Treating Type 2 Diabetes Mellitus: a New York State Medicaid Clinical Guidance Document

Disclaimer: This document is offered as a service to New York State Prescribers to inform about the most current best practices. It does not contain treatment recommendations for type 1 diabetes mellitus or gestational diabetes mellitus. The document will be updated coincident with the availability of new information. Comments and inquiries from healthcare practitioners are welcome and may be sent to pep@nysdoh.suny.edu for prompt reply.

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Introduction

Type 2 diabetes mellitus (T2DM) is an amalgam of metabolic disorders highlighted by loss of glycemic control. T2DM often involves disorders of lipid, carbohydrate, and protein metabolism, and is associated with a host of complications including coronary artery disease, chronic kidney disease, neuropathy, and retinopathy. Type 1 diabetes mellitus (T1DM) is typically characterized as an autoimmune disorder seen earlier in life; however, adults can still develop T1DM. While T2DM is most often seen as a progressive disease occurring as persons advance in age, increasing childhood obesity rates and childhood inactivity have raised the prevalence of T2DM in pediatric populations, especially in those persons with positive family histories for T2DM and in minority populations. Most patients with T2DM will exhibit increased central obesity, resistance to insulin, and inadequate pancreatic insulin secretion. Abdominal obesity can cause additional insulin resistance. In addition to hyperglycemia and insulin resistance, many individuals with T2DM will have comitant high blood pressure and dyslipidemias. This cluster of abnormalities, known as metabolic syndrome or Syndrome X, increases the risk of developing macrovascular complications such as myocardial infarction (MI) or stroke.

The incidence and prevalence of T2DM have increased with obesity rates. In 2005, 1.5 million adults 20 years of age and older were newly diagnosed with diabetes. The number of incident cases rose to 1.6 million in 2007. Data from NHANES 1988-1994 show that the national prevalence of diabetes was 5.4%, compared to 7.7% from years 2003-2006. Diabetes seems to disproportionately affect minority American populations (see Table 1). While the prevalence has increased, the ratio of physician-diagnosed cases of diabetes to overall diabetes cases has also increased over the years, from 65% in 1988-1994 to over 75% in 2003-2006. From these data, it seems that diabetes screening and diagnosis has improved modestly. The increase in national prevalence is reflected in New York State trends (Table 2). State data from 2004 estimate over 1.1 million New Yorkers had diagnosed diabetes, and 451,000 cases were still undiagnosed. This trend is continuing. An estimate of 2008-09 data suggests that almost 1.4 million New Yorkers (9.3% of the state’s population) have been diagnosed with diabetes (excluding gestational diabetes and prediabetes).

There are two major sets of guidelines for the screening, diagnosis, treatment, and monitoring of T2DM. Goals laid out by the American Association of Clinical Endocrinologists (AACE) tend to favor stricter glycemic and metabolic control. American Diabetes Association (ADA) goals are less strict and are therefore easier for

### Table 1: Population-age-difference-adjusted national diagnosed diabetes prevalence rates, adults 20 years of age and older (2004-2006 health survey data)

<table>
<thead>
<tr>
<th>Racial/ethnic group</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic white</td>
<td>6.6%</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>11.8%</td>
</tr>
<tr>
<td>Hispanics</td>
<td>10.4%</td>
</tr>
<tr>
<td>Cuban Americans</td>
<td>8.2%</td>
</tr>
<tr>
<td>Mexican Americans</td>
<td>11.9%</td>
</tr>
<tr>
<td>Puerto Ricans</td>
<td>12.6%</td>
</tr>
<tr>
<td>American Indians*</td>
<td>16.5%</td>
</tr>
<tr>
<td>Alaska Native*</td>
<td>6.0%</td>
</tr>
<tr>
<td>Southern Arizona*</td>
<td>29.3%</td>
</tr>
</tbody>
</table>

*2005 Indian Health Service data

### Table 2: Diabetes-related parameters, New York State 1997-2004

<table>
<thead>
<tr>
<th>New York State Data</th>
<th>1997</th>
<th>1999</th>
<th>2002</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated prevalence of diagnosed diabetes</td>
<td>4.8%</td>
<td>6.0%</td>
<td>7.1%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Hospitalization rate per 1,000 people with diabetes (any cause)</td>
<td>460.3</td>
<td>399.5</td>
<td>380.7</td>
<td>385.3</td>
</tr>
<tr>
<td>Hospitalization rate per 1,000 people with diabetes (diabetes as principal cause)</td>
<td>49.9</td>
<td>41.4</td>
<td>36.5</td>
<td>35.5</td>
</tr>
<tr>
<td>Lower extremity amputations due to diabetes per 1,000 patients with diabetes</td>
<td>7.2</td>
<td>6.0</td>
<td>4.9</td>
<td>4.5</td>
</tr>
<tr>
<td>Incidence of end-stage renal disease per 1,000 patients with diabetes</td>
<td>3.6</td>
<td>3.0</td>
<td>2.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Prevalence of end-stage renal disease per 1,000 patients with diabetes</td>
<td>9.9</td>
<td>5.2</td>
<td>8.0</td>
<td>7.6</td>
</tr>
</tbody>
</table>
patients to reach.\textsuperscript{8} Despite the less strict criteria, about half of diagnosed T2DM patients in the United States remain above ADA glycemic control goals despite recent advances in pharmacotherapy, highlighting the need for optimization and personalization of antihyperglycemic medication regimens.\textsuperscript{9}

### Classification and diagnosis

T2DM is primarily a disease of insulin resistance with progressive insulin deficiency. This is in contrast to T1DM, which is characterized by an autoimmune destruction of the pancreatic beta cells and absolute lack of insulin production. T2DM is diagnosed by either a fasting plasma glucose (FPG) level or by an oral glucose tolerance test (OGTT). A FPG of \( \geq 126 \text{ mg/dL} \) or plasma glucose of \( \geq 200 \text{ mg/dL} \) two hours following a 75-gram oral glucose load constitutes a diagnosis of diabetes.\textsuperscript{8} These criteria are based on the cutoff points over which retinopathy has been shown prevalent.\textsuperscript{10} Diabetes may also be diagnosed by a random plasma glucose of \( \geq 200 \text{ mg/dL} \) when the patient is also exhibiting symptoms of hyperglycemia, such as polyuria, polydipsia, or blurred vision. The 2010 Standards of Medical Care in Diabetes released by the ADA also define a diagnosis of diabetes as a hemoglobin A\textsubscript{1C} (A1C) \( \geq 6.5\% \).\textsuperscript{11} This recommendation was new in 2010 and was based on a recent report by an international expert committee regarding the standardization of the A1C assay.\textsuperscript{12}

In the absence of overt symptoms of diabetes, FPG, OGTT, or A1C should all be repeated on a different day to confirm the diagnosis of diabetes. FPG and A1C are preferred due to greater convenience and reduced cost. If more than one test result is available for a patient on a given day, such as having a FPG \( \geq 126 \text{ mg/dL} \) and an A1C \( \geq 6.5\% \), the diagnosis of diabetes can be confirmed. In addition to the diagnosis of diabetes, patients can be designated as having prediabetes, either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). IFG is defined as FPG in the range of 100-125 mg/dL while IGT is defined as a two-hour plasma glucose in the range of 140-199 mg/dL following an OGTT.\textsuperscript{8} The ADA Standards of Care suggest patients with an A1C in the range of 5.7\% to 6.4\% are at an increased risk for the development of T2DM and should be classified as having prediabetes.\textsuperscript{8} IFG and IGT are not considered clinical conditions on their own, but rather are considered risk factors for development of diabetes and cardiovascular disease. Lifestyle modifications, specifically, loss of 5-10\% of body weight and physical activity, have demonstrated success in delaying the onset of diabetes in patients with IFG and IGT. More information on lifestyle modification is discussed below.

#### Type 2 diabetes in children and adolescents

Until the last decade or so, immune-mediated T1DM was the only type of diabetes considered to be prevalent in children and adolescents. Reports indicate that up to 45\% of children diagnosed with diabetes are now diagnosed with T2DM.\textsuperscript{13,14} To ensure that children with diabetes receive appropriate therapy, an appropriate diagnosis of T1DM or T2DM is crucial. Most children with T2DM are overweight or obese at diagnosis and present with glycosuria, polyuria, and polydipsia without ketoacidosis or weight loss. Additionally, children diagnosed with T2DM typically have at least one parent with diabetes and often have a family history of diabetes over several generations.

