**Data Abstraction**

Two investigators (O.J.P. and J.M.S.), through use of a standardized tool, independently abstracted all data with disagreements resolved by discussion. The following information was sought from each trial: (1) author identification; (2) year of publication; (3) study design and method quality; (4) sample size; (5) inclusion/exclusion criteria; (6) duration of follow-up; (7) drug, dose, and schedule used; (8) use of concurrent lifestyle modification (diet, exercise, or both); and (9) baseline characteristics (age, sex, anthropometrics, HbA\(_1c\), duration of DM, and metformin dose). End points collected included mean change in HbA\(_1c\), number of patients achieving HbA\(_1c\) goal of less than 7%, change in weight, and incidence of hypoglycemia. In cases in which there was more than 1 published article on the same population, the longest duration of follow-up (between 12 and 52 weeks) was incorporated into the meta-analysis, although all records were maintained for determining study design characteristics.

**Statistical Analysis**

Traditional meta-analyses analyzing changes in HbA\(_1c\) and body weight as continuous variables were undertaken. Separate analyses were conducted for each class of oral antidiabetic drug. In all cases, weighted mean differences (WMDs) and associated 95% confidence intervals (CIs) were...
calculated using a DerSimonian and Laird random-effects model. Net changes in each study variable were calculated as the difference between treatment groups in the changes (baseline – follow-up) in these mean values (also referred to as the change score). In instances where variances for net changes were not reported directly, they were calculated from CIs, or individual variances. When the variance for paired differences was not reported, we calculated it from variances at baseline and at the end of follow-up.

As suggested by Follmann et al, we assumed a correlation coefficient of 0.5 between initial and final values. Achievement of HbA\textsubscript{1c} goal of less than 7% and overall hypoglycemic events were meta-analyzed as dichotomous end points, with weighted averages reported as relative risks (RRs) and associated 95% CIs. Again, a DerSimonian and Laird random-effects model was used. The likelihood of statistical heterogeneity was assessed by using the \( I^2 \) statistic (\( I^2 > 50\% \) was considered representative of important statistical heterogeneity). Traditional meta-analysis was performed by using StatsDirect statistical software version 2.4.6 (StatsDirect Ltd, Cheshire, England). \( P < .05 \) was considered statistically significant.

In addition to traditional meta-analysis, a mixed-treatment comparison meta-analysis was conducted to compare the different oral antidiabetic drug treatment classes (sulfonylureas, glinides, thiazolidinediones, AGIs, DPP-4 inhibitors, and GLP-1 analogs). Along with analyzing the direct within-trial comparisons between 2 treatments (such as thiazolidinediones vs placebo), the mixed-treatment comparison framework enables incorporation of indirect comparisons constructed from 2 trials that have 1 treatment in common, such as thiazolidinediones vs placebo and placebo vs sulfonylureas, allowing the indirect comparison of thiazolidinediones with sulfonylureas. This type of analysis safeguards the within-trial randomized treatment comparison of each trial while combining all available comparisons between treatments. Mixed-treatment comparison analyses were conducted by using a Bayesian Markov chain Monte Carlo method and fitted in the freely available Bayesian software, WinBUGS (available at http://www.mrc-bsu.cam.ac.uk/bugs). Mixed-treatment comparison methods were used to calculate the WMDs of HbA\textsubscript{1c} and body weight, and RRs for achievement of HbA\textsubscript{1c} goal of less than 7% and occurrence of hypoglycemia for all treatments relative to placebo (reference), with accompanying 95% credible intervals (Crls). In all cases, a random-effects model was fitted. Residual deviance was calculated for each outcome. Within a Bayesian framework, a residual deviance that approximates the number of unconstrained data points within the model suggests a good fit.

The degree of incoherence between mixed-treatment comparison and traditional meta-analysis results was assessed through qualitative comparison of results for each matched drug-drug comparison derived from both meta-analytic methods. In the absence of marked differences in effect size, the traditional and mixed-treatment comparison meta-analyses were considered to provide coherent results.

To assess the potential confounding effect of heterogeneity on our results, subgroup and sensitivity analyses were performed on the change in HbA\textsubscript{1c} end point, by which trials were stratified by patient or trial characteristics and data from specific trials reanalyzed. Baseline disease severity was considered by performing subgroup analysis according to baseline HbA\textsubscript{1c}, evaluating trials with baseline HbA\textsubscript{1c} of less than 8% and those with baseline HbA\textsubscript{1c} of 8% or more. Trials of shorter duration (12-24 weeks inclusive) and those of longer duration (>24 weeks) were analyzed separately in subgroup analyses. In addition, a sensitivity analysis was performed whereby the meta-analysis was reanalyzed, excluding studies with a Jadad score of less than 3.

