Pharmacy Benefits Management
Strategic Healthcare Group
and the Medical Advisory Panel

The Pharmacologic Management of Type 2 Diabetes Mellitus

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Veterans Health Administration
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Pharmacy Benefits Management (PBM)
Strategic Healthcare Group (SHG)

VHA's PBM SHG has been directed by the Under Secretary for Health to coordinate the development of guidelines for the pharmacologic management of common diseases treated within the VA, establish a national level VA formulary, and to manage pharmaceutical costs, utilization, and measure outcomes as they apply to patient care. The MAP provides support and direction to the PBM SHG staff, located in Washington DC and Hines, Illinois.

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Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Mission

The role of the Medical Advisory Panel (MAP) in the PBM SHG is to consult on the development and refinement of evidence-based pharmacologic management guidelines for the VHA. These guidelines are intended to promote provision of quality, cost effective patient care.

The MAP is comprised of practicing VA physicians from facilities across the nation:

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Development of the Guidelines

Whenever possible, the PBM SHG relies upon evidence-based, multidisciplinary, nationally recognized consensus statements for the basis of VA guidelines. Relevant literature is reviewed and assessed with consideration given to the VA population. Draft guidelines are sent to the field for comment prior to being finalized.

Development of the guidelines relied upon relevant literature (see attached articles).

Use of the Guidelines

The purpose of the guidelines is to assist primary care practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The guidelines attempt to define principles of practice which should produce quality patient care. They are targeted for the needs of primary care practitioners, but are directed to providers at all levels. The guidelines also serve as a basis for monitoring local, regional and national patterns of pharmacologic care.

Guidelines should not be considered inclusive of all appropriate processes of care.

Updating the Guidelines

The PBM SHG will review the guidelines routinely. Updating will occur as new information is made available from well-designed, scientifically valid studies and as outcome data may direct.

A current copy of the pharmacologic management guidelines can be obtained from the Pharmacy Benefits Management home page at http://vaww.pbm.va.med.gov or www.vapbm.org

Referencing the Guidelines

This guideline should be referenced as:
Pharmacy Benefits Management-Medical Advisory Panel. *The Pharmacologic Management of Type 2 Diabetes Mellitus*. VHA PBM-SHG Publication No. 98-0011 Hines, IL: Pharmacy Benefits Management Strategic Health Group, Veterans Health Administration, Department of Veterans Affairs. June 1999.

Tables of Evidence

The referenced articles have been assigned a grade of evidence and strength of recommendation rating, which is based on AHCPR guideline development (Agency for Health Care Policy and Research publication
No. 93-0550, March 1993). A description of this tool is provided below:

Level A – Large, randomized trials with clear-cut results (low risk of error)
Level B - Small, randomized trials with uncertain results (moderate to high risk of error)
Level C – Nonrandomized, contemporaneous controls; nonrandomized, historical and expert opinions; uncontrolled studies, case series, and expert opinions

Acknowledgments*

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*This list does not represent all the clinicians who reviewed the guideline, rather those who wished to be acknowledged. The Pharmacy Benefits Management and Medical Advisory Panel take full responsibility for the content of this guideline.

**This list may not include clinicians who reviewed previous publications of this guideline (refer to Publ. # 96-0004)

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EXECUTIVE SUMMARY

1. Type 2 diabetes mellitus (DM), previously referred to as non-insulin dependent diabetes mellitus, refers to patients who have insulin resistance and relative insulin deficiency. These patients who may go undiagnosed for many years, are at an increased risk for developing macrovascular and microvascular complications.

2. Individual treatment goals must be established with the patient based on extent of disease, co-morbid conditions, and patient preferences.

3. Diet, exercise, and weight loss should be used as initial and/or adjunctive treatment of Type 2 DM.

4. If diet fails, an oral sulfonylurea should be used as first line drug therapy, with an average absolute reduction in HbA1c of 1.5-2%. A second-generation oral sulfonylurea is the preferred agent (Refer to Algorithm 1).

5. Metformin may be used in conjunction with an oral sulfonlyurea when glycemic control fails with an oral sulfonylurea alone. The average absolute decrease in HbA1c is 1.5-2%. Metformin is not recommended as first-line monotherapy at this time since studies have not proven it to be superior to oral sulfonylureas. However, it may be considered as initial monotherapy in overweight patients (BMI > 25).

6. Acarbose may be used in conjunction with an oral sulfonylurea in patients who are inadequately controlled on sulfonylureas. The average absolute reduction in HbA1c is 0.4-1.0%.

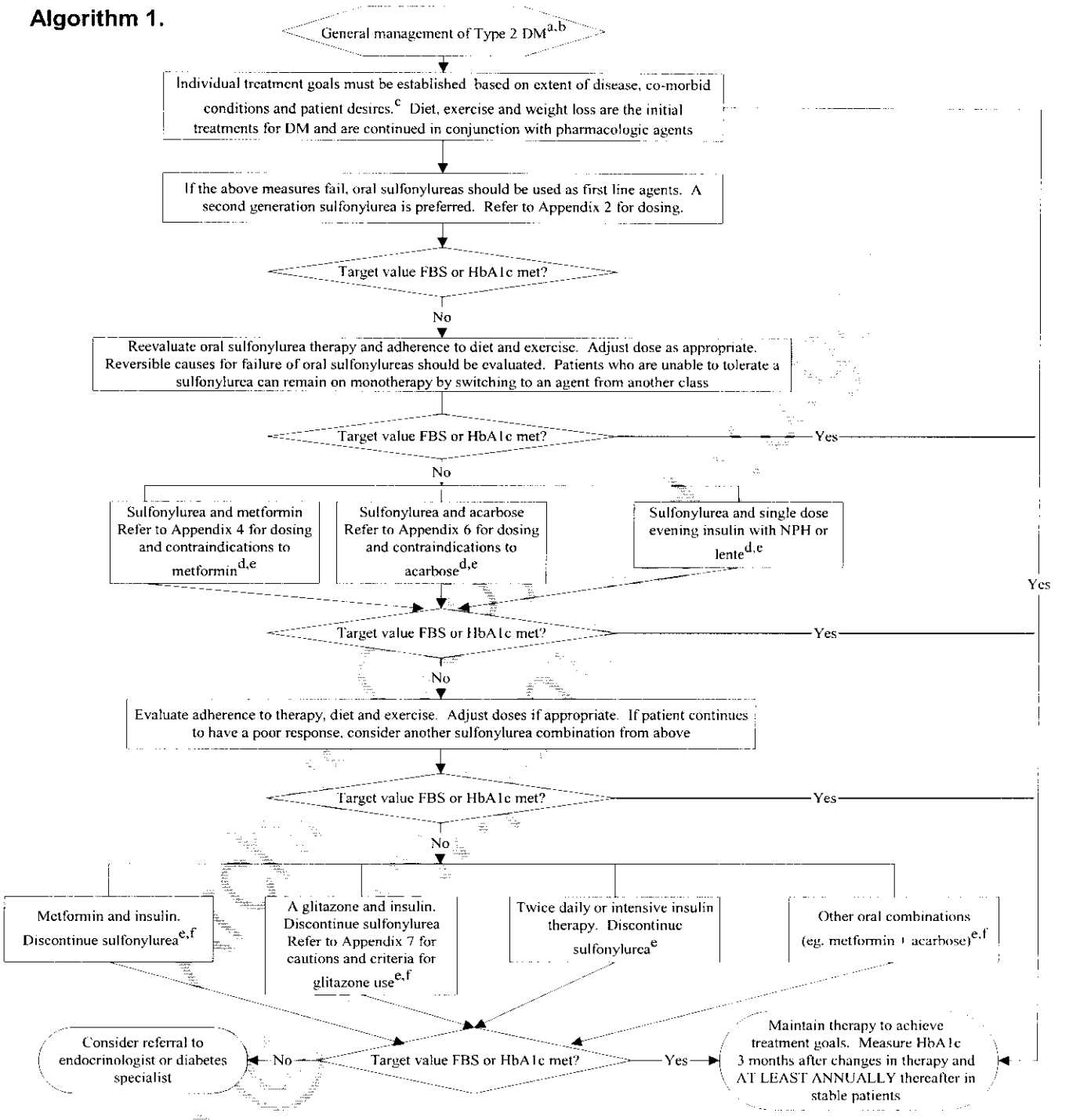
7. Intermediate-acting insulin as a single evening dose may be used in conjunction with an oral sulfonylurea when monotherapy with a sulfonylurea has failed. It may also be used as a single agent, when given in multiple daily doses, if there is failure of glycemic control with combination therapies.

