

III. STANDARDS OF CARE FOR DIABETES IN ADULTS

TABLE 4
A. Quick Reference Guide for Adult Type 1 and 2 Diabetes

	ASSESSMENT FREQUENCY CATEGORIES			
	Initially	Annually	Other	Every Visit
GENERAL				
Comprehensive History and Physical	X			
Brief History and Physical				X
Height and Weight	X			X
Blood Pressure	X			X
Dilated Eye Exam	X ¹	X*		
Dental Exam	X		X twice/yr	
Foot Exam				
Visual	X			X
Comprehensive	X	X		
Referral to Podiatrist		X*		
Referral to diabetes educator	X		X twice/yr*	
EKG	X	X* after age 50		
LABORATORY EVALUATIONS				
Hemoglobin A1c	X		X quarterly	
Lipid Profile	X	X*		
Comprehensive & Basic Metabolic Panel	X	X*		
UA Microalbumin/Creatine Ratio	X ²	X*		
TSH	X	X*		
PREVENTION/INTERVENTION				
Aspirin Therapy	X ³			
Consider ACE Inhibitors/ARB	X* if BP not at goal or nephropathy present			X*
Tobacco Cessation	X			X
Immunizations				
Influenza	X	X		
Pneumococcal	X*			
Pre/Post Pregnancy Counseling	X	X*		
Multi-vitamin of Choice	X	X		
Consider Comorbidities	X	X		
OTHER CONSIDERATIONS				
Diabetes Self-Management Education	X	X*		
Barriers to Care	X			X
SMBG/Blood Glucose Log				X
Medical Nutrition Therapy	X	X		
Physical Activity	X	X		
Weight Management	X	X		
Medication Review	X	X		
Risks & Complications	X	X		

* Or as indicated per level of control

¹ In type 1, screening should start 3-5 years after the diagnosis is made

² In type 1, screening should start 5 years after the diagnosis is made

³ In type 2, start all patients on aspirin at initial visit; in type 1, start only if evidence of CAD exists

B. Initial Evaluation

Medical History

- Symptoms
- Eating patterns
- Exercise patterns
- Risk factors, including cardiac status and baseline EKG
- Presence of infections and history of frequency of infections
- Medications
 - Prescriptions and over-the-counter (including nutrient and herbal supplements)
 - Recreational including alcohol
- Family history
- Lifestyle and cultural preferences
- Tobacco history
- Reproductive and sexual history, including contraception practices
- Immunization status (e.g., Influenza, Pneumococcal, Tetanus, PPD)
- Previous diabetes education (MNT and DSMT)

Physical Examination

- Height, weight, BMI
- Vital signs
- HEENT (head, eyes, ears, nose and throat)
- Thyroid palpation
- Cardiac examination
- Abdominal examination
- Palpation of peripheral pulses
- Feet & hands examination
- Skin examination (acanthosis nigricans, necrobiosis lipoidica)
- Neurological examination (including tuning fork, Achilles tendon reflex and monofilament testing)
- Fundoscopic evaluation
- Referral to other specialties, as indicated

Laboratory Evaluation

- Hemoglobin A1c
- Lipids
- Urine for microalbumin and creatinine
- Blood glucose
- Comprehensive metabolic panel
- TSH
- Others as indicated

C. Yearly Assessments

- Dilated eye exam
- Foot exam (including pulses, tuning fork, Achilles tendon reflex and monofilament testing)
- Lab: lipids, urine microalbumin/creatinine ratio, A1c, others as indicated
- Blood pressure, weight, BMI
- Updated immunization
- Updating self management skills including SMBG
- Tobacco cessation counseling
- EKG (after age 50)
- Dental exam
- Vaccinations as indicated (e.g., Influenza, Pneumococcal, Tetanus, PPD)

D. Targets

Randomized, controlled studies have demonstrated that long-term complications of diabetes can be reduced by intensive glycemic control. The Diabetes Control and Complications Trial showed at nine years the incidence of new retinopathy was 12% in the intensive therapy group versus 54% in the conventional therapy group. After 6.5 years of this study, the prevalence of new microalbuminuria was 16% in intensive therapy versus 27% in conventional therapy. In the same study, the incidence of clinical neuropathy was reduced with intensive insulin therapy by 64%.