### RESULTS

#### Study Characteristics

Of the 410 nonduplicate citations identified from the literature search, 45 full-text articles were screened for eligibility (FIGURE). Assessment of the full-text articles revealed that 2 were not parallel-design RCTs and 12 did not evaluate patients receiving a stable dose of metformin. Thirty-one articles were eligible for inclusion, representing 27 unique RCTs. Twenty-six articles reported a change in HbA\textsubscript{1c}; 13 reported HbA\textsubscript{1c} goal achieved, 15 reported a change in body weight, and 24 reported hypoglycemia. Nine studies were not included in the body weight analysis because measures of variance (SD, SE, or 95% CI) for changes in body weight were not reported in these studies. Attempts to obtain this information from authors were unsuccessful.

A total of 27 RCTs (n=11 198 participants; age range, 53-62 years; 23%-75% were men; mean [range] trial duration, 32 [12-52] weeks; and baseline HbA\textsubscript{1c} range, 6.4%-9.3%) met all of the inclusion criteria (eTable; available at http://www.jama.com) and reported outcomes (TABLE 1). eFigure 1, eFigure 2, eFigure 3, eFigure 4, and eFigure 5 illustrate the network of clinical trials according to the comparison of specific classes of noninsulin antidiabetic drugs for the overall body of literature and for each outcome evaluated.

#### Change in HbA\textsubscript{1c} and HbA\textsubscript{1c} Goal

All classes of antidiabetic drugs were associated with statistically significant reductions in HbA\textsubscript{1c} compared with placebo in both traditional and mixed-treatment comparison meta-analyses (TABLE 2, eFigure 2, and eFigure 6). In the mixed-treatment comparison meta-analysis, sulfonylureas (0.79% reduction; 95% CrI, 0.62%-0.97%), glinides (0.65% reduction; 95% CrI, 0.36%-0.97%), thiazolidinediones (0.85% reduction; 95% CrI, 0.66%-1.08%), AGIs (0.64% reduction; 95% CrI, 0.26%-1.03%),

*References 10, 12, 19, 25, 27, 28, 30, 31, 36, 40.*
DPP-4 inhibitors (0.78% reduction; 95% CrI, 0.64%-0.93%), and GLP-1 analogs (0.97% reduction; 95% CrI, 0.65%-1.30%) were associated with significant reductions in HbA1c compared with placebo. Good model fit was suggested by a calculated residual deviance similar to the number of unconstrained data points (45 and 48, respectively). Review of funnel plots and Egger weighted regression statistic P values suggested a low likelihood of publication bias in all traditional analyses (all \( P > .25 \)). Results of mixed-treatment comparison meta-analysis were coherent with results of traditional meta-analysis (eFigure 2).

All classes of antidiabetic drugs were significantly more likely to achieve the HbA1c goal compared with placebo in both traditional and mixed-treatment comparison meta-analyses (Table 2, eFigure 3, and eFigure 6). In mixed-treatment comparison meta-analysis, sulfonylureas (RR, 2.49; 95% CrI, 1.95-3.32), glinides (RR, 2.25; 95% CrI, 1.48-3.90), thiazolidinediones (RR, 2.71; 95% CrI, 1.74-3.80), DPP-4 inhibitors (RR, 2.51; 95% CrI, 2.04-3.22), and GLP-1 analogs (RR, 2.71; 95% CrI, 2.01-6.24) were associated with increased rates of achieving the HbA1c goal. However, there were insufficient data to evaluate AGIs for this outcome. Good model fit was suggested by a calculated residual deviance similar to the number of unconstrained data points (33 and 28, respectively). Results of mixed-treatment comparison meta-analysis were coherent with results of traditional meta-analysis (eFigure 3).

When evaluating the subgroup of studies in mixed-treatment comparison with baseline HbA1c of less than 8%, we found an association with greater

---

### Table 1. Outcomes Reported by RCTs Evaluating Noninsulin Antidiabetic Drugs Added to Metformin in Patients With Type 2 Diabetes

