Oral Antihyperglycemic Therapy for Type 2 Diabetes
Clinical Applications

Eric S. Holmboe, MD

SeVERAL CLINICAL PRACTICE GUIDELINES for type 2 diabetes are now available. All advocate a hemoglobin A1c level of less than 7%, and at least 1 organization has adopted a target of 6.5%.1-3 Despite the number of agents to choose from, Inzucchi4 notes that the only ones evaluated in randomized controlled trials with regard to clinically important outcomes are insulin, metformin, and the sulfonylureas.5,7 Two important clinical trials have demonstrated that more aggressive glycemic control in type 2 diabetic patients reduced microvascular complications. Questions remain about the effect of all the oral agents and insulin on reducing macrovascular complications.6,7

Primary care physicians provide much of the care for patients with type 2 diabetes.8 Although this article discusses primarily drug treatment, education on self-management, nutrition, and exercise is essential to help patients achieve glycemic control. Self-management training is effective in type 2 diabetes and should be recommended for all patients.9

Recommendations for the use of oral agents for each clinical situation are based on the best evidence available and accepted clinical guidelines. Informed decision making about therapy, however, must involve the patient and include a clear explanation of therapeutic-choice rationale, an assessment of his or her understanding, preferences, and barriers to care, and a discussion of the risks and benefits of each therapy.10-12 An active patient-physician partnership facilitates treatment of this complex, multifaceted disease.13 The TABLE provides a brief summary of the available oral agents and their relative costs. The BOX provides additional resources.

CLINICAL CONTEXT
Patient 1
A moderately obese 49-year-old woman (body mass index, 29 kg/m²) complains of increased thirst, polyuria, and fatigue. Her family history is pertinent for diabetes in her mother and an older brother. A random plasma glucose serum test shows a level of 480 mg/dL (26.6 mmol/L). Her serum electrolyte and anion gap levels are normal.

At this visit, the patient meets American Diabetes Association criteria for having diabetes.14 Given her symptoms and high blood glucose level, the question is whether to start an oral agent or insulin therapy. Guidelines are not prescriptive regarding the choice of the initial agent.1,3,15 One consideration in deciding whether to initiate insulin therapy or an oral agent is glucose toxicity.16,17 High

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levels of glucose are toxic to pancreatic beta cells, impairing insulin secretion in the face of relative insulin deficiency. Although not studied in a randomized controlled trial, initial treatment with insulin has been suggested to allow more rapid control of plasma glucose, recovery of beta cell function, and better subsequent response to oral agents.\textsuperscript{17,18} Additionally, insulin dosage can be adjusted quickly, facilitating more rapid control of hyperglycemia and associated symptoms.\textsuperscript{15-17} Once a stable target glucose level has been achieved, the patient may be able to begin receiving an oral agent. However, insulin therapy does require immediate patient education on injection techniques, use of a home glucose meter, and identification and treatment of hypoglycemic reactions. If available locally, certified diabetes nurse educators can be particularly helpful in this process. Deciding whether to start insulin therapy also requires assessment of the patient’s understanding and wishes.\textsuperscript{10}

When the patient is switched to an oral agent or an oral agent is used as initial therapy, guidelines suggest that either a sulfonylurea or metformin agent is appropriate. However, given that this patient is moderately obese, metformin would be the recommended initial agent.\textsuperscript{4,7,13} It tends to promote weight loss and is equally effective in lowering hemoglobin A\textsubscript{1c} compared with sulfonylurea and thiazolidinedione (TZD) agents.\textsuperscript{4} Given her degree of hyperglycemia, this patient may eventually need 2 oral agents to achieve adequate control.