There are a number of management goals and guidelines for diabetes recommended by various societies and organizations. These guidelines, although based on the available evidence analyzed by experts in the field, may be slightly different. Perhaps the three most commonly utilized guidelines in the United States are from the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE), and the Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP). One should keep in mind that these are only general guidelines and that management goals should be individualized to the patient, with consideration given to individual risk factors (e.g., the patient's age, prognosis, the presence of diabetes complications or comorbidities, and the risk for and ability to perceive hypoglycemia).

TABLE 5
Target Indicators for Glycemic Control in Diabetes

All goals must be individually tailored for patient to provide best control and preserve safety.

Target Indicator	Source		
	ADA ¹	AACE ²	ATPIII ³
Preprandial/Fasting BG*	90 - 130	<110	---
Postprandial/2 hr Fasting BG	<180	<140	---
A1c (%)	<7.0	≤6.5	---
Blood Pressure	<130/80	<130/80	<130/85
Lipids			
LDL	<100 ⁴	<100 ⁴	<100 ⁴
Triglycerides	<150	<150	<150
HDL	>40 men >50 women	>40 men >50 women	>40 men >50 women

1 Summary of targets from Standards of Care. 2007. American Diabetes Association (ADA)

2 Summary of targets from Road Map for Treatment in Type 2 Diabetes. 2007. American Association of Clinical Endocrinologists (AACE)

3 National Cholesterol Education Program/Adult Treatment Panel III (ATP III) guidelines. 2006

4 Lower if multiple risk factors

E. Therapeutic Options

1. Use of Insulin

Insulin is available in different types and concentrations. In the United States, insulin is commercially available in U-100 and U-500 concentrations (100 or 500 units/mL; 1 unit equals ~36 mcg insulin). Outside the United States, U-40 and U-80 are commonly used, which may be useful information when managing patients who travel abroad. Syringes correspond to insulin concentrations.

* BG throughout these Recommendations means plasma or serum glucose. For a discussion on the ways of measuring glucose in the blood and their differences, see the Appendix, page 93.

TABLE 6

Insulin: Types and Action

Type of Insulin	Brand name/formulary status	Concentration	May be mixed with	Onset	Peak	Duration	Administration in relation to meals	Appearance
Prandial or Correction (Rapid Acting)								
Aspart	Novolog	100 units/mL	NPH	10 to 20 min	1 to 3 hours	3 to 5 hours	5 to 10 min before meal	Clear
Glulisine	Apidra	100 units/mL	NPH	10 to 15 min	1 to 1.5 hours	3 to 5 hours	15 min before meal or within 20 min after start of meal	Clear
Lispro	Humalog	100 units/mL	NPH	15 to 30 min	1 to 2 hours	3 to 5 hours	15 min before or immediately after meal	Clear
Prandial or Correction (Short Acting)								
Regular	Novolin R Nova	100 units/mL	NPH	30 to 60 min	2 to 4 hours	4 to 8 hours	30 min before meal	Clear
Regular	Humulin R U-500	500 units/mL	DO NOT MIX	30 to 60 min	2 to 4 hours	4 to 8 hours	30 min before meal	Clear
Regular	Humulin R	100 units/mL	NPH	30 to 60 min	2 to 4 hours	4 to 8 hours	30 min before meal	Clear
Basal (Intermediate Acting)								
NPH	Novolin N	100 units/mL	Aspart, Glulisine, Lispro, and Regular	1 to 2 hours	3 to 6 hours	8 to 18 hours	If mixing, follow guideline for rapid- or short-acting insulin	Cloudy
NPH	Humulin N	100 units/mL	Aspart, Glulisine, Lispro, and Regular	1 to 2 hours	3 to 6 hours	8 to 18 hours	If mixing, follow guideline for rapid- or short-acting insulin	Cloudy
Basal (Long Acting)								
Detemir	Levemir	100 units/mL	DO NOT MIX	0.8 to 2 hours	No peak	Dose dependent 12 hr for 0.2 units/kg; 20 hr for 0.4 units/kg; up to 24 hr	Without regard to meal	Clear, but cannot mix
Glargine	Lantus	100 units/mL	DO NOT MIX	1 to 2 hours	No peak	24 hours	Without regard to meal	Clear, but cannot mix
Basal and Prandial Pre-mixed Combinations								
70% Aspart Protamine/ 30% Aspart	NovoLog Mix 70/30	100 units/mL	DO NOT MIX	10 to 20 min	NA	NA	Within 15 min of meal initiation	Cloudy
70% NPH/ 30% Regular	Novolin 70/30	100 units/mL	DO NOT MIX	30 to 60 min	NA	NA	30 minutes before meal	Cloudy
50% NPH/ 50% Regular	Humulin 50/50	100 units/mL	DO NOT MIX	30 to 60 min	NA	NA	30 minutes before meal	Cloudy
70% NPH/ 30% Regular	Humulin 70/30	100 units/mL	DO NOT MIX	30 to 60 min	NA	NA	30 minutes before meal	Cloudy
75% Lispro protamine/ 25% Lispro	Humalog Mix 75/25	100 units/mL	DO NOT MIX	15 to 30 min	NA	NA	Within 15 min of meal initiation	Cloudy