#### Screening for diabetes in the general population

T2DM is a well-defined disorder that is closely linked with other metabolic abnormalities, such as overweight and obesity, defined as body mass indexes (BMI) of 25-29.9 kg/m\textsuperscript{2} and \( \geq 30 \text{ kg/m}^2 \), respectively.\textsuperscript{15} Other risk factors for T2DM are listed in Figure 1. Screening is recommended in adults if the patient is overweight and has any additional risk factors.\textsuperscript{8} If screening in these patients does not result in a diagnosis of diabetes, repeat
screening is recommended at least every three years. Screening for diabetes should begin at age 45 in asymptomatic patients who do not have a risk factor for the development of T2DM.

**Figure 1: Risk factors for the development of type 2 diabetes mellitus**

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight (BMI 25-29.9 kg/m²) or obese (BMI ≥30 kg/m²)</td>
</tr>
<tr>
<td>Hypertension or being treated for hypertension</td>
</tr>
<tr>
<td>Dyslipidemia, particularly low HDL-C and high triglycerides</td>
</tr>
<tr>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Impaired fasting glucose, impaired glucose tolerance, or prediabetes</td>
</tr>
<tr>
<td>First-degree relative diagnosed with type 2 diabetes mellitus</td>
</tr>
<tr>
<td>High-risk racial or ethnic group (e.g. African American, Latino, Native American)</td>
</tr>
<tr>
<td>Females who have delivered a baby weighing &gt;9 pounds</td>
</tr>
<tr>
<td>Past diagnosis of gestational diabetes</td>
</tr>
<tr>
<td>Polycystic ovarian syndrome</td>
</tr>
<tr>
<td>Other clinical conditions associated with insulin resistance (e.g. abdominal obesity and acanthosis nigricans)</td>
</tr>
<tr>
<td>Use of drugs that increase insulin resistance (e.g. atypical antipsychotics, systemic corticosteroids)</td>
</tr>
</tbody>
</table>

**Screening for diabetes in asymptomatic youth**

The criteria for the diagnosis of diabetes in children and adolescents are the same criteria used for adults. The ADA recommends that children at an increased risk of developing diabetes should be screened every three years beginning at age 10 (or at the onset of puberty, if puberty begins at a younger age) if they meet the following criteria:

Overweight (defined as a BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height) AND having at least two of the following risk factors:

1. Family history of T2DM;
2. Race or ethnicity with increased risk of diabetes (see Figure 1);
3. Signs of insulin resistance or conditions associated with insulin resistance:
   - acanthosis nigricans
   - hypertension
   - dyslipidemia
   - polycystic ovary syndrome
   - small for gestational age birthweight;
4. Maternal history of gestational diabetes during the child’s gestation.

**Complications of diabetes**

The complications of T2DM are well-documented. Damage done to the vasculature by hyperglycemia results in micro- and macrovascular complications over time. Microvascular complications include nephropathy, retinopathy, and neuropathy. Macrovascular complications include cardiovascular disease (CVD) such as MI, peripheral vascular disease, and stroke.

**Nephropathy**

Diabetic nephropathy occurs in up to 40% of patients with T2DM and is the most common cause of end-stage renal disease (ESRD). Microalbuminuria, defined as a urine microalbumin-to-creatinine ratio of 30-299 mg/gram
in a spot urine collection is considered an early marker for diabetic nephropathy. Microalbuminuria is also a marker of increased CVD risk.\textsuperscript{16,17} Patients who progress to macroalbuminuria (urine microalbumin to creatinine ratio of \geqslant 300 mg/gram) are likely to progress to ESRD.\textsuperscript{18,19} Screening for microalbuminuria should occur annually in all patients with T2DM, starting at diagnosis.\textsuperscript{8} Serum creatinine and estimation of glomerular filtration rate (GFR) should also be monitored annually.

Several interventions have been shown to delay the onset of microalbuminuria and progression to diabetic nephropathy. The United Kingdom Prospective Diabetes Study (UKPDS) showed that control of blood glucose and blood pressure can delay the onset of microalbuminuria and reduce the risk of nephropathy.\textsuperscript{20-22} Treatment with angiotensin-converting enzyme (ACE) inhibitors have a renoprotective benefit over other antihypertensive medications, delaying the progression from micro- to macroalbuminuria and slowing the decline in GFR in patients with microalbuminuria.\textsuperscript{23-25} These medications reduce the loss of kidney function by mechanisms that extend beyond their blood pressure-lowering capabilities. Additionally, ACE inhibitors have been shown to reduce the incidence of cardiovascular outcomes in patients with diabetes.\textsuperscript{26} Angiotensin receptor blockers (ARB) are considered equally effective in preventing the progression from micro- to macroalbuminuria in patients with T2DM, though there are no head-to-head trials comparing ARBs to ACE inhibitors.\textsuperscript{27-29} If a patient cannot tolerate a medication from one of the classes, it is recommended to substitute a medication from the other class. Studies examining the benefits and risks of combination therapy with an ACE inhibitor and an ARB have yielded conflicting results. One study showed that combining an ACE inhibitor and ARB produced additional reductions in albuminuria,\textsuperscript{30} but data from the ONTARGET study suggest that the combination of an ACE inhibitor and ARB may actually cause a worsening of kidney function.\textsuperscript{31} The long-term effects of this combination have yet to be evaluated in clinical trials.\textsuperscript{29}

**Retinopathy**

Diabetic retinopathy is the most common cause of new blindness in adults aged 20-74 years.\textsuperscript{11} In addition, glaucoma, cataracts, and other disorders of the eye occur earlier and more frequently in patients with diabetes. The prevalence of retinopathy is strongly related to the duration of diabetes. Other risk factors for retinopathy are chronic hyperglycemia, hypertension, and nephropathy.\textsuperscript{32-34} Screening, in the form of a comprehensive dilated eye exam, is recommended upon diagnosis and annually thereafter for all patients with T2DM and should be performed by a trained optometrist or ophthalmologist.\textsuperscript{8} Similar to other complications of diabetes, the onset and/or progression of retinopathy can be delayed by maintaining glycemic control near normal values.\textsuperscript{20,35} Controlling blood pressure has also been shown to delay progression of retinopathy.\textsuperscript{21} Once diabetic retinopathy is diagnosed, laser photocoagulation surgery is effective in preventing vision loss. Several large-scale trials support the therapeutic benefits of this treatment.\textsuperscript{36,37}

** Neuropathy**

Diabetic neuropathy describes a wide range of clinical manifestations resulting from nerve damage due to chronic, uncontrolled blood glucose concentrations. The manifestations of neuropathy may be focal or diffuse and may affect a variety of organ systems. The most common neuropathies seen in diabetic patients are chronic sensorimotor diabetic peripheral neuropathy (DPN) and autonomic neuropathy. Early recognition and management of neuropathy is important for a variety of reasons. First, up to 50% of DPN is characterized by numbness in the extremities, which may lead to injuries of the feet due to lack of sensation. If the neuropathy is painful, multiple treatment options exist. Second, autonomic neuropathy may involve any organ system in the body. Third, autonomic neuropathy affecting the cardiovascular system can increase morbidity and mortality.
control. Some evidence from observational studies also suggests that avoidance of wide fluctuations in blood glucose is also beneficial in decreasing symptoms of DPN. While many classes of medications are used to treat DPN in practice, at this time only pregabalin and duloxetine are FDA-approved for this indication.

Patients with diabetes should have a comprehensive foot exam on an annual basis to screen for DPN. The exam may be performed by the patient’s primary care practitioner, but patients with previous diabetic foot complications may require intervention by a foot care specialist. In addition, patients should be educated on proper self-care of the feet. This should include daily foot inspection and what to look for, proper procedures for foot drying and moisturizing, proper footwear, and knowing what types of foot problems require a visit to their primary care practitioner or podiatrist.

Unlike DPN, there is no one test that can diagnose autonomic neuropathies. Instead, the signs and symptoms should be carefully screened for during the history and physical examination. Clinical manifestations of autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction or other genitourinary disturbances, “brittle diabetes,” and hypoglycemic unawareness. Each manifestation of autonomic neuropathy should be treated symptomatically with the goal of improving quality of life. For example, patients with erectile dysfunction may benefit from the use of phosphodiesterase-5 inhibitors (e.g. sildenafil) and patients with gastroparesis may benefit from a prokinetic agent such as metoclopramide.