8. The thiazolidinediones (rosiglitazone, and pioglitazone) also referred to as the glitazones, are not recommended as first-line monotherapy agents. Their ability to decrease HbA1c is inferior to sulfonylureas or metformin. There is a role in using these agents in combination regimens in select situations (Refer to section C6).

9. The use of insulin lispro is not recommended for routine use in treatment of Type 2 DM due to inadequate evidence for improved long-term outcomes compared to standard insulin preparations.

10. There is no evidence that supports a clinical benefit of routine daily blood glucose monitoring in stable patients on oral agents. Therefore, if self-monitoring is to be done, a twice-weekly regimen is usually sufficient. Special situations may warrant more frequent monitoring (Refer to section E).

Algorithm 1.



[a] This treatment algorithm is intended to manage the majority of patients with Type 2 diabetes, however it may not be appropriate for all patients

[b] Referral to an endocrinologist or diabetes specialist may be requested at anytime at the providers discretion. The decision to treat patients with Type 2 diabetes should be based on familiarity and experience of the provider.

[c] Refer to text for risk stratification. Target value needs to be individualized. HbA1c would not be expected to stabilize for 3 months after changes in treatment.

[d] A glitazone may be used in combination with a sulfonylurea if treatment with a sulfonylurea in combination with metformin, insulin or acarbose has failed or is contraindicated.

[e] Take into consideration efficacy (see text V.c. Pharmacotherapy), contraindications, and cost (Appendix 8) when selecting a therapeutic regimen.

[f] This treatment option has been studied in patients who have previously failed single drug therapy. There is insufficient evidence to determine which treatment regimen is best for patients failing combination therapy with a sulfonylurea.

I. DEFINITION

Ninety to ninety-five percent of patients with diabetes mellitus (DM) have type 2, formerly referred to as non-insulin dependent or adult onset diabetes. Type 2 patients may however, require insulin for glycemic control.

II. GENERAL PRINCIPLES

DM affects the health of 8-10% of Americans, although it is found with higher frequency in certain ethnic groups and in the elderly. The majority of patients with type 2 DM are overweight adults.

A. CANDIDATES FOR SCREENING (repeat testing every 3 years)

Major Risk Factors for DM[a]
• Age ≥45 years
• Family History (parents or siblings with DM)
• High-density lipoprotein cholesterol (HDL-C) ≤ 35 mg/dL (0.90 mmol/l) and triglycerides (TG) ≥ 250 mg/dL (2.82 mmol/l)
• History of gestational DM or women delivering babies weighing > 9 pounds
• Hypertension (blood pressure ≥140/90 mmHg)
• Obesity (> 20% above ideal body weight or body mass index (BMI) ≥27 kg/m^2
• Previous impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)
• Race/ethinicity (African Americans, Hispanic-Americans, Native Americans, Asian-Americans, Pacific Islanders)

[a] Adapted from American Diabetes Association. Screening for Type 2 Diabetes (Position statement). Diabetes Care 21(Suppl. 1);s20-22, 1998

B. CRITERIA FOR THE DIAGNOSIS OF DM[a]

Fasting Plasma Glucose (FPG)[b]	Random[c] Glucose	Oral Glucose Tolerance Test (OGTT)[d]
≥126 mg/dL (7.0 mmol/l)	≥200 mg/dl (11.1 mmol/l), accompanied by polyuria, polydipsia, or unexplained weight loss	≥200 mg/dL (11.1 mmol/l) at 2 hours

[a] Adapted from the American Diabetes Association. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 1997;20:1183-97

[b] Use of FPG is recommended over OGTT as the preferred method of diagnosis; each of which must be confirmed on a subsequent day by either a FPG, random glucose or OGTT. Fasting is defined as no caloric intake for at least 8 hours

[c] Defined as any time of day, without regard to meals

[d] Definition is based on a 75 gm glucose load

C. OTHER TYPES OF GLUCOSE INTOLERANCE [a]

Type	Fasting Plasma Glucose (FPG) [b]	Oral Glucose Tolerance Test (OGTT)
Gestational diabetes[c]	≥105 mg/dL (5.8 mmol/l)	2 hr. postload glucose ≥ 165 mg/dL (9.2 mmol/l)
Impaired fasting glucose (IFG)	≥ 110 mg/dL (6.1 mmol/l) and <126 mg/dL (7.0 mmol/l)	
Impaired glucose tolerance (IGT)		2 hr. postload glucose ≥140 mg/dL (7.8 mmol/l) and <200 mg/dL (11.1 mmol/l)[d]

[a] Adapted from the American Diabetes Association. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183-97