Type of Insulin	Brand name/formulary status	Concentration	May be mixed with	Onset	Peak	Duration	Administration in relation to meals	Appearance
Inhalation Insulin								
Inhaled Recombinant Human Insulin	Exubera	1 mg, 3 mg unit dose blisters	NA	10 to 20 min	30 to 90 min	6 hours	Within 10 min of meal ingestion	NA

Notes for Table 6:

When combining insulin products in a single syringe, use clear, then cloudy (rapid- or short-acting drawn first)
NovoLog Mix 70/30 and Humalog Mix 70/25 do not contain NPH or Regular insulin

TABLE 7

Pre-Meal Dosing for Inhaled Insulin

Body Weight	Initial pre-meal dose	Total daily dose
30-59.9 kg (66-132 lbs)	1 mg	1 mg per meal + 1 mg per day
60-79.9 kg (133-176 lbs)	3 mg	3 mg per meal + 2 mg per day
80-119.9 kg (177-264 lbs)	5 mg	5 mg per meal + 3 mg per day
120+ kg (265+ lbs)	8 mg	8 mg per meal + 4 mg per day

TABLE 8

Approximate Dosing Equivalent

Dose (mg)	Regular Human Insulin International Units	Approximate Dosing Equivalent
1 mg	3	1
2 mg	6	2
3 mg	8	---
4 mg	11	1
5 mg	14	2
6 mg	16	---

Please note:
On October 18, 2007, the drug company Pfizer announced it would no longer make the inhaled insulin Exubera because too few people were using it. The company stated Exubera was a safe medication. Exubera will continue to be available 3 months after this announcement.
(These clinical recommendations went to print on October 8, 2007.)

* Approximate dosing equivalent of regular human subcutaneous insulin

Insulin Regimens

Many factors affect pharmacokinetics of insulin, including insulin type, injection technique, injection site, etc. In adults, insulin regimen should reflect the normal daily glycemic fluctuations under physiologic conditions. Insulin adjustments are based on average blood glucose readings. Frequently prescribed regimens include:

- *Twice daily injections*, consisting of a mixture of short- or rapid- and intermediate-acting insulins (before breakfast and supper).
- *Multiple daily injections*, consisting of a short- or rapid-acting insulin before meals and a long-acting insulin at bedtime.
- *Insulin pump regimens* of rapid-acting insulin used to mimic a basal-bolus routine.

Dosage Guidelines

Insulin dosages vary greatly and can change over time. The following should be included in the routine review and reassessment of patients:

- Weight change

- Duration of diabetes
- Skin/tissue condition at injection sites
- Exercise patterns
- Daily routine
- Results of SMBG and A1c
- Intercurrent illness

Distribution of Dose

A basal/bolus insulin regimen would generally include 3 components:

1. Basal insulin: this component covers the glucose that enters the circulation from the liver during fasting hours (glycogenolysis). This requirement is usually provided by a long-acting insulin given at bedtime, or two doses of intermediate-acting insulin, approximately 12 hours apart.
2. Prandial insulin: this component covers the glucose that enters the circulation after a meal. This is usually provided by a rapid- or short-acting insulin as several boluses in a day, given prior to meals. An insulin/carbohydrate ratio is utilized in modifying meal boluses. Insulin to carbohydrate ratio must be individualized based on insulin sensitivity.
3. Supplemental insulin (also known as sliding scale or correctional insulin): this component is intended to lower the blood glucose when it is higher than the target and is given in boluses of rapid- or short-acting insulin, when needed.

