Type 2 diabetes is a growing epidemic worldwide and remains a leading cause of cardiovascular disorders, blindness, end-stage renal failure, amputations, and hospitalizations. In diabetes we also see an increased risk of cancer, cognitive decline, chronic liver disease, and other disabling conditions. In 2008, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published a consensus algorithm for the initiation and adjustment of type 2 diabetes therapy. These two organizations have since updated their guidelines as glycemic management has become increasingly complex and new information regarding the safety, efficacy, benefits and risks of the drug classes have emerged. The 2012 recommendations focus more on a patient-centered approach to therapy and are not as algorithmic as prior guidelines. Patient-centered care is defined as “providing care that is respectful of and responsive to individual patient preferences, needs and values and ensuring that patient values guide all clinical decisions.” It is ultimately the patient that makes the decision on how to manage their lifestyle and medications, but with a shared decision-making approach, it is hoped that adherence and effectiveness will enhance outcomes.

Hemoglobin A1c remains the major focus of therapy. The ADA recommends lowering A1c to < 7.0% for most patients in order to reduce the incidence of microvascular disease. However, a more stringent target (6.0-6.5%) may be considered in highly motivated patients that are adherent, have a low risk for hypoglycemia, are newly diagnosed with the disease, have a long life expectancy and no significant cardiovascular disease (CVD). Alternatively, a less stringent A1c goal of 7.5-8.0%, or even higher, may be appropriate for older patients (>65-70 years), for patients with a history of severe hypoglycemia, limited life expectancy and other comorbid conditions, or for patients in which the target is difficult to reach despite therapy and education. Regardless of patient medical history, it is important to individualize these treatment targets to your specific patient.

In addition to individualizing treatment targets, it is also important to individualize therapeutic interventions. All patients should receive diabetes education regarding dietary changes and the importance of physical activity; however, dietary advice must also be personalized. Patients should aim for at least 150 minutes per week of moderate activity (aerobic, resistance, and flexibility training). Highly motivated patients that are near A1c goals (< 7.5%) can be given 3-6 months to make lifestyle changes before medications are implemented.

**ADA-EASD Position Statement: Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach, Glycemic Targets**

- A1c < 7.0% (mean glucose 150-160 mg/dl)
- Pre-prandial glucose < 130 mg/dl
- Post-prandial glucose < 180 mg/dl

**Individualization is key!**

- Tighter targets 6.0-6.5% younger, healthier
- Looser targets 7.5-8.0% older, co-morbidities, hypoglycemia prone
- Avoidance of hypoglycemia

(continued on page 2)
# A Patient-Centered Approach: Properties of Anti-Hyperglycemic Medications