<table>
<thead>
<tr>
<th>Source</th>
<th>Follow-up, wk</th>
<th>Group</th>
<th>Change in HbA1c</th>
<th>Achieved HbA1c Goal &lt;7%</th>
<th>Change in Weight</th>
<th>Overall Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeFronzo, 2009</td>
<td>24</td>
<td>DPP-4 inhibitor</td>
<td>186 (-0.69 (0.95))</td>
<td>81/186</td>
<td>187 (-0.87 (0.9))</td>
<td>1/191</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>175 (0.13 (0.93))</td>
<td>29/175</td>
<td>176 (-0.92 (0.9))</td>
<td>1/179</td>
</tr>
<tr>
<td>Ferrannini, 2009</td>
<td>52</td>
<td>DPP-4 inhibitor</td>
<td>1118 (-0.44 (0.67))</td>
<td>603/1118</td>
<td>1118 (-0.23 (3.6))</td>
<td>23/1389</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sulfonylurea</td>
<td>1072 (-0.53 (0.65))</td>
<td>596/1072</td>
<td>1072 (1.56 (3.9))</td>
<td>224/1383</td>
</tr>
<tr>
<td>Goodman, 2009</td>
<td>24</td>
<td>DPP-4 inhibitor</td>
<td>119 (-0.66 (1.2))</td>
<td>NR</td>
<td>119 (-0.19)</td>
<td>1/125</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>117 (0.17 (1.19))</td>
<td>NR</td>
<td>117 (-0.09)</td>
<td>0/122</td>
</tr>
<tr>
<td>Nauck, 2009</td>
<td>26</td>
<td>DPP-4 inhibitor</td>
<td>210 (-0.6 (1.4))</td>
<td>92/210</td>
<td>-0.3 (0.3)</td>
<td>0/210</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>104 (-0.1 (0.2))</td>
<td>19/104</td>
<td>3/104</td>
<td></td>
</tr>
<tr>
<td>Nauck, 2009</td>
<td>26</td>
<td>GLP-1 analog</td>
<td>242 (-1.0 (1.5))</td>
<td>103/242</td>
<td>242 (-2.8 (0.2))</td>
<td>7/242</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sulfonylurea</td>
<td>242 (-1.0 (1.5))</td>
<td>88/242</td>
<td>242 (1.0 (0.2))</td>
<td>41/242</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>121 (0.1 (1.1))</td>
<td>13/121</td>
<td>121 (-1.5 (0.3))</td>
<td>4/121</td>
</tr>
</tbody>
</table>

(continued)
### Table 1. Outcomes Reported by RCTs Evaluating Noninsulin Antidiabetic Drugs Added to Metformin in Patients With Type 2 Diabetes (continued)