In otherwise healthy patients with type 1 diabetes, the typical total daily dose requirement is about 0.5-1 U/kg. In type 2 diabetes, this requirement is about 1-1.5 U/kg. The proportion of basal and bolus insulins are usually close to 50-50 percent, with the 50% bolus divided by the number of meals.

If initiating insulin pump therapy, the total daily dose of insulin is usually reduced by 25-30%. This reflects the higher efficiency of insulin when delivered in a continuous fashion by pump. The basal dose is distributed in 24 hours, based on different requirements at various times of the day. Bolus doses are divided based on the number and carbohydrate content of meals.

2. Oral Pharmacotherapy

Many advances have been made in the pharmacologic treatment of type 2 diabetes within the past five years. All agents have tissue-specific sites of action to improve glycemia. As stated in AACE Guidelines for Management of Diabetes, “these agents can be used in combination to utilize their respective mechanisms of action for reversing multi-factorial pathophysiology of beta cell dysfunction, insulin resistance, increased hepatic glucose production, and decreased peripheral glucose utilization.”

TABLE 9
Classifications of Non-Insulin Anti-Diabetic Agents

Drug Class	Generic Name	Brand Name	Dosing Range*	Duration (hrs)	Average Cost (month)
Sulfonylureas	Tolazamide	Tolinase	100 mg-1 gm/d	6-12	\$15-\$80
	Tolbutamide	Orinase	500-2000 mg/d	6-12	\$15-\$60
	Chlorpropamide	Diabinese	100-500 mg/d	up to 60	\$9-\$21
	Glimepride	Amaryl	1-8 mg/d	12-24	\$10-\$30
	Glipizide	Glucotrol	2.5-20 mg/d	10-24	\$7-\$40
	Glyburide	Micronase/Diabetabeta	1.25-20 mg/d	10-24	\$8-\$32
Biguanides	Metformin	Glucophage	500-2500 mg/d	10-12	\$25-\$210
Thiazolidinediones	Pioglitazone	Actose	15-45 mg/d	24	\$103-\$165
	Rosiglitazone	Avandia	2-8 mg/d	---	\$67-\$175

Drug Class	Generic Name	Brand Name	Dosing Range*	Duration (hrs)	Average Cost (month)
Incretin-Based Agents					
- Incretin Mimetic Agents	Exenatide	Byetta	10-20 mcg/d	2.4	\$200-\$230
- DPP-IV Inhibitors	Sitagliptin	Januvia	100 mg/d	- - -	\$164
Amylin Analog	Pramlintide	Symlin	45-360 mcg/d	<1	\$52-\$414
α -Glucosidase Inhibitors	Acarbose	Precose	75-300 mg/d	3-4	\$74-\$90
	Miglitol	Glyset	75-300 mg/d	- - -	\$60-\$77
Meglitinides	Nateglinide	Starlix	360 mg/d		
	Repaglinide	Prandin	0.5-16 mg/d	4.5	\$120-\$130

* Although the maximum dose can often be safely exceeded, reaching the maximum dose usually indicates that it is time to move on to another type of therapy because dosing above the maximum dose usually does not produce any significant results, but does increase the cost of therapy.

Sulfonylureas

Mode of Action: The primary effect is to stimulate insulin secretion by blocking the potassium channel of the beta cell. A secondary effect is to decrease hepatic glucose production, and possibly improve insulin sensitivity at the receptor and post-receptor levels.

Profile: Sulfonylurea agents differ in potency, cost, and pharmacokinetics; use as adjunct to diet and exercise; may be used as monotherapy or combination therapy; most useful in thin patients; not effective in type 1 diabetes; not to be used in pregnancy (only Glyburide may be considered during the later part of pregnancy); not recommended for use in association with major surgical procedures or general anesthesia, severe infection, stress, trauma, or predisposition to severe hypoglycemia.