**Cardiovascular disease**

CVD is the leading cause of morbidity and mortality in patients with T2DM. It is also the leading contributor to direct and indirect medical costs for patients with T2DM. Hypertension, dyslipidemia, and obesity, which commonly accompany diabetes, are major risk factors for CVD. Diabetes itself is an independent risk factor for the development of CVD. In order to decrease risk of CVD, comorbid conditions such as hypertension and hyperlipidemia must be addressed and managed. Antiplatelet agents, which are discussed later, are also recommended for some patients. Treatment targets for patients with hypertension and hyperlipidemia are reported in Table 12.
While reductions of microvascular complications with improved glycemic control have been well-documented in large-scale clinical trials, there is less direct evidence for reductions of macrovascular complications. In UKPDS 33, T2DM patients assigned to intensive blood glucose control (mean A1C 7.0%) showed an overall reduction in microvascular complications by 25% over subjects in a “conventional” blood glucose control group (mean A1C 7.9%).20 In contrast, the reduction in macrovascular complications (specifically MI) in the intensive control group did not reach statistical significance. The Diabetes Control and Complications Trial (DCCT), which included only patients with T1DM, had similar results;29 however, when patients from UKPDS and DCCT were followed up after 10 or more years, significant reductions in macrovascular complications were realized.22,40 These results underscore the importance of achieving glycemic control early in the course of the disease as well as controlling other cardiovascular risk factors.

Goals for patients with type 2 diabetes
The two major American organizations that have published guidelines for T2DM, ADA and AACE, have set A1C goals of below 7.0% and below 6.5%, respectively.7,8 While a general A1C goal of less than 7.0% is appropriate for most patients, there is evidence that some patients may benefit from more intensive or less intensive lowering of blood glucose (see discussion of data from trials, below). As discussed above, intensive therapy does reduce incidence of microvascular complications, and may improve macrovascular complications long-term. However, results from trials have shown that there can be more risks than benefits associated with intensive A1C lowering, specifically hypoglycemic events and increased mortality in certain patient subgroups.41-43 These recent analyses highlight the need for additional trial data regarding individualized A1C goal-setting in T2DM patients based on patient characteristics and severity and duration of disease. Data that might lead to more delineated glycemic targets for specific subsets of patients are not definitive enough at this time to divert from the suggested A1C target of less than 7.0%.

Data from trials
Intense blood glucose control can confer more risks than benefits. The ACCORD trial found greater rates of cardiovascular and all-cause mortality with intensive blood glucose lowering (mean A1C 6.4%) compared to standard treatment (mean A1C 7.5%) over a mean 3.5 years of follow-up.41 A subgroup analysis showed that patients who did not have a cardiac event prior to randomization and patients with an A1C less than or equal to 8.0% prior to the start of the study may benefit the most from intensive lowering of glucose.41 Additionally, there were higher levels of hypoglycemic events, serious adverse drug events not related to hypoglycemia, fluid retention, and weight gain in the intensive-treatment group. The ADVANCE trial found no significant differences in major macrovascular events or all-cause mortality between intensive-treatment (mean A1C 6.5%) and standard-treatment (mean A1C 7.3%) groups.42 Most of the difference in the rate of composite primary endpoint of major macro- and microvascular complications of T2DM was related to a significant decrease in new or worsening nephropathy. The intensive-treatment group had significantly higher rates of hospitalization and severe hypoglycemic events. An analysis of various subpopulations found that the intensive glucose lowering seemed to benefit those patients less than 65 years of age, a body mass index less than 28, and no history of micro- or macrovascular disease.42

Though the mean A1C was lower in the intensive-treatment group (7.0% versus 7.9% in the standard-treatment group) in UKPDS 33, there were no differences between groups in diabetes-related or all-cause mortality.20 Like the ADVANCE trial, most of the difference in the relative risk for diabetes-related endpoints was attributable to a significant reduction in microvascular endpoints. A trial in military veterans with long-standing uncontrolled
diabetes showed no significant differences in macrovascular events between intensive blood glucose control and standard control regimens.\textsuperscript{43} Contrary to the above trials, there were also no differences between groups in microvascular events, with the exception of progression of albuminuria. Adverse events (mostly hypoglycemia) occurred in 24.1\% of intensive-treatment participants and 16.7\% of standard-treatment participants.

**Lifestyle interventions for the management of type 2 diabetes**

**Weight management and physical activity**

Weight loss is a recommended intervention for all patients with T2DM or who are at risk for T2DM.\textsuperscript{44} In overweight and obese patients, a modest weight loss (5-10\% of body weight) has been shown to improve insulin resistance in addition to improvements in blood pressure and lipid parameters.\textsuperscript{45}

Physical activity has been shown to aid in weight management, improve blood glucose control, reduce cardiovascular risk, and improve well-being in patients with diabetes and may help to prevent the onset of T2DM in high-risk individuals.\textsuperscript{8,46,47} Studies examining the effect of a structured exercise program for at least eight weeks have shown an average reduction in A1C of 0.66\%, and exercise of higher intensity is associated with an even greater reduction.\textsuperscript{48,49} Aerobic activity (moderate intensity for 150 minutes per week or high intensity for 75 minutes per week) is recommended by the U.S. Department of Health and Human Services.\textsuperscript{50} Similarly, some suggest 30 minutes of exercise five days per week with no more than one day of rest between two days of activity. Patients should be assessed by a clinician prior to commencing an exercise regimen. Patients should be screened for contraindications to certain kinds of exercise or conditions that may predispose them to injury, such as uncontrolled hypertension or complications such as severe autonomic or peripheral neuropathies or proliferative retinopathy. Patients should be encouraged to be as active as they are able.

The ADA recommends consideration of bariatric surgery in some patients with diabetes and a BMI of ≥35 kg/m\textsuperscript{2}, which can result in the improvement of glycemic control.\textsuperscript{8} The long-term benefits and risks of bariatric surgery continue to be studied.

**Medical nutrition therapy (MNT)**

MNT is important in preventing diabetes, managing existing diabetes, and preventing or slowing the development of complications of diabetes. The ADA recommends that patients with prediabetes or diabetes receive individualized MNT provided by a registered dietitian.\textsuperscript{8} Studies have demonstrated that MNT is capable of decreasing A1C by 1-2\% in patients with T2DM.\textsuperscript{51,52} In addition to improving glycemic control, MNT has also been shown to decrease LDL cholesterol by 15-25 mg/dL and has a role in the management of hypertension.\textsuperscript{53,54}

**The role of dietary carbohydrates**

Dietary interventions are instrumental to glycemic control because they reduce postprandial blood glucose. Carbohydrate intake is a major determinant in postprandial blood glucose levels. While low carbohydrate diets such as Atkins™ and South Beach™ diets may seem to be an optimal alternative for patients with diabetes, diets providing fewer than 130 grams of total carbohydrates per day are not recommended.\textsuperscript{8} Carbohydrate-containing foods are important sources of energy, fiber, vitamins, and minerals. These foods are necessary components of the diabetic diet.

Postprandial blood glucose levels are determined by the rate of appearance of glucose in the bloodstream and its clearance from circulation.\textsuperscript{55} While insulin secretion normally keeps blood glucose in a narrow range, patients
with diabetes have defects in insulin secretion and/or action. This impairs the regulation of blood glucose in response to dietary carbohydrate intake. Both the quantity of carbohydrate as well as the source of carbohydrate influence blood glucose levels.

Monitoring carbohydrates is a key strategy in maintaining glycemic control. This may be achieved with carbohydrate counting, carbohydrate exchanges, or estimations based on experience. The recommended daily allowance for dietary carbohydrates, or minimum daily requirement, is 130 grams per day. Intrinsic and extrinsic variables influence the effect of dietary carbohydrates on the blood glucose. Intrinsic variables include, but are not limited to, the specific type of food ingested, type of starch, and style of food preparation. Extrinsic variables include pre-prandial blood glucose levels, available amount of insulin, and degree of insulin resistance, to name a few. Another factor influencing the effect of carbohydrates on the blood glucose is the glycemic index. The glycemic index is defined as the increase in blood glucose above fasting over two hours after ingestion of a constant amount of food (usually in a 50-gram carbohydrate serving size) divided by the response to a reference food (usually glucose or white bread). Foods with a low glycemic index tend to contain fiber, fructose, lactose, and/or fat. The general recommendation of the ADA is that the use of the glycemic index only provides a modest additional benefit over that seen when total carbohydrates are considered alone.

Figure 4: The plate method

Approximately 40-65% of total daily calories should come from carbohydrates (1 gram carbohydrate = 4 calories). Patients may count the grams of total carbohydrate in their foods or use the exchange system, where 15 grams of total carbohydrates is equal to one carbohydrate exchange, or serving. Meals may range from two to five carbohydrate servings (30-75 grams) and snacks are generally limited to one carbohydrate serving (15 grams). Another, simplified way of educating patients is to introduce the “plate method” (Figure 4), where 50% of a 9-inch plate is reserved for vegetables, 25% for carbohydrates, and 25% for protein.