<table>
<thead>
<tr>
<th>Class, Compound</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides (Metformin)</td>
<td>High efficacy in lowering A1c No hypoglycemia Low cost</td>
<td>GI side effects (diarrhea, cramping) Lactic acidosis risk (rare) Vitamin B12 deficiency Contraindications: CKD, acidosis, hypoxia, dehydration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoglycemia Weight gain ? Blunts myocardial ischemic preconditioning Low durability</td>
</tr>
<tr>
<td>Sulfonylureas/ (Glyburide, Glitizide, Glimepiride)</td>
<td>High efficacy in lowering A1c ↓ Microvascular risk (UKPDS) Low cost</td>
<td>Hypoglycemia Weight gain ? Blunts myocardial ischemic preconditioning High cost</td>
</tr>
<tr>
<td>Meglitinides (Repaglinide, Nateglinide)</td>
<td>↓ Postprandial glucose excursions Dosing flexibility</td>
<td>Hypoglycemia Weight gain ? Blunts myocardial ischemic preconditioning High cost</td>
</tr>
<tr>
<td>TZDs (Pioglitazone, Rosiglitazone)</td>
<td>No hypoglycemia High efficacy in lowering A1c ↑ HDL-C</td>
<td>Weight gain Edema/heart failure Bone fractures ↑ LDL-C (rosiglitazone) ↑ MI (meta-analyses, rosiglitazone) ↑ Bladder cancer (pioglitazone) High cost</td>
</tr>
<tr>
<td></td>
<td>↓ Triglycerides (pioglitazone) ↓ CVD events (ProACTIVE, pioglitazone)</td>
<td></td>
</tr>
<tr>
<td>α-Glucosidase inhibitors (Acarbose, Miglitol, Voglibose)</td>
<td>No hypoglycemia ↓ Postprandial glucose excursions ↓ CVD events (STOP-NIDDM) Nonsystemic</td>
<td>Generally modest A1c efficacy GI side effects (flatulence, diarrhea) Frequent dosing Moderate cost</td>
</tr>
<tr>
<td>DPP-4 inhibitors (Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin)</td>
<td>No hypoglycemia Well tolerated Weight neutral</td>
<td>Generally modest A1c efficacy Urticaria/angioedema ? Pancreatitis High cost</td>
</tr>
<tr>
<td>Bile acid sequestrants (Colestevlam)</td>
<td>No hypoglycemia ↓ LDL-C</td>
<td>Generally modest A1c efficacy Constipation ↑ Triglycerides May ↓ absorption of other medications High cost</td>
</tr>
<tr>
<td>Dopamine-2 agonists (Bromocriptine quick-release)</td>
<td>No hypoglycemia ↑ ↓ CVD events (Cycloset Safety Trial)</td>
<td>Generally modest A1c efficacy Dizziness/syncope Nausea Fatigue Rhinitis High cost</td>
</tr>
<tr>
<td>GLP-1 receptor agonists (Exenatide, Liraglutide)</td>
<td>No hypoglycemia Weight loss High efficacy in lowering A1c ? Potential for improved β-cell mass/function ? Cardiovascular protective actions</td>
<td>GI side effects (nausea/vomiting) ? Acute pancreatitis C-cell hyperplasia/medullary thyroid tumors in animals Injectable Training requirements High cost</td>
</tr>
<tr>
<td>Amylin mimetics (Pramlintide)</td>
<td>↓ Postprandial glucose excursions Weight reduction</td>
<td>Generally modest A1c efficacy GI side effects (nausea/vomiting) Hypoglycemia unless insulin dose is simultaneously reduced Injectable Frequent dosing High cost</td>
</tr>
<tr>
<td>Insulins (NPH, Regular, Lispro, Aspart, Glulisine, Glargine, Detemir, Premixed)</td>
<td>Highest efficacy in lowering A1c Theoretically unlimited efficacy ↓ Microvascular risk (UKPDS)</td>
<td>Hypoglycemia Weight gain ? Mitogenic effects Injectable Training requirements “Stigma” (for patients)</td>
</tr>
</tbody>
</table>
A Patient-Centered Approach:  
Management of Hyperglycemia in Type 2 Diabetes

The table on the previous page is a comparison of the advantages and disadvantages that should be taken into consideration when choosing treatments for patients with type 2 diabetes. Unless there are contraindications, metformin is the optimal first-line drug. If a person fails to reach A1c target with metformin monotherapy over approximately 3 months, there is limited data available to guide clinicians as to what therapy to choose next. At this point, patient preferences and your clinical expertise need to be considered to determine the second agent, along with susceptibilities to side effects, the potential for weight gain and risk of hypoglycemia.

Patients with a high A1c (≥9%) have a low chance of obtaining their goal with metformin monotherapy and may be started on a combination of oral agents or with insulin alone. Once patients reach an A1c value of ≥ 10.0-12.0%, insulin therapy should strongly be considered. Ultimately, many patients will end up needing insulin therapy alone or in combination with oral agents to maintain glucose control.

The position statement of the ADA and EASD outlines specific patient factors such as weight, coronary artery disease, heart failure, chronic kidney disease, liver dysfunction and hypoglycemia in order to guide patient-centered approaches. The following is a summary of their recommendations:

**Weight.** The majority of patients with type 2 diabetes are overweight or obese (~80%) and, therefore, even small changes in body weight can improve glycemic control and cardiovascular risk factors. TZDs appear to be more efficacious in patients with higher BMIs, although they have the unwanted side effect of weight gain. GLP-1 receptor agonists, however, are associated with weight reduction, and may be more favorable for obese patients.