[b] Fasting is defined as no caloric intake for at least 8 hours

[c] Performed, unless otherwise indicated, between 24 and 28 weeks gestation (after a non-fasting screening with a 50 g load if 1 hr plasma glucose ≥ 140 mg/dL or 7.8 mmol/l). Positive screen indicates need for diagnositic 100g, 3-hour OGTT. For the diagnostic test to be considered positive, at least 2 of 4 plasma glucose values obtained during the test must meet or exceed values outlined in the 3-hour OGTT. Pregnant women at low risk (< 25 years of age, normal body weight, no family history of DM, and not belonging to an ethnic group with a high prevalence of DM) need not be screened

[d] Definition is based on a 75gm glucose load

III. PATIENT EVALUATION

A. HISTORY

1. Onset and progression of symptoms of hyperglycemia: polyuria, polydipsia and weight loss.
2. History of endocrine disorders, eating disorders, gestational history of hyperglycemia, delivery of an infant weighing > 9 pounds, or complications of pregnancy.
3. Relevant medical history, including diseases that can cause secondary diabetes such as hemochromatosis, pancreatic disease, and endocrine disorders.
4. Family history of diabetes and other endocrine disorders.
5. History of the frequency, severity, and cause of ketoacidosis or hypoglycemia.
6. Lifestyle information, including cultural, psychosocial, educational, and economic factors that may influence management.
7. Diet, exercise, alcohol, and smoking history.
8. Review previous treatment (if any), and past and present degrees of glycemic control.
9. Review symptoms for end-organ damage, especially cardiovascular, ocular, neurologic, renal, and dermatologic.

10. Evaluate for medications that may impair glucose tolerance (Refer to Appendix 1).

B. PHYSICAL EXAM

1. Baseline height, weight, and blood pressure (BP) measurement; check weight and BP on each visit
2. Exclude secondary causes of diabetes (Refer to III. A.3. and A.10.)
3. Evaluate patient for end-organ damage, especially cardiovascular, ocular, neuropathy, dermatologic, renal, and diabetic foot ulcers

C. BASELINE LABORATORY TESTS

Fasting plasma glucose, Hemoglobin A1c (HbA1c), fasting lipid profile, serum electrolytes, BUN/ creatinine, and urinalysis for glucose, ketones, and protein (and culture if abnormal or symptomatic). If proteinuria absent, test for microalbuminuria (timed or 24-hour collection, or the albumin to creatinine ratio in a random, spot collection). Other tests that may be considered are thyroid function tests and electrocardiogram.

IV. TESTS TO GUIDE CLINICAL MANAGEMENT

A. RISK STRATIFICATION OF GLYCEMIC TARGET RANGE (Adapted from VHA Clinical Guideline for the Management of DM and the ADA Standards of Care for DM)

1. Determination of a target value HbA1c is based on patients' life expectancy, presence of microvascular complications, and family history of microvascular complications:

HbA1c Target[a]	Risk Stratification
≤7 % (1% above high-normal range)	Life expectancy ≥15 years in the absence of diabetic complications, or ≥10 years in the presence of early to moderate microvascular disease
≤8% (2% above high-normal range)	Life expectancy 5-15 years in the absence of microvascular disease, or between 5-10 years in the presence of microvascular disease
≤9% (3% above high-normal range)	Life expectancy <5 years, with or without microvascular disease

[a] Based on HbA1c values with a high-normal value of 6%

2. Tailor the target value with patients, taking into account individual patient characteristics:
   - the patient's understanding to carry out the treatment regimen
   - the patient's risks for hypoglycemia

- factors that may increase the risk or decrease the benefit (e.g. advanced age, end-stage renal disease or cerebrovascular disease, or other coexisting diseases that may affect life expectancy)

V. MANAGEMENT

A. GENERAL APPROACH

1. It is important to educate the patient and family about type 2 DM and it's treatment. Together, formulate a plan for achieving glycemic control by encouraging an active, healthy lifestyle that includes exercise and diet and medications when necessary. Obtain agreement of goals in treatment, and provide supportive follow-up.

2. Provide education on glucose monitoring, prevention and treatment of complications, hypoglycemia awareness and treatment, and pharmacologic therapy, as appropriate.

B. NON-PHARMACOLOGIC THERAPY

Lifestyle changes including diet (Refer to Module M in VHA Clinical Guideline) exercise at least 30 minutes per day on most days of the week (as appropriate, after a detailed medical examination), weight loss if indicated, and smoking cessation. Limit alcohol to no more than 2 drinks per day for men and 1 drink per day for women (1 drink = 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of distilled spirits). Diet and exercise should be given at least a 3 month trial before drug therapy is started unless fasting glucose $\geq$ 250 mg/dl or $\leq$ 250 mg/dl with symptoms of hyperglycemia.

C. PHARMACOTHERAPY

1. General Considerations[a]

a. When selecting an agent, consideration must be given to efficacy, contraindications, cost, and patient preferences.

First-line agents	Oral sulfonylurea [a]
Secondary agents	Addition of metformin, acarbose or evening insulin to sulfonylurea

[a] metformin may be considered in overweight patients (BMI > 25)

b. Elderly patients are at a higher risk for drug-associated hypoglycemia, due to altered metabolism and excretion rates, impaired symptom recognition, and potentially attenuated counterreglatory responses. Patients and their families should be instructed to recognize signs and symptoms of hypoglycemia and its management.

c. The effect on HbA1c with monotherapy is variable and seems to depend on whether the patient has been previously treated with another agent. Drug therapy naïve patients have a

greater absolute decrease in HbA1c than do patients receiving prior hypoglycemic drug therapy.

d. When failing to achieve glycemic control with monotherapy, the reduction in HbA1c is greater when a second agent with a different mechanism is added to the failing agent. Switching from one monotherapy regimen to another is not as effective.

2. Oral Sulfonylureas

a. Oral sulfonylureas lower blood glucose by stimulating insulin release from beta cells in the pancreas.

b. A second-generation oral sulfonylurea is the first-line agent, based on safety. HbA1c should be measured 3-6 months after initiation and changes in therapy. A first-generation sulfonylurea can be used as an alternate agent in selected patients. However, chlorpropamide should only be used in patients < 65 years old who are already stable on the medication; it should not be used as a new agent.

c. No difference in long-term efficacy or failure rate has been demonstrated among the sulfonylureas. The average absolute decrease in HbA1c for these agents is 1.5-2%.

d. If the response to a single daily dose does not achieve treatment goals, dividing the dose may be effective. The dose response to these agents flattens out before maximum dosages are reached.

e. Pharmacologic differences in sulfonylureas may have important clinical implications, particularly with regard to risk of hypoglycemia (Refer to Appendix 2). The preferred agents have shorter half-lives, and inactive metabolites.

f. Certain medications may interact with or potentiate the action of sulfonylureas (Refer to Appendix 3).