Dosing:

- **Tolazamide** - Initial: 100-250 mg/day (blood glucose <200 = 100 mg, >200 = 250 mg) with breakfast. Increase by 100-250 mg increments per week. Doses above 500 mg/day should be given in 2 divided doses. Maximum daily dose is 1 gm/day.
- **Tolbutamide** - Initial: 1-2 gm/day as a single dose in the morning or in divided doses throughout day. Maintenance dose is 0.25-3 gm/day; doses greater than 2 gm/day are seldom needed.
- **Chlorpropamide** - 250 mg/day in mild to moderate, middle-aged and stable patients. Older patients start at 100-125 mg/day. Adjust dose by 50-125 mg every 3-5 days. Maintenance dose generally 100-250 mg/day. Avoid doses greater than 750 mg/day.
- **Glimepride** - Initial: 1-2 mg once daily with breakfast. Usual maintenance dose is 1-4 mg/day. After 2 mg/day dose add 2 mg increments at 1-2 week intervals. Maximum dose is 8 mg/day.
- **Glipizide** - Initial: 5 mg/day, increase at 2.5-5 mg increments after several days. Immediate release maximum once daily dose is 15 mg; maximum total daily dose is 40 mg. Doses greater than 15 mg should be divided. Sustained action tablet maximum daily dose is 20 mg.
- **Glyburide** - Regular tabs: 2.5-5 mg/day initially, increase at no more than 2.5 mg increments at weekly intervals. Maintenance is 1-20 mg as once daily or divided doses. Maximum dose is 20 mg/day. Micronized tablets: 1.5-3 mg initially, increase in increments of 1.5 mg/day in weekly intervals. Maintenance dose is 0.75-12 mg/day in single or divided doses. Maximum dose is 12 mg/day.

Warnings: Hypoglycemia due to overdosage, decreased caloric intake, severe or prolonged exercise, ethanol ingestion, or combination with other glucose lowering drugs. Renal or hepatic impairment necessitates dosage adjustment. Chemical similarities exist between sulfonylureas and sulfonamide, thiazides, loop diuretics and carbonic anhydrase inhibitors. Caution should be exercised in patients with sulfonamide allergy. Weight gain is a common side effect of this classification of medications. It may be necessary to discontinue therapy and administer insulin if the patient is exposed to significant stress such as infection, surgery, trauma or fever.

Contraindications: Sulfonylureas are contraindicated in advanced liver or kidney disease, known hypersensitivity to the drug, and diabetic ketoacidosis.

Biguanides

Mode of Action: Metformin has insulin-sensitizing properties and decreases hepatic glucose production by improving insulin action on the liver. A secondary effect is to enhance muscle glucose uptake and utilization.

Profile: Used as monotherapy or in combination with other classes or insulin. Biguanides are usually the first line of medications used in diabetes. This class of drugs is usually weight neutral in most people.

Dosing: Immediate release tablets, begin at 500 mg twice daily or 850 mg once daily. Allow at least one week between increments of 500 mg per week or 850 mg every other week. Meaningful decrease in BG levels are seldom seen with doses less than 1500 mg per day, but GI adverse effects are better tolerated with lower doses and slower titration upwards. Doses of up to 2000 mg/day may be given in divided twice daily dosing, however if greater doses are needed, it may be better tolerated in three daily doses. Maximum daily dose is 2550 mg per day. Extended release tablets begin with 500 mg per day at the evening meal, titrate up at 500 mg increments. If greater than 2000 mg/day is required, convert to immediate release tablets and split doses. The greatest side effects are usually seen in doses above 2500 mg/day.

Warnings: Lactic acidosis is a rare but potentially severe consequence of therapy with metformin. Caution should be exercised in any situations pre-disposing to lactic acidosis. Metformin is substantially excreted by the kidney and care must be exercised in renal (creatinine clearance < 60-70 mL/min) or hepatic insufficiency.