### Table. Summary of Available Oral Agents and Costs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Monthly Retail Cost, $</th>
<th>Comparative Cost, $/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micronase (glyburide), 5 mg, ii bid #120</td>
<td>112</td>
<td>3-4</td>
</tr>
<tr>
<td>Diabeta (glyburide), 5 mg, ii bid #120</td>
<td>101</td>
<td>3-4</td>
</tr>
<tr>
<td>Generic glyburide, 5 mg, ii bid #120</td>
<td>52</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Glynase (micronized glyburide), 6 mg, i bid #60</td>
<td>86</td>
<td>2-3</td>
</tr>
<tr>
<td>Generic micronized glyburide, 6mg, i bid #60</td>
<td>58</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Glucotrol (glipizide), 10 mg, ii bid #120</td>
<td>111</td>
<td>3-4</td>
</tr>
<tr>
<td>Generic glipizide, 10 mg, i bid #120</td>
<td>46</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Glucotrol XL (glipizide GITS), 10 mg/d, ii #60</td>
<td>50</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Amaryl (glimipride), 4 mg/d, i #60</td>
<td>60</td>
<td>2-3</td>
</tr>
<tr>
<td>Biguanides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucophage (metformin), 500 mg, ii bid #120</td>
<td>102</td>
<td>3-4</td>
</tr>
<tr>
<td>Glucophage XR (metformin, extended release), 500 mg/d, iii #120</td>
<td>88</td>
<td>2-3</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precose, 100 mg, i tid #90</td>
<td>78</td>
<td>2-3</td>
</tr>
<tr>
<td>Glyset, 50 mg, i tid #90</td>
<td>73</td>
<td>2-3</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avandia, 4 mg, i bid #60</td>
<td>175</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Actos, 45 mg/d, i #30</td>
<td>169</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Nonsulfonylurea secretagogues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prandin (repaglinide), 2 mg, ii tid #180</td>
<td>165</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Starlix (nateglinide), 120 mg, i tid #90</td>
<td>103</td>
<td>3-4</td>
</tr>
<tr>
<td>Fixed combinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucovance (glyburide/metformin), 5 mg/500 mg, ii bid #120</td>
<td>105</td>
<td>3-4</td>
</tr>
<tr>
<td>Insulins (1 vial, 100 U)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novolin or Humulin NPH</td>
<td>24</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Lantus</td>
<td>44</td>
<td>2-3</td>
</tr>
<tr>
<td>Humalog</td>
<td>45</td>
<td>2-3</td>
</tr>
<tr>
<td>Humalog 75/25</td>
<td>46</td>
<td>2-3</td>
</tr>
</tbody>
</table>

\*Cost is based on the mean of retail costs in 2001 at 3 New Haven County, Connecticut, national chain pharmacies and is adapted from Takeda Pharmaceuticals America; bid indicates 2 times daily; tid, 3 times daily; roman numerals, the number of tablets in each dose; and numbers following a pound sign, the number of tablets in a month’s supply.

\textsuperscript{†}Add approximately $5 to $15 monthly for insulin syringes and alcohol wipes for 1 to 2 injections daily.
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43% of patients receiving triple oral
combination with metformin or a sulfo-
ylurea agent. A recent study found that
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both of which are approved for use in
combination with metformin or a sulfo-
ylurea agent. A recent study found that
43% of patients receiving triple oral
therapy (sulfonylurea, metformin, and
troglitazone) achieved a target hemoglobin
A1c value (<8%) compared with only
6% of patients taking the metformin-
sulfonylurea combination.24

Regardless of approach, the main goal
for this relatively young patient re-
mains optimal glycemic control with a
hemoglobin A1c level below 6.5%. Insulin
therapy is another reasonable op-
tion and is less expensive than adding
a TZD (Table).1,4,15 If rosiglitazone or pio-
glitazone is added, the full effect of the
TZD therapy may not be apparent for 4
to 12 weeks, but a hemoglobin A1c level
should be assessed at 3 months. Al-
though this patient is resistant to start-
ing insulin therapy, better glycemic con-
trol through insulin therapy in the
UKPDS5 and the Kumomato Trial2 led
to a reduction in microvascular compli-
cations. If the target hemoglobin A1c level
is not attained with the addition of a
TZD, then insulin therapy is the best op-
tion. Many patients will eventually re-
quire insulin therapy for adequate gly-
cemic control. In the UKPDS, for
example, approximately 10% of pa-
tients initially assigned to receive a sul-
fonylurea agent had to start receiving
insulin therapy during the trial.6 Talking
to the patient may help her overcome her
reluctance to start insulin therapy.25

Patient 4
A 72-year-old man with a history of hy-
pertension, myocardial infarction, and
New York Heart Association class II
congestive heart failure comes to the
clinician for a routine follow-up visit.
At his last visit 6 months ago, his random
blood glucose level was 180 mg/dL
(10.0 mmol/L). He was not subse-
sequently tested for a fasting blood glu-
cose level but was encouraged to lose
weight and maintain a proper diet. He
now complains of having had poly-
uria and constant thirst for the past 2
months. His random blood glucose level
is tested in your office and is 260 mg/dL
(14.4 mmol/L). His creatinine level was
1.7 mg/dL (129.63 µmol/L) 6 months
ago. The patient weighs 83.3 kg. He is
receiving spironolactone, furosemide
for his hypertension, and an angioten-
sin-converting enzyme inhibitor for
congestive heart failure. What are your
therapeutic options?