g. Approximately 15% of patients may never achieve adequate glucose control (primary failure) and 5-10% per annum loses control of blood glucose (secondary failure).

h. If the patient does not have an initial response to therapeutic doses of a sulfonylurea (primary failure), evaluate patient for possibility of type I diabetes. Make sure patient has no intercurring illnesses or drugs that can interfere with glucose control and assess adherence to diet and drug therapy. For patients experiencing secondary failure, combination therapy with metformin (Hermann 1994 LE=B, DeFronzo 195 LE=A Klein 1991 LE=B, Haupt 1991 LE=C, Trischitta 1992 LE=B), acarbose (Chiasson LE=B), or insulin (Chow 1995 LE=B, Johnson 1996 LE=A, Soneru 1993 LE=C, Yki-Jarvinen 1992 LE=B, Wolffenbuttel 1996 LE=B) is warranted.

i. Sulfonylureas have no appreciable effect on triglycerides, LDL-cholesterol, or HDL-cholesterol.

j. Sulfonylureas can cause weight gains of 2-3 kg.

3. Metformin

a. Metformin is a biguanide oral antihyperglycemic agent. The major blood glucose lowering effect is through decreasing hepatic glucose production with some decrease in peripheral insulin resistance.

b. Metformin may be considered for use as monotherapy if a sulfonylurea cannot be used. (Johansen 1999 Hoffmann 1997 LE=B, UKPDS 34 1998 LE=A) It may be used in combination with an oral sulfonylurea (Hermann 1994 LE=B, Haupt 1991 LE=C,Trischitta 1992 LE=B, De Fronzo 1995 LE=A, Klein 1991 LE=B) acarbose (Rosenstock 1998 LE=B, Chiasson 1994 LE=B), or insulin (Giugliano 1993 LE=B, Robinson 1998 LE=B, Yki-Jarvinen 1999 LE=B) in the event that monotherapy fails to achieve HbA1c goal. The effect of metformin on glycemic control should be additive, due to its different mechanism of action.

c. Efficacy in lowering HbA1c is comparable to oral sulfonylureas; the average absolute decrease in HbA1c is 1.5-2% for monotherapy and when added to other agents.

d. A secondary analysis of results from the UK Prospective Diabetes Study suggested that metformin in overweight patients was associated with only slightly less weight gain over 20 years (2.5kg or 5.5lbs) than oral sulfonylureas or insulin therapy. Metformin also reduced hypoglycemic episodes in aggregate but the impact on major hypoglycemic episodes, defined as an event that required an intervention by a health care provider, was nominal. For example, by intention-to-treat analysis, the incidence of major hypoglycemic episodes for metformin was 0.6% and for sulfonylurea was 1.0% (statistical comparison not provided). In almost all clinical and laboratory endpoints there was no significant difference between metformin and other pharmacologic therapies. For example, each group had similar diabetes-related mortality, macrovascular disease incidence and similar surrogate endpoints such as HbA1c levels and progression to retinopathy. However, the relative risk for any diabetes-related endpoint in aggregate, all-cause mortality, and stroke was lower for the metformin group than for the sulfonylureas or insulin groups. (UKPDS 34 1998 LE=A)

   At present the PBM-MAP recommends the use of sulfonylureas as first-line therapy for most patients with type 2 diabetes. However, metformin may be considered as initial monotherapy in overweight patients (BMI > 25).

e. Starting doses of metformin range from 500mg bid to 850 mg q am. Elderly patients (≥ 65 years old) generally should not be titrated to the maximum dose as renal function decreases with age thereby increasing the risk of lactic acidosis with metformin.

f. Metformin decreases triglycerides and LDL-cholesterol. HDL-cholesterol may increase slightly.

g. The patient should be advised of the transient, dose-related gastrointestinal side effects (i.e. diarrhea, nausea, vomiting, bloating, flatulence, and anorexia).

h. Premenopausal women with polycystic ovary syndrome might resume ovulation with use of metformin. Need for contraception should be discussed with the patient as appropriate.

i. Refer to Appendix 3 for drug interactions.

j. Patients at risk for lactic acidosis should not receive metformin. Specific contraindications include acute or chronic metabolic acidosis, renal dysfunction (SCr $\geq$1.5mg/dl [males] and SCr $\geq$1.4mg/dl [females]), and patients with congestive heart failure requiring pharmacologic management. Avoid use in patients with hepatic disease or excessive ethanol intake. Withhold use in any patient with a condition associated with hypoxemia, dehydration, or sepsis. Temporarily discontinue metformin use at the time of or prior to intravascular radiocontrast studies or surgical procedures. Monitor renal function to prevent lactic acidosis, especially in the elderly. (Refer to Appendix 4)

k. The manufacturer recommends the addition of a second agent for patients not responding to monotherapy with metformin after a 4-week trial using maximal dosages. When metformin is being used as combination therapy, patients not responding to maximal doses of each agent after a 1-3 month trial should be switched to a different regimen.

4. Insulin therapy

a. Insulin is the principal hormone for proper glucose metabolism. Human insulin is manufactured by recombinant DNA technology or chemical modification of pork insulin (Refer to Appendix 5a for various insulin preparations).

b. Use as a second-line agent for failure of oral agents. When used in combination with a sulfonylurea, 10-15 units of NPH or lente can be given at bedtime. (Johnson 1996 LE=A , Chow 1995 LE=B, Wolffenbuttel 1996 LE=B, Soneru 1993 LE=C, Yki-Jarvinen 1992 LE=B, Yki-Jarvinen 1999LE=B)For obese patients (>150% of ideal body weight) 70/30 insulin may be given before dinner. The dose of insulin may be increased by 5-10 units every 1-2 weeks until desired fasting glucose is reached. For therapeutic options with insulin refer to Appendix 5b. Insulin may also be combined with metformin (Giugliano 1993 LE=B, Robinson 1998 LE=B, Yki-Jarvinen 1999 LE=B), acarbose (Kelley 1998 LE=B, Chiasson 1994 LE=B), or troglitazone (Schwartz 1998 LE=A, Buse 1998 LE=B)

c. Efficacy may not increase beyond a single injection per day, though multiple daily dose remains a therapeutic option for some patients (Abraira 1998 LE=B, Chow 1995 LE=B, Wolffenbuttel 1996 LE=B, Soneru 1993 LE=C, Yki-Jarvinen 1992 & 1999 LE=B). Maximum efficacy is up to a 2% absolute reduction in HbA1c.

d. Adverse effects may include hypersensitivity reactions, hypoglycemia, and weight gain.

e. Insulin types and species have different pharmacological properties, and should not be changed inadvertently. (Refer to Appendix 5a) Patients require education on proper insulin administration, mixing if necessary, storage, and syringe disposal. Certain agents may increase or decrease the hypoglycemic effect of insulin (Refer to Appendix 1). Dosage adjustment may be necessary in renal or hepatic impairment, during illness, increased work or exercise, or with a change in eating patterns.

f. Lispro insulin lowers postprandial glucose to a greater extent and may have a lower rate of nighttime hypoglycemia when compared to regular insulin. HbA1c, lipid profile and weight however, were the same for both agents. (Anderson 1997 LE=A) Until there is evidence for improved long-term outcomes, lispro is not recommended for most type 2 patients requiring insulin and should be reserved for use in select cases (eg. frequent nighttime hypoglycemia or frequently elevated postprandial glucose).

g. El Lilly will be phasing out all Iletin I (beef/pork) insulins by 1999. Iletin II (pork only) will continue to be available. Conversion packets from the manufacturer (call 800-545-5979) are available to clinicians wishing to convert patients from Iletin I to human insulin.