Alcohol intake
In patients without contraindications to alcohol consumption, alcohol may be consumed in moderation, defined as one drink per day or less for women and two drinks per day or less for men. Alcohol can have varying effects on blood glucose. In patients taking insulin or insulin secretagogues, alcohol may cause hypoglycemia, and should therefore be consumed with food. Occasional intake of alcoholic beverages should be considered an addition to the regular meal plan and should never replace food products. In addition, the carbohydrate content of the alcoholic beverage must be accounted for, and patients should avoid alcoholic beverages with a high carbohydrate content or mixing alcohol with other beverages or foods with high carbohydrate content. Excessive alcohol intake (three or more drinks per day) on a consistent basis has been shown to contribute to hyperglycemia.

Diabetes self-management education (DSME)
Diabetes self-management education (DSME) is the process of facilitating the knowledge, skills, and abilities necessary for diabetes self-care. The purpose of DSME is to support informed decision making, self-care...
behaviors, problem solving by the patient and to improve clinical outcomes and quality of life in a cost-effective manner. The focus has shifted from the didactic transfer of information to a skills-based approach focused on patient empowerment. There are numerous studies that highlight the benefits of DSME. Some of the outcomes that have shown improvement as a result of DSME include A1C, weight (self-reported), quality of life, healthy coping, and healthcare costs. DSME is also associated with increased use of primary and preventive services and decreased use of acute, inpatient services. DSME is a service that is covered by New York State Medicaid and should be recommended for all patients with diabetes.

Pharmacologic management of type 2 diabetes
This white paper presents an algorithm (Figure 6) that is a condensed and streamlined way for clinicians to treat patients with diabetes. As shown in the algorithm, metformin is recommended as a first-line agent when initiating therapy. Keeping in mind the issues discussed below, the majority of patients will be able to use metformin with good results. Monotherapy is not always appropriate, especially if the patient’s presenting A1C is greater than 1.5% above their goal. In this instance, a sulfonylurea should also be added. Subsequent treatment decisions should be made based on A1C and SMBG readings at office visits.

Biguanides
Metformin is currently the only FDA-approved medication in this category. The primary site of action for a biguanide is at the liver, causing decreased hepatic glucose production. Secondarily, biguanides act at the level of the muscle and adipose tissue to increase glucose uptake and utilization. In addition to reducing blood glucose, metformin has additional benefits. In clinical studies, metformin alone or in combination with a sulfonylurea lowered mean fasting serum triglycerides, total cholesterol, and LDL cholesterol levels and had no adverse effects on other lipid levels. An additional non-glycemic benefit of metformin is either weight stability or modest weight loss. If a pharmacotherapeutic intervention is desired in addition to lifestyle modifications for those patients who are at very high risk of developing diabetes, metformin is the recommended drug of choice.

Metformin use is not without its risks. Certain patients may not be able to use metformin (see Figure 5). There is concern that patients with low creatinine clearance are predisposed to lactic acidosis when using metformin. Newer literature has been published to suggest that established serum creatinine and calculated creatinine clearance cut-off markers can be less stringent, thereby allowing more patients to continue to use metformin and benefit from it. A review of studies showed a weak association between metformin use and the development of lactic acidosis. There is no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of lactic acidosis or increased levels of lactate compared to other anti-hyperglycemic treatments. Though lactic acidosis is extremely rare, it is a serious metabolic complication of metformin use. When it occurs, it is fatal in approximately 50% of cases.

Gastrointestinal side effects are the most common adverse reactions reported with metformin therapy. Diarrhea led to discontinuation in 6% of patients treated with metformin immediate-release tablets. This may be

<table>
<thead>
<tr>
<th>Figure 5: Contraindications to metformin use</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Patients with renal disease or impairment</td>
</tr>
<tr>
<td>- SCr &gt;1.5mg/dl in males</td>
</tr>
<tr>
<td>- SCr &gt;1.4mg/dl in females</td>
</tr>
<tr>
<td>- CrCl &lt;60ml/min;</td>
</tr>
<tr>
<td>- Patients with congestive heart failure requiring pharmacologic management</td>
</tr>
<tr>
<td>- Acute or chronic metabolic acidosis</td>
</tr>
<tr>
<td>- Patients scheduled to receive intravenous radiocontrast media should discontinue use of metformin prior to procedure and 48 hours thereafter.</td>
</tr>
</tbody>
</table>
Figure 6: Suggested treatment algorithm for type 2 diabetes mellitus in adults

Establish goal A1C for patient

Is current A1C <1.5% above their goal A1C?

YES

Lifestyle changes + metformin

Check A1C in 3 months

Has the patient reached their goal A1C?

NO

Optimize metformin dose, check for incomplete adherence, including side effects

Check A1C in 3 months

Has the patient reached their goal A1C?

NO

Add sulfonylurea

Check A1C in 3 months

Has the patient reached their goal A1C?

YES

Optimize drug doses, check for incomplete adherence, including side effects

Check A1C in 3 months

Has the patient reached their goal A1C?

NO

Continue drug regimen, check A1C in 6 months

Optimize insulin therapy and dosing (Tables 3 and 9)

Check A1C in 3 months

Has the patient reached their goal A1C?

YES

Add rapid-acting insulin at largest meal

OR

Add GLP-1 agonist

Check A1C in 3 months

Has the patient reached their goal A1C?

NO

Add basal insulin

Check A1C in 3 months

Has the patient reached their goal A1C?

YES

NO

NO
minimized by dosing metformin with meals and/or slow dose titration (see Figure 7). Patients experiencing GI side effects with immediate-release metformin may be able to tolerate extended-release tablets without similar problems. In addition to GI side effects, decreased vitamin B-12 absorption can occur with metformin use. In controlled clinical trials of metformin, a decrease to subnormal levels of previously normal serum vitamin B-12 levels without clinical manifestation was observed in approximately 7% of patients. Such a decrease is very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B-12 supplementation. Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed at least on an annual basis.

**Figure 7: Metformin slow dosing titration schedule example**

<table>
<thead>
<tr>
<th>Week 1</th>
<th>500 mg once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>500 mg BID</td>
</tr>
<tr>
<td>Week 3</td>
<td>1000 mg AM, 500 mg PM</td>
</tr>
<tr>
<td>Week 4</td>
<td>1000 mg BID</td>
</tr>
</tbody>
</table>

**Sulfonylureas**

Sulfonylureas (SU) were the first class of orally administered drugs available to treat diabetes. SUs are considered secretagogues in that they stimulate insulin release from the beta-cells of the pancreas. SU treatment decreases plasma glucose levels but only partially corrects the insulin secretion patterns characteristic of patients with T2DM. Shapiro et al studied the effects of two months’ treatment with the SU glyburide on glucose and insulin profiles of patients previously poorly controlled on diet alone. Glyburide therapy markedly decreased fasting and 24-hour glucose levels but had almost no effect on glucose increases following meals. Therefore, this agent improved glucose control only by shifting the 24-hour profile downward. Insulin profiles demonstrated that fasting insulin levels were changed little by glyburide treatment, while insulin increments following meals showed modest improvement. Most of the improved post-meal insulin secretion occurred in the late postprandial period. These patterns suggest that the main effect of SUs is to improve the responsiveness of insulin secretion to basal and postprandial glucose levels. The typical response to SU therapy is a reduction in A1C by 1-2% and a reduction in FPG of 50-60 mg/dL.

Some minor differences do exist between the most commonly used SUs. Glipizide lowers blood sugar quicker than glyburide. However, glyburide is more potent than glipizide (meaning that lower doses of glyburide are generally needed compared to glipizide). Glinipiride and glipizide can be used in patients with renal dysfunction because they are metabolized in the liver to inactive metabolites and may be associated with a lower incidence of hypoglycemia. The dose of glipizide, however, should be reduced by half if the creatinine clearance (CrCl) falls below 50 mL/min. Glyburide should not be used when the CrCl is below 50 mL/min. As monotherapy, glyburide has been shown to maintain glycemia for only two to three years.

Hypoglycemia is the most common side effect associated with the use of SUs. Therefore, dose titration, close blood glucose monitoring, and hypoglycemic awareness is required when prescribing these agents. Weight gain (about five pounds) is common when SU therapy is initiated.