<table>
<thead>
<tr>
<th>Source</th>
<th>Follow-up, wk</th>
<th>Group</th>
<th>Change in HbA1c Mean (SD, %)</th>
<th>Achieved HbA1c Goal &lt;7%&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Change in Weight Mean (SD, kg)</th>
<th>Overall Hypoglycemia&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boll,16,16 2008</td>
<td>52</td>
<td>DPP-4 inhibitor</td>
<td>295 −0.6 (1.14)</td>
<td>NR</td>
<td>295 0.2 (3.44)</td>
<td>1/295</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiazolidinedione</td>
<td>281 −0.6 (1.07)</td>
<td>NR</td>
<td>281 2.6 (5.03)</td>
<td>0/281</td>
</tr>
<tr>
<td>Hamann,11 2008</td>
<td>52</td>
<td>Thiazolidinedione</td>
<td>285 −0.78 (1.01)</td>
<td>NR</td>
<td>294 2.7 (5.14)</td>
<td>19/294</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sulfonylurea</td>
<td>288 −0.86 (1.02)</td>
<td>NR</td>
<td>301 1.6 (5.20)</td>
<td>90/301</td>
</tr>
<tr>
<td>Khanolkar,18 2008</td>
<td>24</td>
<td>Thiazolidinedione</td>
<td>25 −1.19 (0.55)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sulfonylurea</td>
<td>25 −1.00 (0.67)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Raz,19 2008</td>
<td>30</td>
<td>DPP-4 inhibitor</td>
<td>95 −1 (1.49)</td>
<td>21/95</td>
<td>96 −0.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1/96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>92 0 (1.22)</td>
<td>3/92</td>
<td>94 −0.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0/94</td>
</tr>
<tr>
<td>Scott,20 2008</td>
<td>18</td>
<td>DPP-4 inhibitor</td>
<td>91 −0.73 (0.66)</td>
<td>50/91</td>
<td>94 −0.4 (1.98)</td>
<td>1/94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>88 −0.22 (0.67)</td>
<td>33/88</td>
<td>91 −0.8 (1.95)</td>
<td>2/91</td>
</tr>
<tr>
<td>Ahren,2,22 2007</td>
<td>52</td>
<td>DPP-4 inhibitor</td>
<td>42 −1.1 (0.2)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>18/42</td>
<td>42 −0.2 (0.47)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0/42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>29 0 (1.22)</td>
<td>3/29</td>
<td>21 −0.2 (0.58)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0/21</td>
</tr>
<tr>
<td>Bosi,23 2007</td>
<td>24</td>
<td>DPP-4 inhibitor</td>
<td>143 −0.9 (1.2)</td>
<td>240/382</td>
<td>−2.5 (0.28)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>29/240</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sulfonylurea</td>
<td>411 −0.66 (0.78)</td>
<td>242/411</td>
<td>187/584</td>
<td></td>
</tr>
<tr>
<td>Nauck,24 2007</td>
<td>52</td>
<td>DPP-4 inhibitor</td>
<td>453 −0.67 (1.09)</td>
<td>213/453</td>
<td>6/464</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>224 −0.02 (0.95)</td>
<td>41/224</td>
<td>187/584</td>
<td></td>
</tr>
<tr>
<td>Garber,26 2006</td>
<td>24</td>
<td>Thiazolidinedione</td>
<td>−0.4 (0.12)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>91/153</td>
<td>−1.5 (0.45)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2/153</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sulfonylurea</td>
<td>71/152</td>
<td>60/152</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ristic,2,23 2006</td>
<td>52</td>
<td>Glinide</td>
<td>110 0.13 (0.15)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>44/110</td>
<td>110 0.42&lt;sup&gt;c&lt;/sup&gt;</td>
<td>19/110</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sulfonylurea</td>
<td>99 0.1 (0.67)</td>
<td>49/99</td>
<td>99 0.91&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10/99</td>
</tr>
<tr>
<td>DeFronzo,25 2005</td>
<td>30</td>
<td>GLP-1 analog</td>
<td>113 −0.8 (1.06)</td>
<td>NR</td>
<td>113 −2.8 (3.52)</td>
<td>6/113</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>113 0.1 (1.06)</td>
<td>NR</td>
<td>113 −0.3 (3.91)</td>
<td>6/113</td>
</tr>
<tr>
<td>Feinglos,26 2005</td>
<td>16</td>
<td>Sulfonylurea</td>
<td>61 −0.65 (0.78)</td>
<td>42/61</td>
<td>61 0.4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9/61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>61 −0.18 (0.78)</td>
<td>17/61</td>
<td>61 −1.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2/61</td>
</tr>
<tr>
<td>Matthews,21 2005</td>
<td>52</td>
<td>Thiazolidinedione</td>
<td>36 −1.2 (1.84)</td>
<td>NR</td>
<td>317 1.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4/317</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sulfonylurea</td>
<td>317 1.4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NR</td>
<td>313</td>
<td>35/313</td>
</tr>
<tr>
<td>Gómez-Perez,26 2002</td>
<td>26</td>
<td>Thiazolidinedione</td>
<td>36 −1.2 (1.84)</td>
<td>NR</td>
<td>317 1.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4/317</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sulfonylurea</td>
<td>317 1.4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NR</td>
<td>313</td>
<td>35/313</td>
</tr>
<tr>
<td>Marr,22 2002</td>
<td>24</td>
<td>Glinide</td>
<td>34 −0.51 (0.12)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NR</td>
<td>160 1.0 (2.53)</td>
<td>5/160</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>34 0.3 (1.49)</td>
<td>NR</td>
<td>152 0.1 (2.47)</td>
<td>1/152</td>
</tr>
<tr>
<td>Charpentier,24 2001</td>
<td>20</td>
<td>Sulfonylurea</td>
<td>147 −0.74 (0.97)</td>
<td>NR</td>
<td>147 0.60 (2.86)</td>
<td>22/147</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>75 0.07 (1.21)</td>
<td>NR</td>
<td>75 −0.74 (2.58)</td>
<td>11/75</td>
</tr>
<tr>
<td>Van Gaal,25 2001</td>
<td>32</td>
<td>AGI</td>
<td>76 −0.21 (1.13)</td>
<td>NR</td>
<td>76 −2.5 (3.8)</td>
<td>0/76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>75 0.22 (1.17)</td>
<td>NR</td>
<td>75 −0.7 (2.5)</td>
<td>0/75</td>
</tr>
<tr>
<td>Fonseca,26 2000</td>
<td>26</td>
<td>Thiazolidinedione</td>
<td>−1.2 (0.36)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NR</td>
<td>110 1.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5/113</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>NR</td>
<td>NR</td>
<td>113 −1.2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2/113</td>
</tr>
<tr>
<td>Halimi,27 1999</td>
<td>26</td>
<td>AGI</td>
<td>59 −0.7 (1.2)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>70 0.2 (1.3)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Moses,28,29 1999</td>
<td>12</td>
<td>AGI</td>
<td>27 −1.41 (1.20)</td>
<td>16/27</td>
<td>27 2.41 (2.6)</td>
<td>9/27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>27 −0.33 (1.25)</td>
<td>5/27</td>
<td>27 −0.86 (2.65)</td>
<td>0/27</td>
</tr>
<tr>
<td>Rosenstock,30 1998</td>
<td>24</td>
<td>AGI</td>
<td>73 −0.57&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NR</td>
<td>74 −0.98&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1/74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>74 0.08&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NR</td>
<td>74 −0.88&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2/74</td>
</tr>
</tbody>
</table>