5. **Alpha-glucosidase inhibitors**

a. Acarbose and miglitol are α-glucosidase inhibitors that work by delaying the digestion of carbohydrates thereby decreasing postprandial hyperglycemia.

1. Acarbose may be considered for use as monotherapy if a sulfonylurea cannot be used. (Coniff 1994 LE=B, Hanefeld 1991 LE=B, Hoffman 1994 LE=B, Hoffman 1997 LE=B) It may be used in combination with a sulfonylurea (Chiasson 1994 LE=B), metformin (Chiasson 1994 LE=B, Rosenstock 1998 LE=B), or insulin (Kelley 1998 LE=B, Chiasson 1994 LE=B) in the event of failure with monotherapy. The effect of acarbose on glycemic control should be additive, due to its different mechanism of action.

   Miglitol may be considered for use as monotherapy if a sulfonylurea cannot be used. (Segal 1997 LE=B , Johnston 1998a =A) It may also be used in combination with a sulfonylurea in cases where monotherapy has failed (Johnston 1998b LE=A, Johnston 1998c LE=A)

2. Acarbose or miglitol may be considered in patients with elevated postprandial plasma glucose, or impaired glucose tolerance.

b. The efficacy of acarbose or miglitol in lowering HbA1c is inferior to that of the oral sulfonylureas and metformin; monotherapy in previously diet-treated patients resulted in an absolute reduction from baseline in HbA1c of 0.4-1.0%. Combination therapy results in decreases of 0.12-0.6% from baseline.

c. Gastrointestinal side effects tend to limit tolerance of acarbose or miglitol. The recommended starting dose for either agent is 25mg TID with the first bite of each main

meal. However, some patients may benefit from a slower titration period (eg. start at 25 mg per day for 2 weeks, followed by 25 mg BID for 2 weeks, and then 25 mg TID for 8 weeks). Further dosage increases may be made at 4-8 week intervals. The maximum dose for acarbose is 100mg TID (50 mg TID for patients < 60 kg). The maximum dose for miglitol is 100mg TID.

d. The patient should be advised of the transient, dose-related GI side effects (diarrhea, abdominal pain, and flatulence). Initiating therapy at a reduced dosage may reduce these side effects.

e. Reduction in plasma triglycerides may occur with acarbose without a change in LDL or HDL cholesterol. Miglitol does not significantly reduce triglycerides.

f. Body weight does not significantly change with use of these agents.

g. If a patient becomes hypoglycemic from a combination of acarbose or miglitol and a hypoglycemic agent, oral glucose (dextrose) should be given to treat the reaction, since sucrose (table sugar) or a complex carbohydrate (starches) will not be readily effective.

h. Refer to Appendix 6 for contraindications to the use of acarbose or miglitol.

6. Thiazolidinediones ("glitazones")

a. Rosigltazone and pioglitazone are in the drug class known as thiazolidinediones. They work by enhancing insulin sensitivity in skeletal muscle, hepatic, and adipose tissue without directly stimulating insulin secretion from the pancreas. They also have a small effect on inhibiting hepatic glucose output.

b. Troglitazone was withdrawn from the market on March 21, 2000. Patients who are currently receiving troglitazone may either be converted to rosiglitazone or pioglitazone or be reassessed to see whether other agents such as metformin or insulin can be used.
   - For those patients converted to rosiglitazone or pioglitazone, the manufacturers recommend the following:
     1. Allow for a one-week washout period between troglitazone and rosiglitazone or pioglitazone
     2. Obtain a baseline ALT. If the is ALT normal, rosiglitazone or pioglitazone may be initiated.
   - There is no established dose equivalency between troglitazone and rosiglitazone or pioglitazone. The manufacturer of rosiglitazone recommends that all patients start at 4mg/day and the manufacturer of pioglitazone recommends starting either at the 15mg or 30mg dose regardless of the prior dose of troglitazone.

     Alternatively, the following approximation may serve as a guide to initial dosing.

Troglitazone ≤ 400mg once daily	Rosiglitazone 4mg once daily or 2mg bid	Pioglitazone 15mg once daily
Troglitazone 600mg once daily	Rosiglitazone 8 mg once daily or 4mg bid	Pioglitazone 30mg once daily

b. Rosiglitazone and pioglitazone should be reserved for selected patients due to their modest effect on reducing HbA1c compared to sulfonylureas or metformin, unknown long-term safety profile, and high cost.

c. Rosiglitazone and pioglitazone should not be used as monotherapy since there is no advantage in reducing HbA1c over sulfonylureas (SU) or metformin. When used as monotherapy in patients receiving no prior therapy with hypoglycemic agents, the average absolute decrease in HbA1c was 0.2-0.7% from baseline values. In a very small group of treatment naïve patients, pioglitazone given as 45mg once daily resulted in further decreases in HbA1c. Studies with larger numbers of patients are needed to substantiate this finding.

d. The use of rosiglitazone or pioglitazone as part of a combination regimen with SU, metformin, or insulin should be restricted as outlined below.