Although determining a fasting glu-
cose level and a baseline hemoglobin
A1c level will be helpful, the patient now
has symptomatic diabetes and warr-
ants pharmacologic treatment. Al-
though it appears that diet did not con-
tral his blood glucose level, reinforcing
the importance of diet and lifestyle
should still be attempted.26 Evidence ex-
ists that suggests consulting a nutrition-
ist or diabetes educator improves
glycemic control.27,28

Regarding drug therapy, there are sev-
eral important issues to consider for this
older diabetic patient. First, what should
the target hemoglobin A1c level be? No

Box. Resources for Primary Care Physicians and Patients

Guidelines
American Diabetes Association. Standards of medical care for patients with dia-

Institute for Clinical Systems Improvement (ICSI). Web site available at: http://
www.ici.org. Printed copies can be obtained from ICSI, 8009 34th Ave S, Suite
1200, Bloomington, MN 55423.


All guidelines listed above are also available at: http://www.guideline.gov (Na-
National Guideline Clearinghouse).

Organizations
American Diabetes Association, 1701 N Beauregard St, Alexandria, VA 22311.
Phone: (800) 842-6323. Information and educational brochures are available for
patients. The association has offices across the United States.

American Dietetic Association. Diabetes Care & Educational Practice Group,
216 W Jackson Blvd, Suite 800, Chicago, IL 60606. Phone: (800) 366-1655. Web
site available at: http://www.eatright.org. Good source for information about nu-
tritional therapy in diabetes.

www.hcfa.gov. The CMS concentrates on diabetes improvement efforts for Medi-
care patients. Quality of care programs for the CMS are managed across the United
States by peer-review organizations, all of which have educational material and
ongoing projects designed to help the primary care provider care for Medicare pa-
ents with type 2 diabetes.

cdc.gov/nccdphp/ddt/ddthome.htm.

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cdc.gov/nccdphp/ddt/ddthome.htm.

.nih.gov.

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outcome data for elderly diabetics exist. However, several studies have found that lower hemoglobin A1c levels are associated with lower costs for patients in all age groups, especially those with cardiovascular disease,29-31 and better control of diabetes improves the quality of life for older diabetic patients.32-34 Second, what are the appropriate oral agents for this patient? Given his underlying cardiovascular disease, metformin would be an ideal agent, but his history of congestive heart failure and elevated serum creatinine levels are absolute contraindications. Remaining agents to lower blood glucose levels are a sulfonylurea, a rapid-acting secretagogue taken with a meal, or a TZD. A major concern about starting sulfonylurea treatment in older patients is hypoglycemia, which can be profound and prolonged because of the long half-life of the second-generation agents. If a long-acting sulfonylurea is chosen, the lowest possible starting dose (eg, 2.5 mg of glipizide) should be initiated and the patient fully educated about hypoglycemic reactions and treatment. His mild renal insufficiency also places him at increased risk for hypoglycemia. If hypoglycemia is a major concern related to other underlying health issues (eg, the patient is at significant risk for falls or lives alone), a rapid-acting secretagogue taken with meals may be safer because of its shorter half-life. The disadvantage is the frequent dosing schedule required with these agents. Acarbose could be tried, but the magnitude of glucose-level reduction is less than that with other agents, the adverse gastrointestinal effects may be difficult for this older patient with congestive heart failure, and again the drug must be taken several times a day. A TZD may be prescribed but should be used only cautiously in this patient with class II congestive heart failure. Because of their propensity to expand plasma volume, TZDs are clearly contraindicated for patients with class III and IV congestive heart failure. Therefore, for this patient an oral agent may not be the best treatment and in fact may increase the risk of adverse events because of his multiple comorbidities. Despite the mild degree of hyperglycemia, insulin may be the best choice as an initial agent in this patient. It has several advantages: flexibility with regard to dose and dosing adjustments and multiple preparations that allow physicians to tailor a treatment regimen that best meets the needs and goals of the patient.

CONCLUSIONS

Decisions about treatment with oral agents require a number of important considerations, including drug efficacy and adverse effects, strength of evidence, patient preferences, cost, and effective use of nonpharmacologic therapies such as diet and exercise. Patient involvement in self-management is critical to successful glycemic control, and all therapeutic choices must involve a comprehensive dialogue and negotiation between patient and physician. Organizations to obtain resources for caring for diabetic patients are provided in the Box. For the majority of patients, the overarching goal is to lower the hemoglobin A1c level to as close to normal and as safely as possible.

REFERENCES

11. Guyatt GH, Sackett DL, Cook DJ, for the Evidence-Based Medicine Working Group. Users’ guides to the medical literature. I: how to use an article about a treatment or prevention. II: what were the results and will they help me in caring for my patients? JAMA. 1994;271:59-63.