**Insulin**

Though manufactured outside of the human body with recombinant DNA technology, human insulin is an exact replica to what our bodies naturally produce. Analog insulins are molecularly similar to human insulin but engineered with slight differences that slow down or speed up their absorption. This provides alternative therapeutic choices.
Tables 4 through 8 on the following page compare the onset, peak, and duration of action of insulin formulations after subcutaneous injection. These values are approximate since many factors can affect the pharmacokinetics of insulin.\textsuperscript{70} Onset, peak, and duration of action are important factors to consider when choosing an insulin regimen because it allows the prescriber and the patient to best cover and match any hyperglycemia that may be occurring. Rapid-acting insulin analogs (insulins lispro, aspart, and glulisine) have less variability in absorption than regular insulin.\textsuperscript{71} Rapid-acting analogs may provide better postprandial glucose control and less nocturnal hypoglycemia than regular insulin, but it is unclear that these benefits translate into long-term improvements in outcome.\textsuperscript{72}

Since insulin is the oldest medication available to treat diabetes, by default we have the most experience using it. This does not necessarily translate to prescriber comfort in prescribing it. Other factors considered when using insulin are patient adherence, A1C decrease needed to reach goal, and cost. Using once-daily dosing insulin (in combination with oral anti-diabetic therapy) can have enormous benefit in getting A1C to goal.

Consider only rapid-acting insulin when bolus insulin is warranted and long-acting insulin when basal insulin is warranted. Short-acting human insulin is not recommended for bolus therapy due to its action profile and patient preference.\textsuperscript{73,74} Intermediate-acting human insulin is not recommended as basal insulin due to its action profile and variability.\textsuperscript{75} If rapid-acting insulins are to be started at each meal in a patient using an SU, the SU should be discontinued.

**Long-acting insulins**
Comparing the clinical efficacy of insulin glargine to detemir is a bit more inconclusive than just comparing their pharmacokinetic profiles. In a study that compared these once-daily glargine to twice-daily detemir, it was found that little clinical difference can be seen between these two agents, although insulin glargine did have lower mean fasting plasma glucose levels while having higher rates of nocturnal and major hypoglycemia.\textsuperscript{76}

**Insulin initiation and titration**
When a patient is started on basal insulin therapy (starting doses of 10 units or 0.2 units/kg), the dose should be adjusted using the patient’s fasting blood glucose readings (Table 3). If hypoglycemia occurs, or the fasting glucose level is <70 mg/dL, reduce bedtime dose by 4 units or 10% - whichever is greater. If post-prandial insulin is warranted based on SMBG readings, then a rapid-acting insulin is recommended. Intensive therapy with both basal and post-prandial insulin will require patient education and time management. A referral to a certified diabetes educator should be made at this time to educate the patient on carbohydrate counting. Table 9 can be used as an aid to troubleshooting insulin dosing based on SMBG. As with oral therapy, A1C should be checked every 3 months to assess overall goal attainment.

Individualization is the key to successful insulin therapy. Some basic parameters (Tables 3 and 9) can be utilized, but no two patients will be managed the same.

<table>
<thead>
<tr>
<th>Fasting blood glucose level</th>
<th>Increase insulin dose by</th>
</tr>
</thead>
<tbody>
<tr>
<td>121-140 mg/dL</td>
<td>2 units</td>
</tr>
<tr>
<td>141-160 mg/dL</td>
<td>4 units</td>
</tr>
<tr>
<td>161-180 mg/dL</td>
<td>6 units</td>
</tr>
<tr>
<td>&gt;180 mg/dL</td>
<td>8 units</td>
</tr>
</tbody>
</table>

Titration should stop if blood glucose drops below 70 mg/dL during the night

From time to time it may be prudent to convert patients from one type of insulin to another. The reasons for the need to convert will vary widely, but some of the most common can be due to clinical efficacy or cost issues. Table 10 will aid in making an insulin switch from NPH to long-acting or long-acting to long-acting.
### Table 4: Rapid-acting insulins

<table>
<thead>
<tr>
<th></th>
<th>Insulin lispro&lt;sup&gt;78&lt;/sup&gt;</th>
<th>Insulin aspart&lt;sup&gt;79&lt;/sup&gt;</th>
<th>Insulin glulisine&lt;sup&gt;80&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>15 to 30 minutes</td>
<td>10 to 20 minutes</td>
<td>10 to 15 minutes</td>
</tr>
<tr>
<td>Peak</td>
<td>30 minutes to 2.5 hours</td>
<td>40 to 50 minutes</td>
<td>1 to 1.5 hours</td>
</tr>
<tr>
<td>Duration</td>
<td>3 to 6.5 hours</td>
<td>3 to 5 hours</td>
<td>3 to 5 hours</td>
</tr>
<tr>
<td>Meal timing</td>
<td>Given within 15 minutes before or immediately after meals. Give pump bolus immediately before meal.</td>
<td>Give 5 to 10 minutes before meals. Give pump bolus immediately before meal.</td>
<td>Given within 15 minutes before or within 20 minutes after starting a meal.</td>
</tr>
</tbody>
</table>

### Table 5: Short-acting insulins

<table>
<thead>
<tr>
<th></th>
<th>Regular human insulin&lt;sup&gt;81,82&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>30 to 60 minutes</td>
</tr>
<tr>
<td>Peak</td>
<td>1 to 5 hours</td>
</tr>
<tr>
<td>Duration</td>
<td>6 to 10 hours</td>
</tr>
<tr>
<td>Meal timing</td>
<td>Given approximately 30 minutes before meals. Give pump bolus 20 to 30 minutes before a meal.</td>
</tr>
</tbody>
</table>

### Table 6: Intermediate-acting insulins

<table>
<thead>
<tr>
<th></th>
<th>NPH insulin (zinc-protamine suspension)&lt;sup&gt;83,84&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>1 to 2 hours</td>
</tr>
<tr>
<td>Peak</td>
<td>6 to 14 hours</td>
</tr>
<tr>
<td>Duration</td>
<td>16 to 24+ hours</td>
</tr>
<tr>
<td>Meal timing</td>
<td>NPH can be given separately from rapid- or short-acting insulin. In these cases, it does not have to be given with meals; it can be given in the morning and/or at bedtime.</td>
</tr>
</tbody>
</table>

### Table 7: Long-acting insulins

<table>
<thead>
<tr>
<th></th>
<th>Insulin glargine&lt;sup&gt;85&lt;/sup&gt;</th>
<th>Insulin detemir&lt;sup&gt;86&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>1.1 hours</td>
<td>0.8 to 2 hours (dose-dependent)</td>
</tr>
<tr>
<td>Peak</td>
<td>No significant peak</td>
<td>Relatively flat; 4 to 14 hours</td>
</tr>
<tr>
<td>Duration</td>
<td>24 hours</td>
<td>Dose-dependent: 12 hours for 0.2 units/kg, 20 hours for 0.4 units/kg, up to 24 hours. Binds to albumin.</td>
</tr>
<tr>
<td>Meal timing</td>
<td>Not applicable</td>
<td>Evening dose can be given at dinner or bedtime. In twice-daily regimens, it can also be given 12 hours after the morning dose.</td>
</tr>
</tbody>
</table>

### Table 8: Insulin premixtures

<table>
<thead>
<tr>
<th></th>
<th>70% NPH/30% regular&lt;sup&gt;87,88&lt;/sup&gt;</th>
<th>50% NPH/50% regular&lt;sup&gt;89&lt;/sup&gt;</th>
<th>75% insulin lispro protamine/25% insulin lispro&lt;sup&gt;90&lt;/sup&gt;</th>
<th>70% insulin aspart protamine/30% insulin aspart&lt;sup&gt;91&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>30 to 60 minutes</td>
<td>Faster than 30 minutes</td>
<td>Faster than 30 minutes</td>
<td>Faster than 30 minutes</td>
</tr>
<tr>
<td>Peak (mean)</td>
<td>4.4 hours</td>
<td>3.3 hours</td>
<td>2.6 hours</td>
<td>2.4 hours</td>
</tr>
<tr>
<td>Peak (range)</td>
<td>1.5 to 16 hours</td>
<td>2 to 12 hours</td>
<td>1 to 6.5 hours</td>
<td>1 to 4 hours</td>
</tr>
<tr>
<td>Duration (effective)</td>
<td>10 to 16 hours</td>
<td>2 to 5.5 hours</td>
<td>Up to 24 hours</td>
<td>15 to 18 hours</td>
</tr>
<tr>
<td>Duration (maximum)</td>
<td>18 to 24 hours</td>
<td>Up to 24 hours</td>
<td>Up to 24 hours</td>
<td>Up to 24 hours</td>
</tr>
<tr>
<td>Meal timing</td>
<td>Give approximately 30 minutes before meals. Individualize based on blood glucose.</td>
<td>Give within 15 minutes of a meal. Individualize based on blood glucose.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Glucagon-like peptide-1 agonists

GLP-1 agonists are also known as incretin mimetics. Incretins are peptide hormones secreted by cells in the gastrointestinal tract. The two major incretins that affect blood glucose metabolism are GLP-1 and glucose-dependent insulintropic polypeptide (GIP). They are normally secreted into the circulation in response to food intake in an effort to regulate glucose homeostasis.