Contraindications: Patients prone to metabolic acidosis or hypoxic states, including renal dysfunction with serum creatinine >1.5 mg/dL for males or >1.4 mg/dL for females, or liver dysfunction; dye procedures (temporarily discontinue drug for 24 hr pre- and 48 post-IV iodinated contrast and follow-up with a BUN-to-creatinine ratio test). Use cautiously in patients >80 years old.

Thiazolidinediones (TZDs)

Mode of Action: This class of medications enhances tissue sensitivity to insulin in muscle through activation of intracellular receptors. A secondary effect is suppression of hepatic glucose production. There is no stimulatory effect on insulin secretion.

Profile: Used as monotherapy or in combination with sulfonylureas and metformin; both TZDs are FDA approved for use in combination with insulin therapy. Useful in patients with insulin resistance or azotemia. May take several weeks for onset of action and several months for peak action. Assess serum transaminase levels at start of therapy and every 2-3 months for 1 year, then periodically.

Dosing:

- **Pioglitazone** - Initial dosing is 15-30 mg once daily. If response is inadequate, increase in 15 mg increments up to maximum daily dose of 45 mg.
- **Rosiglitazone** - Initial dose is 4 mg in a single or divided daily dose. If there is insufficient response after 8-12 weeks of therapy, increase to 8 mg per day in a single or divided dosage. Clinically, the greatest decreases in glucose and A1c were seen with the 4 mg twice daily dosing.

Warnings: Weight gain, increase in total cholesterol, edema, and heart failure. Currently there is much controversy as to whether or not Avandia can increase overall cardiovascular morbidity and mortality. No adjustment of dose is needed with mild to moderate renal impairment. However, clearance is significantly lower in hepatic impairment. Treatment should not be started if the patient exhibits active liver disease or increased transaminases.

Contraindications: Known hypersensitivity or allergy to the drug or its components, severe renal impairment, clinical evidence of active liver disease, abnormal transamines >2.5 times upper limit of normal for pioglitazone or >2.5 times upper limits of normal for rosiglitazone, and CHF (NY Heart Assoc. Class III and IV).

Incretin-Based Agents

Incretin hormones cause increased insulin synthesis and release from pancreatic beta cells and inhibit the release of glucagon from pancreatic alpha cells. Decreased glucagon secretion results in decreased hepatic glucose synthesis. Incretin hormones along with glucose-dependent insulinotropic polypeptide regulate normal glucose homeostasis, and are released throughout the day, but are increased with response to meals.

- Incretin Mimetics: Exenatide

Mode of Action: This analog of the hormone GLP1 is among a group of hormones that have direct and indirect influences on the increased secretion of insulin, promotion of beta cell growth and replication, and the slowing of gastric emptying. The medication may lead to decreased food intake.

Profile: Exenatide is approved for use in type 2 patients that are already on metformin, sulfonylureas, or both and are not experiencing optimal glycemic control with mono or combination oral therapy. It is also approved for use with thiazolidinediones. Addition to metformin therapy seldom requires decreased dose of metformin. However, presence of hypoglycemia upon addition to sulfonylureas dictates that the sulfonylurea dose be decreased. The medication promotes weight loss in most people.

Dosing: Initial dosing is 5 mcg subcutaneously (thigh, abdomen, upper arm) twice daily within 60 minutes prior to meals. After 1 month the dose may be increased to 10 mcg twice daily, based on response and tolerance. Gradual dose escalation decreases side effects.

Warnings: Nausea is the most common side effect with exenatide. Nausea decreases with decreased food intake. Initiation of therapy in patients with severe GI disease has not been studied. Other common side effects include diarrhea, vomiting, headache and dizziness. Renal adjustment of dosing is not necessary with creatinine clearance levels above 30 mL/minute, however, below 30 mL/minute Exenatide is not recommended. Exenatide can cause hypoglycemia, generally characterized as mild to moderate in severity. Hypoglycemia is much more pronounced when Exenatide is added to a sulfonylurea (sulfonylurea dose should be decreased at the initiation of Exenatide).

Contraindications: Exenatide requires the presence of insulin, so use in type 1 diabetes or ketoacidosis is not recommended. Exenatide use is not recommended in severe renal failure and gastroparesis. Dose dependent gastrointestinal side effects are common and may respond to gradual titration and continued use.