Rosiglitazone or pioglitazone + sulfonylurea (SU)	**Rosiglitazone or pioglitazone + metformin**	**Rosiglitazone or pioglitazone + insulin**
• Failed monotherapy with an SU ***and*** • Failed or have a contraindication to combining an SU with metformin, an alpha-glucosidase inhibitor, or insulin (or patient adamantly refuses insulin)	• Failed monotherapy with metformin ***and*** • Failed or have a contraindication to combining metformin with an SU, an alpha-glucosidase inhibitor, or insulin (or patient adamantly refuses insulin)	• Insulin in doses > 75 units/day ***and*** • HbA1c > 9% or exceeds target HbA1c value by > 1% ***and*** • Failed or have contraindications to other insulin/oral hypoglycemic regimens
The average absolute decrease in HbA1c when combining a glitazone with a SU is 0.9-1.3%	The average absolute decrease in HbA1c when combining a glitazone with metformin is 0.5-0.8%	The average absolute decrease in HbA1c when combining a glitazone with insulin is 0.6-1.2%

e. Liver function tests abnormalities, jaundice, hepatitis, liver transplant and death have been reported with troglitazone. Phase II and III trials have shown that rosiglitazone and pioglitazone do not cause hepatotoxicity any more than placebo. *Post-marketing studies are needed to confirm the lack of hepatotoxic potential.* Rosiglitazone and pioglitazone should not be used if the patient has evidence of liver disease or an ALT > 2.5x the upper limit of normal. **See Appendix 7 for the required monitoring**

f. Plasma volume has been shown to increase with these agents, causing abnormalities in hematologic parameters such as hemoglobin and hematocrit. Patients with New York Heart Association (NYHA) Class III and IV CHF/angina have not been included in the clinical trials. Until safety data is available, the use of rosiglitazone and pioglitazone are not recommended for these patients. Very few patients with NYHA Class I and II CHF have

been included in the clinical trials; therefore, close monitoring of the patients' fluid status is necessary.

g. Rosiglitazone and pioglitazone may induce ovulation in premenopausal anovulatory patients. Need for contraception should be discussed with the patient as appropriate.

h. Increases in low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and total cholesterol have been observed these agents. LDL-C is increased the least with pioglitazone. The LDL/HDL ratio is preserved, although with rosiglitazone, there is a lag time of several months before HDL-C rises relative to LDL-C. Triglycerides decrease with pioglitazone, whereas the effect with rosiglitazone is variable.

i. Weight gains of 1-4 kg may occur with these agents.

j. Rosiglitazone and pioglitazone do not inhibit any of the major cytochrome P450 isoenzymes.

7. Repaglinide

a. Repaglinide is an oral hypoglycemic agent indicated for treatment of type 2 diabetes either as monotherapy (Goldberg 1998 LE=B, Wolffenbuttel 1999 LE=A) or in combination with metformin (Moses 1999 LE=B) for those who failed treatment with either agent alone. Like sulfonylureas, it works by stimulating pancreatic secretion of insulin.

b. Repaglanide has a faster onset and shorter duration of action than sulfonylureas, therefore postprandial glucose is affected to a greater extent than fasting blood glucose.

c. When used as monotherapy in patients failing diet therapy, decreases in HbA1c ranged from 1-2.7% (number of patients studied was small). The majority of patients studied had received prior hypoglycemic drug therapy. The change in HbA1c ranged from increased values to small decreases of 0.1-0.3%. Combination with metformin resulted in a mean decrease of 1.4% from baseline.

d. The starting dose is 0.5mg in patients with HbA1c < 8%. If the HbA1c is ≥ 8%, a dose of 1 or 2mg may be initiated. Repaglinide should be taken 15 minutes before a meal. Maximum dose is 4mg per meal. Dosing may be individualized so that if a patient misses a meal, the corresponding dose would be omitted. Repaglinide may be used in patients with renal or hepatic impairment; however, dosage adjustments need to be made with caution.

e. Repaglinide has no significant effect on plasma lipids.

f. Body weight may increase by 2-3kg.

g. Repaglinide is metabolized by CYP3A4. Concurrently administered drugs that are inhibitors or inducers of CYP3A4 may decrease or increase the metabolism of repaglinide respectively.

h. The most commonly reported adverse effect was hypoglycemia and was generally comparable to that seen with sulfonylureas.

D. FOLLOW-UP

The patient should be scheduled for appropriate follow-up to evaluate response and tolerability to therapy. Reassess goals and management of acute and chronic problems.

E. SELF MONITORING OF BLOOD GLUCOSE (SMBG)

1. Patients on stable doses of medications do not need frequent SMBG unless the information is being used to alter self-management or when providers are considering altering medications. In most cases, periodic HbA1c is sufficient to ascertain diabetic control. (Faas 1997 LE= B, Oki 1997 LE=C, Wieland 1997 LE=C)

2. Patients who demonstrate good glycemic control while on a stable oral regimen (stable patients) may require fewer or no strips. When metabolic control worsens or changes (illness, change in exercise or diet, etc.), testing requirements may increase. Each provider must ascertain that the patient has proficiency in SMBG technique. Initial and ongoing justification for SMBG use must be provided and should be linked to health outcomes.

RECOMMENDATIONS FOR SMBG	
Patients on Oral Agents	• For **stable** type 2 DM: No more than 50 strips per 150 days. This would allow for twice-weekly testing. Increased numbers of strips may be needed for a limited time period for the following indications: 1) initiation of therapy and/or active adjustment of oral agents 2) prevention and detection of hypoglycemia when symptoms are suggestive of such, or if documented hypoglycemia unawareness 3) detection of hyperglycemia when symptoms or urine glycosuria (for the occasional patient using urine test strips) are suggestive
Patients on Insulin	• The frequency of monitoring should be individualized based on the frequency of insulin injections, hypoglycemic reactions, level of glycemic control, and patient/provider use of the data to adjust therapy

RECOMMENDATIONS FOR SMBG	
	• A combination of pre and postprandial tests should be performed, up to 4 times per day

VI. Suggested Therapeutic Measures for Implementation of Type 2 DM Guideline

A. DOCUMENT ENDPOINTS

At a minimum, a biannual HbA1c should be done

B. EVALUATE ADVERSE DRUG EVENTS

Hypoglycemic events reported in the medical record

C. EVALUATE APPROPRIATENESS FOR USE

1. Patients on a thiazolidinedione have documented failure or contraindications to metformin, acarbose or insulin (or patient refuses insulin)
2. HbA1c checked within 3 months after starting oral therapy, and adjustment of therapy if no improvement
3. SMBG strips prescribed appropriately

D. OTHER QUALITY OF CARE MEASURES

1. Serum creatinine and LFT measurement within 30 days of starting metformin
2. LFT testing performed as indicated in Appendix 7 for the thiazolidinediones.

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Appendix 1. Drugs That May Impair Glucose Tolerance

Beta-blockers, calcium antagonists, diazoxide, diuretics, estrogens, glucocorticoids, isoniazid, l-asparaginase, niacin, oral contraceptives, pentamidine, phenothiazines, phenytoin, rifampin, sympathomimetics, thyroid products

Appendix 2. Oral Sulfonylureas[a]

SULFONYLUREA	POTENCY	DOSING INTERVAL	DAILY DOSE [b] (MG/DAY)	PLASMA HALF-LIFE (HRS)	DURATION OF ACTION (HRS)	ACTIVE METABOLITES
First Generation						
Chlorpropamide	Low	qd	100-500	36	up to 60	yes
Tolazamide	Low	qd-bid	100-1000	7	12-24	yes
Tolbutamide	Low	bid-tid	250-2000	4.5-6.5	6-12	no
Second Generation						
Glimepiride	High	qd	1-4	9	≥24	yes
Glipizide[c]	High	qd-bid	2.5-20	2-4	10-16	no
Glipizide XL	High	qd	5-10	2-5	≥24	no
Glyburide	High	qd-bid	1.25-10	10	≥24	weak

[a] Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc.,1996:130e-130m.

b Reflects commonly used doses (maximum dose not shown). The maximum daily dose may be necessary for some patients.