T2DM is associated with GLP-1 deficiency. In normal individuals, GLP-1 binds to receptors to stimulate release of insulin from the pancreas only in the presence of elevated glucose (mealtime). GLP-1 agonists bind to incretin receptor sites, resulting in increases in glucose-dependent secretion of insulin by pancreatic beta cells. Incretin mimetics also reduce glucagon secretion and food intake and slow gastric emptying. As a patient’s
blood sugar normalizes, insulin release slows. Thus, hypoglycemia is possible with GLP-1 agonists, but is not overly common.

Exenatide is the oldest product in this category, gaining FDA approval in 2005. A second agent in the category, liraglutide, was released to market in early 2010. Both agents are injectable, however exenatide requires twice-daily dosing while liraglutide is once-daily. The most common side effects include GI upset which tends to diminish over time. Weight loss can also be seen with these agents.

Table 9: General approaches to adjusting insulin dose

<table>
<thead>
<tr>
<th>Problem</th>
<th>Cause</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting hyperglycemia</td>
<td>Not enough basal insulin at bedtime OR</td>
<td>Check 3 a.m. blood sugar. If high, increase bedtime basal insulin. If low, decrease basal insulin at bedtime.</td>
</tr>
<tr>
<td></td>
<td>Too much basal insulin at bedtime (rebound from overnight hypoglycemia)</td>
<td></td>
</tr>
<tr>
<td>Pre-lunch hyperglycemia</td>
<td>Not enough rapid-acting insulin at breakfast OR</td>
<td>Increase amount of rapid-acting insulin at breakfast – adjust correction dose or the insulin-to-carbohydrate ratio OR Increase morning NPH.</td>
</tr>
<tr>
<td></td>
<td>Not enough morning NPH</td>
<td></td>
</tr>
<tr>
<td>Pre-supper hyperglycemia</td>
<td>Not enough rapid-acting insulin at lunch OR</td>
<td>Increase amount of rapid-acting insulin at lunch – adjust correction dose or the insulin-to-carbohydrate ratio OR Increase morning NPH.</td>
</tr>
<tr>
<td></td>
<td>Not enough morning NPH</td>
<td></td>
</tr>
<tr>
<td>Bedtime hyperglycemia</td>
<td>Not enough rapid-acting insulin at supper</td>
<td>Increase amount of rapid-acting insulin at supper – adjust correction dose or the insulin-to-carbohydrate ratio.</td>
</tr>
<tr>
<td>Fasting or nocturnal hypoglycemia</td>
<td>Too much basal insulin at bedtime</td>
<td>Decrease bedtime NPH or basal insulin.</td>
</tr>
<tr>
<td>Pre-lunch hypoglycemia</td>
<td>Too much rapid-acting insulin at breakfast OR</td>
<td>Decrease amount of rapid-acting insulin at breakfast OR Decrease morning NPH.</td>
</tr>
<tr>
<td></td>
<td>Too much morning NPH</td>
<td></td>
</tr>
<tr>
<td>Pre-supper or bedtime hypoglycemia</td>
<td>Too much rapid-acting insulin at lunch or supper</td>
<td>Decrease amount of rapid-acting insulin at lunch or supper</td>
</tr>
</tbody>
</table>

Table 10: Tips for insulin conversion

| NPH to insulin detemir       | • Convert unit-per-unit. 86                                               |
|                              | • Some patients on basal-bolus insulin may require more detemir than NPH. 86 |
|                              | • Give detemir once daily, or divided twice daily if necessary for control. 86 |
|                              | • Do not mix detemir with other insulins. 86                              |
| NPH to insulin glargine      | • NPH once daily: convert unit-per-unit and give once daily. 85          |
|                              |   • If hypoglycemia is present, reduce dose by 20%.                      |
|                              |   • NPH twice daily: reduce daily dose by 20% and give once daily. 85     |
|                              | • Do not mix glargine with other insulins. 85                             |
| Insulin detemir to insulin glargine | • Convert unit-per-unit. 92,93                                        |
|                              | • Give once daily, or divided twice daily if necessary for control. 94    |
|                              | • A lower daily dose may be needed. 95                                   |
|                              | • Do not mix glargine with other insulins. 85                             |
| Insulin glargine to insulin detemir | • Convert unit-per-unit. 86,92,93                                       |
|                              | • Give once daily, or divided twice daily if necessary for control. 86    |
|                              | • A higher daily dose may be needed, especially if divided twice daily. 95|
|                              | • Do not mix detemir with other insulins. 86                             |

Treating Type 2 Diabetes Mellitus: A New York State Medicaid Clinical Guidance Document
Other medications
There are several other classes of medications that are available for the treatment of T2DM. These medications are considered as second-line agents, to be used if the above treatments are contraindicated or not well-tolerated.

Meglitinides
Meglitinides are indicated as an adjunct to diet and exercise to lower blood glucose in patients with T2DM. In addition, they are also indicated for use in combination therapy with metformin and thiazolidinediones (TZD). Meglitinides stimulate insulin release from pancreatic beta cells. The extent of insulin release appears to be glucose-dependent with an increase in insulin secretion during episodes of hyperglycemia and diminishing insulin secretion at lower glucose levels. The drugs in this class are unique because they are relatively short-acting. Thus, they are used to target post-meal glucose spikes by reducing prandial glucose elevations.

Repaglinide may be taken two to four times a day and should have the dose slowly increased over time, while nateglinide is typically taken three times a day with each main meal and needs no dose adjustment. To reduce the risk for low blood sugar, meglitinides are to be taken up to 30 minutes before meals, and those who skip meals should also skip their scheduled dose of the drug.

Based on pharmacokinetic profiles, nateglinide has a quicker onset lowering blood glucose levels after meals than repaglinide; however, the clinical implications of this are unknown. Meglitinides may be advantageous in individuals who have sporadic meal schedules or who do not eat regular, full meals, since the dose may be omitted if a meal is skipped. Since meglitinides and SUs both stimulate pancreatic beta cells to produce insulin, patients having a poor response to SU therapy are not likely to respond if a meglitinide is added. However, if a patient is experiencing hypoglycemia with an SU, then a switch to a meglitinide may be warranted.67,96

Alpha-glucosidase inhibitors
Acarbose and miglitol are the only available alpha-glucoaldase inhibitors (AGI). Miglitol is only indicated to be used in combination with an SU, while acarbose can be used with SUs, metformin, and insulin. Both AGIs appear to be similar in their ability to lower blood glucose levels after meals (50-60 mg/dL).

In contrast to SUs and meglitinides, AGIs exert their antihyperglycemic effect from a reversible inhibition of membrane-bound intestinal alpha-glucoside hydrolase enzymes. In addition, acarbose also reversibly inhibits pancreatic alpha-amylase. Membrane-bound intestinal alpha-glucosidases hydrolyze oligosaccharides and disaccharides to glucose and other monosaccharides in the brush border of the small intestine. Both acarbose and miglitol cause a delay in glucose absorption and therefore lower postprandial hyperglycemia. AGIs are taken three times daily with the start of each main meal. Both acarbose and miglitol are typically started at the lowest possible dose and titration should be individualized based on effectiveness and tolerance of adverse events. Dose increases should be slow in order to minimize side effects. Upwards of 25-45% of patients discontinue use of these agents due to GI side effects including flatulence and stomach upset.67,97 Low blood sugar should be treated with glucose if hypoglycemia occurs while a patient is using an AGI, as more complex carbohydrates will not be absorbed.

Thiazolidinediones
TZDs make up a unique class of drugs that act primarily by increasing insulin sensitivity of the skeletal muscle and adipose tissue. Secondarily they work to decrease hepatic glucose production. The ability of these drugs to
lower blood glucose is dependent on the presence of insulin. When using a TZD, it may take two weeks to see a reduction in blood glucose and two to three months to see full effect.\textsuperscript{98,99} Pioglitazone and rosiglitazone are the only two TZDs marketed in the United States.