- Dipeptidyl Peptidase-IV Inhibitors (DPP-IV): Sitagliptin

Mode of Action: Sitagliptin inhibits dipeptidyl peptidase-IV which breaks down endogenous incretin hormones. Incretin hormones are rapidly destroyed by DPP-IV enzyme.

Profile: This agent is used at a dose of 100 mg per day as monotherapy or in combination with metformin or thiazolidinediones.

Dosing: 100 mg once daily.

Warnings: The most common adverse effects of sitagliptin are upper respiratory tract infections, nasopharyngitis, and headache. Hypoglycemia was not elevated in combination use with metformin or pioglitazone. There are no current studies combining sitagliptin with agents known to cause hypoglycemia such as sulfonamides or insulin. Renal insufficiency does change dosing; decrease the daily dose to 50 mg for creatinine clearances of 30-50 mL/minute or serum creatinine between 1.7-3 mg/dL in men or 1.5-2.5 mg/dL in women. In severe renal impairment (creatinine clearance less than 30 mL/min or serum creatinine greater than 3 mg/dL) drop the daily dose to 25 mg. Sitagliptin requires the presence of insulin, so use in type 1 diabetes or ketoacidosis is not recommended.

Contraindications: Dosage reduction should be considered in patients with moderate or severe renal impairment and use of this medication has not been studied in severe hepatic failure. Administration is contraindicated with allergy to Sitagliptin or any component of the formulation.

Amylin Analogs - Pramlintide

Mode of Action: This synthetic analog of Amylin, which is co-secreted with insulin, decreases postprandial glucose elevations via the following mechanisms: 1) prolongation of gastric emptying time; 2) decreased glucagon secretion; and 3) centrally mediated appetite suppression resulting in reduced caloric intake.

Profile: Adjunctive treatment with insulin in type 1 patients, or type 2 patients with insulin and with/without concurrent sulfonylurea and/or metformin that have not obtained optimal glycemic control.

Dosing:

- **Type 1 diabetes:** 15 mcg subcutaneously immediately prior to meals. Titrate in 15 mcg increments every 3 days if not experiencing significant nausea. Target dose is 30-60 mcg before meals. Consider discontinuation if intolerant of 30 mcg dose. When initiating pramlintide therapy, decrease current insulin dose (rapid and mixed analogs) by 50% to avoid hypoglycemia.
- **Type 2 diabetes:** 60 mcg subcutaneously immediately prior to meals; after 3-7 days increase to 120 mcg prior to meals if no significant nausea occurs. If nausea occurs at 120 mcg, reduce dose to 60 mcg.

Warnings: Pramlintide has been associated with an increased incidence of insulin induced severe hypoglycemia, generally seen within 3 hours of doses. Frequent pre- and post-dose glucose readings are necessary. Renal dosing adjustment is not required; dialysis patients have not been evaluated. Caution: potential for patient errors due to confusion with measurement of doses (see table below).

The table below is a combination of the tables included in professional and patient education inserts. The first three columns under 'professional' are what is contained in the professional insert. The last two columns illustrate how information is presented in patient leaflets. Issues of concern expressed by the Institute for Safe Medication Practices are that the measurements in professional inserts relate to volume in units, and cc or mL, while patient information describes measurements only in units. Go to <http://www.ismp.org/> for more information and counseling tips on how to decrease risk of accidental overdose with pramlintide.

TABLE 10
Professional vs. Patient Information for Pramlintide

Pramlintide Professional Table			Pramlintide Patient Handout Table	
Dosage Prescribed (µg)	Increment using U-100 Syringe (Units)	Volume (cc or mL)	<i>Pramlintide Dose Conversion</i>	
			If your dose amount is:	Draw up this amount in syringe
15	2.5	0.025	15 micrograms	2½ units
30	5.0	0.050	30 micrograms	5 units
45	7.5	0.075	45 micrograms	7½ units
60	10.0	0.100	60 micrograms	10 units
120	20.0	0.200	120 micrograms	20 units

Contraindications: Known hypersensitivity to pramlintide or any component of the formulation (including Metacresol); diagnosis of gastroparesis (caution with drugs that cause hypomotility); or hypoglycemia unawareness.