Abbreviations: AGI, α-glucosidase inhibitor; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin A1c; NR, not reported; RCTs, randomized controlled trials.

<sup>a</sup>May not add up to total sample size due to attrition.

<sup>b</sup>Reported as No./total No.

<sup>c</sup>Reported without measures of variance; could not be meta-analyzed.

<sup>d</sup>Difference between groups (referent given), given as mean (SE).

<sup>e</sup>Data provided by author via personal communication.
scores in HbA1c with sulfonylurea, glinide, thiazolidinedione, and DPP-4 inhibitor treatment compared with placebo (Table 3). In patients with baseline HbA1c of 8% or more, there was also an association with greater decreases in HbA1c with sulfonylurea, glinide, thiazolidinedione, AGI, DPP-4 inhibitor, and GLP-1 analog treatment compared with placebo. When evaluating the subgroup of studies in mixed-treatment comparison lasting 12 to 24 weeks, an association was found with greater decreases in HbA1c with sulfonylurea, glinide, thiazolidinedione, and DPP-4 inhibitor treatment compared with placebo. In studies lasting more than 24 weeks in duration, there was also an association with greater HbA1c reductions with sulfonylurea, glinide, thiazolidinedione, AGI, DPP-4 inhibitor, and GLP-1 analog treatment compared with placebo. All of the above-mentioned subgroup analyses provided results consistent with our base case analysis. With sensitivity analysis, there was no significant change from results reported above when studies with a Jadad score of less than 3 were excluded from the analysis.

**Body Weight**

Sulfonylurea, glinide, and thiazolidinedione treatments were associated with increases in body weight compared with placebo in mixed-treatment comparison, with gains in body weight of 2.06 kg (95% CI, 1.15-2.96 kg), 1.77 kg (95% CI, 0.46-3.28 kg), and 2.08 kg (95% CI, 0.98-3.17 kg), respectively (eFigure 4 and eFigure 6). There was no weight change with AGIs (WMD, -1.80 kg; 95% CI, -3.79 to 0.21 kg) or DPP-4 inhibitors (WMD, -0.14 kg; 95% CI, -0.94 to 0.63 kg). The GLP-1 analogs were associated with significant weight loss (WMD, -1.74 kg; 95% CI, -3.11 to -0.48 kg). Good model fit was suggested by a calculated residual deviance similar to the number of unconstrained data points (27 and 29, respectively). Results of mixed-treatment comparison meta-analysis were coherent with results of traditional meta-analysis (eFigure 4).

**Hypoglycemia**

In mixed-treatment comparison meta-analysis, sulfonylurea (RR, 4.57; 95% CI, 2.11-11.45) and glinide (RR, 7.50; 95% CI, 2.02-29.62) were associated with greater hypoglycemia compared with placebo. When evaluating the subgroup of studies in mixed-treatment comparison lasting 12 to 24 weeks, an association was found with greater HbA1c decreases in sulfonylurea, glinide, and thiazolidinedione treatment compared with placebo. When evaluating the subgroup of studies in mixed-treatment comparison lasting 12 to 24 weeks, an association was found with greater HbA1c decreases in sulfonylurea, glinide, and thiazolidinedione treatment compared with placebo. When evaluating the subgroup of studies in mixed-treatment comparison lasting 12 to 24 weeks, an association was found with greater HbA1c decreases in sulfonylurea, glinide, and thiazolidinedione treatment compared with placebo.