[c] Absorption is delayed by food, take 30 minutes before a meal.

Appendix 3. Drug interactions with oral hypoglycemic agents

There is a potential for drug interactions between sulfonylureas and highly protein bound drugs (eg. nonsteroidal anti-inflammatories, salicylates, sulfonamides, chloramphenicol, probenecid, monoamine oxidase inhibitors, tricyclic antidepressants, beta-blockers). These interactions are more likely to occur with the first generation agents. Monitor patients for hypoglycemia or loss of glucose control when these agents are added or withdrawn.

Cationic drugs that are eliminated by renal tubular secretion (eg. amiloride, digoxin, morphine, procainamide, quinidine, ranitidine, triamterene, trimethoprim, vancomycin) can potentially interact with metformin by competing for elimination by the renal tubular transport system.

Troglitazone has the potential to induce CYP3A isoenzyme at doses given in clinical practice and may thereby decrease the concentration of drugs metabolized (eg. cisparide, astemizole, cyclophosphamide, clonazepam, carbamazepine, atorvastatin, amlodipine, cyclosporine) by this enzyme.

Repaglinide is metabolized by CYP 3A4, therefore drugs which induce (eg. troglitazone, rifampin, barbiturates) or drugs which inhibit CYP 3A4 (eg. ketoconazole, erythromycin) may result in a decreased or increased concentration of repaglinide respectively. Repaglinide is also >98% protein to albumin, therefore other highly protein bound drugs may interact.

The table below lists interactions that are either on file with the manufacturer or published in small studies or case reports.

Antidiabetic Agent	Interacting Drug	Result
Glipizide	MgOH or $NaHCO_3$ containing products	Enhanced absorption rate of glipizide and glucose reduction
Glyburide, glipizide	Cimetidine	May ↑ serum concentration of antidiabetic agent
Glyburide, glipizide	Cyclosporine	May ↑ concentration of cyclosporine
Glyburide	Gemfibrozil	May potentiate action of glyburide
Glyburide	Rifampin	May ↓ glyburide concentrations
Glyburide	Fluoroquinolones	May potentiate action of glyburide
Glipizide	Fluconazole	May ↑ glipizide concentration
Sulfonylueas (type not specified)	Oral miconazole	Can result in hypoglycemia
Glimepiride	Propranolol	↑ concentration of glimepiride
Acarbose	Warfarin	May ↑ absorption of warfarin with ↑ INR
Acarbose, miglitol	Digestive enzymes	May ↓ effectiveness of acarbose or miglitol
Acarbose, miglitol	Digoxin	May ↓ digoxin concentration
Acarbose, miglitol	Charcoal absorbants	May ↓ effectiveness of acarbose or miglitol
Miglitol	Propranolol	May ↓ bioavailability of propranolol by 40%
Miglitol	Ranitidine	May ↓ bioavailability of ranitidine by 60%
Metformin	Furosemide	Furosemide may ↑ metformin concentration and metformin may ↓ furosemide concentration
Metformin	Nifedipine	May ↑ concentration of metformin
Metformin	Cimetidine	May ↑ concentration of metformin

Appendix 4. Metformin Drug Therapy [a]

- **Do not use in patients with renal dysfunction (Scr > 1.5mg/dl for males or > 1.4mg/dl in females), in patients with congestive heart failure requiring pharmacologic management, or in patients with acute or chronic metabolic acidosis.**
- **Temporarily discontinue metformin use at the time of or prior to intravascular iodinated radiocontrast studies and withhold for 48 hours after procedure. Reinstitute only after renal function has been reevaluated and found to be normal.**
- **Should not be used in patients ≥ 80 years of age unless normal creatinine clearance, and the dose should not be escalated to the maximum in elderly patients due to increased susceptibility to lactic acidosis.**
- **Avoid use in patients with hepatic disease or excessive ethanol intake.**
- **Withhold metformin in the presence of any condition associated with hypoxemia, dehydration or sepsis.**

DOSE	CAUTIONS/MONITOR
•Check S_{cr} and LFTs prior to starting therapy •Starting dosage is either 500mg bid or 850mg q am •If on 500mg bid, dosage increase may be made by 500mg increments weekly up to 1000mg bid; doses ≥2500 should be given tid with meals • If on 850mg qam, dosage increase of 850mg may be made every other week (given as 850mg bid). Maximum dose: 2550 mg/day (850mg tid) • The usual maintenance dose is 850 mg bid with meals; the dose response curve usually flattens out after 2000mg/day	•Inform patient to take with food to avoid possible GI symptoms (diarrhea, nausea, vomiting, bloating, flatulence, anorexia) •Counsel patient to be aware of possible metallic taste in mouth •Monitor BUN, creatinine, and electrolytes within 2 weeks of initiation or dosage change •Caution patients against use with alcohol as alcohol potentiates the effects of metformin on lactate metabolism

[a] Adapted from Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc., 1998:130n-130u.

Appendix 5a. Comparison of Insulin Preparations[a,b]

INSULIN[a]	ONSET (HRS)	PEAK (HRS)	DURATION (HRS)[C]	COMPATIBLE MIXED WITH:	APPEARANCE
RAPID-ACTING					
Regular	0.5-1	1-5	6-10	all	Clear
Lispro	0.25-0.5	0.5-2.5	3-6.5	ultralente-NPH[d]	Clear
INTERMEDIATE-ACTING					
NPH	1-2	6-14	16-24+	regular	Cloudy
Lente	1-3	6-14	16-24+	regular	Cloudy
LONG-ACTING					
Ultralente	4-6	8-20	24-28	regular	Cloudy

[a] Adapted from AHFS Drug Information, American Society of Health-System Pharmacists, Inc., 1998.

[b] Onset, peak, and duration are parameters for non-human insulin preparations; in general, human preparations have shorter times of duration.

[c] Duration may depend on type of preparation and route of administration as well as patient related variables. In general, the larger the dose of insulin, the longer the duration of activity.

[d] The effects of mixing insulin lispro with insulins of animal source or insulins produced by manufacturers other than Eli Lilly have not been studied.