**CAD.** Coronary artery disease (CAD) can be exacerbated by hypoglycemia which can cause myocardial ischemia, so medications that cause hypoglycemia need to be avoided in these patients. Additionally, certain sulfonylureas have been shown to aggravate myocardial ischemia but the clinical relevance of this remains unknown. Metformin may have some cardiovascular benefits and can be favorable in patients with CAD. In a single study, pioglitazone reduced cardiovascular events in patients with established macrovascular disease; however, it should not be considered in patients with heart failure. There is limited data regarding GLP-1 receptor agonists, DPP-4 inhibitors, α-glucosidase inhibitors and bromocriptine in reducing cardiovascular events.

**Heart failure.** TZDs (pioglitazone, rosiglitazone) are contraindicated in patients with heart failure. Although metformin was previously contraindicated in heart failure, it can now be used in patients with stable cardiovascular status, renal function, and/or mild ventricular dysfunction. Incretin therapies are currently being studied in heart failure.

**Chronic kidney disease.** Moderate to severe renal function (GFR < 60ml/min) occurs in about 20-30% of patients with type 2 diabetes. Patients with CKD need to be monitored for signs and symptoms of hypoglycemia and fluid retention while taking antihyperglycemic drugs with renal excretion. Current guidelines advise against metformin in patients with a serum creatinine of ≥ 1.4mg/dl in women and ≥ 1.5mg/dl in men due to its renal elimination and risk of lactic acidosis. In the UK, the National Institute for Health and Clinical Excellence (NICE) guidelines, state metformin can be used down to a GFR of 30ml/min, with a dose reduction at 45 ml/min. With CKD patients caution is advised for most insulin secretagogues, especially glburide, which has a longer duration of action and active metabolites that can accumulate in patients with chronic kidney disease. DPP-4 inhibitors (except linagliptin) need to have dose reductions. GLP-1 receptor agonists (exenatide) are contraindicated in stage 4-5 CKD (GFR < 30ml/min). All insulins are also eliminated more slowly in renal impairment, so doses need to be closely monitored. Pioglitazone is not eliminated renally and can be used in all stages of CKD, as long as the patient is monitored for fluid retention.

**Liver dysfunction.** There has been some evidence that pioglitazone may benefit patients with fatty liver, but it should not be used in active liver disease or with an alanine transaminase (ALT) level greater than 2.5 times the upper limit of normal. Sulfonylureas also can cause abnormal liver function tests, although it is rare. Secretagogues should be avoided in patients with severe liver disease, due to concerns regarding hypoglycemia. Medications that can be used in liver dysfunction include meglitinides, incretin-based drugs (in mild liver disease and no history of pancreatitis), and insulin.

Although this article presents a more patient-centered approach to type 2 diabetes treatment, there is still a need for more comparative evidence on glycemic control and patient/disease characteristics that can be used to drive therapy decision-making, especially as new medications are introduced into the market.

**Reference:**
Focus on Exenatide Extended-Release
By Ashley Savage, Pharm D Candidate

Exenatide extended-release injectable suspension (Bydureon®) is a recently approved, once weekly, GLP-1 receptor agonist for adjunctive treatment to diet and exercise for the treatment of type 2 diabetes. This adds to the growing class of GLP-1 receptor agonists. There are two products available for daily dosing exenatide and liraglutide. This is the first once weekly formulation.

**Background:** In addition to insulin resistance, patients with type 2 diabetes have a decreased “incretin response” after meals. The gut releases incretin hormones as a result of eating a meal. These hormones have been identified as glucagon-like peptide-1 (GLP-1) and glucose dependent insulonotropic peptide (GIP). GLP-1 stimulates a glucose-dependent insulin release from beta cells in the pancreas, inhibits release of glucagon from alpha cells in the liver, slows gastric emptying, and finally reduces appetite. It is thought the reduction of appetite and slowing of gastric motility contribute to weight loss in patients taking exenatide extended release.

**Mechanism of Action:** exenatide extended release is a GLP-1 receptor agonist with a microsphere delivery system allowing for extended drug delivery.

**Efficacy:** Clinical trials data have shown decreases in A1c from 1.5-1.9% with the extended release formulation. Twice daily exenatide has shown A1c decreases from 0.5-1%. On average patients lose 2.3kg over 26 weeks.