### Table 2. Results of Traditional Meta-analysis Comparing Noninsulin Antidiabetic Drugs With Placebo on Change in HbA1c, HbA1c Goal Achieved, Change in Body Weight, and Overall Hypoglycemia

<table>
<thead>
<tr>
<th>Group vs Placebo</th>
<th>% Change in HbA1c</th>
<th>HbA1c Goal Achieved</th>
<th>Change in Body Weight, kg</th>
<th>Overall Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WMD (95%CI)</td>
<td>RR (95%CI)</td>
<td>RR (95%CI)</td>
<td>RR (95%CI)</td>
</tr>
<tr>
<td>All drugs</td>
<td>-0.79 (-0.90 to -0.68)</td>
<td>10.25 (1.99 to 3.28)</td>
<td>0.14 (-1.37 to 1.65)</td>
<td>19.14 (0.89 to 2.30)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>-0.79 (-1.15 to -0.43)</td>
<td>3.38 (2.02 to 5.83)</td>
<td>1.99 (0.86 to 3.13)</td>
<td>3.26 (0.76 to 9.19)</td>
</tr>
<tr>
<td>Glinides</td>
<td>-0.71 (-1.24 to -0.18)</td>
<td>1.30 (1.47 to 7.58)</td>
<td>0.91 (0.35 to 1.46)</td>
<td>7.92 (1.45 to 43.21)</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>-1.00 (-1.62 to -0.38)</td>
<td>1.69 (1.24 to 2.33)</td>
<td>2.30 (1.70 to 2.90)</td>
<td>2.04 (0.50 to 8.23)</td>
</tr>
<tr>
<td>AGIs</td>
<td>-0.65 (-1.11 to -0.19)</td>
<td>0 NA</td>
<td>1.80 (-2.83 to -0.77)</td>
<td>2.60 (0.08 to 4.55)</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>-0.79 (-0.94 to -0.63)</td>
<td>2.44 (1.78 to 3.33)</td>
<td>-0.09 (-0.47 to 0.30)</td>
<td>0.67 (0.30 to 1.50)</td>
</tr>
<tr>
<td>GLP-1 analogs</td>
<td>-0.99 (-1.19 to -0.78)</td>
<td>1.96 (2.37 to 6.79)</td>
<td>-1.76 (-2.90 to -0.62)</td>
<td>0.94 (0.42 to 2.12)</td>
</tr>
</tbody>
</table>

Abbreviations: AGIs, α-glucosidase inhibitors; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin A1c; NA, not applicable; RR, relative risk; WMD, weighted mean difference.

### Table 3. Results of Sensitivity and Subgroup Mixed-Treatment Comparison Meta-analysis of Change in HbA1c Presented as WMD

<table>
<thead>
<tr>
<th>Group vs Placebo</th>
<th>Base Case (n = 26)</th>
<th>&lt;8% (n = 9)</th>
<th>≥8% (n = 16)</th>
<th>12-24 (n = 11)</th>
<th>&gt;24 (n = 15)</th>
<th>Jadad Score &gt;3 (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>-0.79 (-0.97 to -0.62)</td>
<td>-0.57 (-0.75 to -0.39)</td>
<td>-0.97 (-1.35 to -0.62)</td>
<td>-0.53 (-0.88 to -0.20)</td>
<td>-0.99 (-1.26 to -0.78)</td>
<td>-0.80 (-0.99 to -0.62)</td>
</tr>
<tr>
<td>Glinides</td>
<td>-0.65 (-0.97 to -0.36)</td>
<td>-0.44 (-0.85 to -0.04)</td>
<td>-0.65 (-1.10 to -0.26)</td>
<td>-0.86 (-1.15 to -0.24)</td>
<td>-0.86 (-1.38 to -0.42)</td>
<td>-0.86 (-0.99 to -0.35)</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>-0.85 (-1.08 to -0.66)</td>
<td>-0.62 (-0.88 to -0.39)</td>
<td>-1.02 (-1.30 to -0.69)</td>
<td>-0.75 (-1.14 to -0.24)</td>
<td>-0.95 (-1.27 to -0.73)</td>
<td>-0.95 (-1.14 to -0.66)</td>
</tr>
<tr>
<td>AGIs</td>
<td>-0.64 (-1.03 to -0.26)</td>
<td>NR</td>
<td>-0.65</td>
<td>NR</td>
<td>-0.63</td>
<td>-0.64</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>-0.78 (-0.93 to -0.64)</td>
<td>-0.51 (-0.69 to -0.34)</td>
<td>-0.89 (-1.11 to -0.68)</td>
<td>-0.76 (-1.02 to -0.53)</td>
<td>-0.76 (-1.13 to -0.71)</td>
<td>-0.76 (-0.94 to -0.62)</td>
</tr>
<tr>
<td>GLP-1 analogs</td>
<td>-0.97 (-1.30 to -0.65)</td>
<td>NR</td>
<td>-0.99</td>
<td>NR</td>
<td>-0.98</td>
<td>-0.97</td>
</tr>
</tbody>
</table>

Abbreviations: AGIs, α-glucosidase inhibitors; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin A1c; NR, not reported; WMD, weighted mean difference.