Appendix 5b. Insulin Regimen Examples[a-c]

Bedtime Dosing of NPH or Lente Insulin in Addition to an Oral Agent	•Begin with 10-15 units at bedtime •Example: A dose equal to the morning glucose/18[a] •Verify that the pre-dinner glucose remains in control
Split Mixed Regimen with NPH/Regular[c]	•Inject 2/3 of the total insulin requirement in the morning, with a NPH/Regular ratio of 70/30 •Inject 1/3 of the total insulin requirement in the evening, with a NPH/Regular ratio of 50/50[b]
Once-daily Morning NPH insulin	• Good for elderly or non-compliant patients • Inject 30-60 minutes before breakfast • Usual dosage < 40 units/day

[a] Adapted from Edelman SV, White D, Henry RR. Intensive insulin therapy for patients with type II diabetes. Current opinion in endocrinology and diabetes 1995;2:333-340.

[b] These are a few examples, optimal regimen depends on the individual patient

[c] Always counsel patients to mix regular insulin in syringe first, followed by NPH; mixtures of regular and lente insulins should be injected immediately. Inject regular insulin 30-60 minutes before a meal; Lispro insulin should be injected within 15 minutes before a meal; mixtures of lispro and Humulin N or Humulin U should be administered immediately. Manufacturer specific storage guidelines should be followed

Appendix 5c.

GENERAL GUIDELINES FOR INSULIN ADJUSTMENT IN THE TYPE 2 DM PATIENT ON SPLIT REGIMENS
• If the morning fasting blood sugar is off target, adjust the evening NPH or switch evening NPH to bedtime • If the evening serum glucose is off target, adjust the morning NPH • If the evening glucose continues to be off target, have the patient check the pre-lunch glucose • If the pre-lunch glucose is off target, adjust the morning Regular insulin • If the bedtime glucose is off target, adjust the evening Regular insulin • Generally, the patient's basic insulin dose (the dose the patient will be taking daily) can be adjusted by 1-2U at a time and should be based on the individual patient's response to insulin

Appendix 6. Alpha-glucosidase inhibitors (acarbose and miglitol)

DOSE	CAUTIONS/MONITOR	CONTRAINDICATIONS
Initial starting dose: 25 mg tid **Alternate starting dose:** 25 mg qd x 1-2 weeks followed by 25 mg bid for 1-2 weeks with subsequent increase to 25 mg tid. Once a 25mg tid dosing regimen is reached, further increases may be made at a 4-8 week interval. **Maintenance dosage:** 50 mg tid **Maximum dosage:** Acarbose 100 mg tid (< 60 kg 50 mg tid) Miglitol 100mg tid	•Inform patient to take dose with the first bite of each main meal •Patients should maintain a diet high in complex carbohydrates and low in simple sugars to achieve maximum benefit and minimize adverse effects •Inform patient of possible GI symptoms (diarrhea, abdominal pain, flatulence) that may occur during the first few weeks of therapy •Acarbose, especially at doses greater than 50 mg TID may cause serum AST/ALT elevation; monitor serum levels every 3 months during the first year of treatment •Renal impairment has been shown to increase plasma concentrations of acarbose and miglitol; their use is not recommended in patients with SCr > 2.0mg/dl	•Hypersensitivity to the drug •Presence of diabetic ketoacidosis •Presence of intestinal complications (ulceration, obstructions, digestion or absorption disorders) • Presence of cirrhosis for acarbose. Miglitol pharmacokinetics are not altered in cirrhosis and may be used

Appendix 7. Thiazolidinedione ("glitazones") Drug Therapy

DOSE	CAUTIONS/MONITOR	WARNINGS
If using in combination with a sulfonylurea, metformin,or insulin, the current dose should be continued when adding a glitazone. **Rosiglitazone** • Start at 4mg/day (single dose or divided into 2 doses). May increase to 8mg/day (single dose or divided into 2 doses) after 12 weeks if glycemic control is inadequate. • Maximum dose is 8mg daily (single or bid dosing) and can be given without regard to meals. • Dosage adjustment is not required in patients with renal insufficiency **Pioglitazone** • Start at 15 or 30mg once daily. Maximum dose is 45mg daily and can be given without regard to meals. • Insulin dosage should be decreased by 10-25% after fasting glucose levels decrease to less than 100mg/dl. • Dosage adjustment is not required in patients with renal insufficiency	Liver function test abnormalities, jaundice, hepatitis, liver transplant and death have been reported with troglitazone. **Rosiglitazone and pioglitazone** • Do not initiate in patients with ALT > 2.5x the upper limit of normal. • Liver function tests and bilirubin should be tested every 2 months for 1 year, then periodically thereafter. If ALT is > 3x upper limit of normal, recheck another level as soon as possible. If ALT remains > 3x the upper limit, discontinue use. Monitor for signs and symptoms suggestive of hepatic dysfunction such as nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine or jaundice. Patients should be instructed to inform their physician should they develop these symptoms.	• Plasma volume may increase with rosiglitazone or pioglitazone thereby potentially exacerbating congestive heart failure. Patients with New York Heart Association Class III and IV were not included in clinical trials therefore use in these patients is not recommended. • Patients with NYHA Class I or II should have their fluid status monitored closely.

Appendix 8. Selected Costs for Type 2 DM Drug Therapy

For current VA prices, check the Pharmacy Benefits Management website (www.dppm.med.va.gov).

DRUG	USUAL DOSE[a]	FEDERAL SUPPLY SCHEDULE (FSS) COST/MONTH
Oral Sulfonylureas		
1st generation		
Chlorpropamide	250 mg po qd	$ 5.84
Tolazamide	250 mg po bid	$ 2.91
Tolbutamide	500 mg po bid	$ 4.97
2nd generation		
Glimepiride	4 mg po qd	$ 7.18
Glipizide	10 mg po bid	$ 1.08
Glipizide XL	10mg po qd	$ 10.27
Glyburide	5mg po bid	$ 1.53
Insulin		
Lente Human - U100/10mL	individualized	$ 4.49
Lispro Human - U100/10mL	individualized	$ 15.39
NPH Human - U100/10mL	individualized	$ 4.49
Regular Human - U100/10mL	Individualized	$ 4.49
Ultralente Human - U100/10mL	individualized	$ 15.39
70/30 Human - NPH/regular 10ml	individualized	$ 4.49
Metformin	850 mg po bid	$ 30.56
Acarbose	50 mg po tid	$ 24.00
Miglitol	50 mg po tid	$ 30.98
Rosiglitazone	4mg po bid	$ 90.00
Pioglitzone	30mg po qd	$ 85.20
Repaglinide	1mg po tid	$ 40.13

[a] Usual dose; does not reflect equivalent doses