TZD treatment may also have effects on lipid parameters. Rosiglitazone as monotherapy was associated with increases in total cholesterol, LDL, and HDL and a decrease in free fatty acids. The change in triglycerides during therapy with rosiglitazone was variable and generally not statistically different from placebo.\textsuperscript{67,98} In studies, patients treated with pioglitazone had mean decreases in triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol.\textsuperscript{67,99}

When used alone or in combination with any other antidiabetic agent (including insulin), TZDs can cause fluid retention, which can lead to or exacerbate heart failure. Post-marketing cases of heart failure have been reported in patients both with and without previously known heart disease using pioglitazone or rosiglitazone. Patients with New York Heart Association (NYHA) class III and IV cardiac status were not studied during pre-approval clinical trials. For these reasons, TZDs should not be prescribed for heart failure patients.\textsuperscript{98,99} Patients should be monitored for signs and symptoms of heart failure, and the TZD should be discontinued if any deterioration in cardiac status occurs. In addition to weight gain caused by fluid retention, TZDs can also cause weight gain via increases in subcutaneous adipose tissue.

In the summer of 2010, an FDA Advisory Panel reviewed the use of rosiglitazone (Avandia\textsuperscript{®}) and whether it should be removed from market. The FDA permitted that the drug be allowed to remain available if the following actions were taken: (1) develop a restricted access program under a Risk Evaluation and Mitigation Strategy (REMS); (2) document in the patients’ medical record that complete risk information was provided; (3) documentation by the health care provider that the patient either currently uses rosiglitazone or they want to start using it instead of pioglitazone; (4) the physician, pharmacist and patient will need to be enrolled in the restricted access program.\textsuperscript{100} In addition to aforementioned restrictions, pharmacists are still required to provide patients with a medication guide with every rosiglitazone prescription. Pioglitazone does not have to comply with a restricted access program but a medication guide is required to be dispensed with the drug. Combination products containing rosiglitazone require the same oversight and reporting as the stand-alone drug.

\textit{Dipeptidyl peptidase-4 (DPP-4) inhibitors}

GLP-1 and GIP are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4). Agents in this class inhibit the DPP-4 enzyme, thereby allowing GLP-1 and GIP to circulate freely. The potential for this class of drugs to interfere with the immune response is of concern as upper respiratory tract infections have been reported with their use.

\textit{Amylin analogs}

Pramlintide is a synthetic analog of amylin. Amylin is a hormone that is normally secreted at the same time as insulin. Since amylin concentrations would be directly affected based on how much insulin was being produced, one can conclude that a T1DM patient would have no naturally occurring amylin and T2DM patients would have diminished levels. Pramlintide does require multiple daily pre-meal injections. Gastrointestinal upset and hypoglycemia are its major side effects. Currently, it has FDA approval for use only in combination with insulin in either a T1DM or T2DM patient.
Table 11: Expected A1C decrease of various interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Expected A1C decrease as monotherapy (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle management/MNT</td>
<td>1.0 – 2.0</td>
<td>Broad benefits</td>
<td>Insufficient for most within first year</td>
</tr>
<tr>
<td>Metformin</td>
<td>1.0 – 2.0</td>
<td>Weight neutral/modest weight loss</td>
<td>GI side effects; contraindicated with renal insufficiency</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.0 – 2.0</td>
<td>Rapidly effective</td>
<td>Weight gain; hypoglycemia</td>
</tr>
<tr>
<td>Insulin</td>
<td>&gt;1.5</td>
<td>No dose limit</td>
<td>Multiple injections; weight gain; hypoglycemia; analogs are expensive</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>0.5 – 1.0</td>
<td>Weight loss</td>
<td>Multiple daily injections (exenatide); GI side effects; expensive</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>0.5 – 1.5</td>
<td>Rapidly effective</td>
<td>Weight gain; multiple daily dosing; expensive</td>
</tr>
<tr>
<td>AGIs</td>
<td>0.5 – 0.8</td>
<td>Weight neutral</td>
<td>GI side effects; multiple daily dosing; expensive</td>
</tr>
<tr>
<td>TZDs</td>
<td>0.5 – 1.4</td>
<td>Improved lipid profile</td>
<td>Fluid retention; CHF; weight gain; bone fractures; MI (rosiglitazone)</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>0.5 – 0.8</td>
<td>Weight neutral</td>
<td>Expensive</td>
</tr>
</tbody>
</table>

**Treatment of diabetes in children and adolescents**

The pathophysiology of T2DM in children and adolescents appears to be similar to the pathophysiology of T2DM in adults. Therefore, it is a reasonable assumption that pharmacotherapy used for adults with diabetes would also be effective in children with diabetes. Other than insulin and immediate-release metformin, however, no other diabetes medication is FDA-approved for use in children, which means that little efficacy and safety data are available.

Treatment goals for children with diabetes are not entirely clear. The ADA does not give specific treatment targets, but rather states that patients should achieve blood glucose and A1C levels as close to normal as possible.\textsuperscript{13} When targets are set for near-normal values, there is an inherent risk of hypoglycemia. This risk must be balanced against the benefit of reduction of complication risk. Targets must be individualized patient to patient.

The clinical status of the child at the time of diagnosis may be used to guide initial therapy.\textsuperscript{13} In children who are ill at diagnosis, such as those presenting with dehydration or ketosis and/or acidosis, insulin is a reasonable first choice for therapy. In children who are not ill (or who are less ill) at diagnosis, diet, exercise, and an oral agent are appropriate therapy. Additionally, a practitioner may choose to withhold oral therapy for three to six months while a child implements MNT.

When blood glucose goals are not met with diet and exercise alone, treatment with an oral agent is indicated. Metformin is considered the first-line agent for children with T2DM and may be used at normal adult dosages.\textsuperscript{13} Because metformin may also normalize ovulatory function in girls and young women with polycystic ovary syndrome, the risk of unplanned pregnancy increases, and counseling should be a part of the treatment for all girls and women of childbearing age taking metformin. Side effects of and contraindications to metformin therapy are similar in children as in adults.

If blood glucose goals are not met with metformin monotherapy, an SU may be added, starting at low doses.\textsuperscript{13} A meglitinide would have an effect similar to an SU, but its quick onset and shorter duration of action may be...
preferable in children with irregular eating schedules. As in adults, children should be educated about hypoglycemia recognition and management when using either an SU or a meglitinide.

In children who present with very elevated blood glucose levels or present with severe symptoms and/or ketosis, initiation of therapy with insulin is recommended. The regimen may consist of once-daily insulin, a twice-daily insulin regimen, or an intensive basal-bolus regimen, depending on the needs of the patient. Once glucose control is attained, reduction or discontinuation of insulin and addition of metformin is an option. In children presenting with very high blood glucose levels, monitoring for urine ketones during initiation of therapy may be helpful in identifying patients who may actually have T1DM.

Co-morbidity considerations

Hypertension management
Hypertension is a condition that often coincides with diabetes and increases the risk of CVD which is the major cause of morbidity and mortality for patients. Controlling hypertension has been shown to reduce the progression of CVD in patients with diabetes and also reduces the risk of microvascular complications such as retinopathy, nephropathy, and neuropathy.

There are observational data to show increases in cardiovascular and all-cause mortality as SBPs rise incrementally above 140 mmHg. Most existing guidelines used expert opinion to conclude that patients with T2DM should be treated to lower blood pressure levels (<130/80 mmHg) than patients without diabetes. According to NHANES 1999-2000 data, only 35.8% of T2DM patients met blood pressure goals of below 130/80 mmHg. A less-stringent systolic blood pressure (SBP) goal (<140 mmHg) could be reasonable for T2DM patients with very high blood pressures, as this would reduce the number of medications a patient will need to lower their SBP to goal. In theory, this should reduce side effects, simplify the antihypertensive regimen, and reduce cost to the patient. At this time, we continue to support the expert opinion-based target of <130/80 mmHg pending the availability of new data or strong rationale and consensus from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

Table 12: Hypertension and lipid goals/management for T2DM patients

| Blood pressure goal | • <130/80 mmHg if achievable with 3 or fewer medications  
|                     | • <140/90 mmHg otherwise |
| Blood pressure pharmacotherapy | • ACE inhibitor or ARB  
|                                 | • Add diuretic if needed:  
|                                 |   o GFR ≥30 mL/min: thiazide-type diuretic  
|                                 |   o GFR <30 mL/min: loop diuretic |
| LDL-C goal | • <100 mg/dL –OR–  
|           | • <70 mg/dL if patient has coronary artery disease –OR–  
|           | • 30-40% decrease from baseline if <100 mg/dL cannot be achieved |
| HDL-C goal | • >40 mg/dL for men  
|           | • >50 mg/dL for women |
| TG goal | • <150 mg/dL |
| Lipid pharmacotherapy | • Statins to achieve LDL goal  
|                       | • Fibric acid derivatives if TG >400 mg/dL and HDL <35 mg/dL  
|                       | • Niacin to increase HDL |
Blood pressure should be measured at every routine diabetes visit. Lifestyle management including exercise, weight loss (if overweight), and the Dietary Approaches to Stop Hypertension (DASH) diet, should be instituted in all hypertensive patients regardless of pharmacological management.\(^8\) Sodium intake should be <1,500 mg/day for those with hypertension, those middle aged or older, or black patients. For all other patients, sodium intake should be <2,300 mg/day. Lower sodium diets potentiate antihypertensive treatment.\(^{107,108}\)

Antihypertensive agents that regulate the renin-angiotensin system, especially ACE inhibitors and ARBs, have been shown to benefit patients with both hypertension and diabetes due to their renal protective functions.\(^{102}\)

**Recent trial data**
The blood pressure arm of the ACCORD trial tested whether or not more intensive lowering of blood pressure resulted in decreased macrovascular endpoints.\(^{109}\) Mean SBPs were 119.3 mmHg in the intensive-treatment group and 133.5 mmHg in the standard-treatment group. The difference between groups in the primary outcome (the composite of nonfatal MI, nonfatal stroke, and cardiovascular mortality) was not significant.