©2010 American Medical Association. All rights reserved.
additional meta-analysis revealed HbA1c of noninsulin antidiabetic drugs. Tra-
indirect evidence) of different classes determined the comparative efficacy on and traditional meta-analysis, we to metformin, in which HbA1c reduc-
similar to a previous meta-analysis supporting their efficacy.1 Through con-
sory mention due to the limited data remaining drug classes (glinides, AGIs, listed as tier 2 drugs. However, the re-
enatide may also be selected and are 
other comorbidities that can be af-
ected by body weight.42 Potential in-
creases in body weight due to antidia-
betic drugs may negatively influence patient health by increasing the risk of cardiovascular disease43 and should be a consideration when selecting drug therapy. Our mixed-treatment comparison meta-analysis demonstrated that the different classes of drugs provided similar reductions in HbA1c (range, 0.64%-0.97%) compared with placebo. The US Food and Drug Administra-
tion considers a margin of 0.4% to be the upper margin of noninferior-
ity between drugs.41 Despite this, the ADA guidelines do not suggest that these drugs have similar glucose-
lowering ability. The rate of HbA1c goal attainment was also similar among classes of drugs (RR range, 2.25-3.20) using mixed-treatment comparison meta-analysis, with no statistically sig-
ificant differences between noninsul-
lin antidiabetic drugs.

In addition to demonstrating com-
parative efficacy of antidiabetic drugs, our meta-analysis also evaluated their associations with hypoglycemia and weight gain. In patients with type 2 DM, many are obese or overweight and have other comorbidities that can be af-
ected by body weight.42 Potential in-
creases in body weight due to antidia-
betic drugs may negatively influence patient health by increasing the risk of cardiovascular disease43 and should be a consideration when selecting drug therapy. Our mixed-treatment comparison meta-analysis demonstrated that glinides, sulfonylureas, and thia-
zolidinediones were associated with weight gain ranging between 1.77 kg and 2.08 kg compared with placebo. Glinides and sulfonylureas likely pro-
mote weight gain by increasing insul-
in secretion. Thiazolidinediones likely promote weight gain by increasing fluid retention.44-45 Glucagon-like pep-
tide-1 analogs, AGIs, and DPP-4 in-
hibitors resulted in weight loss or no 
change in weight. Compared with sul-
fonylureas and thiazolidinediones, 
GLP-1 analogs were associated with an approximately 4-kg difference in weight, which in some patients may be close to the clinically relevant weight reduction value of 5% typically associ-
ated with decreased insulin resistance and improvements in serum lipids and blood pressure.42 Glucagon-like pep-
tide-1 analogs may promote weight loss by increasing satiety and prolonging gastric emptying time.46 α-Glucosi-
dase inhibitors likely promote weight loss by decreased caloric absorption and as a result of gastrointestinal adverse ef-
effects.3

The ADA guidelines emphasize the 
prevention of hypoglycemia as critical to the treatment strategy in type 2 DM.42 Therefore, considering a drug’s hypoglyce-
mia rate is warranted when select-
ing a drug. Although mild hypoglyce-
mia produces bothersome symptoms, excessive decrease in blood glucose is associated with complications, including coma, cardiac arrhythmias, or myocar-
dial ischemia.47 Of the studies that reported hypoglycemia, patients receiv-
ing sulfonylureas or glinides experi-
enced higher rates of hypoglycemia than placebo (RR range, 4.57-7.50). This increased risk is likely related to the increase in insulin release, which may occur independent of the presence of a glucose load.48 The remaining 
drugs did not exhibit statistically significant differences in hypoglycemia risk compared with placebo.

In addition to the efficacy and safety aspects evaluated by this meta-
analysis, considerations of contrain-
dications (eg, heart failure, renal dys-
function), other adverse effects (eg, bone fracture, pancreatitis, or cardio-
vascular, gastrointestinal, and renal dysfunction), other therapeutic ben-
efits (eg, pleiotrophic effects), or cost may guide selection of therapy. Due to the limited reporting of these outcomes in RCTs, these were not included in our traditional or mixed-
treatment comparison meta-analyses. Although DPP-4 inhibitors and GLP-1 analogs are associated with no change in weight or weight loss, they

95% CrI, 2.12-41.52) treatments were associated with increased risk of hypoglycemia compared with placebo (eFigure 5 and eFigure 6). Thiazoli-
dinediones (RR, 0.56; 95% CrI, 0.19-
1.69), AGIs (RR, 0.42; 95% CrI, 0.01-
9.00), DPP-4 inhibitors (RR, 0.63; 95% 
CrI, 0.26-1.71), and GLP-1 analogs (RR, 0.89; 95% CrI, 0.22-3.96) were not as-
associated with increased risk of hypoglycemia compared with placebo. Good model fit was suggested by a calcu-
lated residual deviance similar to the number of unconstrained data points (50 and 50, respectively). Results of mixed-treatment comparison meta-
analysis were coherent with results of traditional meta-analysis (eFigure 5).