Alpha-Glucosidase Inhibitors

Mode of Action: These medications act locally in the small intestine by inhibiting the α -glucosidase enzyme to slow digestion of ingested carbohydrates, delay glucose absorption, and reduce the increase in postprandial blood glucose.

Profile: Used as monotherapy or in combination with other medications. Effectiveness has been demonstrated with all agents and insulin and this class of agents modestly reduces glycosylated hemoglobin. Alpha-Glucosidase inhibitors have a high discontinuation rate due to GI side effects.

Dosing:

- **Acarbose** - Initial dose is 25 mg three times daily with first bite of each meal. Increase dose based on effect and tolerance. Maintenance dose is 50-100 mg three times daily. Maximum dose in patients less than 60 kg is 50 mg three times daily; in patients greater than 60 kg it is 100 mg three times daily.
- **Miglitol** - Initial dose is 25 mg three times daily with the first bite of meals. Dose is increased to 50 mg three times daily after 4-8 weeks. Maximum dose is 100 mg three times daily.

Warnings: Alpha-glucosidase inhibitors can increase hypoglycemia caused by sulfonylureas. Treatment emergent elevations in transaminases can occur in up to 15% of patients, and are generally asymptomatic and reversible. Gastrointestinal side effects (pain, diarrhea, flatulence) are very common, but tend to abate with time. The mechanism of action makes treatment of hypoglycemia more problematic; complex sugars will not be effective; glucose tablets or IV glucose may be needed.

Contraindications: Major GI disorder (i.e., inflammatory bowel disease, chronic ulceration, malabsorption, or partial intestinal obstruction).

Meglitinides

Mode of Action: Meglitinides are insulin secretagogues, lowering blood glucose by stimulating release of insulin in response to a glucose load. They close adenosine triphosphate-dependent potassium channels in beta cell membranes, resulting in increased calcium influx that induces insulin secretion. They lower both fasting and postprandial blood glucose, with greatest effect postprandially.

Profile: Usually taken 15-30 minutes before meals; can be used as monotherapy or in combination with metformin.

Dosing:

- **Nateglinide** - Initial and maintenance dose is 120 mg three times daily within 15-30 minutes before meals. Patients close to A1c goal may be started at 60 mg three times daily.
- **Repaglinide** - Patients not previously treated or whose A1c <8% start at 0.5 mg within 15-30 minutes of each meal. If already treated or A1c greater than 8%, start at 1-2 mg before each meal. Dosing adjustments are made on fasting blood glucose readings and preprandial doses can be doubled up to 4 mg per dose. Allow at least 1 week before dose adjustments. Maximum daily dose is 16 mg per day.

Warnings: Use caution in patients with moderate to severe hepatic or renal impairment. Hypoglycemia may occur due to over dosage, decreased caloric intake, after severe or prolonged exercise, ethanol ingestion, or combination with other glucose lowering agents. It may be necessary to discontinue therapy and administer insulin if the patient is exposed to significant stress such as infection, surgery, trauma or fever.

Contraindications: Diabetic ketoacidosis, with or without coma; known hypersensitivity to the drug or its inactive ingredients.

TABLE 11**Available Anti-Diabetic Combination Products**

Generic Names	Brand Names	Strengths Available
Glyburide/Metformin	Glucovance	1.25 mg/250 mg, 2.5 mg/500 mg, 5 mg/500 mg
Glipizide/Metformin	Metaglip	2.5 mg/250 mg, 2.5 mg/500 mg, 5 mg/500 mg
Rosiglitazone/Metformin	Avandamet	1 mg/500 mg, 2 mg/500 mg, 2 mg/1,000 mg, 4 mg/500 mg, 4 mg/1,000 mg
Pioglitazone/Metformin	ActoPlus Met	15 mg/500 mg, 15 mg/850 mg
Pioglitazone/Glimepride	Duetact	30 mg/2 mg, 30 mg/4 mg
Rosiglitazone/Glimepride	Avandaryl	4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg
Sitagliptin/Metformin	Janumet	50 mg/500 mg, 50 mg/1,000 mg

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