A retrospective look at the INVEST study suggests that aiming for an SBP below 140 mmHg may be just as effective as a goal below 130 mmHg.\(^{110}\) Data presented at the 59th Annual Scientific Session of the American College of Cardiology showed that patients with T2DM and coronary artery disease seemed to have no difference in cardiovascular events or death whether they had SBPs below 130 mmHg or within 130-139 mmHg.

**Dyslipidemia management**
T2DM patients have a higher prevalence of dyslipidemia, which increases the risk of developing CVD.\(^{102}\) Patients with diabetes should have their fasting lipid profile measured at least annually.\(^{8}\) Lifestyle modifications focusing on reducing saturated fat, trans fat, and cholesterol intake should be instituted in all patients with diabetes regardless of fasting lipid profile. Pharmacological management should begin with getting LDL-C to goal (see Table 12).\(^{8}\) This can be efficiently accomplished with the use of statin drugs (e.g. atorvastatin, lovastatin).

Statin therapy should be started in most patients regardless of baseline lipid levels if the patient has either overt CVD or does not have overt CVD, but is greater than 40 years old and has at least one or more CVD risk factors.\(^{8}\) Fibrates are likely ineffective for prevention of cardiovascular morbidity or mortality, and should be used only if a patient’s triglyceride level is very high (>400 mg/dL) and HDL is very low (<35 mg/dL).

**Recent trial data**
An arm of the ACCORD trial tested whether or not fenofibrate would be of benefit in reducing cardiovascular morbidity and mortality in T2DM patients.\(^{111}\) Fenofibrate or a placebo was added to open-label simvastatin. There was no difference between groups in the occurrence of the primary outcome (first occurrence of cardiovascular mortality, nonfatal MI, or nonfatal stroke). In a retrospective analysis of the data, the authors found only the trend of a benefit for fenofibrate in a subgroup of patients with low HDL and high triglycerides.

**Antiplatelet therapy**

**Primary prevention**
Low-dose aspirin (LDA) therapy (81 mg daily) can be considered as primary prevention in patients with diabetes that have a >10% 10-year cardiovascular risk,\(^{8}\) although there is a growing body of evidence to suggest adding LDA does not reduce cardiovascular events in most subsets of patients with T2DM.\(^{112,113}\) There is insufficient evidence to use aspirin therapy in low-risk patients (those not conforming to the criteria outlined above).\(^{8}\)
Secondary prevention
LDA should be used in patients with a history of CVD.\textsuperscript{8} If a patient requires antiplatelet therapy but cannot take aspirin due to a documented allergy, clopidogrel 75 mg per day should be used. Concomitant use of aspirin and clopidogrel is reasonable for up to one year status-post acute coronary syndrome.

Glycemic control monitoring
Hemoglobin A\textsubscript{1C} (A1C) testing
Hemoglobin A1C, the three-month average of blood glucose values, is the gold standard for monitoring glycemic control in patients with T2DM. A1C testing should be performed in T2DM patients who have achieved their individualized goal twice yearly, and in T2DM patients who have not achieved their individualized goal every three months.

In the black population as a whole, A1C can run 0.2-0.3 percentage points higher than in the white population.\textsuperscript{114} The mechanism by which this occurs is unknown. Though this information may be considered when treating and screening patients, a difference in A1C of 0.3% is negligible and should not change treatment approaches.

Self-monitoring blood glucose (SMBG)
While the ADA advocates SMBG for all patients who use insulin, there has been some controversy in the literature about the usefulness of SMBG in T2DM patients who are not using insulin. Two studies have found that neither occasional SMBG nor more intensive SMBG is any different from not self-monitoring at all in lowering A1C levels.\textsuperscript{115,116} A meta-analysis by Welschen et al. found similar A1C decreases (~0.4%) as one of the two trials that did not show a significant difference between monitoring groups, but this difference was reported as statistically significant.\textsuperscript{117} In addition to relatively small decreases in A1C, SMBG in T2DM patients not using insulin was associated with higher costs and lower quality of life survey scores.\textsuperscript{118}

SMBG can be a useful tool for guidance of therapy, even in T2DM patients who do not use insulin therapy. A1C testing does not take into account wide diurnal variability in blood glucose levels. Monitoring at certain times of the day to check fasting blood glucose or post-prandial blood glucose can help guide drug therapy. Glycemic variability is more common in T2DM patients who do not use insulin but have severe insulin deficiency. In these instances, the combination of A1C testing and SMBG would be best to determine glycemic control.\textsuperscript{8} Also, teaching patients to monitor at home can help them to avoid hypoglycemic and hyperglycemic events, especially as drug therapy is being changed.

In T2DM patients who use insulin, SMBG three times daily or more is recommended to assess the efficacy and safety of the regimen.\textsuperscript{119} The actual frequency of testing will depend upon the number of injections per day. Generally, the more rapid- or short-acting insulin injections per day, the more frequent the patient should test. T2DM patients on basal insulin and not prandial insulin should be testing at least before breakfast in the morning and at bedtime or before dinner. More frequent testing may be necessary in patients who have a history of severe hypoglycemia. In those patients who do not use insulin, less stringent SMBG (once or twice daily) is still recommended in order to guide drug regimens, teach patients how eating habits, exercise, and medications can have an impact on their blood glucose, and check for very high and very low blood sugar and avoid hyper- or hypoglycemic events. This is especially important in patients with wide diurnal glycemic variability.
Patients should be instructed to increase frequency of SMBG at certain times. Additional testing when a new drug is added, the dose of an existing drug is changed, or a drug is discontinued helps the practitioner know how the drug is affecting both fasting and postprandial glucose readings. Since acute illness increases blood glucose, patients should be instructed to keep a closer eye on their readings when they are sick. Discordant SMBG and A1C results can also signal the need for increased monitoring. This will help to identify times of the day when blood glucose is running too high or too low. Some practitioners will also have patients with very high A1C test blood sugar more often to ensure their blood sugar does not rise too high to spark a hyperglycemic emergency or drop too low too quickly as a result of medication therapy.

Effective April 1, 2009, New York State Medicaid expanded their maximum monthly limits of SMBG supplies to allow for three times daily or greater glucose testing. Both lancets and test strips have quantity limits of 200 units for a 30-day supply. Patients who require testing eight times daily or more can receive additional test strips and lancets with prior approval.

**Summary**

The prevalence of T2DM is increasing as obesity and overweight rates increase. Proper diabetes management, including drug and non-drug therapy, is the key to reducing morbidity and mortality across New York State and the country. Screening and diagnosing at-risk child and adult patients is simpler than in years past given the many options available for confirming a diagnosis. Fasting plasma glucose tests are easily performed and reliable for diagnosis. While lifestyle changes are an important tool, most patients will require drug therapy due to the progressive nature of T2DM. Upon diagnosis, most patients should be managed with metformin and/or an SU alone or in combination with insulin, depending on how close they are to their A1C goal. In addition to managing blood sugar, patients with T2DM may need therapies to treat neuropathies, retinopathies, and nephropathy. Additionally, medication adherence should be stressed at every office visit, and treatment should be titrated to goal using A1C as a surrogate marker. Treating to target decreases the risk of microvascular complications associated with diabetes and may decrease the risk of macrovascular complications long-term. Statin drugs should be utilized to decrease LDL cholesterol below 100 mg/dL where possible. Lastly, aspirin therapy should be used appropriately in patients where indicated and not contraindicated.
References


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