**Clinical trials:** In the DURATION trials (Diabetes therapy Utilization: Researching changes in A1C, weight and other factors Through Intervention with exenatide ONce weekly), once weekly exenatide extended release was compared with twice daily exenatide with patients who were on a combination of sulfonylurea and metformin. Exenatide extended-release showed better control of A1c then twice daily exenatide. GLP-1 agonist are add on therapies for the management of type 2 diabetes, thus it stands to reason why in clinical trials they are studied in conjunction with other commonly used medications.

**Dosing and Administration:** Supplied as 2mg of powder with a solvent that is mixed to form a suspension for injection. The dose is 2mg by subcutaneous injection once weekly. The patient may administer a missed dose as soon as noticed provided the next regularly scheduled dose is due at least three days later. The kit is pictured below.

**Adverse effects:** Similar to twice-daily exenatide, of which the most common adverse effects are nausea, vomiting, diarrhea, local injection site erythema and pruritus. GI side effects are decreased in exenatide extended-release patients but there is an increased incidence of local injection site reactions. Exenatide does not typically cause hypoglycemic episodes but can contribute to them if a patient is on a sulfonylurea.

**Noteworthy remarks:** Exenatide extended-release is listed in the FDA REMS (Risk Evaluation and Mitigation Strategies) program. There is also a boxed warning for risk of thyroid C-cell tumors, and risk for the development of acute pancreatitis. Patients at risk for thyroid cancer or acute pancreatitis should not use exenatide extended release.

**Place in Treatment:** Exenatide extended-release is an attractive, but expensive, option for patients who would benefit from weight reduction and further decreases in their A1c. It has the advantage of working 24 hours to reduce glucose levels. While it is an injectable drug, patients may be more open to just one shot per week. More post-marketing data will be needed to show its true place in treatment.

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**Goal**

The goal of the Diabetes Dispatch is to increase the reader’s knowledge of diabetes treatments and technologies and to provide the most current information on new drugs, therapies, and devices.

**ACPE #**

- Release Date: July 18, 2012
- Expiration Date : July 18, 2015
- ANMC HED Activity # 11-30010

The speakers/authors disclose that they do not have significant financial interests in any product or class of products discussed directly or indirectly in this activity, including research support.
Continuing Education Quiz  
Diabetes Dispatch: Summer 2012

1) Patient-centered care is defined as  
   a. Paternal  
   b. Ensures that patient values guide all clinical decisions  
   c. Care that is respectful and responsive to individual patient preferences, needs and values  
   d. Both b and c  

2) True or False: A1c remains the major target of therapy.  

3) What is the most appropriate A1c goal for a 75 year old patient with a history of severe hypoglycemia?  
   a. 7.5-8.0%  
   b. 7.0-7.5%  
   c. 6.5-7.0%  
   d. 6.0-6.5%  

4) Patients should aim for at least _____ minutes per week of moderate activity.  
   a. 60  
   b. 90  
   c. 120  
   d. 150  

5) Which of the following is a disadvantage of metformin?  
   a. No weight gain  
   b. GI side effects  
   c. No hypoglycemia  
   d. Low cost  

6) True or False: Sulfonylureas have high efficacy in lowering A1c.  

7) In the UK, the National Institute for Health and Clinical Excellence (NICE) guidelines, state metformin can be used down to a GFR of 30ml/min, with a dose reduction at 45 ml/min?  
   a. Yes  
   b. No  

8) Which of the following medications should be avoided in patients with pancreatitis/acute pancreatitis?  
   a. Sitagliptin  
   b. Linagliptin  
   c. Exenatide  
   d. All of the above  

9) Bydureon® decreases A1c by _________?  
   a. 0.5-1%  
   b. 1-1.5%  
   c. 1.5-1.9%  
   d. 2.0-2.5%  

10) Which are considered the most common side effects of Bydureon®:  
   a. Nausea  
   b. Vomiting  
   c. Injection site erythema  
   d. All of the above are common side effects

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5) The teaching and learning methods were effective 1 2 3 4 5  
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7) The program was presented in a fair and unbiased manner  
   Yes  No
8) Overall, I was satisfied with the activity  
   Yes  No

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