COMMENT

The ADA recommends drug therapy for treatment of type 2 DM based on the drug’s ability to reduce hyperglyce-
mia.1 The ADA recommends that pa-
tients inadequately treated with met-
formin monotherapy (and lifestyle modification) should be initiated on either sulfonylureas or insulin.4 Piogli-
itazone and the GLP-1 analog ex-
enate may also be selected and are 
listed as tier 2 drugs. However, the re-
maining drug classes (glinides, AGIs, and DPP-4 inhibitors) get only cur-
sory mention due to the limited data supporting their efficacy.3 Through con-
ducting this mixed-treatment compar-
ison and traditional meta-analysis, we determined the comparative efficacy (comparisons resulting from direct and indirect evidence) of different classes of noninsulin antidiabetic drugs. Tra-
ditional meta-analysis revealed HbA1c reductions ranging between 0.62% and 1.00% in patients treated with various adjunctive drugs (added to inad-
quate, stable metformin) vs placebo. Patients treated with each adjunctive drug also had an increased RR of achiev-
ing an HbA1c goal of less than 7% (RR range, 1.69-3.96) compared with placebo.

Our change in HbA1c results were similar to a previous meta-analysis evaluating antidiabetic drug additions to metformin, in which HbA1c reduc-
tions ranged between 0.42% and 0.85% vs placebo.3 The previous meta-
analysis evaluated trials of sulfonyl-
ureas, glinides, thiazolidinediones, AGIs, and GLP-1 analogs, but not DPP-4 in-
hibitors.3 Furthermore, the meta-
analysis by Monami et al3 did not use methods for incorporating indirect comparisons, and therefore was un-
able to assess the comparative efficacy of drugs. Our mixed-treatment compar-
ison meta-analysis demonstrated that the different classes of drugs pro-
vided similar reductions in HbA1c (range, 0.64%-0.97%) compared with placebo. The US Food and Drug Ad-
m\n
©2010 American Medical Association. All rights reserved.
are not available as generic products. Monthly costs for sitagliptin or exenatide range between US $200 and $250, but sulfonylureas may have monthly costs as low as $5.49.

Our meta-analysis had limitations. Limitations typically observed in traditional meta-analysis, such as variations in treatment regimens or populations (heterogeneity), also apply to mixed-treatment comparison meta-analysis. Although estimates from the mixed-treatment comparison meta-analysis cannot simply be assumed accurate, we believe the reliability and robustness of our results are supported by (1) well-defined and strict inclusion and exclusion criteria, (2) observed goodness of model fit, (3) qualitative assessment demonstrating strong coherence, and (4) similarity of conclusions in subgroup and sensitivity analysis. Although many trials reported changes in body weight, data from some trials could not be metaanalyzed because measures of variance (SD, SE, or 95% CI) were not reported. The underreporting of weight outcomes in these trials may reflect an underappreciation of the effect of treatment on body weight by investigators. Associations of weight gain or loss on serum lipids or blood pressure could not be assessed in our meta-analysis because these end points were not reported. Future studies should report these end points. We could not assess the effect of AGIs on attainment of an HbA1c goal because trials evaluating AGIs did not report this end point. Therefore, we are unable to provide conclusions about the ability of AGIs to reach HbA1c goal. Another limitation of our meta-analysis is that the duration of type 2 DM in patients in the studies ranged between 4.6 and 10.7 years, which may influence the efficacy of certain classes of drugs. In particular, sulfonylureas may have decreased efficacy in patients who have had DM for at least 6 years, because of pancreatic β-cell decline that goes along with the disease progression.60 Addi-

tionally, the duration of prior metformin use may influence responsiveness to additional antidiabetic drugs, but this was not assessed due to the underreporting of this patient characteristic. Although the duration of prior metformin treatment may differ between trials, the use of randomization would likely have attenuated intrastudy variation.


References 10, 12, 19, 25, 27, 28, 30, 31, 36, 40.

©2010 American Medical Association. All rights reserved.


